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Case report

Divalent cation-responsive myotonia and muscle paralysis in skeletal muscle sodium channelopathy

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Abstract

We report a patient with paramyotonia congenita/hyperkalemic periodic paralysis due to Nav1.4 I693T mutation who had worsening of myotonia and muscle weakness in the setting of hypomagnesemia and hypocalcemia with marked recovery after magnesium administration. Computer simulations of the effects of the I693T mutation were introduced in the muscle fiber model by both hyperpolarizing shifts in the Nav1.4 channel activation and a faster recovery from slow channel inactivation. A further shift in the Nav1.4 channel activation in the hyperpolarizing direction as expected with low divalent cations resulted in myotonia that progressed to membrane inexcitability. Shifting the channel activation in the depolarizing direction as would be anticipated from magnesium supplementation abolished the myotonia. These observations provide clinical and biophysical evidence that the muscle symptoms in sodium channelopathy are sensitive to divalent cations. Exploration of the role of magnesium administration in therapy or prophylaxis is warranted with a randomized clinical trial.
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Keywords: Myotonia; Paramyotonia congenita; Periodic paralysis; Muscle weakness; Sodium channel; Magnesium

1. Introduction

Skeletal muscle sodium channelopathy and childhood-onset aplastic anemia are rare. Concurrence of these rare diseases in the same subject has not previously been reported. Myotonia and muscle weakness are cardinal symptoms in sodium channel disorders of the skeletal muscle. Experimental studies have shown that reduced concentrations of extracellular Mg^{2+} and Ca^{2+} ions exacerbate myotonia in the ClC-1 chloride channel inhibited skeletal muscle fibers [1,2]. Effects of serum divalent cation concentrations on myotonia and muscle weakness in patients are not yet known.

We present a patient with paramyotonia congenita/hyperkalemic periodic paralysis and aplastic anemia who had worsening myotonia and prolonged muscle paralytic episodes in the setting of drug-induced hypomagnesemia and hypocalcemia. His symptoms improved with the normalization of the serum divalent cation concentration. We provide supporting biophysical data using a mathematical simulation model of single skeletal muscle fibers. The Institutional Review Board approved the study and the patient provided written informed consent for the contribution to this study.

2. Case report

A 19-year-old man reported episodes of muscle stiffness followed by weakness that lasted ≤30 min since the age of 3 years. Muscles in the face, arms and legs were affected. Episodes occurred about once a week and did not interfere with his quality of life. The episodes were triggered by rest after exercise, prolonged sleep, and hunger. His symptoms improved during the teenage years such that he only noticed transient right upper arm stiffness about 2–3 times in a month. A similar history in his father suggested dominant inheritance.

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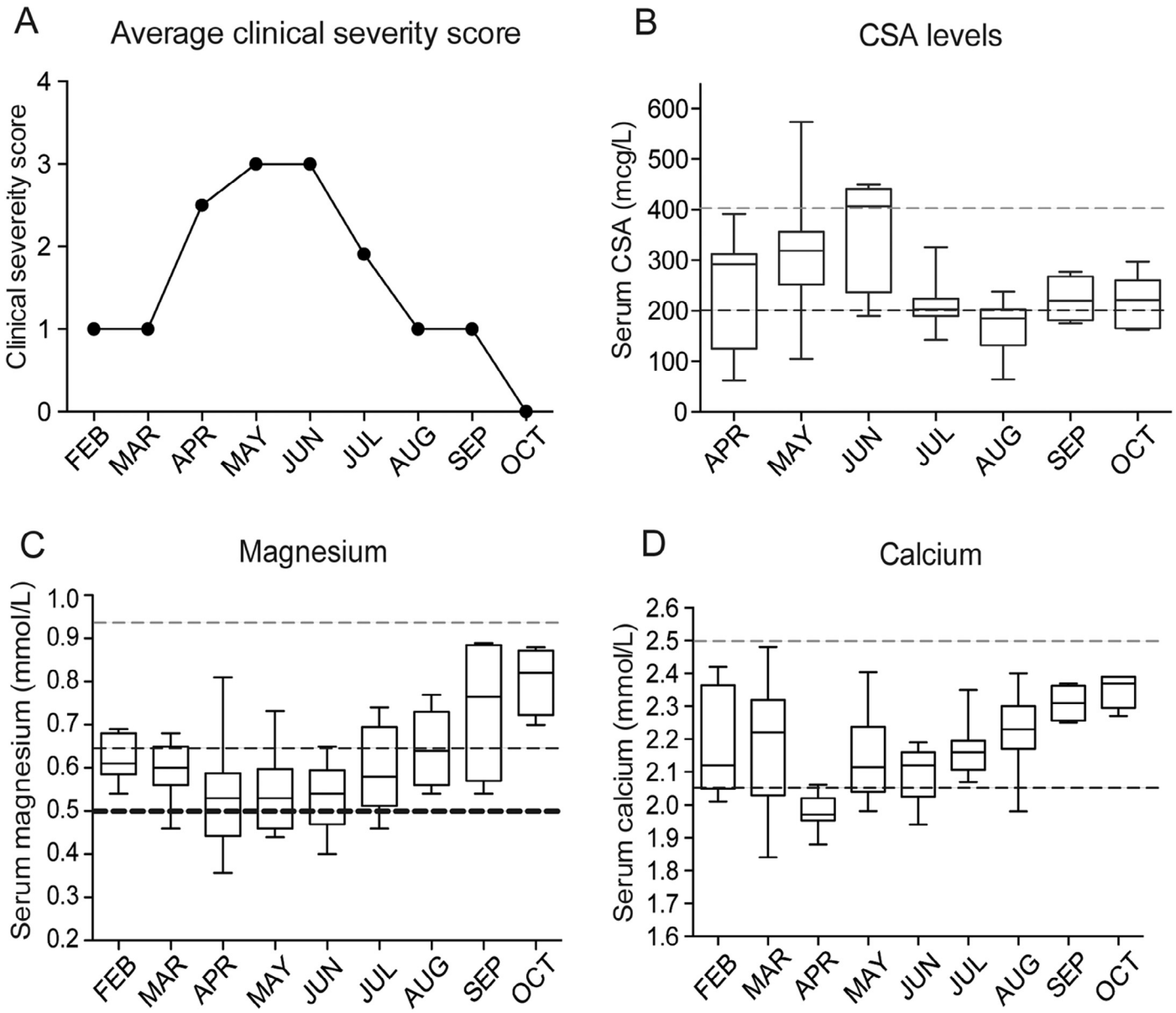

Fig. 1. Clinical and laboratory findings over time (A–D). Clinical severity score (A) was adapted from the GBS disability scoring system (0: A healthy state, 1: Minor symptoms and capable of running, 2: Needs help with walking, 3: Chair bound or bedridden). Average monthly CSA (B), Mg^{2+} (C) and Ca^{2+} (D) concentrations. Monthly data are shown in box and whiskers format with 5% and 95% confidence intervals. Light and dark lines indicate the normal laboratory reference range for divalent cations and therapeutic range for CSA. Heavy dark line (C) defines a critically low magnesium level.

He was treated with multiple courses of immunosuppressive therapy (IST) including cyclosporine (CSA) for aplastic anemia from the age of 9 years. Due to worsening aplastic anemia, he received an allogeneic hematopoietic stem cell transplant using haploidentical CD34+ cells from his mother combined with a single umbilical cord blood unit at the age of 20 years. In the weeks following the transplant he developed daily symptoms of stiffness followed by generalized flaccid paralysis lasting for >8 hours (Fig. 1A). Bulbar, respiratory and sphincter muscles were not affected. Previously reported triggers such as rest after exercise, cold environment, hunger and excess sleep were absent. In between the episodes, his muscle strength was normal. Eyelid myotonia was present and worsened on repetitive exercise. Repetitive forceful handgrip exercise induced myotonia. Cooling of the forearms resulted in muscle weakness. Thyroid hormone levels were normal. Electromyography showed myotonia and myopathic changes in the limb muscles. DNA testing confirmed the presence of a previously characterized p.I693T mutation in the domain II S4-S5 linker of the alpha subunit of the voltage gated skeletal muscle sodium channel (Nav1.4) [3,4]. Post-transplant IST consisted of CSA given at doses to maintain levels in the therapeutic range (200–400 mcg/L) (Fig. 1B) and mycophenolate mofetil 1000 mg twice daily. Although serum K^+ levels remained within physiological range, serum Mg^{2+} and Ca^{2+} levels dropped below 0.5 mmol/L and 2.2 mmol/L, respectively (Fig. 1C and D). Mg^{2+}