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Case Report

Epilepsy in Christianson syndrome: Two cases of Lennox–Gastaut syndrome and a review of literature

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ABSTRACT

Christianson syndrome (CS) is an X-linked intellectual disorder caused by mutations in the *SLC9A6* gene. Clinical features of CS include an inability to speak, truncal ataxia, postnatal microcephaly, hyperkinesis, and epilepsy. Almost all patients with CS develop drug-resistant epilepsy—its most serious complication. We report two cases of CS with drug-resistant epilpesy associated with the Lennox–Gastaut syndrome (LGS). One patient experienced generalized tonic seizures since 9 months of age with cognitive regression, which evolved to include atonic seizures at the age of 7 years. Electroencephalography (EEG) showed generalized slow spike–wave complexes and generalized paroxysmal fast activity. Seizures remained drug-resistant despite multiple anti-seizure drugs. The second patient experienced generalized tonic seizures since the age of 17 months and arrested development. EEG showed generalized slow spike–wave complexes, with frequent atonic seizures since the age of 6 years. Electrical status epilepticus during slow-wave sleep (ESES) developed at the age of 7 years. Our cases illustrate that CS may cause LGS in addition to other developmental and epileptic encephalopathies of the neonatal and infantile period. We suggest that generalized tonic or tonic–clonic seizures and generalized slow spike–wave complexes in interictal EEG be included as potential electroclinical features of epilepsy in CS.

1. Introduction

Christianson syndrome (CS) is an X-linked condition that was first reported by Christianson et al. in South African families who displayed severe intellectual disability, epilepsy, mild craniofacial dysmorphology, ophthalmoplegia, speech absence, acquired microcephaly, and cerebellar and brainstem atrophy [1]. Later, patients were also reported from other regions in Europe [2]. *SLC9A6* was identified as the causative gene; moreover, clinical features in patients with CS may overlap with those seen in Angelman syndrome [2]. Pescosolido et al., based on a study on 12 families note the characteristic symptoms of CS include an inability to speak, moderate to severe intellectual disability, epilepsy in 100% of patients, truncal ataxia, postnatal microcephaly or growth arrest of head circumference, and hyperkinesis [3]. Female carriers are known to manifest mild to moderate intellectual disabilities, behavioral issues, and psychiatric illnesses [4].

Epilepsy in CS is often drug-resistant and is a leading concern for family members [3]. While there have been several reports of electrical status epilepticus during slow-wave sleep (ESES) [5–7], few reports provide detailed description regarding the long-term course of epilepsy in CS.

We describe two cases of CS presenting with Lennox–Gastaut syndrome (LGS) and the progression of epilepsy in CS along with a review of the relevant literature.

2. Patient description

2.1. Patient 1

The patient was born via normal vaginal delivery at a gestational age of 40 weeks with a birth weight of 3134 g. His development was normal

Abbreviations: CS, Christianson syndrome; DEE, developmental and epileptic encephalopathy; EEG, electroencephalography; ESES, electrical status epilepticus during slow-wave sleep; LGS, Lennox–Gastaut syndrome.

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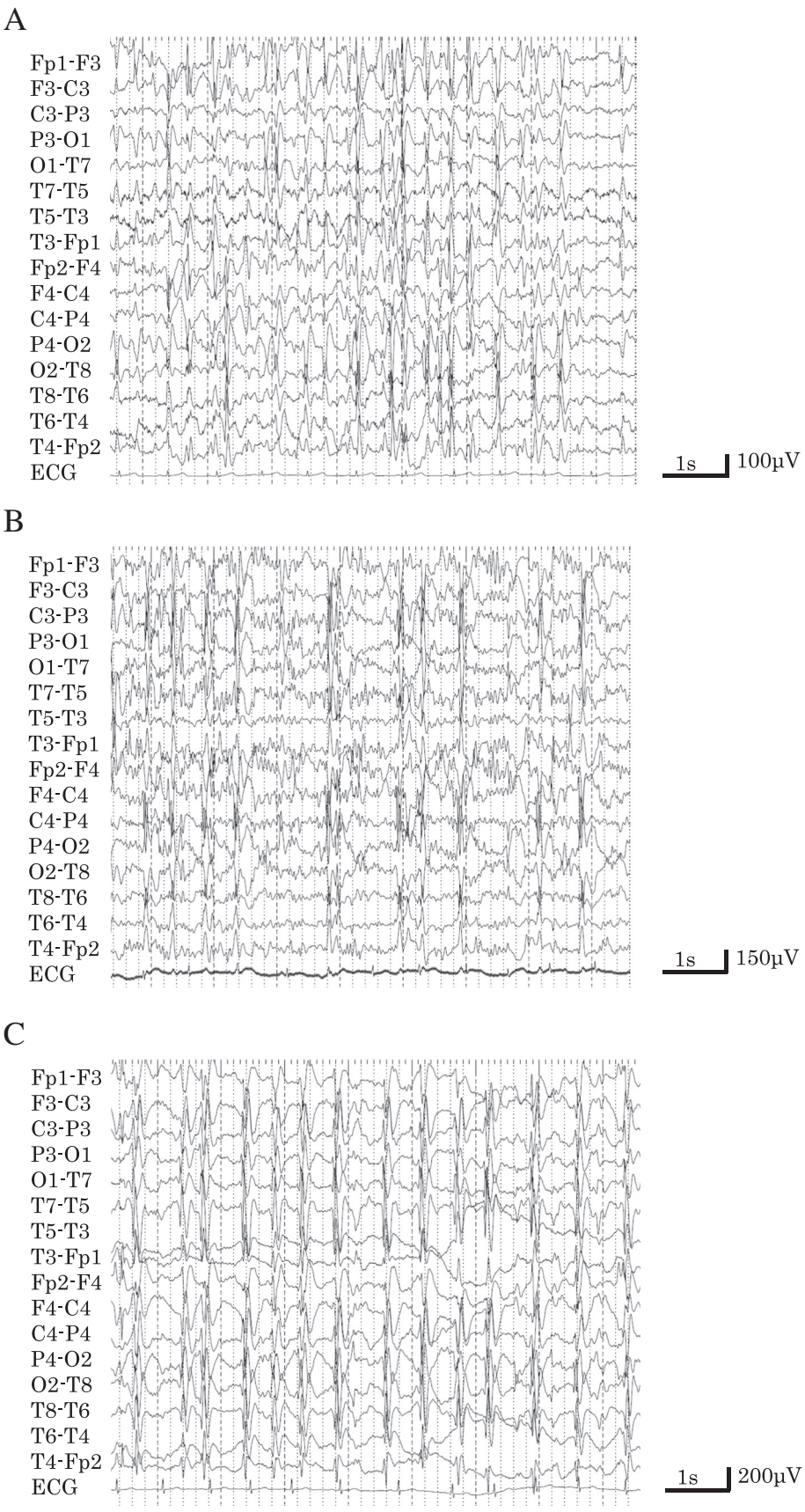

Fig. 1. A. EEG of patient 1. Sleep EEG at 7 years of age shows frequent 2.0–2.5 Hz generalized slow spike–wave complexes. B. EEG of patient 2. Sleep EEG at 6 years of age shows frequent 1.5–2.0 Hz generalized slow spike–wave complexes. C. EEG of patient 2. Sleep EEG at 7 years of age shows continuous generalized spike–waves forming more than 85% of the sleep recording, which is consistent with electrical status epilepticus during slow-wave sleep (ESES).

during early infancy; he could sit at 9 months and subsequently crawled appropriately. However, generalized tonic seizures developed several times a day from the age of 9 months, and he was referred to our hospital at the age of 11 months. At presentation, he had microcephaly (43.4 cm, 1.8 SD) and mild developmental delay. Blood tests and brain MRI revealed no abnormal findings. However, a sleep electroencephalography (EEG) showed frontal and occipital spike–wave complexes and generalized slow spike–wave complexes. Seizure occurrence temporarily decreased following treatment with valproate and clonazepam. However, weekly seizures persisted, and they became drug-resistant at the age of 3 years when psychomotor regression was also observed. Until the age of 3 years, the child had an ataxic gait but gradually progressed to the point of being unable to walk with severe intellectual disability and without the ability to speak. Topiramate was included in the drug regimen at the age of 5 years but seizures were not controlled. By the age of 7 years, he experienced weekly atonic seizures in addition to weekly tonic seizures and he was diagnosed with LGS. Sleep EEG showed frequent generalized slow spike–wave complexes (Fig. 1A), followed by generalized paroxysmal fast activity by the age of 12 years. Seizures spontaneously decreased at the age of 14 years but weekly tonic seizures during sleep persisted. Brain MRI at 16 years of age showed mild atrophy in the cerebrum and cerebellum.

Exome analysis using the TruSight One Sequencing Panel and the MiSeq platform (Illumina, Inc., San Diego, CA, USA) for the patient's leukocyte DNA identified an *SLC9A6* mutation (NM_006359.3:c.1402C>T: p.Arg468*). His younger sister was found to be a carrier for the same mutation and suffered from mild intellectual disability and epilepsy that was well-controlled with valproate. This mutation was not detected in their mother's peripheral blood sample and the patient was considered to be a mosaic carrier.

2.2. Patient 2

The patient was born via a normal vaginal delivery at a gestational age of 37 weeks with a birth weight of 2945 g. At the age of 4 months, he could hold his head and roll over; at the age of 14 months, he could sit. At the age of 17 months, he started experiencing generalized tonic seizures, for which valproate was administered. Seizure frequency increased to daily, and hence, clobazam was included in the drug regimen. At that time, he showed arrested motor and intellectual development and he was referred to our hospital at the age of 3 years. At presentation, he had microcephaly (46.7 cm, −1.9 SD), severe intellectual impairment without speech, ataxic gait, truncal hypotonia, and hyperkinesis. Daily generalized tonic seizures continued despite adding topiramate, lamotrigine, levetiracetam, and carbamazepine to his antiseizure drug therapy. EEG showed frequent generalized slow spike–wave complexes (Fig. 1B). At the age of 6 years, falling due to atonic seizures became frequent and he was diagnosed with LGS. Brain MRI at this age (6 years) showed T2 hyperintensity and atrophy of the lower cerebellum. At the age of 7 years, his daytime level of consciousness declined and EEG demonstrated ESES (Fig. 1C). At the age of 8 years, atonic seizures disappeared with rufinamide; however, daily generalized tonic seizures during sleep persisted.

Table 1
Previous reports of epilepsy in CS.

	n	Age at onset	Seizure type (n)	EEG findings	Epilepsy classification (n)	SLC9A6 mutation (NM_006359.3)
Mathieu et al. [7]	5	<2 y	Myoclonic (2) GTC (4) Tonic–clonic (1) Atonic (1) Gelastic seizure (1)	Diffuse spike and Polyspike–waves (4) ESES (3) Fast background activity (3) Diffuse alpha (1)	ND	40-Mb deletion in Xq26.3 p.Trp491* p.Gly351Asp
Masurel-Paulet et al. [9]	2	ND	GTC (1)	Normal (1)	ND	c.430-9_430-5delTTTTA
Coorg and Weisenberg [6]	1	1 y	Generalized seizure	Diffuse generalized discharges ESES	ND	p.Trp538*
Zanni et al. [5]	1	<2 y	Tonic–clonic	ESES	ND	c.1255-1G>A
Pescosolido et al. [3]	14	4 m to 3 y	Infantile spasms Tonic Tonic–clonic Myoclonic Drop seizure Staring spells	Frequent generalized spike–wave complexes Irregular generalized spike–wave pattern Multifocal spikes	LGS (3) Infantile spasms (1)	p.Gly351Asp p.Arg440Lysfs*4 p.Trp538* p.Trp491* c.512_519dupAGAAGTAT (p.Phe151fs*1) c.498-1G>A p.Glu64* p.Arg468* c.1237-557_UTRdel p.Glu515*
Mingot et al. [13]	1	2 y	GTC	Bilateral frontal slow-waves Spike–waves Generalized bursts of spikes	ND	c.820C>T (p.Gln274*)
Tzschach et al. [10]	1	11 m	ND	ND	ND	314 kb deletion in Xq26.3
Takahashi et al. [14]	1	4 y	Multiple types	5–6 Hz theta 3 Hz diffuse high voltage slow waves	ND	c.441delG (p.Ser147fs) (NM_001042537)
Schroer et al. [15]	7	<2 y	GTC (5) Tonic–clonic (2) Partial seizure (1) Atypical absence (1) Atonic seizure (1)	ND	LGS (1)	p.Arg468* p.Gln375*
Gilfillan et al. [2]	8	9 to 26 m	Multiple seizure types (1)	Epileptiform discharges (8) Abnormal fast activity (3) Slow frequency of 1.5–3 Hz with high voltage (1)	ND	c.764_769delAAAGTG (p.Glu255_Ser256del) c.1402C>T (p.Arg468*) c.507+3_507+6delAAGT (p.Val144_Arg169 del)
Christianson et al. [1]	16	<1 y	Tonic and Tonic-clonic (1)	ND	ND	c.512_513delAT (p.His171Lysfs*60)

EEG = electroencephalography, ESES = electrical status epilepticus during slow-wave sleep, GTC = generalized tonic–clonic seizure, ND = no data.

Whole-exome sequencing of the patient's leukocyte DNA revealed a novel *SLC9A6* mutation (NM_006359.3:c.477_481del:p.Ile160Leufs*5), which is considered pathogenic according to the American College of Medical Genetics and Genomics guidelines [8]. This mutation was not detected in their parents' peripheral blood sample and therefore was considered de novo.

3. Review of the literature

Table 1 summarizes the findings from previous reports of epilepsy in CS. All known CS patients with information about epilepsy to date were included. Onset of epilepsy ranges from infancy to 26 months of age. Seizure types seen are generalized tonic–clonic seizures or tonic seizures in most cases, atonic seizures or drop attacks in several cases, and partial seizures in only a few patients.

EEG findings have been predominantly described as generalized slow spike–wave complexes. Several cases of high-voltage slow waves or abnormal fast activity were reported. Three reports corresponded to five cases of ESES. The age when ESES was first observed varied from 4 to 8 years, and all seizures were refractory except in one case where felbamate was effective in a patient reported by Coorg and Weisenberg [6].

Only two reports to date have classified epilepsy and both included LGS. Only one case of epileptic spasms was reported. Although most cases are resistant to antiseizure drug therapy, there are reports of milder cases [9] and patients whose seizures responded to antiseizure medication such as diazepam [10].

4. Discussion

We have described the course and progression of two cases of CS subsequently developing LGS with both patients showing similar generalized slow spike–wave complexes in EEG and one child also exhibiting ESES. We propose that LGS may be relatively common in patients with CS in addition to ESES. When taken together with the previous reports, generalized tonic or tonic–clonic seizures and generalized slow spike–wave complexes in interictal EEG tests are common in CS, although other seizure types and EEG results may occur. Even though epilepsy in CS has often been reported as drug-resistant, there is limited information on the course of epilepsy in CS. Therefore, this report provides additional information on patients with epilepsy and CS.

Interictal EEG in both our patients showed frequent generalized slow spike–wave complexes that were very similar to those reported by Pescosolido et al. [3], Zanni et al. [5], and Mathieu et al. [7]. Although the precise details of the EEG including spike–wave complexes (whether “slow” spike–wave or not) cannot be determined from previous reports, we note generalized spike–wave complexes are a characteristic feature of interictal EEG in CS. Interestingly, a few previous reports have described high-voltage slow waves similar to those seen in Angelman syndrome [2], and although it has been reported that CS symptoms are similar those of Angelman syndrome, it has now become clear that neither such wave forms nor symptoms are frequently encountered [3].

Our literature survey identified five cases of ESES at ages between 4 and 8 years, and our second patient developed drug-resistant ESES at the age of 7 years. ESES that develops in early childhood is considered to be one of the features of epilepsy in CS.

Only two reports to date have classified epilepsy and both included LGS; therefore we suspect the frequency of LGS may be higher based on the limited amount of information on epilepsy classification in available reports. Mutations in *GABRB3*, *ALG13*, *SCN8A*, *STXBP1*, *DNM1*, *FOXG1*, and *CHD2* have been reported to result in LGS [11]. All of these genetic mutations may be associated with epilepsy or developmental delays and are known to cause other developmental and epileptic encephalopathies as phenotypes apart from LGS. *SLC9A6* encodes the endosomal Na^{+}-H^{+} exchanger 6 (NHE6) [2], and NHE6 has been reported to be required for neuronal arborization and synapse development [12]. There is also a case report of spasms and CS in a patient with a developmental and epileptic encephalopathy though there is very little information on how developmental processes are affected. The onset of epilepsy in CS occurs in late infancy, and so it may tend to present with LGS phenotypes rather than as early infantile epileptic encephalopathy or West syndrome.

Our first patient had drug-resistant seizures and developed severe intellectual disability; however, the seizures decreased by age 14 years, which is similar to the disease course reported by Mathieu et al. [7]. Therefore, it appears that seizures may decrease spontaneously in some patients during adolescence.

In summary, CS may be associated with LGS rather than manifesting as other forms of developmental and epileptic encephalopathies in the neonatal and infantile period, along with ESES. The presentation and progression of the two cases described here and those of previous reports suggest that generalized tonic or tonic–clonic seizures and generalized slow spike–wave complexes in interictal EEG may be characteristic features in patients with epilepsy and CS.

Ethical statement

The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Informed consent was obtained from the parents of the patients.

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Declaration of competing interest

The authors have no financial or personal relations that could pose a conflict of interest.

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