Neurology Asia 2014; 19(4) : 409 – 412

Cold allodynia as the presenting symptom in a case of acquired neuromyotonia (Isaacs syndrome) with multiple autoantibodies

[1]Khean-Jin Goh, [1]Suhailah Abdullah, [2]Won Fen Wong, [3]Swan-Sim Yeap, [1]Nortina Shahrizaila, [1]Chong-Tin Tan

[1]Division of Neurology, Department of Medicine; [2]Department of Medical Microbiology, University of Malaya, Kuala Lumpur and Rheumatology Unit, [3]Subang Jaya Medical Centre, Subang Jaya, Malaysia.

Abstract

We report a patient who presented with severe cold-induced allodynia and hyperhidrosis, and found to have acquired neuromyotonia (Isaacs syndrome) with high voltage-gated potassium channel (VGKC) antibody titre,positive contactin-associated protein 2 (CASPR2) and leucine-rich glioma-inactivated 1 (LGI1) antibodies. The patient also had positive anti-dsDNA and acetylcholine receptor (AChR) antibodies without clinical features of SLE or myasthenia gravis, suggesting a strong underlying autoimmune tendency. CT thorax showed no thymoma. Her symptoms improved with intravenous immunoglobulin infusion but recurred despite maintenance oral corticosteroids and carbamazepine. She has since been on regular IVIG infusions. Cold allodynia is an unusual presentation in acquired neuromyotonia.

INTRODUCTION

Acquired neuromyotonia (Isaacs syndrome) is a rare disorder of peripheral nerve hyperexcitability, characterised clinically by continuous muscle twitching, cramps and stiffness associated with hyperhidrosis.[1-3] There is an underlying autoimmune basis with the presence of voltage-gated potassium channel complex (anti-VGKC) antibodies in these patients, as well as in the related Morvan syndrome, where in addition, there are neuropsychiatric symptoms such as insomnia, confusion, amnesia, hallucinations.[4-7] The auto-antibodies do not bind specifically to potassium channel subunits but to proteins that co-precipitate with the potassium channel antigenic complex, viz. the leucine-rich, glioma-inactivated 1 (LGI1) protein and the contactin-associated protein 2 (CASPR2).[8-10] In a series of patients with positive VGKC-complex antibodies, it was suggested that LGI1 antibodies was seen more often in autoimmune encephalitis while CASPR2 antibodies in neuromyotonia and Morvan syndrome.[7,8,11,12]

In acquired neuromyotonia, motor symptoms usually predominate but sensory symptoms have been noted in up to a third of patients, usually consisting of numbness or tingling of the limbs.[5] Predominantly sensory symptoms at presentation are uncommon but have been reported in a few patients while chronic pain has also been reported in patients with anti-VGKC positivity.[13,14] With the recognition of specific autoantibodies, the clinical spectrum of acquired neuromyotonia may continue broaden to include atypical phenotypes. We report an unusual presentation of a patient with peripheral nerve hyperexcitability and positive anti-VGKC complex antibodies whose initial complaints were cold-induced allodynia of the extremities.

CASE REPORT

A 53-year-old ethnic Chinese woman was referred to the Neurology Clinic of the University of Malaya Medical Centre, Kuala Lumpur, Malaysia with complaints of painful burning sensation of her hands and feet on exposure to cold for about a year. This occurred for example, when she washed her hands in cold water or when her limbs were exposed to cold air from an air-conditioner. Initially episodic, her symptoms became more persistent and pronounced till she had to wear thick gloves and socks while in her air-conditioned office. There were no changes in skin colour to suggest Raynaud phenomenon. She admitted to generalised lethargy and multiple

Address correspondence to: Khean-Jin Goh, Division of Neurology, Department of Medicine, University of Malaya, Kuala Lumpur, MALAYSIA. Tel: +603 79492555, Fax: +603 79556936, Email: gohkj@ummc.edu.my

joint aches but had no complaints of muscle twitching, cramps or stiffness nor any numbness and tingling. However, she did notice increased sweating for the last 6 months. There was no history of cognitive problems and she denied any insomnia, amnesia or hallucinations. She had a history of type 2 diabetes mellitus for the past 17 years on oral gliclazide and metformin as well as insulin injections.

Neurological examination showed no abnormal findings in terms of muscle power, reflexes and sensory examination. No visible myokymia, fasciculations or cramps were noted. There was hyperhidrosis of the palms and soles. There were no cutaneous or systemic manifestations of connective tissue disease.

Routine investigations showed satisfactory diabetes control (glycoslyated haemoglobin (HbA1c) 6.4%) and normal thyroid function but she had positive anti-nuclear antibody (ANA) 1:160 (homogenous) and strongly positive anti-double-stranded DNA antibody (anti-dsDNA) of 1149 iu/mL (normal <200 iu/mL). However, complement levels were normal and anti-cardiolipin antibody, cryoglobulin and extractable nuclear antigen (ENA) screen were negative and despite having positive anti-dsDNA, she did not fulfil the American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE). In addition, serum anti-acetylcholine receptor antibody (AChR-Ab) was positive at 0.65 nmol/L (normal < 0.25 nmol/L). CT scan of the thorax showed no thymoma while CT of the abdomen and pelvis did not reveal any intra-abdominal or pelvic malignancy.

Nerve conduction studies (NCS) and electromyography (EMG) carried out showed normal motor and sensory studies of the median, ulnar, common peroneal, tibial and sural nerves while all F-wave studies showed repetitive after-discharges. EMG showed spontaneous neuromyotonic discharges consisting of doublets, triplets and multiplets in the deltoid (Figure 1), biceps brachii and vastusmedialis. No spontaneous activity was seen in the first dorsal interosseous and tibialis anterior. There were no fibrillation or fasciculation potentials. Based on EMG findings, further immunological tests showed a markedly elevated anti-VGKC antibody at 5150 pM (normal < 100 pM) confirming Isaacs syndrome. Further characterisation of the autoantibodies was performed using Autoimmune Encephalitis Mosaic 1 kit (Euroimmun AG), a cell-based assay kit. The results were positive for LGI1 and CASPR2 antibodies in the patient's serum (Figure 2).

The patient was treated with intravenous immunoglobulin (IVIG) at a dose of 100 g over 5 days with gradual improvement and near complete remission of both her cold allodynia and hyperhidrosis. She was subsequently maintained on oral prednisolone 10 mg daily and azathioprine 125 mg daily but developed neutropaenia from the latter which had to be stopped. Cold-induced allodynia and hyperhidrosis recurred after about 4 months and this time she also noted development of mild muscle cramps and stiffness but no fasciculations. Carbamazepine was started and together with low dose prednisolone but afforded only slight relief of her sensory as well as motor symptoms. She has required maintenance IVIG at about 3 to 4 monthly intervals to improve her symptoms ever since.

DISCUSSION

Our patient widens the clinical phenotype of anti-VGKC peripheral nerve disorders in that she presents with severe cold-induced allodynia, initially without symptoms or signs of muscular overactivity. With a history of diabetes mellitus and positive connective tissue disease markers, other diagnostic possibilities would have been painful sensory polyneuropathy secondary to diabetes or Raynaud syndrome in the context of an underlying connective tissue disease.

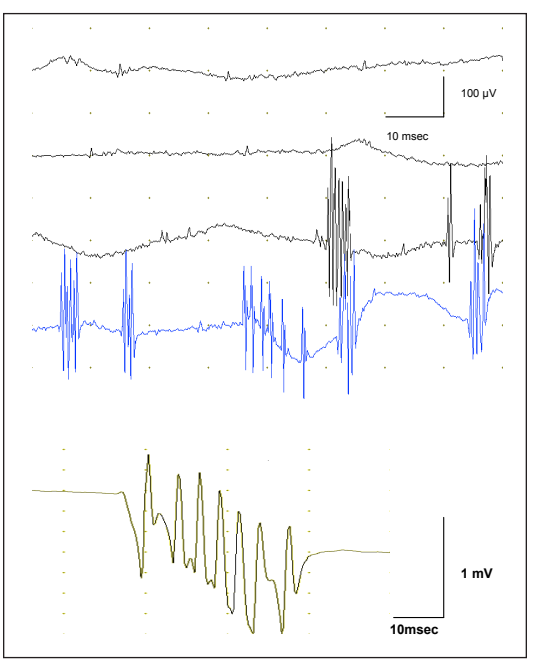

Figure 1: Needle electromyography of multiplet discharges in the right deltoid muscle (intraburst frequency of 150 – 250 Hz)

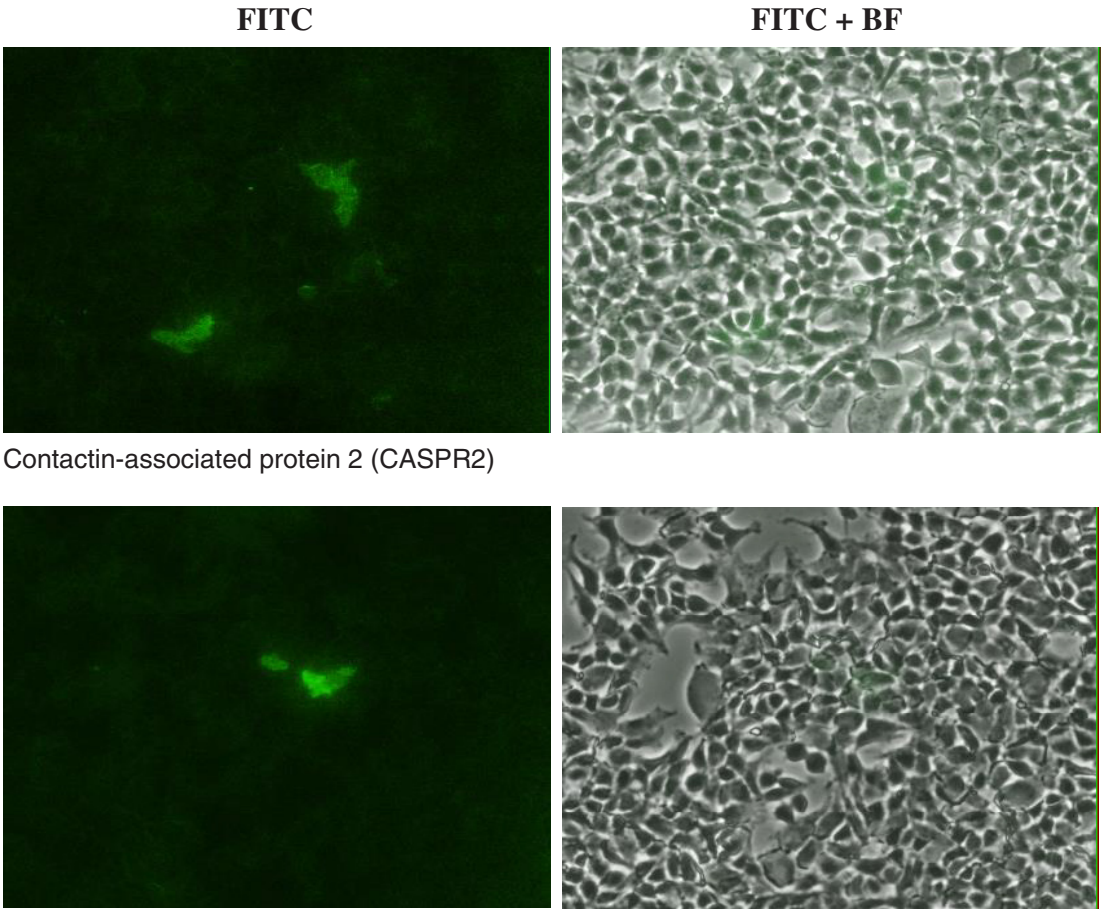

Figure 2: Presence of autoantibodies in patient serum. Chimeric cells transfected with different antigens were stained with the serum of patient and with fluorescein isothiocyanate (FITC) - conjugated anti IgG antibody. Data presented were the cells viewed under FITC (left panel) and under brightfield (BF) merged with FITC (right panel). Unstained cells represented non-transfected cells.

However, the lack of objective clinical signs of neuropathy did not support the former while absence of involvement of individual digits and lack of skin colour changes on exposure to cold excluded the latter.

Sensory symptoms in Isaacs syndrome have been reported previously and included paraesthesias and dysaesthesias as well as paroxysmal electrical sensations.[5,13] In a series of 316 patients with positive anti-VGKC antibodies, pain was reported in 159 (50.3%) of patients although the nature of pain was heterogeneous and included not only neuropathic pain but also nociceptive pain and pain attributed to psychogenic causes.[14] CASPR2-IgG positivity was reported to be significantly associated with pain.[14] Cold-triggered symptoms are also seen in an unusual form of acute neuropathy due oxaliplatin, a chemotherapeutic drug used in colorectal cancers, which also causes peripheral nerve hyperexcitability, but involving the Na+ channels instead.[15-17] Patients complain of transient cold-induced paraesthesias, dysaesthesias and jaw tightness and have neuromyotonic discharges within 24 to 48 hours after oxaliplatin infusion.[15,16]

Despite having high titres of anti-VGKC and positive LGI1 and CASPR2 antibodies, our patient had a pure peripheral nerve presentation. It has been suggested that LGI1 positivity is associated with the presence of cortical symptoms but this patient underscores the fact that specific antibody positivity is not pathognomonic for a particular neurological presentation.[8,9,11] There was also strong serological evidence for a more diffuse underlying autoimmune tendency with positivity

to other auto-antibodies viz. ANA, anti-dsDNA and AChR-Ab. Interestingly, over a follow-up period of 5 years; she has not developed other systemic symptoms or signs to suggest systemic lupus erythematosus (SLE). Isaacs syndrome has previously been reported in association with SLE.[18]

In summary, our patient's symptoms expand the spectrum of sensory symptoms in Isaacs syndrome, which should be considered in unusual cases of neuropathic pain as it potentially responds to treatment. Serological evidence (although no clinical features) of other autoimmune conditions in the patient suggests that she had underlying autoimmune tendency.

REFERENCES

1. Isaacs H. A syndrome of continuous muscle-fibre activity. *J NeurolNeurosurg Psychiatry* 1961;24:319-25.
2. Newsom-Davis J, Mills KR. Immunological associations of acquired neuromyotonia (Isaacs' syndrome). Report of five cases and literature review. *Brain* 1993;116:453-69.
3. Maddison P. Neuromyotonia. *ClinNeurophysiol* 2006;117:2118-27.
4. Hart IK, Waters C, Vincent A, *et al*. Autoantibodies detected to expressed K^+ Channels are implicated in neuromyotonia. *Ann Neurol* 1997;41:238-46.
5. Hart IK, Maddison P, Newsom-Davis J, Vincent A, Mills KR. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 2002;125:1887-95.
6. Liguori R, Vincent A, Clover L, et al. Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001;124:2417-26.
7. Irani SR, Pettingill P, Kleopa KA, *et al*. Morvan syndrome: clinical and serological observations in 29 cases. *Ann Neurol*2012;72:241-55.
8. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome, and acquired neuromyotonia. *Brain* 2010;133:2734-48.
9. Lai M, Huijbers MGM, Lancaster E, *et al*. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010;9:776-85.
10. Lancaster E, Huijbers MGM, Bar V, *et al*. Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann Neurol* 2011;69:303-11.
11. Klein CJ, Lennon VA, Aston PA, *et al*. Insights from LGI1 and CASPR2 potassium channel complex autoantibody subtyping. *JAMA* 2013;70(2):229-34.
12. Lancaster E, Dalmau J. Neuronal autoantigens—pathogenesis, associated disorders and antibody testing. *Nat Rev Neurol* 2012;8:380-90.
13. Herskovitz S, Song H, Cozien D, Scelsa SN. Sensory symptoms in acquired neuromyotonia. *Neurology* 2005;65:1330-1.
14. Klein CJ, Lennon VA, Aston PA, McKeon A, Pittock SJ. Chronic pain as a manifestation of potassium channel-complex autoimmunity. *Neurology* 2012;79:1136-44.
15. Lehky TJ, Leonard GD, Wilson RH, Grem JL, Floeter MK. Oxaliplatin-induced neurotoxicity: acute hyperexcitability and chronic neuropathy. *Muscle Nerve* 2004;29:387-92.
16. Pasetto LM, D'Andrea MR, Rossi E, Monfardini S. Oxaliplatin-related neurotoxicity: how and why? *Crit Rev Onco Hem* 2006;59:159-68.
17. Krishnan AV, Goldstein D, Friedlander M, Kiernan MC. Oxaliplatin-induced neurotoxicity and the development of neuropathy. *Muscle Nerve* 2005;32:51-60.
18. Taylor PW. Isaacs' syndrome (autoimmune neuromyotonia) in a patient with systemic lupus erythematosus. *J Rheumatol* 2005;32(4):757-8.