Epileptic Disord 2019; 21 (1): 117-21

Berardinelli-Seip syndrome and progressive myoclonus epilepsy

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Received August 28, 2018; Accepted December 01, 2018

ABSTRACT – Berardinelli-Seip syndrome, or congenital generalized lipodystrophy type 2 (CGL2), is characterized by a lack of subcutaneous adipose tissue and precocious metabolic syndrome with insulin resistance, resulting in diabetes, dyslipidaemia, hepatic steatosis, cardiomyopathy, and acanthosis nigricans. Most reported mutations are associated with mild, non-progressive neurological impairment. We describe the clinical and EEG data of a patient with progressive myoclonus epilepsy (PME), CGL2, and progressive neurological impairment, carrying a homozygous *BSCL2* nonsense mutation. The patient had epilepsy onset at the age of two, characterized by monthly generalized tonic-clonic seizures. By the age of three, he presented with drug-resistant ongoing myoclonic absence seizures, photosensitivity, progressive neurological degeneration, and moderate cognitive delay. Molecular analysis of the *BSCL2* gene yielded a homozygous c.(1076dupC) p.(Glu360*) mutation. Application of a vagus nerve stimulator led to temporary improvement in seizure frequency, general neurological condition, and EEG background activity. Specific *BSCL2* mutations may lead to a peculiar CGL2 phenotype characterized by PME and progressive neurodegeneration. Application of a vagus nerve stimulator, rarely used for PMEs, may prove beneficial, if only temporarily, for both seizure frequency and general neurological condition.

Key words: lipodystrophy type 2, Berardinelli-Seip syndrome, *BSCL2*, progressive myoclonus epilepsy, neurodegenerative encephalopathy, EEG, vagus nerve stimulator

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doi:10.1684/epd.2019.1038

Berardinelli-Seip syndrome, or congenital generalized lipodystrophy type 2 (CGL2), is characterized by a lack of subcutaneous adipose tissue and precocious metabolic syndrome with insulin resistance, resulting in diabetes, dyslipidaemia, hepatic steatosis, cardiomyopathy, and acanthosis nigricans. Genotype-phenotype correlations and an autosomal recessive inheritance were proposed with regards to a number of mutations in the *BSCL2* gene, that encodes Seipin. Most reported mutations are associated with mild, non-progressive neurological impairment. In 2016, Opri *et al*. published a small case series

of three patients with a rare association between CGL2, progressive myoclonus epilepsy (PME) and severe progressive neurological impairment (Opri *et al*., 2016). In one patient, a novel compound heterozygous *BSCL2* gene mutation was found, resulting in two different frameshift mutations. Here, we describe clinical and EEG data of a further patient with PME, CGL2, and progressive neurological impairment, carrying a homozygous *BSCL2* nonsense mutation.

Methods

After obtaining informed consent from the patient's parents, genetic molecular analysis was performed. Blood genomic DNA was extracted from whole peripheral blood. Exons and exon-intron boundaries of *BSCL2* were analysed by PCR amplification and direct sequencing (the first nucleotide of the ATG initiation codon was considered as the first nucleotide of the gene).

Case study

The patient was a male born in Macedonia in 2013. Pregnancy was reported as uneventful and psychomotor development as normal. At the age of 12 months, he developed monthly tonic seizures and antiepileptic drug (AED) therapy with valproic acid (VPA) was introduced in his home country, resulting in good seizure control. He moved to Italy at the age of two and a new medical evaluation was undertaken. Lack of subcutaneous adipose tissue, moderate psychomotor delay with speech impairment, and severe hyperactivity prompted metabolic testing.

Hypertriglyceridaemia, hypertransaminasaemia, and hepatic steatosis were documented and a low fat diet was implemented. Cerebral MRI was normal.

Molecular analysis of the *BSCL2* gene yielded a homozygous c.(1076dupC)/p.(Glu360*) mutation. Seizure recurrence followed the parents' autonomous suspension of VPA, and was characterized by generalized tonic seizures and episodes of loss of consciousness, perioral cyanosis, and bilateral eye retropulsion. The EEG correlate of such episodes was characterized by brief diffuse discharges of spike-wave (SW) complexes, followed by slow waves (*figure 1*). Seizure control was briefly obtained after gradual introduction of lamotrigine (LTG). During the following three months, the patient developed numerous daily absence seizures with eyelid myoclonias and forward head tilt, and VPA was reintroduced as add-on. After one month, there was a recurrence of absence seizures and an appearance of frequent drop attacks. The patient was eventually hospitalized for non-convulsive status epilepticus. A significant, albeit temporary, reduction in absence seizure and drop attack frequency was obtained with introduction of ethosuximide (ESM) and substitution of LTG with clonazepam (CZP). CPZ, however, severely worsened hyperactivity which led to accidental head trauma with subdural haemorrhage and transitory left facial nerve palsy. At this stage, ataxic gate and severe psychomotor delay were also evident. Serial brain MRI scans did not show signs of cerebral atrophy. Worsening of the general neurological condition paralleled degeneration of EEG background activity, especially during sleep, and an increase in photosensitivity, which was evident even at 1-Hz photic stimulation. A steady increase in seizure frequency gave way to relapsing refractory non-convulsive status, controlled with second-line IV administration of phenobarbital (PB) (*figure 2*). Introduction of PB therapy resulted in temporary improvement in seizure control but worsening of ataxic gait. A vagal nerve stimulator (VNS) was implanted (cyclic stimulation: 30 sec on; 5 min off; 30 Hz; 500 msec). The VNS was gradually calibrated to 1.2 mA with temporary improvement in seizure frequency, general neurological condition, and EEG background activity. After three months, PB was substituted with perampanel because of a relapse in drop attacks and the appearance of prolonged generalized tonic seizures. After two months of follow-up, tonic seizures disappeared and drop attack frequency and absence seizure frequency and duration were reduced with improvement in general neurological condition (gait, speech, and social interaction).

Discussion

Evidence that a form of PME exists in the context of CGL2 has already been suggested (Tseng *et al*., 2009; Guillén-Navarro *et al*., 2013; Opri *et al*., 2016). Guillèn-Navarro *et al*. described six patients affected by a fatal neurodegenerative syndrome who had homozygous or compound heterozygous *BSCL2* gene mutations. Five out of six patients developed myoclonic seizures between two and four years of age. This peculiar clinical presentation was named "Celia's encephalopathy" (CE), characterized by the presence of intranuclear aggregates of mutated, misfolded Seipin which are thought to have a pathogenic role in neurodegeneration by inducing endoplasmic reticulum stress in neurons (Ruiz-Riquelme *et al*., 2015). Even though there were no available data to demonstrate a pathogenic role for Seipin aggregates, PAS-positive inclusions were also found in the patients described by Tseng *et al*. and Opri *et al*. While the *BSCL2* transcripts of the patients described by Guillèn-Navarro *et al*. lacked exon 7, those described by Opri *et al*. presented with a heterozygous mutation

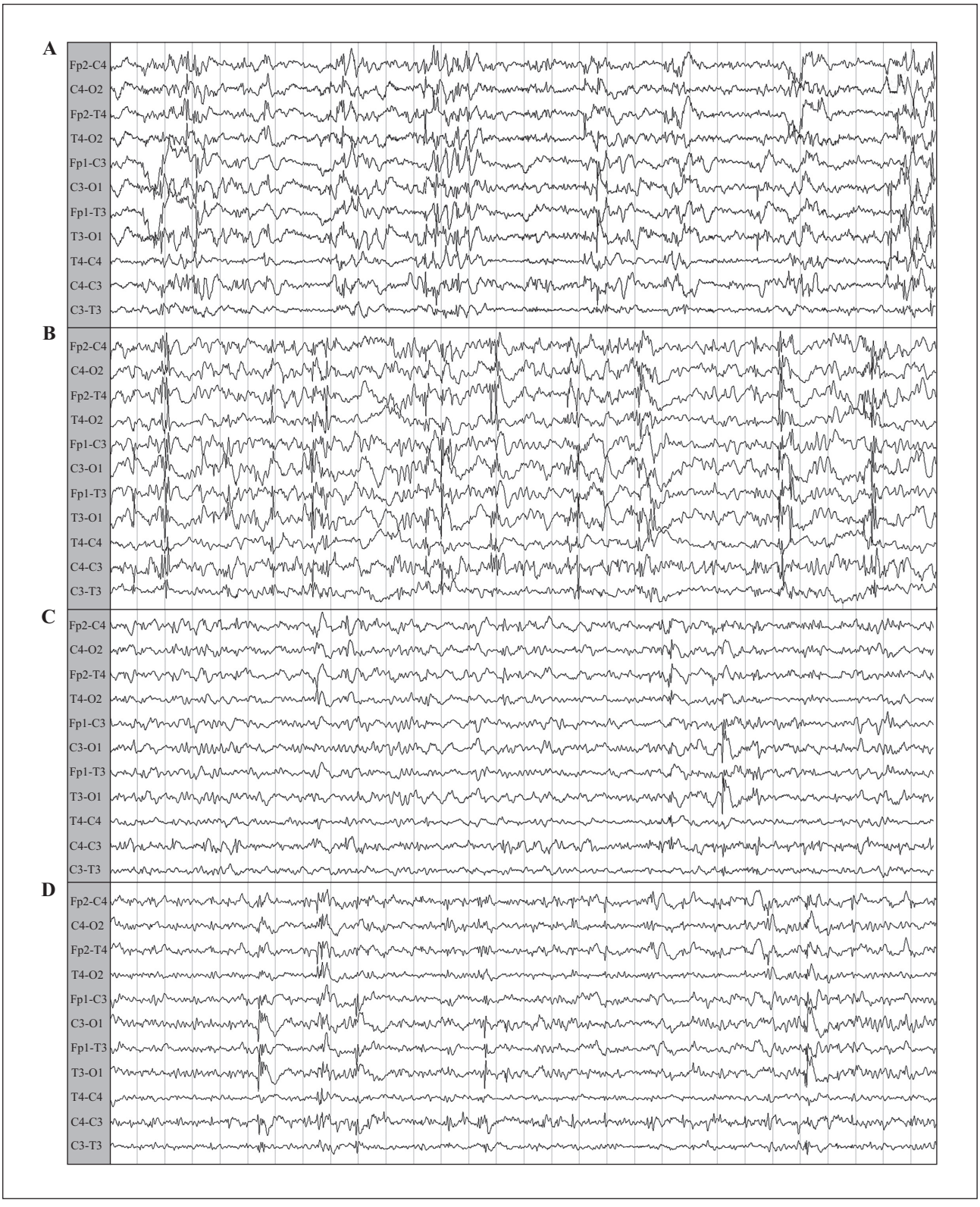

Figure 1. (A-D). Continuous EEG recording showing the EEG correlate of episodes characterized by brief diffuse discharges of spike-wave (SW) complexes, followed by slow waves.

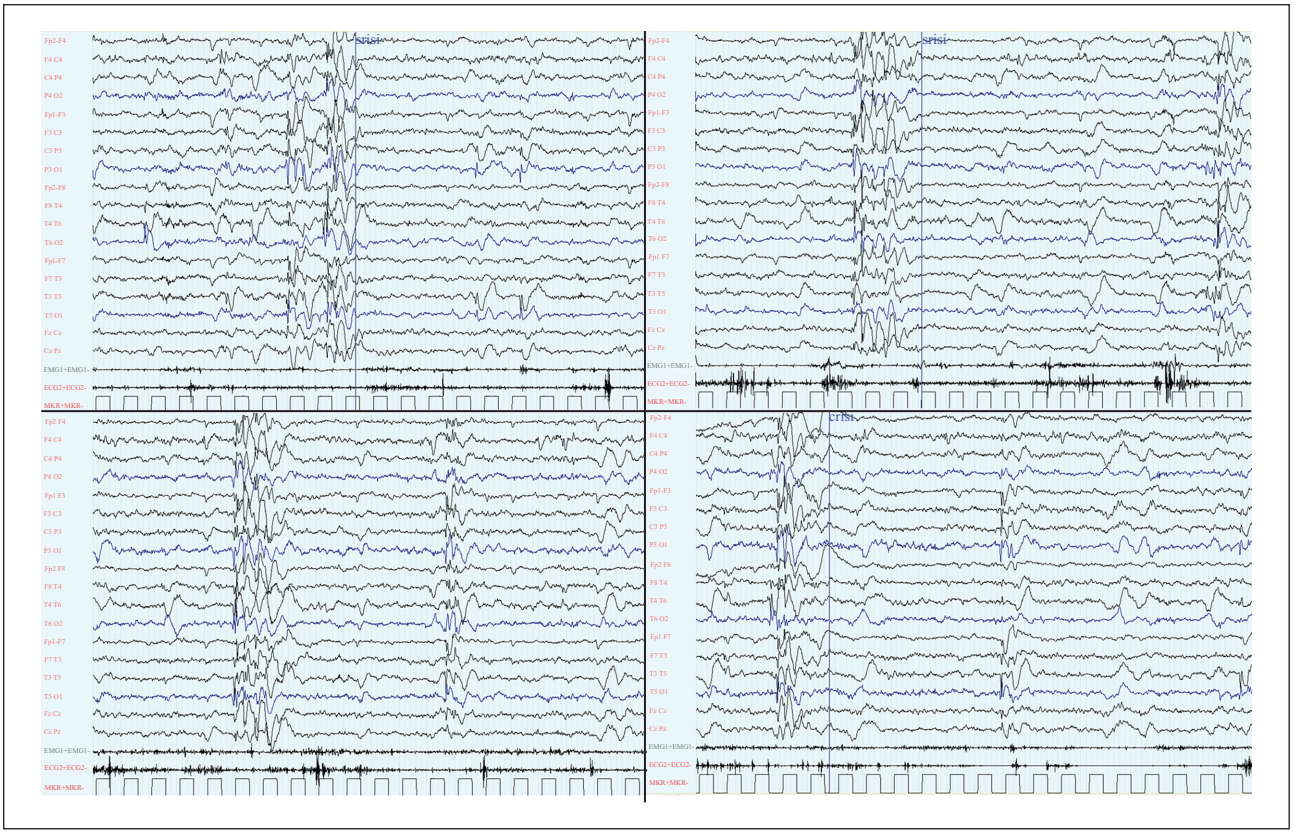

Figure 2. EEG revealing relapsing refractory non-convulsive status, controlled with second-line IV administration of phenobarbital.

involving exons 8 and 9. Thus, the authors argued that the pathogenic mechanism described for CE might not be unique to *BSCL2* exon 7 skipping. Our patient presented with a homozygous c.1076dupC mutation, involving exon 9 and resulting in a premature stop codon. Even though histological evidence of neuronal inclusion was not available, in the light of such a mutation, we believe that the presence of misfolded aggregates was very likely. Interestingly, there was no MRI evidence of brain atrophy in our case, in contrast to other patients, although these patients were described with a longer follow-up period. However, our report seems to validate the hypothesis that this peculiar type of CGL2 is not uniquely linked to exon 7 and provides further evidence towards a link between specific *BSCL2* mutations and a peculiar CGL2 phenotype characterized by PME and progressive neurodegeneration. Our report may also provide some insight into the possible role of VNS implantation. VNS is rarely used in PME but appeared to prove beneficial, although only temporarily, regarding both seizure frequency and the general neurological condition. Changes in amperage and stimulation pattern during follow-up might hopefully yield more data on potential effectiveness. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Is CGL2 usually associated with progressive neurological impairment?

(2) Is CGL2 usually associated with epilepsy?

(3) What seems to be the pathogenetic mechanism behind the neurodegenerative CGL2 phenotype associated with epilepsy?

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