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# PAINFUL CRAMPS AND GIANT MYOTONIC DISCHARGES IN A FAMILY WITH THE NAV1.4-G1306A MUTATION

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ABSTRACT: *Introduction:* Two previously reported Norwegian patients with painful muscle cramps and giant myotonic discharges were genotyped and compared with those of members of 21 families harboring the same mutation. *Methods:* Using primers specific for *SCN4A* and *CLCN1*, the DNA of the Norwegian family members was amplified and bidirectionally sequenced. Clinical and neurophysiological features of other families harboring the same mutation were studied. *Results:* A G1306A mutation in the Nav1.4 voltage-gated sodium channel of skeletal muscle was identified. This mutation is known to cause myotonia fluctuans. No giant myotonic discharges or painful muscle cramps were found in the other G1306A families. *Conclusions:* Ephaptic transmission between neighboring muscle fibers may not only cause the unusual size of the myotonic discharges in this family, but also a more severe type of potassium-aggravated myotonia than myotonia fluctuans.

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In 2003, Torbergsen *et al*. reported an unusual nondystrophic painful myotonic disorder with stiffness and cramps in skeletal muscles including the tongue in a 34-year-old Norwegian woman and her 14-year-old daughter.[1] Extended electromyographic (EMG) studies revealed some unusual findings. In addition to ordinary myotonic discharges, intensive bursts of positive waves with amplitudes up to 16 mV were observed (called "giant myotonic discharges" because their amplitude exceeded 10 mV, an amplitude above which high-amplitude motor unit potentials are conventionally called "giant"), whereas the maximum size of typical positive waves is about 1 mV. Recordings performed with concentric needle EMG, single-fiber EMG (SFEMG), and a dual-channel EMG were interpreted to show ephaptic transmission between neighboring muscle fibers. At that time, sequencing of the 2 myotonia genes, *SCN4A* and *CLCN1*, was not completed.

*SCN4A* mutations cause sodium channel myotonia (also called potassium-aggravated myotonia, or PAM) or paramyotonia congenita. The mutations are situated in different protein areas. PAM is divided into 3 subtypes of severity, myotonia fluctuans,[2,3] moderate myotonia,[3] and myotonia permanens.[3] All 3 subtypes are characterized by myotonia after exercise without substantial cold sensitivity, whereas in paramyotonia congenita there is myotonia with exercise and exposure to cold. The stiffness is frequently followed by flaccid weakness, which lasts several hours, even after immediate rewarming. *CLCN1* mutations are responsible for chloride channel myotonia, which is characterized by myotonia after rest and improvement with exercise (warm-up phenomenon).[4]

**Abbreviations:** CK, creatine kinase; *CLCN1*, gene encoding the major chloride channel of skeletal muscle, ClC-1; EDTA, disodium ethylenediamine tetraacetate; EMG, electromyography; MUP, motor unit potential; *SCN4A*, gene encoding the α subunit of the voltage-gated sodium channel of skeletal muscle, Nav1.4; SFEMG, single-fiber electromyography; SNEL, severe neonatal episodic laryngospasm

**Key words:** ephaptic transmission; G1306A; muscle pain; mutation; myotonia; positive waves

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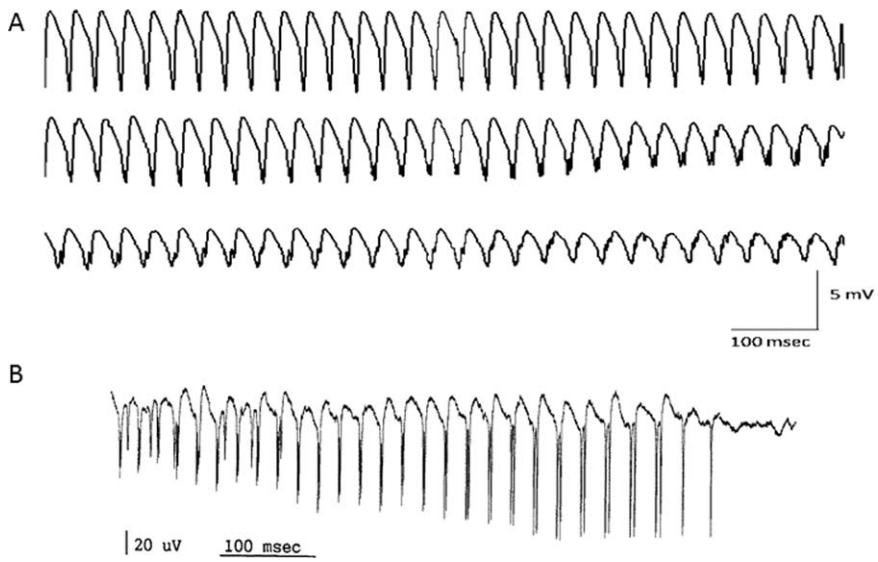


**FIGURE 1.** Spontaneous EMG activities of patient 1 **(A)** and a typical Nav1.4-G1306A patient **(B)**. Both myotonic bursts consist of positive waves. Although the typical patient shows normal potential amplitudes, patient 1 exhibits very high amplitudes, and specifically giant myotonic discharges. Note the different amplitude calibrations in **(A)** and **(B)**.

Here we describe the results of genetic sequencing in conjunction with the clinical presentation and electrophysiological findings of the Norwegian family and discuss, in comparison, the 21 G1306A families from the Ulm Neuromuscular Center.

## METHODS

Whole blood was taken from the patients for extraction of genomic DNA. Using primers specific for the exons and exon–intron boundaries of *SCN4A*[3] and *CLCN1*,[4] the DNA was amplified by polymerase chain reaction, and the products were sequenced bidirectionally. All studies were conducted according to the Declaration of Helsinki. Informed consent was obtained from the Norwegian family and the members of the G1306A families of the Ulm group.

The EMG examinations were performed on various muscles (deltoid, vastus lateralis, extensor digitorum, and flexor digitorum) using a Keypoint device (Medtronic, Copenhagen) in the Norwegian patients, and a Multiliner device (Toennies, Hochberg, Germany) in the German patients. Spontaneous activity and motor unit potentials were recorded conventionally with concentric needle electrodes. SFEMG was performed in the Norwegian patient. In the German patients, muscle contractions and corresponding electrical activity were studied at normal and increased serum potassium levels in patient 1 (see Case Reports) together with Dr. K. Ricker. Two wire electrodes were used to record the EMG activity during contraction. The length of the exposed tips was about 3 mm, and the interelectrode distance was approximately 10 mm. Contractions of the flexor digitorum muscle were measured under isometric conditions.

## CASE REPORTS

**Patient 1.** This 48-year-old woman was examined by some of the present investigators 14 years ago because of pronounced symptoms of myotonia, without clinical or EMG signs of a myopathy. Her painful myotonia and unusual myotonic findings on EMG were described in detail previously.[1]

Her symptoms have mainly remained unchanged, although she has noticed some worsening over time. Her symptoms are stiffness and painful cramps in skeletal muscles. The muscle cramps are localized to the muscles in the thighs or in the legs, toes, face, and tongue. The symptoms in the trunk muscles become so pronounced that her breathing is uncomfortable during the night. Her muscle pain may be severe, sometimes to the extent that she has to see a doctor for acute care at night to receive analgesic medication. She feels a little more uncomfortable in the cold. She has experienced neither muscle weakness nor cardiac symptoms. Initially, anti-myotonic medications such as mexiletine, carbamazepine, and acetazolamide were tested, but without obvious effect. Since that time she has not had any treatment.

As an infant she was seen in the hospital several times because of respiratory problems, which seem to have been related to respiratory infections, and no relation to her myotonic disease was suspected.

Clinical examination shows strong and well-developed muscles. She opens her closed eyes and fists without obvious delay. There is no warm-up effect, but she feels stiffer within minutes after exercise. Tapping on the forearm extensor muscles

with a reflex hammer causes prolonged extension of the wrist. A painful contraction occurs when she protrudes the tongue[1] (see video in Supplementary Material available online). EMG shows classic myotonic discharges in addition to intense activity of complex positive waves with high amplitude (up to 16 mV; Fig. 1A), as described previously.[1]

Creatine kinase (CK) level was normal. MRI of the thighs and legs showed normal musculature. Echocardiogram was normal without signs of hypertrophy and with normal relaxation time.

**Patient 2.** Patient 2 is the 28-year-old daughter of the index patient. She has complained of painful muscle cramps since she was a teenager. The muscle cramps started after the electrodiagnosis was made and have increased gradually over the years. She has pain every day, particularly in the morning. The cramps can occur in any muscle and may move from 1 region of the body to another. The cramps are mostly provoked by exercise, and she feels stiffer in a cold environment. There is no typical warm-up phenomenon. When her face is cold or she is eating ice cream, she feels stiffness in her tongue, throat, and facial muscles. Sometimes she feels that swallowing can be difficult and feels that she may choke. She has complained of episodic tachycardia, but extensive cardiologic examinations have not revealed any heart disease. In infancy and up to the age of 2.5 years she had several episodes of respiratory arrest and was hospitalized for urgent care. Her muscles are well developed. Clinical examination is otherwise normal. EMG showed similar changes as in her mother with rather continuous myotonic discharges and positive waves of very high amplitude. Concentric needle EMG revealed neither myopathic nor neuropathic changes. CK was normal. She has not had any antimyotonic treatment.

**Genetic Studies.** Genetic studies revealed an *SCN4A* c.3917G>C mutation predicting a G1306A amino acid substitution in the Nav1.4 sodium channel in both patients. This mutation was excluded in the asymptomatic relatives of the index patient (mother and son of the index patient). DNA as well as clinical information concerning her father was not available. *CLCN1* mutations affecting the chloride channel were not identified in either parent, and the search for mutations related to dystrophic myotonic disorders was also negative.

## DISCUSSION

This Norwegian family meets the characteristic features of myotonia fluctuans, such as delayed myotonia *after* exertion and the distribution of the most affected muscles.[3] However, some clinical and electrophysiological findings are different. Whereas myotonia fluctuans is a mild form of sodium channel myotonia that remains unnoticed by some patients,[3] the myotonia in this family was striking. The summation of synchronous action potentials from neighboring fibers may explain the increased strength of the myotonic contractions. In the EMG, this summation leads to the giant myotonic discharges, the most surprising and unusual finding in this family. Such giant discharges have not been reported previously for potassium-aggravated myotonia in the literature nor have they been observed in the 21 G1306A families known to us from the Ulm Neuromuscular Center.[5] As mother and daughter both have giant myotonic discharges, this phenomenon could be genetically determined. The synchronous electrical activity may be the result of ephaptic transmission between fibers.[1] This is indicated by high-amplitude signals that are generated by highly synchronized muscle fiber action potentials (small jitter[1]) and by the phenomenon of desynchronization when the shape changes and amplitude decreases.

Nav1.4-G1306 is localized in the III–IV intracellular loop, which contains the fast inactivation particle. Due to pathologically increased reopenings of the mutant channels, sodium conductance is elevated, and the muscle fibers slowly depolarize.[4,6] Whereas slow depolarization inactivates normal sodium channels (accommodation), mutant sodium channels flicker between the gating states and generate repetitive action potentials, that is, myotonia. The mutant channels confer a dominant gain of function on the channel as well as on cell excitability. Corresponding to the severity of the disruption of the inactivation gate structure on the protein level, there are 3 clinical severities to be distinguished, of which myotonia fluctuans (G1306A) is the least severe. Even the most severe phenotypes of moderate myotonia (G1306V) and myotonia permanens (G1306E) do not show higher amplitude myotonic discharges, but rather increased frequency.

Although muscle pain has been reported in myotonia patients[7–10] and seems to occur more often in sodium channel than in chloride channel mutation carriers,[11–14] it is not a frequent symptom in G1306A carriers; that is, pain was found in only 1 of the 21 G1306A families at the Ulm Neuromuscular Center. In contrast, pain was a dominant symptom in the Norwegian family. The mechanism for the pain is unclear. The extreme cramps in the tongue muscles are also peculiar.[1] Myotonia in the tongue muscles is well known,[15] but impressive painful cramps and contraction, as seen in these patients, have not been recognized.

Laryngospasm (severe neonatal episodic laryngospasm, or SNEL) has been reported in some children with sodium channel mutations.[16,17] Patient 2 in our study had symptoms in infancy that suggested this condition. The fact that 3 families at the Ulm Neuromuscular Center who reported similar postnatal respiration symptoms are also the families who reported the most muscle pain shows that SNEL may also be seen in G1306A mutations, not only in the G1306E mutations reported earlier. Taken together, this could suggest that the larger the discharges, the more severe the muscle cramping and pain. Interestingly, the more severe phenotype does not lead to more myolysis, because the CK levels in the Norwegian family were normal. This is in contrast to the frequently elevated CK values in such patients, with average elevations of 2–3-fold seen in the 21 Ulm families.

We conclude that the synchronous muscle fiber activity of the Norwegian family led to a more severe form of sodium channel myotonia than expected from the well-known Nav1.4-G1306A substitution. Further study is needed to determine whether the dominant pain is related to this synchronous activity.

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