■ Original article

Epileptic Disord 2021; 23 (6): 865-874

Epileptic Disorders

Epilepsy features in *ARID1B*-related Coffin-Siris syndrome

Jacopo Proietti[1,2], Elisabetta Amadori[3], Pasquale Striano[3,4], Emilia Ricci[5], Duccio Maria Cordelli[5], Cristina Bana[6], Robertino Dilena[6], Elena Gardella[7], Jens Erik Klint Nielsen[8], Francesco Pisani[9], Tommaso Lo Barco[10,11], Elena Fiorini[1,12], Elena Fontana[1,12], Francesca Darra[1,10,12], Bernardo Dalla Bernardina[12], Gaetano Cantalupo[1,10,12]

[1] U.O.C. di Neuropsichiatria Infantile, Dipartimento ad Attività Integrata Materno Infantile – AOUI di Verona, Verona, Italy
[2] PhD program Applied Sciences of Life and Health, University of Verona, Verona, Italy
[3] Pediatric Neurology and Muscolar Diseases Unit, IRCCS "G. Gaslini" Insitute, Genova, Italy
[4] Department of Neurosciences, Rehabilitation, Ophtalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy
[5] IRCCS Istituto delle Scienze Neurologiche di Bologna, UO Neuropsichiatria dell'età Pediatrica, Bologna, Italy
[6] UOC Neurofisiopatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
[7] Department of Clinical Neurophysiology, Filadelfia Epilepsy Hospital, Dianalund, Denmark
[8] Department of Clinical Medicine, Zealand University Hospital, Roskilde, Denmark
[9] U.O. di Neuropsichiatria Infantile, AOU di Parma, Parma, Italy
[10] Child Neuropsychiatry, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy
[11] PhD program Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy
[12] Centro Ricerca per le Epilessie in età Pediatrica (CREP), Azienda Ospedaliera Universitaria di Verona, Verona, Italy

Received January 27, 2021;
Accepted May 15, 2021

ABSTRACT

Objective. Coffin-Siris syndrome (CSS) is a rare congenital malformation syndrome, caused by mutations in the *ARID1B* gene in over half of the cases. While the clinical characteristics of the syndrome have been increasingly described, a detailed evaluation of the epileptic phenotype in patients with *ARID1B* alterations and CSS has not been approached yet. We report seven patients with *ARID1B*-related CSS, focusing on epilepsy and its electroclinical features.

Methods. The evolution of epilepsy and EEG findings of children with CSS are described and compared with patients previously reported in the literature.

Results. The patients described here reveal common features, consistent with those of patients previously described in the literature.

Significance. The epilepsy phenotype of CSS due to *ARID1B* pathogenic variants may be described as focal epilepsy with seizures, variable in frequency, arising from motor areas, with onset in the first years of life and susceptibility to fever, and interictal perisylvian (centrotemporal) epileptiform abnormalities that are enhanced during sleep with possible evolution to an EEG pattern of continuous spike and wave during sleep (without documented developmental regression). Additional information emerging from other patients is needed to confirm this definition.

Key words: Coffin-Siris Syndrome, *ARID1B* gene, focal epilepsy, childhood, Rolandic trait, fever susceptibility

• **Correspondence:**
Gaetano Cantalupo
University of Verona,
AOUI Verona,
P.le A. Stefani 1,
37126 Verona, Italy
<gaetano.cantalupo@univr.it>,
<gcantalupo@gmail.com>

doi:10.1684/epd.2021.1356

Coffin-Siris syndrome (CSS) is a rare syndrome, caused by mutations in several genes encoding components of the BAF complex [1, 2]. Among those, *ARID1B* is the most frequently mutated gene (51–75% of CSS) [3-5]. In the large majority of patients reported in the literature, pathogenic variants occur *de novo* and are truncating (nonsense, frameshift, splice-site, and deletions of various numbers of exons including whole-gene deletions). A genotype-phenotype correlation is not evident.

Since the first description by Coffin and Siris in 1970, more than 60 patients have been reported and clinical characteristics of the syndrome have been increasingly outlined [6]. Cardinal features of

CSS include variable degrees of developmental and cognitive delay predominantly affecting speech, hypotonia, dysmorphic facial features (including sparse scalp hair, thick eyebrows, long eyelashes) and hypertrichosis [7]. Other frequently encountered characteristics are feeding difficulty, laryngomalacia, recurrent infections, vision and hearing impairments, digital abnormalities (aplasia or hypoplasia of the fifth distal phalanx or nail) and scoliosis, cardiac and renal anomalies, and cryptorchidism. Endocrinological abnormalities (including growth hormone deficiency, hypothyroidism and diabetes mellitus) can be found. Neuroradiological abnormalities are frequently found but not pathognomonic [3-6, 8, 9]. To date, information in the literature on the epilepsy features of subjects with CSS and confirmed pathogenic *ARID1B* mutation is sparse and the EEG documentation is lacking. We describe the evolution of epilepsy and the EEG findings of several children with CSS and compare with patients previously reported in the literature.

Methods

We report seven patients with ARID1B-related CSS (six patients with pathogenic mutations and one patient with a whole-gene deletion), focusing on epilepsy and its electroclinical features which are extensively presented in the results section. Patients 1 to 3 were regularly followed in the Child Neuropsychiatry Unit in Verona. Patients 4 to 7 were collected from three other Italian tertiary centres and Filadelfia Epilepsy Centre in Denmark, after a call for cases conducted in the framework of the Italian League Against Epilepsy.

Furthermore, a literature review was performed on PubMed. We searched for reports published from 1976 to 2020, using the following search terms: ((“Seizures”[Mesh]) OR (“Epilepsy”[Mesh])) AND ((“Coffin-Siris syndrome” [Supplementary Concept]) OR CSS OR “Coffin-Siris” OR ARID1B). Furthermore, we manually searched pertinent reports quoted in the selected literature.

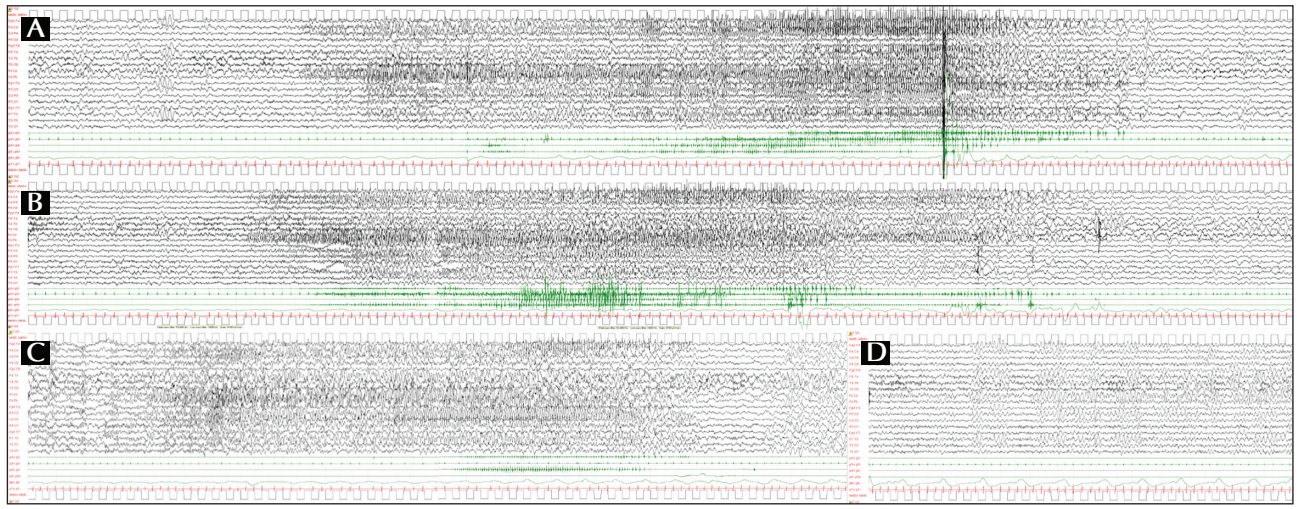
Finally, we performed a descriptive comparison of epilepsy features between our cohort and previously reported patients; among the latter, we considered only reported patients with adequate information on the epilepsy phenotype.

Results

All patients reported presented with variable dysmorphic facial features, along with developmental and cognitive impairment, detected before epilepsy onset in all cases. The developmental and cognitive impairment was difficult to quantify since only one of the patients received a standardized assessment, but was considered at least moderate in all cases by the referring physician. Speech was severely delayed in all cases, and not developed in five out of seven. Motor milestones were also delayed, with predominant hypotonia invariably present in the first months of life and autonomous walking achieved between two and three years in six out of seven cases. General clinical and neurological traits are summarized in *supplementary table 1*.

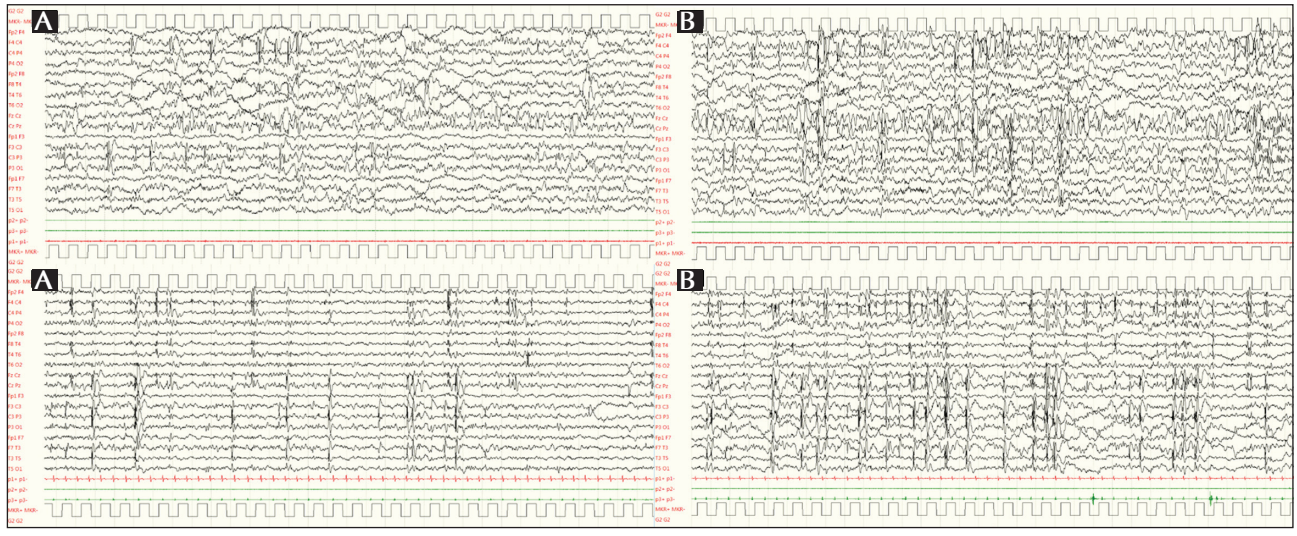
Patient 1 is a four-year-old boy who had a stormy epilepsy onset at one year and four months of age, when he experienced focal motor seizures during both sleep and wakefulness, without fever. The seizure frequency was daily at onset and rapidly increased up to 70 seizures per day, despite polytherapy with carbamazepine, nitrazepam, and valproic acid. Seizures, each lasting up to 80 seconds and self-limiting, were characterized by changes in breathing, upper and lower limb hypertonia evolving to a tonic-vibratory phase, followed by clonic twitches asynchronously affecting both sides of the body. The ictal EEG showed a focal discharge of polyspikes involving the vertex region soon involving the motor areas of both hemispheres, asynchronously (with alternating side predominance) and sometimes independently (*figure 1*). The interictal EEG showed intermittent medium-voltage theta activity in the vertex region, spreading to the centro-temporal areas of both hemispheres, in the absence of clear-cut epileptiform abnormalities at this stage. Due to the progressive worsening, about 25 days after seizure onset levetiracetam, phenobarbital and phenytoin were sequentially added, with a gradual reduction in seizure frequency and duration, obtaining complete seizure freedom 45 days after onset. Comprehensive metabolic testing and array-CGH were negative. After a first negative 45-gene panel, a second targeted 149-gene panel for epilepsy revealed a *de novo* heterozygous stop-gain mutation [c.5547del (p. Leu1850*)] in *ARID1B*. During the 24-month follow-up period, the antiepileptic therapy was gradually simplified with a transition to carbamazepine monotherapy. Since then, only one isolated seizure has occurred by the age of two years and three months, during fever. At the age of three years and six months, interictal epileptiform abnormalities, asynchronous over the Rolandic regions of both hemispheres, became evident during drowsiness and sleep (*figure 2A*).

Patient 2 is a nine-year-old boy, whose epilepsy onset occurred at age two years and 10 months, characterized by isolated tonic-vibratory seizures, occurring exclusively during sleep, each lasting less than one minute, varying in frequency from one up to five per year. Seizures occurred in a cluster only once, during fever. The interictal EEG by the age of three years and six



■ **Figure 1.** New-onset status epilepticus at the age of one year and four months in Patient 1. (A) The ictal discharge arises from the vertex region and simultaneously or a few seconds later, spreads to the Rolandic regions of both hemispheres, often asynchronously. (B) The discharge involves earlier the right central region and lasts longer in the right hemisphere. (C) By contrast, the discharge more markedly involves the central regions of the left hemisphere with simultaneous activation of polygraphic channels on the right side of the body. (D) The interictal EEG shows intermittent medium-voltage theta activity on central-temporal areas of both hemispheres and on the vertex; epileptiform abnormalities are not evident at this stage.

months showed epileptiform abnormalities asynchronously on the Rolandic regions of the two hemispheres, later on increasing in frequency especially during sleep, to an EEG pattern of continuous spike and wave during sleep (CSWS) by the age of six years (*figure 2B*). This EEG pattern was not associated with cognitive, behavioural or neurological worsening, and was therefore not consistent with the electroclinical syndrome of encephalopathy related to status epilepticus during sleep (ESES). The array-CGH analysis



■ **Figure 2.** Interictal epileptiform abnormalities on the Rolandic regions during drowsiness (left) and sleep (right) in Patient 1 at the age of three years and six months (A) and in Patient 2 at the age of five years and six months (B).

revealed a 5.4-Mb *de novo* deletion (del 6q25.2q25.3) including *ARID1B*.

Patient 3 is a girl, nine years and six months old, who displayed only one seizure with convulsive semiology, during fever and during wakefulness, at the age of one year and nine months. The interictal EEG showed unusual theta activity over the frontal-centro-parietal areas at the time of the febrile seizure and by the age of four years, isolated sharp waves, asynchronously in the centro-parietal regions of both hemispheres and over the vertex, increasing in frequency during sleep. The mentioned interictal epileptiform abnormalities persisted, with similar characteristics up to the last evaluation performed at the age of seven years and 10 months. The CSS-specific genetic testing, based on clinical suspicion, revealed a *de novo* heterozygous frameshift mutation leading to a premature stop [c.1382_1391delGGGCGGCGGC (p.Ala464SerfsTer35)] in *ARID1B*.

Patient 4 is an 11-year-old boy, who displayed focal clonic seizures (with hemifacial and upper limb jerks) and tonic seizures by the age of two years and six months, occurring initially only during fever and later also during apyrexia, that persisted in the following years despite several anti-seizure medications (valproate and carbamazepine as monotherapy, then valproate combined with clobazam and ethosuximide). From the age of four years, the interictal EEG showed centro-temporal epileptic abnormalities asynchronously on the two hemispheres, enhanced during sleep and evolving – by the age of six years – to an EEG pattern of CSWS. The presence of concomitant neurological or cognitive regression was not clear and a treatment cycle with ACTH did not improve the EEG pattern. By the age of seven years and nine months, increasing epileptiform abnormalities were seen also during wakefulness with a further deterioration in background EEG activity (*figure 3*). Diffuse spike-wave and polyspike-wave discharges with hard-to-notice clinical correlate (sometimes subtle jerking, suggestive of myoclonic-atonic phenomena) were recorded both in sleep and awake EEG recordings. Metabolic investigations were unremarkable. Whole-exome sequencing revealed a novel heterozygous *de novo* mutation [c.2270C>T (p.Ala757Val)] in exon 6 of *ARID1B*. This variant (NM_020732) is not reported in GnomAD, dbSNP150, 1000 Genomes Phase 3, or ESP. It is predicted as pathogenic (Class IV) following the ACMG criteria and based on common bioinformatic predicting software (PolyPhen=2; MuuTaster= disease-causing; DANN=0,9992; Provean=deleterious).

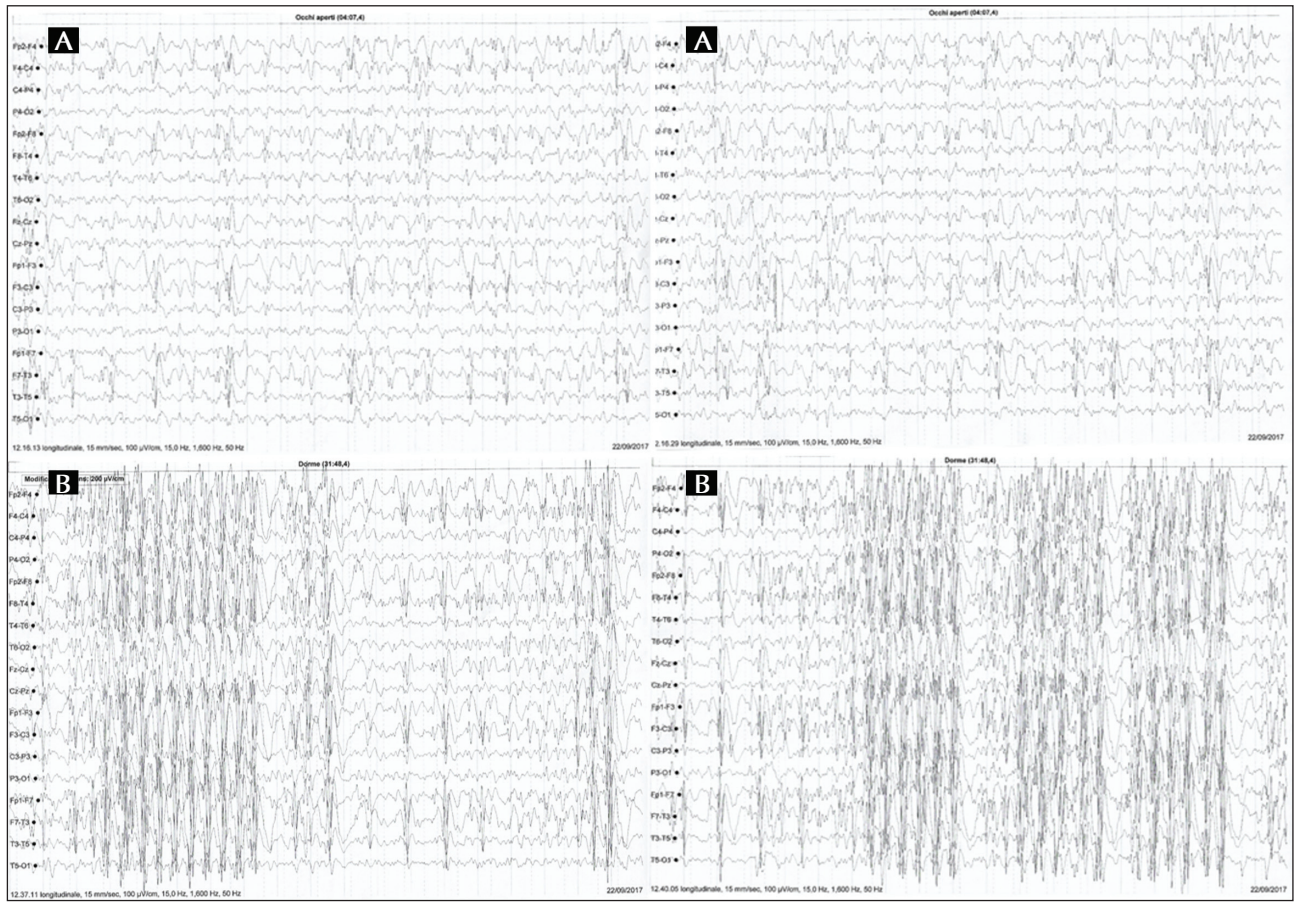
Patient 5 is an eight-year-old girl. She presented with seizures at the age of four years and 11 months, mainly during sleep, with focal onset (motion arrest, staring, and oroalimentary automatisms) and evolving to a tonic or tonic-clonic phase, each interrupted with benzodiazepines. After a frequency of up to four per month initially, seizures were controlled with carbamazepine therapy. The interictal EEG at epilepsy onset showed medium-voltage asynchronous spike-waves in both hemispheres, predominant in the posterior regions at the age of five (*figure 4A*). After, by the age of six years, interictal EEG abnormalities were prevalent over the centrotemporal regions of both hemispheres, increasing in frequency during sleep (*figure 4B*). A sleep EEG was not performed after the age of six. CSS-specific genetic testing, based on clinical suspicion, revealed a *de novo* heterozygous frameshift mutation [c.5265_5266delAG (p.Glu1756LysfsTer3)] in *ARID1B*.

Patient 6, a 10-year-old girl, experienced her first epileptic seizure at nine years and two months during drowsiness, with impaired awareness, drooling and predominant right upper limb hypertonia and clonic movements, self-remitting after about one minute. After a week, sleep EEG was recorded over an afternoon (*figure 5*), showing multifocal isolated spikes and spike-waves, sometimes in short sequences, asynchronous on the fronto-centro-temporal regions of both hemispheres, and activated by sleep. One low-voltage fast-activity discharge arising from the left hemisphere, lasting 10 seconds and not associated with clinical manifestations, was also recorded during drowsiness (an electrographic-only seizure). Antiseizure therapy with levetiracetam was then started, with subsequent reduction of interictal abnormalities during both wakefulness and sleep, as well as seizure freedom at the last visit. A *de novo* heterozygous stop-gain mutation [c.382G>T p.Glu1276*] in *ARID1B* was identified.

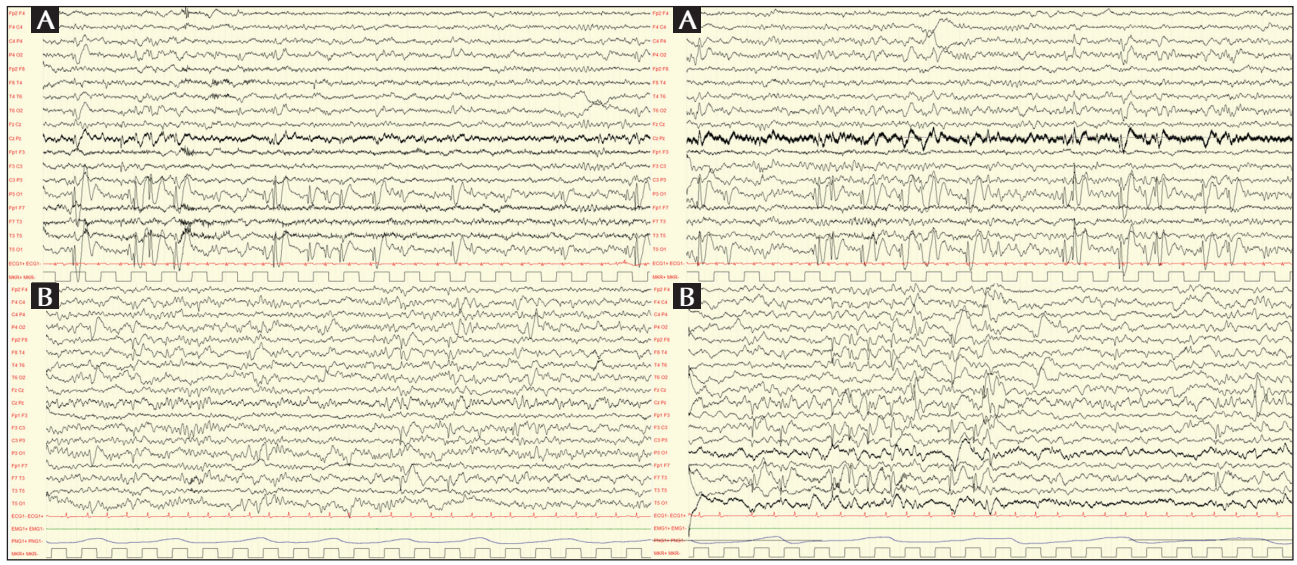
Patient 7 is a 14-year, six-month-old boy. At the age of six years and six months, he presented with a first tonic seizure, during sleep, with sustained head and eye deviation to the right, self-terminating after three to five minutes. In the following year, three more asymmetric tonic seizures occurred, exclusively in sleep, with similar semiology and duration. After valproate introduction and optimization, he is still seizure-free after five years. The interictal EEG at onset was characterized by isolated focal spikes, often followed by slow waves over the right temporal and parietal lobes, sometimes spreading to homologous contralateral regions and markedly activated both in amplitude and frequency during sleep (without becoming continuous); focal abnormalities appeared to be mitigated in subsequent EEGs. Genetic testing revealed a *de novo* mutation c.2002_2006delinsTTC; p.(Asn668PhefsTer18) in the A*RID1B* gene.

Literature review

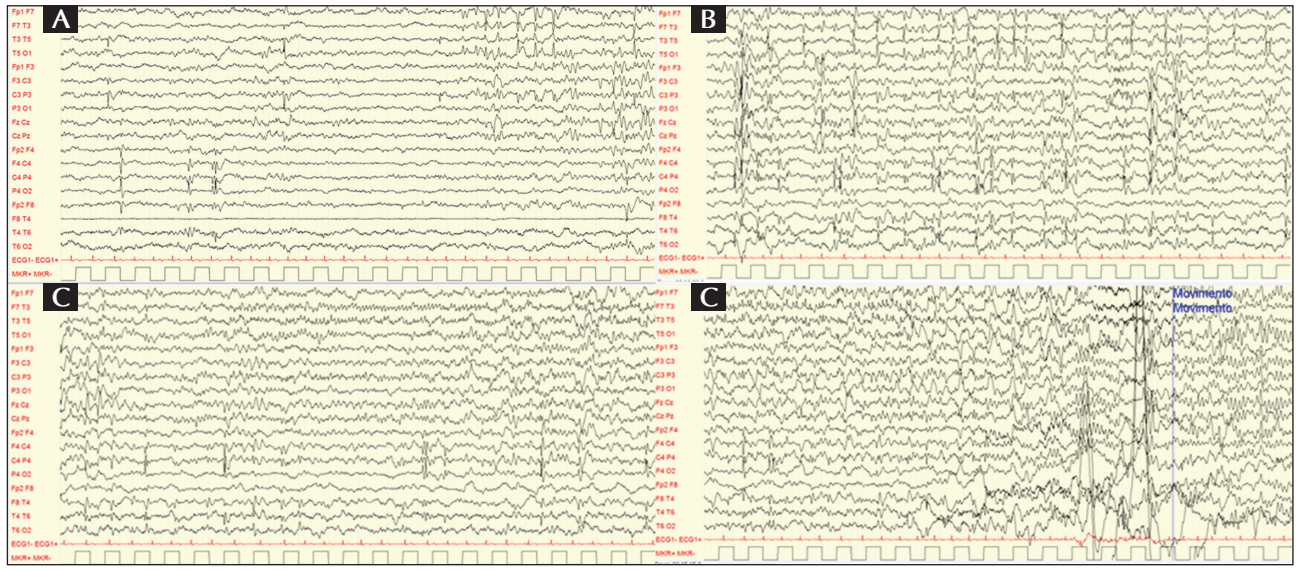
Among the 143 subjects with pathogenic variants in *ARID1B*, recently collected by Van der Sluijs and



■ **Figure 3.** EEG of Patient 4 at the age of seven years and nine months showing subcontinuous epileptiform abnormalities over the central-temporal regions in the awake state (A) and diffuse high-amplitude spike-wave discharges during sleep (B).



■ **Figure 4.** Interictal abnormalities on the posterior regions at the age of five in Patient 5 (A) become clearly dominant over the central-temporal regions of both hemispheres by the age of six years (B).



■ **Figure 5.** Interictal multifocal epileptiform abnormalities, asynchronous on both hemispheres (A), are activated by sleep (B) at the age of nine years and three months in Patient 6. One electrographic seizure consisting of low-voltage fast activity arising from the left hemisphere and lasting for10 seconds occurs during drowsiness in the same recording (C).

colleagues within the framework of an international survey, approximately one third (27.5%) experienced seizures. The age at onset of the seizures varied from birth to 14 years, with a median age at seizure onset of four years. All patients responded well to standard antiseizure drugs, while four did not receive medications. Additional individuals (5.6%) had an "abnormal EEG" (not further specified), without apparent clinical seizures. More specific information about epileptic features in this population was not provided in this survey, which mainly focused on the general clinical phenotype. Notably, the semiology of seizures was not mentioned and details on single patients were not provided [6].

Detailed descriptions can be found in single case reports. In 1976, Sylvester *et al*. reported a patient who had epileptic fits in infancy, which diminished in frequency by the age of two and a half and ceased at 14 years [10]. Bender *et al*., in 2011, described a patient diagnosed with partial epilepsy at the age of four years. She experienced "simple" and "complex partial" seizures with clonic activity that involved either side of the body, predominantly the arm, associated with Todd's paralysis, lasting up to 30 minutes. She also experienced secondary generalized tonic-clonic seizures, as well as a burst of prolonged seizure activity lasting for more than 30 minutes (status epilepticus). Seizures, predominantly nocturnal, occurred monthly and were prominent during febrile illnesses. EEG at four years of age was abnormal due to the presence of sharp wave-and-spike discharges arising independently in the central region of both hemispheres, and by the age of 7.5 years, revealed medium-amplitude sharp waves in the centrotemporal regions of both sides asynchronously; sleep architecture was abnormal due to the lack of well-formed vertex sharp transients and sleep spindles [11]. In 2016, Takenouchi *et al*., reported a patient with seizure onset at the age of three years and EEG abnormalities treated with valproic acid [12]. In the same year, Sonmez *et al*., described the case of a girl who had a seizure with fever at two months of age and developed, by the age of 13, recurrent afebrile generalized tonic-clonic seizures (three to four times monthly), successfully treated with oxcarbazepine after six months [8]. Recently, Curcio *et al*. reported an epilepsy phenotype in three patients with CSS, two of whom were carrying a mutation in the *ARID1B* gene; these latter presented with focal-onset seizures by the age of five years, isolated and brief in duration, both during wakefulness and sleep, which were satisfactorily treated with carbamazepine and valproic acid, respectively. EEG recordings documented focal paroxysms in the left frontal-central-temporal region in the first patient and right temporal-occipital spikes and spike-and-waves enhanced by sleep in the second [13].

Summary of findings

The analysis of the patients presented in the present paper and of those previously described in the literature reveals common epilepsy features, summarized in *table 1*.

In our series, the mean age at seizure onset was four years and two months (median of two years and 10 months), as opposed to three years and three months (median of three years and six months) among the previously reported patients. One out of seven patients experienced status epilepticus (SE) (14%), and one out of the six single cases previously published similarly had SE (17%). Fever susceptibility was present in four out of seven patients in our series (57%), and two out of six previously published cases (33%). Six out of seven patients in our series experienced focal seizures. Among those, five patients had motor-onset seizures and one had non-motor-onset seizures. The predominant seizure type was tonic in five cases and clonic in two cases (two patients experienced both clonic and tonic seizures); one patient (Patient 5) experienced focal non-motor seizures evolving to tonic or tonic-clonic. The seizures occurred in sleep in all cases, as well as in wakefulness in two patients (Patient 1 and 4, during phases with transient worsening). Among the six previously published patients, three had focal-onset seizures, one had apparently generalized seizures, while the seizure semiology was not mentioned in two cases. Four out of six previously reported patients achieved seizure remission within adolescence (the evolution of epilepsy was not described in the remaining two cases).

Focal interictal epileptiform abnormalities, predominant in the motor areas, represented a common EEG trait in our patients. This finding emerged during follow-up EEG recordings, performed between three and a half years and four years in patients who had had epilepsy onset earlier in life (Patients 1 to 4), but was encountered during the first recorded EEG for those who experienced their first seizure after the age of four years (Patients 6 and 7). In one case (Patient 5, who experienced focal non-motor seizures), the epileptic focus was occipital at onset and changed to centro-temporal by the age of six years. The focal paroxysmal abnormalities were enhanced by sleep in all cases, reaching a continuous or subcontinuous pattern in sleep in three out of seven patients (by the age of six in all three cases). Similarly, all previously published patients whose EEG features were described (four out of six) showed focal interictal paroxysmal abnormalities with comparable localization, enhanced by sleep in two cases [11, 13].

Discussion

Based on the electroclinical features of this cohort, the epilepsy phenotype of *ARID1B*-related CSS is that of a focal epilepsy with multifocal seizures originating from both hemispheres, variable in frequency, with onset in the first years of life, fever susceptibility, and interictal perisylvian/Rolandic (centrotemporal) paroxysmal abnormalities enhanced during sleep with possible evolution to an EEG pattern associated with CSWS (without documented developmental regression). The possible self-limiting evolution observed in the cases described in the literature is consistent with the features from only one patient (Patient 7) in our series since the actual age in the remining patients was prepuberal at the time of the study.

Tonic-clonic seizures, mentioned by Sonmez and collaborators in their case report [8], are most likely focal to bilateral tonic-clonic seizures. Both our series and other previously reported single patient descriptions, providing details on ictal semiology and EEG features, support the hypothesis of focal epilepsy.

The EEG features emerging from our series are similar to those observed in other genetically determined syndromic entities in which a "Rolandic trait" is frequently encountered, such as Fragile X syndrome [14] and SATB2-associated syndrome [15].

The change in location of interictal EEG abnormalities observed in our Patient 5, who showed medium-voltage asynchronous spike-waves in the posterior regions at onset, and thereafter clearly preponderant centro-temporal abnormalities by the age of six years, can be interpreted in analogy to what is proposed for the concept of "childhood seizure-susceptibility syndrome"; in which the dysfunctional hyperexcitability parallels the postero-anterior gradient of brain maturation, thus generating distinct effects at different ages [16, 17].

In our patients with marked activation of focal abnormalities during sleep, the possible cognitive regression associated with subcontinuous epileptiform discharge in sleep was difficult to evaluate because of their pre-existing significant neurodevelopmental impairment. This implies that our patients cannot be diagnosed as ESES, although a phase of epileptic encephalopathy and regression cannot be excluded.

Taken together, the following are phenomena observed in self-limiting focal epilepsies of childhood (SLFEC): (1) presence of epileptiform abnormalities resembling a "Rolandic trait", with (2) possible age-related postero-anterior change in location, and (3) marked activation of focal abnormalities during sleep. However, it is worth emphasizing the relatively higher proportion of febrile seizures in

▼ **Table 1.** Epilepsy features in our series and patients described in previously published case reports.

	Age at first seizure	Epilepsy onset	SE	ASMs*	Fever susceptibility	Age at remission	Seizure semeiology (state)	FIPA (region)	FIPA activation in sleep
Our series									
Patient 1	1y4m	Id	Y	CBZ	Y	NA	T, TV (w, s)	Y (V, C-P)	Y
Patient 2	2y10m	Id	N		Y	NA	T, TV (s)	Y (C-P)	Y (continuous)
Patient 3	1y9m	-	N	-	Y	-	TC (w)	Y (V, C-P)	Y
Patient 4	2y6m	Id	N	CBZ, VPA, CLB, ESM	Y	NA	C, T, M, AA (w, s)	Y (C-T)	Y (continuous)
Patient 5	4y11m	Id	N	CBZ	N	NA	NM to T/TC (s)	Y (O to C-T)	Y
Patient 6	9y3m	Id	N	LEV	N	NA	T, C (s)	Y (F-C-T)	Y
Patient 7	6y6m	Id	N	VPA	N	7y6m	T (s)	Y (P-T)	Y (continuous)
Mean/ percentage	4y2m	Id	14% (1/7)	-	57% (4/7)	-	-	100% (7/7)	100% (7/7)
Literature									
Sylvester *et al.*, 1976 [10]	<2y	Id	N	NA	N	14y	NA	NA	NA
Bender *et al.*, 2011 [11]	4y	Id	Y	NA	Y	NA	C (s>w)	Y (C-T)	Y (continuous)
Takenouchi *et al.*, 2016 [12]	3y	Id	N	VPA	N	NA	NA	Y (NA)	NA
Sonmez *et al.*, 2016 [8]	2m	13y	N	OXC	Y	14y	GTC	NA	NA
Curcio *et al.*, 2020 [13]	5y	Id	N	CBZ	N	6y	TC (w, s)	Y (F-C-T)	NA
	5y6m	Id	N	VPA	N	7y6m	NM, TC (w, s)	Y (T-O)	Y
Mean/ percentage	3y3m	5y5m	17% (1/6)	-	33% (2/6)	-	-	100% (5/5)	100% (2/2)
Cases overall mean/ percentage	3y9m	4y8m	15% (2/13)	-	46% (6/13)	-	-	100% (12/12)	100% (9/9)

SE: status epilepticus; ASMs: antiseizure medications (*excluded those administered during SE); CBZ: carbamazepine; VPA: valproate; CLB: clobazam; ESM : ethosuximide; LEV: levetiracetam; OXC: oxcarbazepine; FIPA: focal interictal paroxysmal abnormalities; NA: not applicable; T: tonic; C: clonic; M: myoclonic; TV: tonic-vibratory; TC: tonic-clonic; AA: atypical absences; NM: focal non-motor; y:year; m:month.

our *ARID1B*-related CSS series and the possible occurrence of SE. ■

Supplementary material.
Supplementary table and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Acknowledgements and disclosures.
We acknowledge the Genetic Commission of the Italian League Against Epilepsy (LICE) within the framework of which this collection of cases was conducted.
PS developed this work within the framework of the DINOGMI Department of Excellence of MIUR 2018-2022 (legge 232 del 2016).
None of the authors have any conflict of interest to declare.

References

1. Kosho T, Okamoto N, Coffin-Siris Syndrome International Collaborators. Genotype-phenotype correlation of Coffin-Siris syndrome caused by mutations in SMARCB1, SMARCA4, SMARCE1 and ARID1A. *Am J Med Genet C Semin Med Genet* 2014; 166C(3): 262-75.

2. Tsurusaki Y, Okamoto N, Ohashi H, Kosho T, Imai Y, Hibi-Ko Y, *et al*. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat Genet* 2012; 44(4): 376-8.

3. Santen GW, Aten E, Vulto-van Silfhout AT, Pottinger C, van Bon BW, van Minderhout IJ, *et al*. Coffin-Siris syndrome and the BAF complex: genotype-phenotype study in 63 patients. *Hum Mutat* 2013; 34(11): 1519-28.

4. Wieczorek D, Bogershausen N, Beleggia F, Steiner-Haldenstätt S, Pohl E, Li Y, *et al*. A comprehensive molecular study on Coffin-Siris and Nicolaides-Baraitser syndromes identifies a broad molecular and clinical spectrum converging on altered chromatin remodeling. *Hum Mol Genet* 2013; 22: 5121-35.

5. Tsurusaki Y, Okamoto N, Ohashi H, Mizuno S, Matsumoto N, Makita Y, *et al*. Coffin-Siris syndrome is a SWI/SNF complex disorder. *Clin Genet* 2014; 85: 548-54.

6. van der Sluijs PJ, Jansen S, Vergano SA, Adachi-Fukuda M, Alanay Y, Al Kindy A, *et al*. The ARID1B spectrum in 143 patients: from nonsyndromic intellectual disability to Coffin-Siris syndrome. *Genet Med* 2019; 21(6): 1295-307.

7. Schrier Vergano S, Santen G, Wieczorek D, Wollnik B, Matsumoto N, Deardorff MA. Coffin-Siris Syndrome. 2013 Apr 4 [updated 2018 Feb 8]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle, 1993-2020.

8. Sonmez FM, Uctepe E, Gunduz M, Gormez Z, Erpolat S, Oznur M, *et al*. Coffin-Siris syndrome with cafeau-lait spots, obesity and hyperinsulinism caused by a mutation in the ARID1B gene. *Intractable Rare Dis Res* 2016; 5: 222-6.

9. Baban A, Moresco L, Divizia MT, Rossi A, Ravazzolo R, Lerone M, *et al*. Pituitary hypoplasia and growth hormone deficiency in Coffin-Siris syndrome. *Am J Med Genet A* 2008; 146A: 384-8.

10. Sylvester PE, Rundle AR, Richards BW. The syndrome of Coffin, Siris and Wegienka: report of a case. *J Ment Defic Res* 1976; 20: 35-54.

11. Bender HA, Zaroff CM, Karantzoulis S, Nakhutina L, Macallister WS, Luciano D. Cognitive and behavioral functioning in Coffin-Siris syndrome and epilepsy: a case presentation. *J Genet Psychol* 2011; 172(1): 56-66.

12. Takenouchi T, Yoshihashi H, Sakaguchi Y, Uehara T, Honda M, Takahashi T, *et al*. Hirschsprung disease as a yet undescribed phenotype in a patient with ARID1B mutation. *Am J Med Genet Part A* 2016; 9999A: 1-4.

13. Curcio MR, Ferranti S, Lotti F, Grosso S. Coffin-Siris syndrome and epilepsy. *Neurol Sci* 2020; 42: 727-9.

14. Musumeci SA, Colognola RM, Ferri R, Gigli GL, Petrella MA, Sanfilippo S, *et al*. Fragile-X syndrome: a particular epileptogenic EEG pattern. *Epilepsia* 1988; 29(1): 41-7.

15. Lewis H, Samanta D, Örsell JL, Bosanko KA, Rowell A, Jones M, *et al*. Epilepsy and electroencephalographic abnormalities in SATB2-associated syndrome. *Pediatr Neurol* 2020; 112: 94-100.

16. Panayiotopoulos CP. Benign childhood partial epilepsies: benign childhood seizure susceptibility syndromes. *J Neurol Neurosurg Psychiatry* 1993; 56(1): 2-5.

17. Caraballo RH, Aldao Mdel R, Cachia P. Benign childhood seizure susceptibility syndrome: three case reports. *Epileptic Disord* 2011; 13(2): 133-9.

TEST YOURSELF

(1) Which period is epilepsy onset in *ARID1B*-related CSS patients most common?
A. in the neonatal period
B. during childhood
C. in adolescence
D. in adulthood

(2) Which of the following epileptic features are shared by *ARID1B*-related CSS patients and self-limited focal epilepsies of childhood?

A. the recurrence of multifocal seizures originating from both hemispheres
B. the presence of focal interictal paroxysmal abnormalities
C. the possible evolution to an EEG pattern of CSWS
D. all of the above

(3) Which of the following features distinguish *ARID1B*-related CSS from self-limited focal epilepsies of childhood?

A. impaired motor and cognitive development from birth
B. speech delay prior to epilepsy onset
C. a relatively higher proportion of febrile seizures
D. all of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.