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Letter to the Editor

Neuropathic pain, dysautonomia, and nerve hyperexcitability: Expanding the spectrum of LGI1 autoimmunity

Antibodies to Leucine-rich Glioma Inactivated 1 (LGI1) protein have primarily been associated with limbic encephalitis (van Sonderen et al., 2016). However, a more widespread autoantibody testing has recently allowed to expand the spectrum of LGI-1 autoimmunity, and peripheral impairment is increasingly reported, whether or not in association with central nervous system involvement (van Sonderen et al., 2016; Klein et al., 2012; Gadoth et al., 2017). The clinical and electrophysiological phenotype associated with LGI1-positive peripheral neuropathy has not been fully elucidated yet, and neurologists are not necessarily familiar with this entity. Here we describe the case of a patient with a one-year history of severe neuropathic pain and autonomic dysfunction who was ultimately diagnosed with a small-fiber peripheral neuropathy associated with LGI1 antibodies. The aim of this report is to highlight the importance to test for LGI1 antibodies when facing severe neuropathic pain and dysautonomia with no apparent cause.

This 42year-old man developed progressive pain involving the lumbar region and lower limbs. The patient had no apparent motor defects, but he required two canes for walking because of intense fatigability. He was initially investigated by electroneuromyography and spine MRI, which displayed normal findings. Six months later, he developed night sweats, constipation, dysuria and erectile dysfunction. He also started to experience diffuse pruritus and weight loss (−15kg). Pain became extremely intense, leading to opioid medication overuse. Due to progressive clinical deterioration, he underwent a second panel of assessments at our Institution. Electroneurography (including F waves and H-reflexes) displayed normal findings except for the presence of after-discharges in the lower limbs on motor nerve conduction studies (Fig. 1, panel A and B). On needle examination, no neuromyotonic or myokymic discharges were detected. Sudoscan test showed an impairment of the autonomic nerves at all four limbs. CSF analysis showed no inflammatory changes and no oligoclonal bands. Screening for infection (HIV, syphilis, Lyme disease, hepatitis B and C), systemic autoimmunity (sarcoidosis, vasculitis) and amyloidosis were negative. Onconeural antibodies were absent, and total body ^{18}FDG-PET was normal. One year after symptom onset, LGI1 antibodies were ultimately detected on serum. Subclinical limbic involvement was ruled out by contrast brain MRI, EEG, and neuropsychological testing. The patient received high-dose steroids (6-methylprednisolone 1g/day for 3days) followed by daily oral prednisolone (1mg/kg/day), together with monthly cycles of intravenous immunoglobulin (0.4g/kg/day for 5days). At last follow-up, six months later, he reported a remarkable improvement of pain and of dysautonomic features. At control examination, the abnormalities detected on Sudoscan test and on motor nerve conduction studies (Fig. 1, panel C and D) had resolved.

The present report describes a case of small-fiber peripheral neuropathy associated with LGI1 antibodies. Typical correlates of limbic dysfunction, such as hyponatremia or sleep disturbances, were absent, and neurological impairment was restricted to peripheral nerves. Sensory neuropathy was characterized by severe neuropathic pain and intense pruritus, which are emerging as prominent clinical features in this entity (Gadoth et al., 2017). Autonomic dysfunction included hyperhidrosis and constipation, but also dysuria and erectile dysfunction (van Sonderen et al., 2016), which are infrequent in other types of immune-mediated dysautonomia. Classical hallmarks of voltage-gated potassium channel autoimmunity, such as continuous muscle twitching or myokymia, were absent, and peripheral nerve hyperexcitability was limited to the presence of after-discharges on motor nerve conduction studies. This electroneurographic feature, which reflects increased spontaneous activity (Maddison, 2006), was detected in our patient despite the absence of clinical manifestations of nerve hyperexcitability.

The diagnosis of LGI1-positive peripheral neuropathy was reached only one year after symptom onset, as the opioid overuse, together with the normality of the initial paraclinical testing, first suggested a psychogenic disorder. Neurologists should keep in mind to test for LGI1 antibodies when facing severe neuropathic pain or dysautonomia without apparent cause, especially when in presence of clinical-paraclinical signs of nerve hyperexcitability. Manifestations of peripheral nerve hyperexcitability are reported in about one-fourth of LGI1 positive patients (Gadoth et al., 2017), and recognizing post-discharges on motor nerve conduction studies - like in our patient - may represent a precious diagnostic clue. However, LGI1-positive painful neuropathy without neuromyotonia on needle examination has also been reported (Lahoria et al., 2017).

Testing for LGI1 antibodies may be the only mean to reach an accurate diagnosis, as CSF analysis (van Sonderen et al., 2016) and nerve biopsy (Lahoria et al., 2017) may display no inflammatory alterations. The importance of performing an appropriate diagnostic work-up is ultimately emphasized by the observation that the neuropathic pain associated with LGI1 neuropathy poorly responds to analgesics but dramatically improves upon immune therapy administration (Klein et al., 2012; Lahoria et al., 2017).

Ethical standards

This study performed in accordance with the ethical standards of the Declaration of Helsinki. The patient provided informed consent for data publication.

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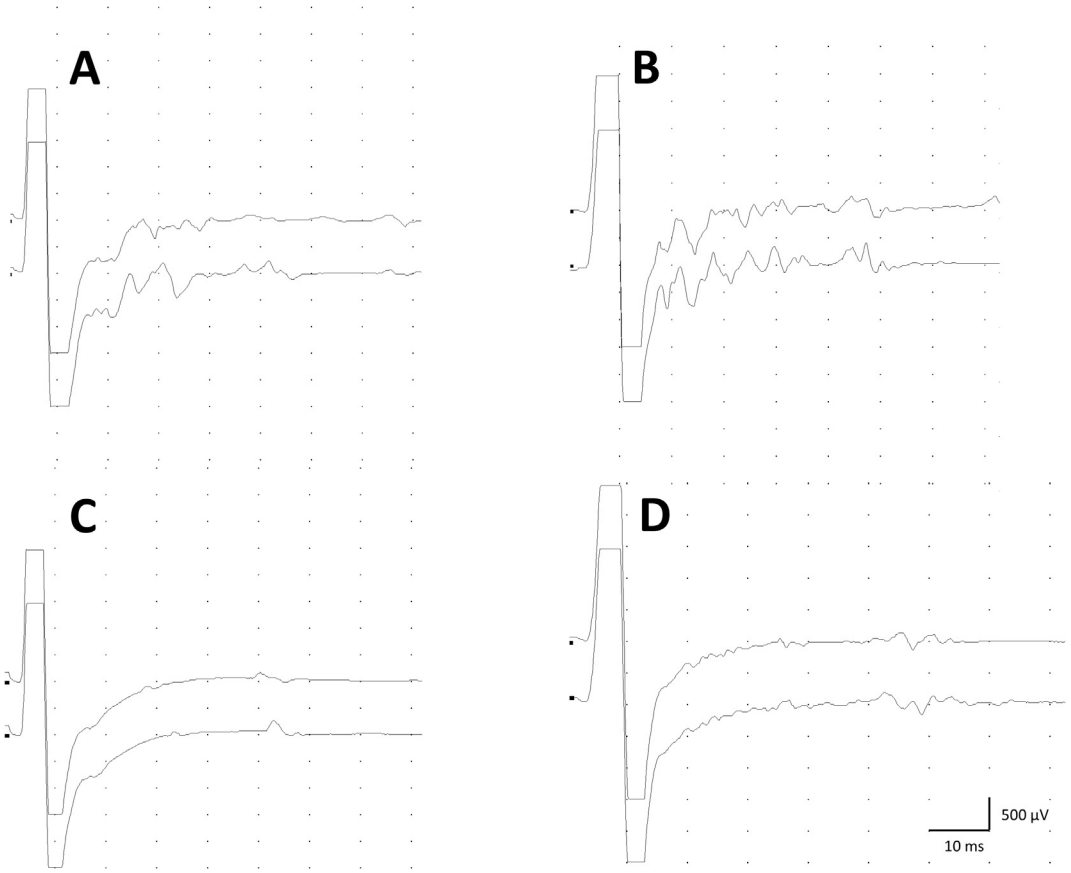

Fig. 1. Motor nerve conduction studies of peroneal and tibial nerves with recording from the tibialis anterior (panel A, C) and from the abductor hallucis (panel B, D) after supramaximal stimulation (representative single trials are shown). At the time of diagnosis, after-discharges of variable duration and shape following the compound motor action potential were detected (panel A, B). The same recordings after immune therapy administration displayed almost complete resolution of the after-discharges (panel C, D).

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Conflicts of interest

The authors have no conflict of interest to disclose.

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