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Case report

Paroxysmal neuromyotonia: A new sporadic channelopathy

Teeratorn Pulkes [a,*], Charungthai Dejthevaporn [a], Metha Apiwattanakul [b], Chutima Papsing [a], Michael G. Hanna [c]

[a] *Division of Neurology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
[b] *Department of Neurology, Prasat Neurological Institute, Bangkok, Thailand*
[c] *MRC Centre for Neuromuscular Diseases and Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London, UK*

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Abstract

Neuromyotonia is a heterogeneous group of genetic and autoimmune channelopathies resulting in hyperexcitability of peripheral nerves. We report an unusual case of neuromyotonia, which to our knowledge has not been previously described. The patient developed intermittent attacks of severe painful muscle stiffness accompanied by sweating, myokymia and raised serum creatine kinase. Genetic analysis of *KCNA1*, *KCNQ2* and *SCN4A* genes did not identify pathogenic mutation. Serum voltage-gated potassium channel antibody was also negative. He was successfully treated with acetazolamide and carbamazepine. This appears to be a new neuromuscular disease, "paroxysmal neuromyotonia", the etiology of which is still unknown.

Keywords: Neuromyotonia; Channelopathies; Acetazolamide

1. Introduction

Neuromyotonia is characterized by muscle stiffness and cramps, myokymia, and pseudomyotonia in association with continuous motor unit activity [1]. Most cases are considered to be autoimmune-mediated usually related to voltage-gated potassium channel (VGKC)-complex antibodies [2]. Recent study demonstrated that VGKC antibodies did not bind to Kv1 subunits but its major target was contactin-associated protein-2 (CASPR2) [3]. CASPR2 is co-localized with Kv1.1 and 1.2 at the juxtaparanodes in myelinated axons. It is possible that antibodies to CASPR2 cause down-regulation of CASPR2/Kv1.1/Kv1.2 complexes resulting in hyperexcitability of peripheral nerves [3]. Although patients with a rare inherited form often develop myokymia as a part of episodic ataxia type 1, only a few cases of inherited pure neuromyotonia are described [4,5]. To our knowledge, neuromyotonia always exhibits a chronic illness. Here, we report clinical, electrophysiological, immunological and genetic studies of an interesting patient with a new clinical syndrome of paroxysmal neuromyotonia.

2. Case report

A 53-year-old Thai man presented with paroxysmal attacks of severe painful muscle stiffness. At age 40 years, he experienced the first stereotypic attack. Attacks commenced with a feeling of tiredness and fatigue in both legs shortly followed by vigorous rippling muscle contraction in both thighs and marked generalized sweating. His legs subsequently became generally stiff and painful to the point of a stiff paralysis. In a typical attack, similar symptoms progressively affected muscles in abdomen, chest, arms and hands, but not facial muscles. The attack lasted 5–6 h. He did not observe dark urine during or after the attacks. During the first few years, it occurred only a few

* Corresponding author. Address: Division of Neurology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama 6 Road, Bangkok 10400, Thailand. Tel./fax: +66 22011386.
E-mail address: ratpk@mahidol.ac.th (T. Pulkes).

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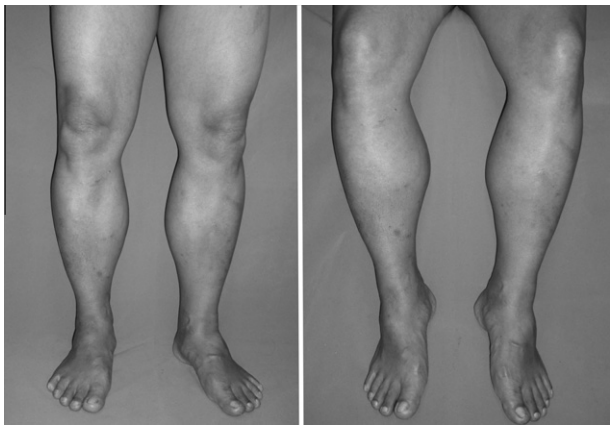

Fig. 1. Demonstrates marked leg muscle hypertrophy.

times a year but the frequency, duration and severity gradually increased. Long-periods of heavy exercise and hot conditions induced the attacks. In contrast, rest and cold conditions could sometimes help to ameliorate the attacks. Four years ago, he was able to walk only a short distance before the attack started. He developed the attack once or twice a week with two days duration. He has no family history of neuromuscular diseases. Treatments with quinine, phenytoin, carbamazepine and prednisolone were all ineffective. Laboratory records showed that serum antinuclear antibody (ANA) was positive in 2007 and 2010 (peripheral pattern 1:160 and homogeneous pattern 1:160). Chest X-ray was periodically performed which showed no evidence of thymoma or lung carcinoma.

Neurological examination four years ago was unremarkable. However he clearly had generalized muscle hypertrophy despite lack of physical exercise (Fig. 1). He was clinically diagnosed with potassium-aggravated myotonia. 250-mg of oral acetazolamide daily was prescribed. For the next 3 years, the attacks occurred only 4 times. During the first week of the attacks, serum creatine kinase was markedly increased to 1864–6482 U/L (normal 30–200 U/L) and it normalized after a month. (Table 1) He was frequently hospitalized in attacks because of severe pain. We observed one attack and noted the following features: it commenced with myokymia in his thighs (VDO supplement 1). Half an hour later, legs were progressively stiff and he was unable to passively flex his joints. His body then became rigid and his arms and hands were subsequently affected. He had dramatic and excessive generalized sweating. At this stage myokymia became subtle. He had tachycardia rate of about 100 beats per minute. We gave him 200-mg of carbamazepine. He was given intravenous 10-mg of diazepam and 25-mg of pethidine for relieving pain. The attack lasted for 6 h and pain had completely disappeared by the next morning.

Table 1
Shows serum creatine kinase level during and after neuromyotonia episodes.

Weeks after onset of each neuromyotonia episode	Creatine kinase level (unit/litre)			
	02/2007	07/2007	09/2007	10/2007
0	6482	2454	1864*	2058
2	na	na	481	na
3	na	na	na	189
4	280	366	na	na
7–8	174	144*	na	126

Abbreviation: na = not available.

* Blood samples were taken on consecutive days, which a regular follow-up was on the 8th Sep 2007 and the attack was started on the 9th Sep 2007.

About 2 years ago, he started to experience the attacks again every 1–3 months. In view of an increased frequency we prescribed 200-mg of carbamazepine combined with 250-mg of acetazolamide daily and since commencing this regime he has had no further attacks, having been followed up for 18 months.

Electromyography (EMG) was performed on gastrocnemius, vastus medialis and rectus femoris. Both ictal (late phase of the attack demonstrated on VDO supplement 2) and interictal EMG showed continuous motor unit activity which is composed of frequent fasciculations, doublets, triplets and runs of myokymic discharges (Fig. 2). The motor units were of normal configuration and the recruitment patterns were also normal (up to 7 mV). Nerve conduction study was unremarkable.

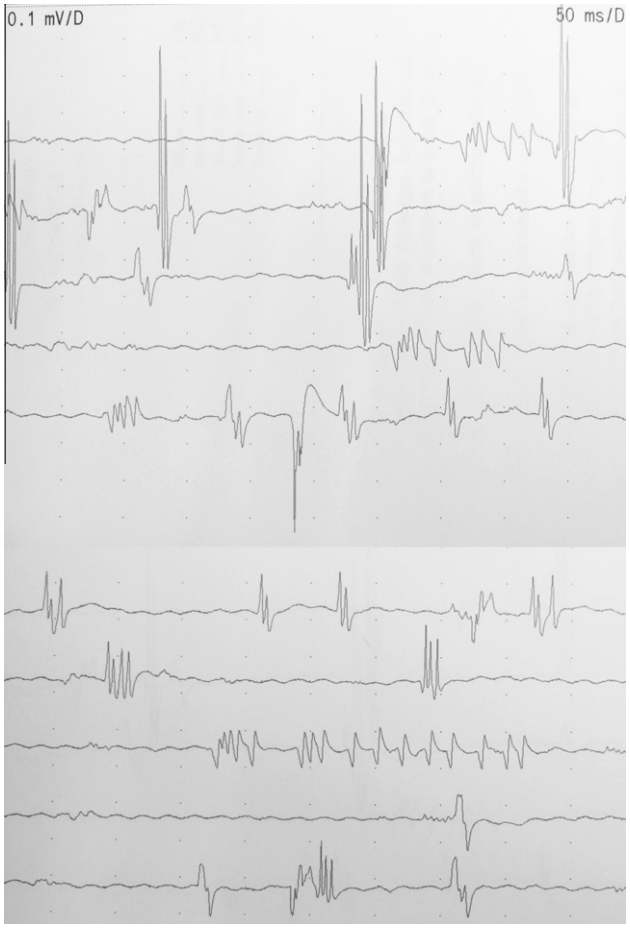

Fig. 2. Electromyography (interictal period) shows frequent fasciculations, myokymic discharges and continuous motor unit activity.

Direct sequencing of all exons in *KCNA1* [6], *KCNQ2* [7] and *SCN4A* [8] genes did not identify any pathogenic mutations. Eleven primer-pairs set for sequencing all exons and exon–intron boundaries of *KCNQ2* were newly designed. VGKC-complex antibodies were negative by using immunofluorescent and immunoprecipitating techniques. Other antibodies were screened including antibodies to GAD, ANNA-1, ANNA-2, ANNA-3, PCA-1, PCA-2, PCA-Tr, amphiphysin, CRMP-5, NMDA, AMPA, GABA-b, SRP-54, which were all negative.

3. Discussion

We report a unique patient with clinical and electrophysiological features of neuromyotonia including myokymia, muscle stiffness and continuous motor unit activity in association with autonomic dysfunction. Patients with classical neuromyotonia almost invariably exhibit a chronic clinical course despite sometimes experiencing paroxysmal painful spasms [9]. An episodic syndrome of hyperhidrosis associated with VGKC-complex antibodies has also been described. However that patient did not exhibit neuromuscular manifestations [10]. We report a unique patient with clinical and electrophysiological features of neuromyotonia. The patient was clinically similar to autoimmune neuromyotonia except for the paroxysmal course and markedly distressing pain was a notable and extreme feature. Paroxysmal attacks also correlated with a striking increase in serum creatine kinase.

During the neuromyotonia attack, muscle membrane appeared to be severely disrupted corresponding to a marked increase in serum creatine kinase (Table 1). This may have also resulted in a release of myoglobin into bloodstream causing myoglobinuria. Lack of history of dark urine in this case may not entirely exclude the possibility of dark urine, since the patient might not fully observe color of his urine because of the distressing pain. Laboratory testing for myoglobin level in urine is not available in Thailand, therefore we were unable to demonstrate the existence of myoglobinuria in this patient.

Unlike acquired neuromyotonia, this patient did not respond to monotherapy of carbamazepine and phenytoin. But low dose of carbamazepine later showed some benefit when taken with acetazolamide. This data suggest that the patient may have different pathophysiological mechanisms compared to classical neuromyotonia.

The etiology of neuromyotonia is usually either autoimmune or genetic. Acetazolamide and carbamazepine showed a clear benefit in this patient suggesting that the primary defect might involve the function of a cellular channel. Acetazolamide is an effective treatment of inherited channelopathies such as episodic ataxia and periodic paralysis. The benefit may result from its functional properties including an ability to alter cellular pH and sarcolemmal potassium conductance [11]. Therefore, responsiveness to acetazolamide may not be limited to channelopathies of inherited form. The syndrome was also late in onset, without a family history, and the patient repeatedly had high ANA serum titres. However, the nature of the disease exhibits frequent paroxysmal attacks ranging from a few hours to every a few days since several genetic channelopathies exhibit an episodic nature. Autoimmune-mediated diseases however, in association with a pathogenic antibody, are unlikely to show disease activity which can rise and fall in such a short period of time. So the natural history of paroxysmal neuromyotonia suggests that a genetic defect may be a primary underlying process. Genetic analysis in this study does not exclude the possibilities of an intronic mutation in the *KCNA1*, *KCNQ2* or *SCN4A* genes, or an unknown mutation in other genes.

In summary, we report a sporadic case of paroxysmal neuromyotonia characterized by episodic painful muscle stiffness, myokymia and excessive sweating. Acetazolamide combined with carbamazipine appear to be effective. We did not identify antibodies to VGKC-complex and mutation in *SCN4A*, *KCNA1* and *KCNQ2* genes. The pathogenesis of the newly described clinical syndrome is still unknown.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2012.01.004.

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