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Clinical letter

Novel epilepsy phenotype associated to a known *SCN8A* mutation

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The *SCN8A* gene, localized on chromosome 12q13, encodes the sodium channel alfa-subunit Nav1.6, which is expressed in excitatory and inhibitory neurons. Mutations in this gene are found predominantly in patients with epileptic encephalopathies and have been identified as a cause in 1–1.4% of the cases [1]. Generally, these patients present with early onset epilepsies that are refractory to treatment, severe intellectual disability, and autistic features.

The neurological aspects of the syndrome are also characterized by motor disorders such as ataxia, tremor, and impaired coordination starting in the first months of life [2]. In the last few years, some reports have also described mutations of this gene in epileptic syndromes with less severe prognosis, particularly Benign Familial Infantile Seizures (BFIS) or paroxysmal choreoathetosis [3].

Our patient is a male now aged 10 years 7 months. He is the first child of unrelated parents. Family history is negative for epilepsy.

He was born by vaginal delivery after an uneventful pregnancy. There was minimal breathing distress (Apgar 5 at 1'/9 at 5'), but oxygen was given and no intubation was needed. Transfontanellar ultrasound scan was normal.

The patient presented his first generalized tonic seizure at the age of 15 months during febrile exanthema. No epileptiform abnormalities were reported in the EEG recording. He suffered five additional generalized tonic seizures, always during fever episodes.

At the age of 3 years and 6 months, neurological examination was normal. The patient underwent brain MRI that showed a subcortical cavernous angioma on the frontal right side. In the meantime, treatment with Sodium Valproate was started. After the start of the treatment, he never had another seizure and his development was described as normal.

He underwent his first EEG recording at our Institute at the age of 4 years and 8 months. Background activity was well organized, both during wakefulness and sleep, some slow wave abnormalities, increased during sleep, were recorded over bilateral fronto-temporal regions (Fig. 1A and B).

At age 6, due to complete seizure remission for more than 2 years and the absence of epileptiform abnormalities during EEG recordings, drug treatment tapering was started.

Mutation analysis for the *SCN1A* gene resulted negative.

A few days after the complete interruption of the therapy (6 yrs and 8 mos), the patient presented generalized tonic seizures without fever. EEG and MRI data were unchanged; Sodium Valproate was re-introduced at low dose (10 mg/kg).

In the meantime, from the beginning of primary school his parents started to report some learning difficulties, therefore he was submitted to a neuropsychological examination.

After the reintroduction of antiepileptic therapy the patient resumed a good seizure control, except for an instance of prolonged seizure cluster associated to a streptococcal infection, at age 8 years and 9 months, and a second instance with features of an epileptic status, associated to *mycoplasma pneumoniae*, which required intravenous treatment with phenytoin, at age 9 years and 9 months.

EEG recordings confirmed well-organized background activity and bilateral slow wave abnormalities over the fronto-temporal areas.

The dose of Sodium Valproate was progressively increased (23 mg/kg). The patient did not experience any seizures in the following 10 months.

Since the first report of learning difficulties, the patient underwent repeated neuropsychological evaluations (summarized in Fig. 2). Full Scale IQ (FSIQ) and the primaries index scores had a favorable evolution with a gradual increase in the scores. Nevertheless, mild difficulties in arithmetic operation speed and mathematical problem-solving persisted.

At age 9 years, the patient underwent a genetic test consisting of a diagnostic NGS panel containing 79 genes mutated in epilepsy and epileptic encephalopathy. The screening discovered a *de novo* p.Asn1877Ser variant in *SCN8A* (rs587780455), described as pathogenic in ClinVar and reported several times, according to Dr. Michael Hammer's website (https://www.scn8a.net/VariantSearch.aspx). In the meantime it discovered a p.Ser91Phe variant in *CHRNA2*, a p.Arg2980Leu variant in RYR3 and a p.Asp568Asn variant in CACNA1H; all these variants are not found in any human variants database and they are inherited from his unaffected father.

Other ten patients have the same *SCN8A* mutation. All four patients for whom data are available presented Infantile Benign Focal Epilepsy and inherited the mutation from a parent showing the same epileptic syndrome. Data on the remaining six patient are unavailable.

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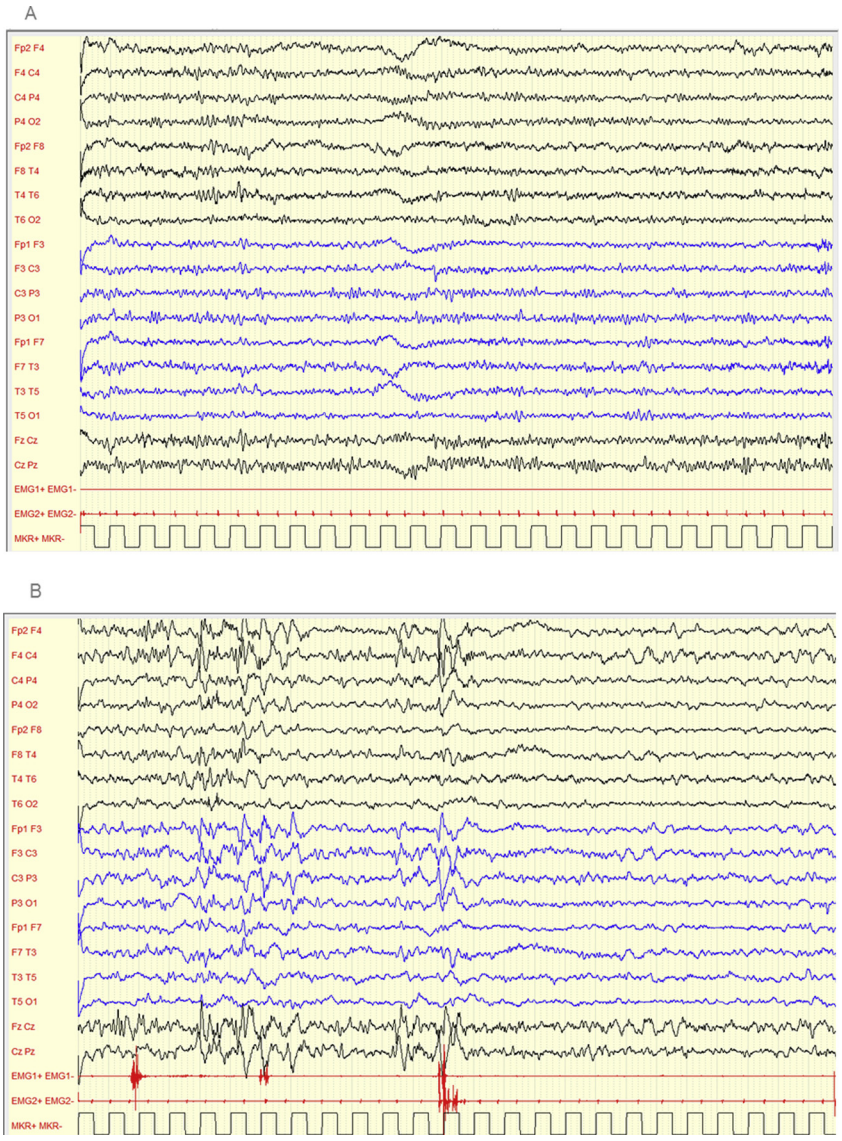

Fig. 1. (A) EEG during wakefulness, at the age of 4 years and 8 months, shows a well organised background activity. (B) EEG recording during sleep shows slow waves abnormalities over the anterior regions of both emishperes. Background activity is well oganised; numerous myoclonic jerks.

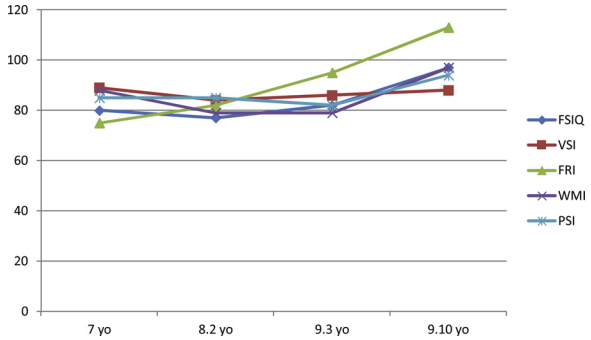

Fig. 2. data about different FSIQ evaluations, divided into Visual Spatial Index (VSI), Fluid Reasoning Index (FRI), Working Memory Index (WMI), and Processing Speed Index (PSI).

Our patient further expands the phenotypic spectrum that characterizes mutations of the *SCN8A* gene, since he showed generalized tonic seizures that were almost entirely fever-related. We classified him as being affected by Generalized Epilepsy with Febrile Seizures Plus (GEFS +) and therefore we initially looked for a *SCN1A* mutation. The extension of the genetic analysis through an NGS panel allowed us to identify additional variants. To our knowledge, this is the first case with this kind of phenotype and a mutation in *SCN8A*. Moreover, fever sensitivity is not considered a characteristic feature of epilepsies caused by *SCN8A* mutations [4].

Our patient showed a positive evolution of his neuropsychological picture despite unstable seizure control. After all, this fluctuating control could be so far justified by the choice of a therapy lacking a sodium-blocking drug. Our experience however suggests that it is not advisable to proceed with a drug withdrawal in these patients.

The EEG recordings, both during wakefulness and sleep, have never shown epileptiform discharges, and this feature is infrequent in patients with mutations in *SCN8A*.

Clinical history and serial follow-up data, both neuropsychological and EEG, demonstrate that our patient's cognitive impairment is not associated to the electro-clinical pattern but to the genetic mutation itself.

The slight neuropsychological deficits (memory, attention tasks) we found did not show a deterioration over time, while, on the contrary, the patient showed a significant improvement in his FSIQ score.

In the same period, the patient underwent intensive

neuropsychological rehabilitative training that fostered an improvement in his learning achievements, giving him more confidence in his skills and abilities. For this reason, it is important to highlight the extreme importance of neuropsychological rehabilitation in the follow-up of these epileptic patients, with the goal to strengthen their cognitive skills regardless of seizures' evolution.

The same mutation, located in a highly conserved portion of the protein, it has already been described in association with very different phenotypes that vary from BFIS to severe epilepsy with developmental disorders. This variability could be the result of other genetic protective factors [3] or epigenetic factors; furthermore at the moment it is also impossible to give a precise meaning to the other inherited variants, found with NGS test and their contribution to the phenotype heterogeneity.

Conflict of interest

None.

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