

Clinical, Electrophysiological, and Serological Evaluation of Patients with Cramp–Fasciculation Syndrome

Kramp Fasikülasyon Sendromlu Hastaların Klinik, Elektrofizyolojik ve Serolojik Olarak Değerlendirilmesi

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ABSTRACT

Introduction: Cramp–fasciculation syndrome (CFS) is a rare peripheral nerve hyperexcitability syndrome. There are only a few reports on clinical and serological profile of a CFS cohort that was followed up by a single outpatient clinic.

Methods: Clinical, electrophysiological, and serological features of 6 CFS patients (5 men, 1 woman; 27–65 years old) were investigated.

Results: All patients presented with cramps, fasciculations, muscle pain, and autonomic symptoms, and 2 also reported numbness and burning sensation in limbs, suggestive of neuropathic pain. Antibodies to uncharacterized voltage-gated potassium channel (VGKC)-complex proteins were found in 2 patients and to contactin-associated protein-like 2 (CASPR2) in 1 patient. None of the patients had a tumor. Most of the patients revealed prolonged after-discharges following tibial nerve stimulation. Nerve

conduction studies and R-R interval variability tests were normal, whereas sympathetic skin responses were increased in amplitude in 3 seronegative patients. Five patients showed favorable response to carbamazepine or pregabalin treatment, whereas 1 VGKC-antibody-positive patient was resistant to carbamazepine and immunosuppressant treatment.

Conclusion: Neuropathic pain and VGKC-complex antibodies may be encountered in CFS patients. Although autonomic symptoms are commonly found in CFS, routine autonomic system tests which are done in electrophysiology laboratories might yield normal results.

Keywords: Cramp–fasciculation syndrome (CFS), peripheral nerve hyperexcitability, voltage-gated potassium channel (VGKC)-complex proteins, neuropathic pain

ÖZ

Amaç: Kramp-fasikülasyon sendromu (KFS) nadir görülen bir periferik sinir hipereksitabilite sendromudur. Tek bir merkezden takip edilen KFS hastalarının klinik ve serolojik özelliklerinin bildirildiği az sayıda yazı vardır.

Yöntem: Altı KFS (5 erkek/1 kadın, yaş aralığı: 27-65 yıl) hastasının klinik, elektrofizyolojik ve serolojik özellikleri incelendi.

Bulgular: Bütün hastalarda kramp, fasikülasyon, kas ağrısı ve otonom belirtiler görülürken ikisinde ayrıca nöropatik ağrıyı düşündüren ekstremitelerde uyuşma ve yanma hissi mevcuttu. İki hastada tanımlanmamış voltaja duyarlı potasyum kanalı kompleks proteinlerine [voltage-gated potassium channel (VGKC)-complex proteins] karşı oluşmuş antikorlar, bir hastada "contactin-associated protein-like 2 (CASPR2)" antikorunu bulundu. Hastaların hiçbirinde tümör yoktu.

Tibial sinir stimülasyonu sonucunda hastaların çoğunda uzamış ard boşalimler görüldü. Sinir iletim çalışmaları ve R-R interval değişkenliği testleri normalken seronegatif olan 3 hastada sempatik deri yanıt amplitüdüleri artmıştı. Beş hasta karbamazepin ve pregabalin tedavisine iyi cevap verirken VGKC-antikoru pozitif olan bir hasta karbamazepin veya immünsüpresyon tedavisine dirençli idi.

Sonuç: Nöropatik ağrı ve VGKC-kompleks antikor birlikteliği KFS hastalarında görülebilir. Otonom belirtiler KFS'li hastalarda sık bulunmasına rağmen elektrofizyoloji laboratuvarlarında uygulanan rutin otonom sistem test sonuçları normal kalabilir.

Anahtar kelimeler: Kramp-fasikülasyon sendromu (KFS), periferik sinir hipereksitabilitesi, voltaja duyarlı potasyum kanal-kompleks proteinleri, nöropatik ağrı

INTRODUCTION

Cramp–fasciculation syndrome (CFS) is a rare peripheral nerve hyperexcitability (PNH) syndrome, characterized by disabling muscle cramps and twitches. CFS presents with a lower rate of clinical and electrophysiological signs of PNH as compared to the more severe member of the same spectrum-neuromyotonia (Isaacs' syndrome) (1,2,3,4). Voltage-gated potassium channel (VGKC)-complex antibodies are often found in CFS patients. While these antibodies are usually directed against leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) in other PNH syndromes, they are mostly against uncharacterized VGKC-complex antigens in CFS patients (2). In this study, we



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report clinical and electrophysiological features of 6 CFS patients together with their detailed antibody screening and autonomic test findings.

METHODS

Patients

All consecutive CFS patients (27–65 years old; 5 men, 1 woman) followed up in our outpatient clinic were recruited, and their demographic, clinical, and laboratory data were recorded (Table 1). CFS was defined by the presence of muscle cramps and fasciculations in the upper and lower limbs on the neurological exam. None of the patients had any electrolyte disturbance, another neuromuscular disorder, or clinical and electrophysiological evidence for anterior horn disease or another autoimmune disease. Cranial magnetic resonance imaging (MRI) was normal in all patients. They were screened for occult malignancy with thorax and abdominal computerized tomography (CT), tumor markers, and fludeoxyglucose positron emission tomography (Cases 1 and 5), and none of the patients were found to have a tumor. The study was approved by the Institutional Review Board, and all patients gave their consents.

Electrophysiological Studies

In all patients, routine sensory and motor nerve conduction studies (NCSs; at least 2 nerves in 1 upper and 1 lower extremity), F wave studies (recorded from at least 1 hand and 1 foot muscle), and needle electromyography (at least 1 distal and 1 proximal muscle in 1 upper and 1 lower extremity) were performed. Presence of after-discharges was evaluated by stimulation of the right posterior tibial nerve by trains of 5 stimuli given at 0.5-, 1-, 3-, and 5-Hz intra-train frequencies. Discharges which began during or immediately following the trains that were clearly distinct from the baseline without fluctuations, implying voluntary motor activity were accepted as after-discharges. Discharge intensities were graded on a scale of 0–3, as described in a previous report (5).

Sympathetic skin responses (SSRs) recorded simultaneously from the right hand and foot following electrical stimulation (0.1-s duration, 20–40 mA in intensity) of the left median nerve at the wrist level. Recordings were made by disk electrodes placed as palm/sole (active) and the dorsum of the hand/foot (reference) arrangement. Band pass was 0.1–1000 Hz, sensitivity was 1–2 mV/division, and sweep speed was 1 s/

division (6). SSR responses >6.3 mV in amplitude for hand and >3.0 mV for foot were considered as to be increased (7). For R-R interval variation (RRIV), 1-min-long electrocardiograms of the supine patient during rest and hyperventilation were recorded with the oscilloscope program using triggering mode. The recording disk electrodes were placed on the wrist and 5th intercostal space at the midclavicular line. Then, RRIV was calculated manually by the percentage of difference between the earliest and the latest R waves (range of the R-R intervals) /mean of R-R intervals*100 (8).

Immunologic Studies

Antibodies to N-methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), LGI1, CASPR2, and gamma-aminobutyric acid B receptor (GABA_BR) were investigated by a cell-based immunofluorescence assay (Euroimmun, Luebeck, Germany). For uncharacterized VGKC-complex antibodies, radioimmunoassay (RIA) using brain extracts labeled with ¹²⁵I-dendrotoxin (normal value <100 pM) were used (9). Paraneoplastic antibodies (Hu, Yo, CV2, Ri, Ma2, and amphiphysin) were evaluated by a commercial immunoblot kit (Euroimmun).

RESULTS

All patients presented with cramps, fasciculations, muscle pain, and autonomic symptoms, and 2 of them (Cases 4 and 5) also reported numbness and burning sensation in the limbs, which were suggestive of neuropathic pain. Three patients had insomnia (Case 2, 4 and 5), and 1 of them had fatigue. All patients complained of hyperhidrosis, and all except Case 2 exhibited additional autonomic symptoms, such as erectile dysfunction, lightheadedness, constipation, and palpitation. Their follow-up durations were between 1 and 10 years (Table 1). They were diagnosed as having CFS 1 month to 1.5 years after the beginning of their complaints. Neurological examination was normal in 2 patients, while increased deep tendon reflexes (Cases 1 and 6) and reduced vibration sensation in the lower limbs (Cases 3 and 4) were found in some patients. Cases 2–6 showed significant response to carbamazepine or pregabalin treatment, whereas symptoms of Case 1 was only moderately decreased following carbamazepine, gabapentin, pregabalin, pulse steroid, intravenous immunoglobulin, azathioprine, and cyclophosphamide treatments (Table 1).

Table 1. Clinical, electrophysiological, and serological features of CFS patients

Case no.	Age (years), gender	Anti-bodies	Duration of follow-up	Neurological exam	Muscle pain	Neuro-pathic pain	Cramp	Fasci-culation	Hyper-hidrosis	OAS	NCSs	ADs ≤3Hz	ADs 5 Hz	SSR/RRIV	Treat-ment response
1	48,M	VGKC-complex	3 years	DTR↑	+	-	+	+	+	+	N	+++	+++	N/N	CBZ+IST/moderate
2	34, M	CASPR2	2 years	Normal	+	-	+	+	+	-	N	-	-	N/N	CBZ/complete
3	27,M	-	1 year	Vibration↓ LL	+	-	+	+	+	+	N	+	+	↑/N	CBZ/complete
4	65,M	-	2 years	Vibration↓ LL	+	+	+	+	+	+	N	+	+	↑/N	PRG/complete
5	54,M	VGKC-complex	3 years	Normal	+	+	+	+	+	+	N	+	+++	N/N	CBZ/complete
6	30,F	-	10 years	DTR↑	+	-	+	+	+	+	N	+++	+++	↑/N	CBZ/complete

M: male; F: female; CBZ: carbamazepine; PRG: pregabalin; DTR: deep tendon reflexes; ↑: increased, vibration; ↓ LL: reduced vibration sense in the lower limbs; OAS: other autonomic symptoms; VGKC: uncharacterized voltage gated potassium channel antigens; CASPR2: contactin-associated protein-like 2; IST: immunosuppressive treatment; SSR: sympathetic skin response; RRIV: R-R interval variability; NCSs: nerve conduction studies; ADs: after-discharges; N: normal

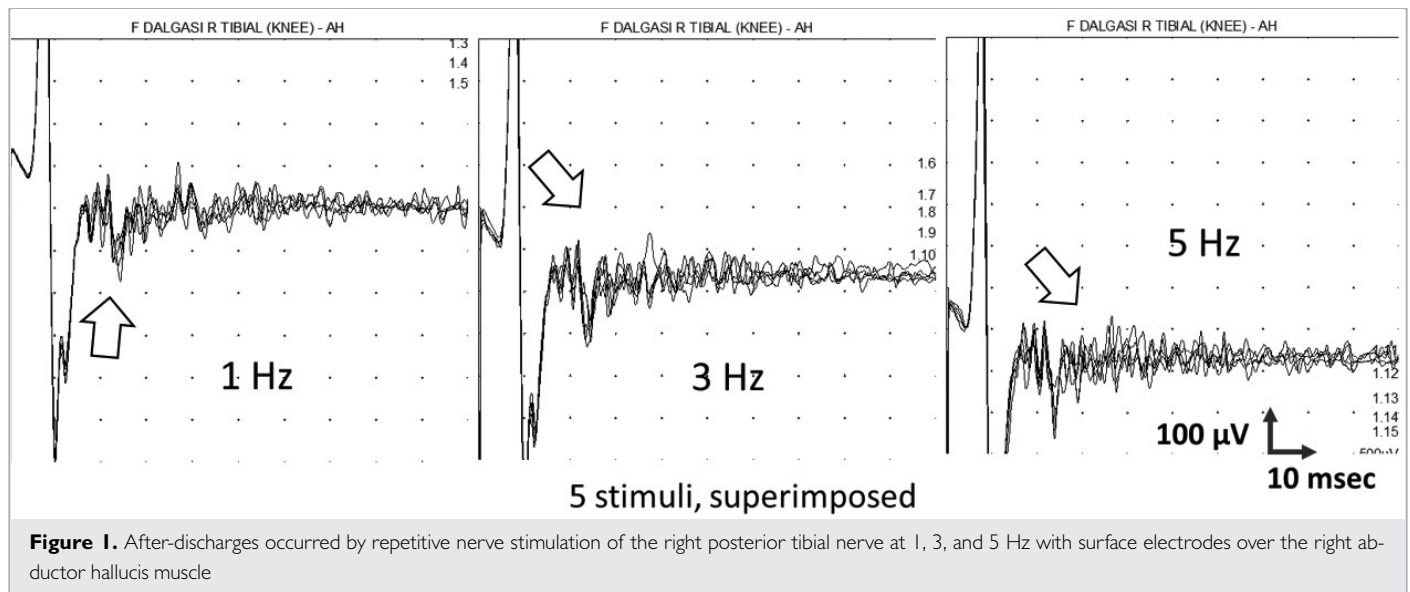


Figure 1. After-discharges (AH) occurred by repetitive nerve stimulation of the right posterior tibial nerve at 1, 3, and 5 Hz with surface electrodes over the right abductor hallucis muscle

Sensory and motor NCSs were normal in all patients. After-discharges were obtained in all patients except Case 2 (Figure 1). Needle electromyography showed abnormal spontaneous activity (random or semirhythmically discharging fasciculations and myokymic discharges) in all patients. R-R interval variations were normal in all the cases, whereas SSR was increased in amplitude in Cases 3, 4, and 6 (Table 1).

None of the patients had evidence of other tested paraneoplastic antibodies, including Hu, Yo, CV2, Ri, Ma2, and amphiphysin. Patients were not screened for the presence of unclassified antibodies. Two patients (Cases 1 and 5) displayed antibodies to uncharacterized VGKC-complex antigens (both >500 pM), and 1 (Case 2) had CASPR2 antibody. None of the other investigated ion channel antibodies could be detected.

DISCUSSION

As a rare syndrome, CFS has mostly been reported in the form of case reports, and there are only a few reports on CFS cohorts followed up by single outpatient clinics (2,4). Overall, in line with previously reported cohorts, our CFS patients showed male predominance, no tumor association, VGKC-complex antibody positivity, high prevalence of autonomic symptoms, and presence of chronic pain. While the sensory complaints and reduced vibratory sensation in the distal extremities in our patients can easily be attributed to the mild peripheral nerve involvement found in the idiopathic/autoimmune peripheral nerve hyperexcitability syndromes, the mechanisms leading to the increased tendon reflexes in 2 cases are more difficult to be interpreted (1). It might be speculated that the same central mechanisms as those causing insomnia in 3 patients can be effective in CFS, thereby reminding that this syndrome is a member of a larger coalition of syndromes with peripheral and central nervous system involvement (1).

Similar to previously reported cases, most of our patients, including seropositive ones, responded to membrane-stabilizing agents with no immunosuppression requirement (2). Moreover, our antibody results corroborate the notion that CFS patients do not necessarily display antibodies to uncharacterized VGKC-complex antigens and might also present with antibodies to well-characterized antigens such as CASPR2 (2).

However, in contrast with a recent report (2), we failed to find an association between VGKC-complex antibody positivity and autonomic test findings. Although autonomic symptoms are frequently observed in CFS

patients (1,2,3,10), autonomic studies might often give negative results. In previous studies, autonomic reflex screen and thermoregulatory sweat tests have given positive results only in a small fraction of CFS patients (2,4). Likewise, R-R interval variability test was normal in our patients, and SSR measurements gave large amplitude results in 3 patients. It is more likely that the large SSR responses were due to the already sweaty patients at the baseline. Nevertheless, none of the patients with increased SSR had VGKC-complex antibodies, indicating the presence of different pathogenic mechanisms in seronegative CFS. It was reported that after-discharges in seropositive patients were significantly longer in duration (5). We found similar after-discharge characteristics in seropositive and seronegative patients.

In conclusion, VGKC-complex antibodies were found in most of our patients. A parallelism between the antibody profile and some clinical characteristics may be found in larger series. Identification of novel anti-neuronal antibodies and non-VGKC-related disease mechanisms might be required for better identification of CFS cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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