A Case of Congenital Paramyotonia with Atypical Features in a Family with a New Variation of SCN4A Gene

Fusco Carlo1, Elena Pavlidis1, Carlotta Spagnoli1, Grazia Gabriella Salerno1, Daniele Frattini1 & Pisani Francesco2

1Child Neurology and Psychiatry Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy
2Child Neurology and Psychiatry Unit, University of Parma, Italy

Correspondence to: Dr. Fusco Carlo, Child Neurology and Psychiatry Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

Copyright © 2018 Dr. Fusco Carlo, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received: 10 May 2018
Published: 06 June 2018

Keywords: SCN4A; Sodium-Channelopathies; Paramyotonia Congenita; EMG

Abstract

SCN4A variations have been identified in various neuromuscular disorders, which are collectively named “sodium channelopathies”.

We report the case of a patient who presented paramyotonia congenita with motor paroxysmal episodes since the neonatal period and some peculiar features. He showed a pathogenic heterozygous variant c.4690G>A (p.V1564) on exon 24 of SCN4A gene inherited by the mother, that showed only mild clinical features.

This case provides other possible clinical features related to the SCN4A gene variations and further highlights the significant clinical heterogeneity of SCN4A-related channelopathies, even in members of the same family with an identical genetic variation.
Introduction

Gene SCN4A, which is located on chromosome 17q23-25, encodes for the voltage-sensing alpha subunit of the skeletal muscle sodium channel [1].

Over 40 different mutations have been reported in the SCN4A gene. These are associated with different neuromuscular disorders like hypo- and hyper-kalaemic periodic paralyses, paramyotonia congenita, sodium channel myotonias and congenital myasthenic syndrome, which are collectively named “sodium channelopathies” [1-3].

Here we report the case of a child affected from paramyotonia congenita due to a SCN4A variant, inherited by his mother, with some peculiar and atypical clinical features.

Case Report

This patient is a 17 years-old boy, born at term, by non-consanguineous parents. The pregnancy and delivery were uneventful. Apgar scores at first and fifth minutes were 9 and 10 respectively. The mother presented occasional episodes of stiffness in lower limbs and hands, resembling myotonia. At 5 days of life the infant was admitted to the NICU since he had motor paroxysmal episodes. The episodes were characterized by tonic contraction of one side of the body involving the face (right eye closure, deviation of the head and mouth to the right), arm and leg (extended) and the trunk (deviated to the right); sometimes the episodes involved both sides and they usually lasted few seconds but in some occasions they were longer or in cluster, lasting from minutes to hours. The EEG recordings were always normal. During the course of his life, the child underwent several investigations with an extensive diagnostic work-up.

Routine blood exams, parathormone, total cholesterol, triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, immunoglobulins, apolipoproteins, routine urine examination were all negative. The metabolic work-up (including plasmatic lactate and ammonium, plasmatic and urinary aminoacids, urinary organic acids, biotinidase, blood copper and serum ceruloplasmine) was normal. CSF exam and lactate, and CSF neurotransmitters were negative. Brain CT scan and MRI were unremarkable, as well as serial EEG (both during wakefulness and sleep). Auditory evoked potentials and somatosensory evoked potentials were negative. Abdominal ecography, EKG, ecocardiography. Eye and fundus oculi examinations were unremarkable. His motor development was normal, however the child showed delayed language milestones, hyperactivity and behavioural abnormalities.

The patient experienced attacks of spontaneous sustained stiffness, both during wakefulness and sleep, not associated with sustained exercise or muscle cooling, leading occasionally to transient paralysis of these muscles. Furthermore, exposure to cold never produced temporary episodes of mild to severe muscle weakness. He was treated with clonazepam, diazepam, clobazam, valproate, acetazolamide, carbamazepine, phenytoin, but without any improvement. Treatment with mexiletine was refused. The episodes have continued so far.
The EMG performed when the child was 10 years old showed, rapidly repetitive, spontaneous, low amplitude discharge (paramyotonia) and complex repetitive discharges in deltoid muscles. CGH - array and gene panels for epilepsy, pediatric movements disorders and congenital myotonia disease (SCN1A, PRRT2, MR1, SLC2A1 and CLCN1 genes) were negative. A pathogenic heterozygous variant c.4690G>A (p.V1564) on exon 24 of SCN4A gene was detected. The same variant was also detected in his mother. Consequently, an EMG study was performed in the mother and showed a complex repetitive discharges in gastrocnemius muscles.

Written informed consent from patient’s parents was obtained. following a full explanation of the procedures undertaken.

Discussion

Paramyotonia congenita (OMIM #168300) is a non-dystrophic myopathy caused by mutations in the SCN4A gene. SCN4A gene, which is located on chromosome 17q23-25, encodes for the voltage-sensing alpha subunit of the skeletal muscle sodium channel. More than 40 different types of SCN4A mutation have been identified so far, most of which are single-base substitutions producing missense variations [1]. The SCN4A gene comprises 24 exons with a 5.5-kb open reading frame and is associated with several neuromuscular disorders, including hyperkalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia, hypokalemic periodic paralysis, and congenital myasthenic syndrome [1,2]. Exons 22 and 24 are recognized as ‘hot spots’ for paramyotonia congenita [1].

Paramyotonia congenita may be confuse with myotonia congenita caused to CLCN1 gene mutations. Both diseases present with generalized weakness since childhood, in paramyotonia congenita stiffness is exacerbated by repeated and prolonged movements and exertion and are also cold-sensitive, differently from what happens to patients with myotonia congenita. Infact, in congenital myotonia the patients show a pronounced warm-up phenomenon, in which the myotonic attack is relieved with repeated muscle contractions.

Our patient presented some peculiar clinical features compared to the “classical paramyotonia congenita”. First of all, the onset of the stiffness is usually in infancy or in early childhood, whereas our patient had an early neonatal onset. Moreover, the episodes of stiffness were severe, frequent and repetitive in our case, when the attacks usually occur once or twice a month and are often mild to moderate in intensity in childhood and adult patients [4]. Unlike other patients with paramyotonia congenita [4,5], the episodes of stiffness were usually spontaneous and not evoked by continuous muscle contractions.

Furthermore, in paramyotonia congenita the weakness usually follows the muscle cramps or the stiffness episodes, whereas our patient rarely experienced transient paralysis or muscle weakness of short duration. Moreover, this patient did not show cold-sensitive stiffness or weakness. The first cases reported did show cold-sensitivity and periodic paralysis [6] and these findings were confirmed by other authors reporting paralysis and weakness after cold exposure [7]. However, cases without weakness and without cold-sensitive weakness/paralysis were recognised [8,9].

Surprisingly, in our case, the same variation of the child has been found also in the mother, that showed discharges on EMG with only mild clinical symptoms during her life. A similar phenomenon has been previously reported by Rossignol et al. [10], that described 25% (11/44) of patients presenting with myotonic discharges on EMG without a clinical manifestation.

Finally, the clinical picture and the EMG findings were not suggestive for other clinical phenotypes due to SCN4A gene variations.

The EMG features of the our patient and his mother showed abnormally prolonged insertional activity (rapidly repetitive, spontaneous, low amplitude discharge and complex repetitive discharge) without myotonic discharge, indicating irritability of the muscle or instability of the muscle membrane. Moreover, a decremental response on repetitive stimulation after exercise or cold exposure was not present, as usually reported in patients suffering from paramyotonia congenita. In conclusion, although the wide spectrum of SCN4A variations is well-known [1-3], this case further highlights other clinical features related to the SCN4A gene variations. This report provides further evidence that SCN4A channelopathies display significant clinical heterogeneity, even in members of the same family with an identical genetic defect where other genetic or environmental factors may influence the expression of the symptomatology due to SCN4A gene variations.

Bibliography


