Received: 25 November 2019 | Revised: 30 March 2020 | Accepted: 2 April 2020

DOI: 10.1002/ejp.1572

SHORT COMMUNICATION

EJP European Journal of Pain

Heterogeneous presentation of caspr2 antibody-associated peripheral neuropathy – A case series

Erik Ellwardt[1] | **Christian Geber**[1,2] | **Johannes Lotz**[3] | **Frank Birklein**[1]

[1]Focus Program Translational Neurosciences (FTN), Rhine Main Neuroscience Network (rmn2), Department of Neurology, University Medical Center of the Johannes-Gutenberg University Mainz, Mainz, Germany

[2]DRK Schmerz-Zentrum, Mainz, Germany

[3]Institute of Laboratory Medicine, University Medical Center of the Johannes-Gutenberg University Mainz, Mainz, Germany

Correspondence
Erik Ellwardt, Focus Program Translational Neurosciences (FTN), Rhine Main Neuroscience Network (rmn2), Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstraße 1, 55131 Mainz, Germany.
Email: erik.ellwardt@unimedizin-mainz.de

Funding information
This work was supported by the Deutsche Forschungsgemeinschaft to Frank Birklein (Bi 579/10) and to Erik Ellwardt (CRC-TR 128).

Abstract

Contactin-associated protein 2–like (caspr2) antibodies have been discovered recently. Since then a multitude of patients with caspr2 antibodies presenting with different neurological symptoms have been reported. Here, we describe three patients with caspr2 antibodies with different types of pain/no pain in combination with peripheral neuropathy. The first patient, a 33-year-old woman, presented with erythromelalgia-like pain and autonomic symptoms; the second patient, a 58-year-old man, with paresthesia and pain while walking together with signs of peripheral motor neuron hyperexcitability in combination with optic neuritis, and the third patient, a 74-year-old man, without any pain but with polyneuropathy and encephalopathy. These cases illustrate the spectrum of symptoms in anti-caspr2 diseases. The pain in such cases can be treated causally.

1 | INTRODUCTION

Painful peripheral neuropathies are common. The most prevalent causes of peripheral neuropathies are diabetes, toxins like alcohol or chemotherapeutics, or autoimmune diseases (Visser, Notermans, Linssen, Berg, & Vrancken, 2015). However, routine tests do not usually uncover the underlying cause of a significant proportion of peripheral neuropathies. This is, in particular, true for small-fibre neuropathies.

While the reason that patients with the same disease develop painful or painless neuropathies has been a conundrum for many years (Schley et al., 2012), it has recently become clear that neuronal hypersensitivity mediated by genetic variants of nociceptor-specific voltage-gated sodium channels (VGSC) is highly prevalent in small-fibre neuropathies (Eijkenboom et al., 2019). These mutations lead to a leftward shift of the opening kinetics of these VGSCs and thereby facilitate and increase firing rates of the primary afferent fibres. Such mechanisms have been shown to contribute to pain in diabetic neuropathy (Blesneac et al., 2018; Craner, Klein, Renganathan, Black, & Waxman, 2002) or erythromelalgia (Eberhardt et al., 2014). The latter is characterized

by a combination of recurrent burning pain, warmth, redness and sometimes oedema at the extremities, which might be triggered by physical activity or heat, but often occurs spontaneously (Tang, Chen, Tang, & Jiang, 2015).

The family of ion channels that lead to repolarization and control neuronal excitation are potassium channels. They have also been identified as important regulators of nociceptive pain. Voltage-gated potassium channels (VGKC) help to maintain nociceptive afferent sensory nerve thresholds. It was also recently shown that genetic variants of potassium channels (Langford et al., 2015), translation of suppressing non-coding RNAs (Zhao et al., 2013) and epigenetic silencing of VGKC genes (Laumet et al., 2015) are linked to chronic neuropathic pain.

While genetic influences predispose for pain susceptibility with manifestation of pain mainly during early life, there might also be acquired dysfunctions of VGKCs which lead to pain without obvious predisposition. Through the discovery of autoimmune mechanisms underlying encephalopathy, peripheral neuropathy and neuromuscular disorders (e.g. as paraneoplastic syndromes) (Armangue, Leypoldt, & Dalmau, 2014) we know about the detrimental effects of inactivating autoantibodies against ion channels and receptors. Best known in clinical neurology are autoantibodies against Ca^{2+} channels or NMDA receptors. Most interesting for pain research, however, are inactivating autoantibodies directed against potassium channel structures leading to nerve hyperexcitability. Such diseases are called neuromyotonia (Isaac's syndrome; [Maddison, 2006]) or Morvan's syndrome in the case of central nervous system involvement (Liguori et al., 2001; van Sonderen et al., 2016).

Here, we report about three patients with autoantibodies against contactin-associated protein-like 2 (caspr2), which is an associated extracellular protein to the VGKC. These patients presented with very different pain phenotypes. The first presented with erythromelalgia-like symptoms with spontaneous attacks of burning pain and skin reddening at rest. The second patient had a minor variant of neuromyotonia, the fasciculation–crampus syndrome, and a clinical picture of "painful legs and moving toes" and pain while walking. The third patient had severe polyneuropathy without pain and progressive dementia.

2 | METHODS

2.1 | Bedside sensory examination

Written informed consent for publication was obtained from all patients. Comprehensive clinical neurological and technical investigations were performed. Pain intensity was assessed on an 11-step verbal rating scale. The bedside sensory examination was performed with a cocktail stick to assess pinprick hypo/hyperalgesia and a piece of cotton wool to assess touch sensation (Cruccu et al., 2010). Both stimuli were applied with a supra-threshold force (patient senses touch or a slightly painful pricking). Vibration sense is tested with a tuning fork and temperature is tested semi-quantitatively and further elaborated in quantitative sensory testing (QST). Depending on the clinical presentation, e.g. in polyneuropathies, intraindividual changes (semi-quantitative) in, e.g. mechanical pain and non-painful touch sensation can be detected by testing from proximal to distal sites of the extremities. Thereby, the site for subsequent QST is identified, which are normally hands and feet like in our cases.

2.2 | Quantitative sensory testing (QST)

QST was performed on the right foot and hand dorsum according to the protocol of the German Research Network on Neuropathic Pain (Rolke et al., 2006). QST assesses among others sensory loss (hypesthesia, hypalgesia) and gain (hyperalgesia, allodynia) for thermal and mechanical stimuli in comparison to age- and gender-matched normal values.

In detail, the following parameters were assessed: CDT – cold detection threshold, WDT – warm detection threshold, TSL – thermal sensory limen, CPT – cold pain threshold, HPT – heat pain threshold, PPT – pressure pain threshold, MPT – mechanical pain threshold, MPS – mechanical pain sensitivity, MDT – mechanical detection threshold, VDT – vibration detection threshold, DMA – dynamic mechanical allodynia, PHS – paradoxical heat sensation.

The resulting values were than transformed in an age- and gender-adjusted z-score and graphically depicted to easily appreciate a gain or loss of function due to neuropathy.

2.3 | Nerve conduction

Motor (tibial, peroneal and ulnar) and sensory (sural and ulnar) nerve conduction (NCV) were assessed. Measurements were performed according to our laboratory standards. Amplitudes of muscle compound action potentials (MCAP) were measured peak to peak and sensory nerve action potentials (SNAP) baseline to peak. Reference data were taken from our laboratory (Hopf, 1996). Electromyography was performed in the tibialis anterior, vastus lateralis, abductor halluces brevis and gastrocnemius muscles. Signs of acute nerve damage (denervation) and motor unit potentials were analysed.

2.4 | Autonomic function tests

The sympathetic skin response (SSR) and the heart rate variability (HRV) were evaluated using the FAN® device

(Schwarzer) as described previously (Haegele-Link, Claus, Ducker, Vogt, & Birklein, 2008).

2.5 | Immunofluorescence assay

The caspr2 autoantibody was detected by an indirect immunofluorescent assay which was based on specific transfected cells (human embryonic kidney cells [HEK]). Furthermore, the applied immunofluorescent slide could detect antibodies against the LGI1, NMDA-R, DPPX, AMPA1/2, and GABAB structures (autoimmune mosaic 6, Euroimmun, Lübeck, Germany). The assay was performed in accordance with the manufacturer's recommendations. The slides were stored at 4–8°C and analysed within 2 days. The basic dilution was 1:10 for serum. If positive fluorescence was detected, the titre was elicited by consecutive tenfold dilutions (1:10, 1:100, 1:1,000, etc.). Evaluation of the test result was carried out by two independent observers.

3 | RESULTS

Patient 1 was a 33-year-old woman who presented with sporadic reddening at different locations of her body (hands, breast and legs) in combination with spontaneous burning and stinging pain at the same body sites for more than 1 year. The spontaneous skin reddening was accompanied with hyperthermia and mild oedema in the extremities. On the basis of these symptoms, a clinical diagnosis of erythromelalgia was given. Additionally, she reported general symptoms such as vertigo, headache, visual disturbances, memory problems and intermittent tachycardia. She had lost 10 kg of weight within 1 year.

Clinical neurological investigation was unremarkable with the exception of minor hypoesthesia and hypalgesia at the feet. At the time of first presentation pain was 4 on the 0–10 verbal rating scale (VRS). The pain flares, however, were rated as 9/10. The accompanied reddening of the skin was documented by the patient (Figure 1). She had also been diagnosed by our dermatologists as having hyperkeratotic eczema. Nerve conduction studies were normal for motor (peroneal nerve NCV 48.6 m/s; MSAP 14mV) and sensory nerve function (sural nerve NCV 48 m/s; SNAP 22.2μV). Autonomic function tests were physiological and QST revealed hyperalgesia for heat at the feet (Figures 2 and 3). A genetic testing for small-fibre neuropathy causing genes including sodium channels (ATL1, GLA, SCN9A, SCN10A, SCN11A, TTR and TRPA1) was negative. Extensive blood investigations revealed physiological results with the exception of serum Caspr2 autoantibodies (titre 1:100). This finding was confirmed in independent samples which were sent to a reference laboratory (Eurimmune, Lübeck, Germany).

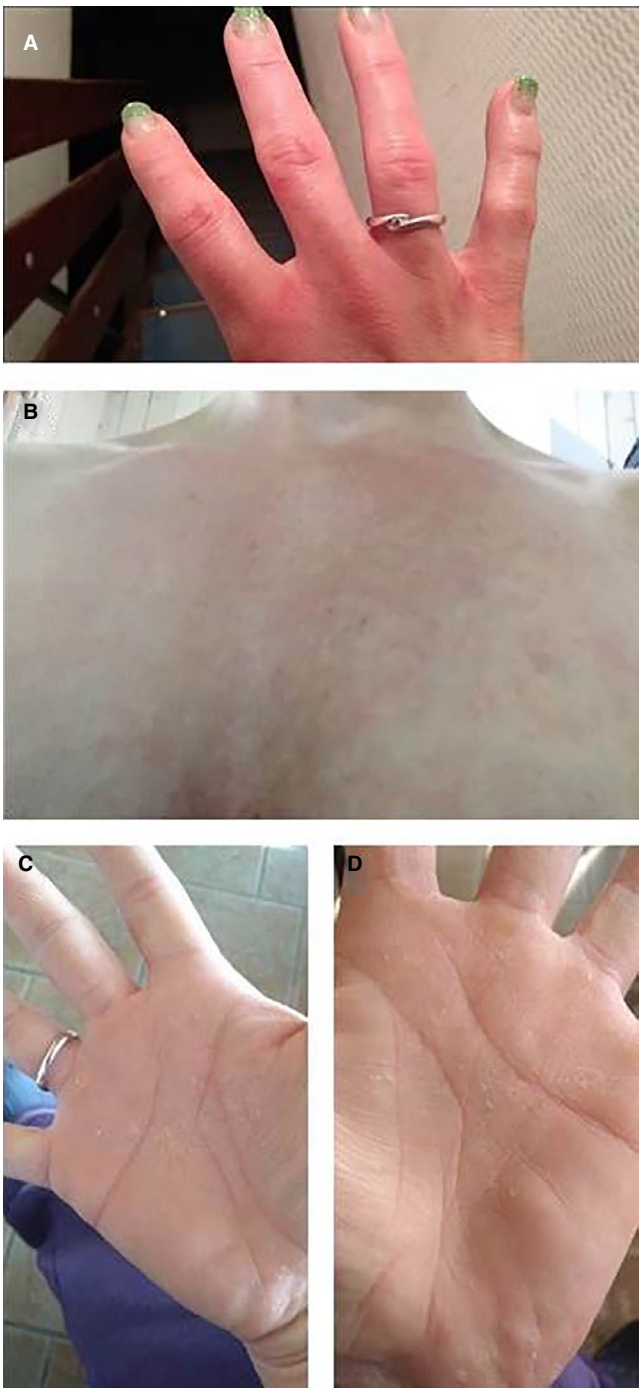

FIGURE 1 Photo documentation of patient 1 with erythromelalgia. During an episode, skin becomes erythematous, hot and swollen (a and b). After several months the skin becomes broken due to repetitive scratching (c and d)

No further autoantibodies were detected; a search for malignancies was negative.

Initial symptomatic treatment with carbamazepine was partially effective to control pain, but hydromorphone was not. Immune treatments with intravenous immunoglobulins (IVIG) and steroids were not successful; monthly plasmapheresis controlled neuropathic pain attacks only temporarily.

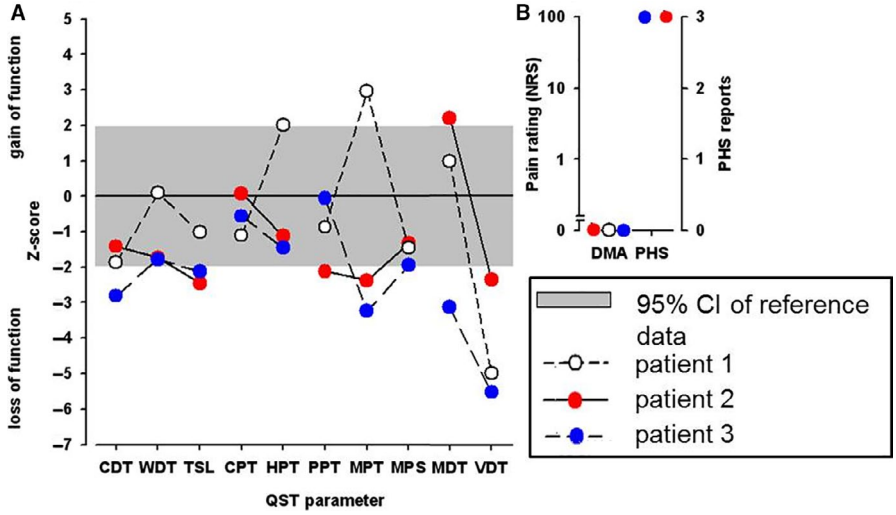

FIGURE 2 QST z-profiles of the feet from all three patients. Depicted are the age- and gender-adjusted z-values. Normal range is indicated by the grey bar (95% CI of age- and gender-matched reference population). Patients 2 and 3 mainly show a loss of perception for non-painful and painful sensory stimuli (polyneuropathy loss-of-function pattern (Baron et al., 2017)), while patient 1 had decreased perception of non-painful sensory stimuli fitting to small-fibre neuropathy in combination with hyperalgesia to heat and pinprick stimuli indicating peripheral and central nociceptive sensitization. CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, numeric rating scale; PHS, paradoxical heat sensation; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold

Usually after 2 weeks the pain burden was similar to baseline, so that we stopped this therapy again. A symptomatic treatment with duloxetine and pregabalin currently leads to a stabilization of symptoms.

Patient 2 was a 58-year-old man. The primary reason for admission to our hospital was acute vision loss at the right eye under the suspicion of optic neuritis. Additionally, he reported painful tingling radiating from his feet to the proximal legs for about 6 months. Pain was generally rated as 5/10, which intensified while walking (8/10). Additionally, he reported fatigue, unintentional weight loss of 10 kg and fasciculation, myoclonic jerks and cramps in different muscles. The neurological examination confirmed fasciculation at the gastrocnemius and small foot muscles with characteristic involuntary moving toes at rest, reduced vibration sense at the big toe and reduced Achilles tendon reflexes. However, the further clinical sensory testing was unremarkable. Brain MRI scans showed contrast uptake in the right optical nerve but were otherwise unremarkable. Cerebrospinal fluid (CSF) analysis revealed mild pleocytosis of 20 leukocytes/µl and increased protein levels (740 mg/L). Repeated investigations gave no indication of malignancy. Neurography revealed a predominant motor neuropathy (peroneal nerve NCV 39 m/s; MSAP 9.8mV and sural nerve NCV 41.9 m/s; SNAP 10µV) and electromyography confirmed the visible muscle fasciculation. QST revealed decreased thermal perception and hypalgesia to pressure and pinprick stimuli at his feet (Figure 2). Autonomic testing revealed absent SSR at the feet and reduced heart -rate variability (Figure 3).

Based on these findings we diagnosed peripheral nerve hyperexcitability (fasciculation–crampus syndrome). Autoantibodies against caspr2 (titre 1:10.000) and voltage-gated potassium channel complex (VGKC, 536 pmol/l, threshold <85 pmol/l) measured with radio-immune assay (Eurimmune, Lübeck, Germany) were detected in the serum samples (Figure 4). Symptomatic treatment with the sodium channel blocker carbamazepine was effective but induced an adverse drug reaction. A treatment switch to lacosamide led to pain reduction of 80% and abolished the muscle cramps. We abstained from immune therapy because of the good response to the symptomatic treatment. The optic neuritis remained unexplained; an association of optic neuritis and Caspr2 or VGKC autoantibodies has not been reported, but it is likely that the optic neuritis has an autoimmune origin (inflammatory CSF changes). High-dose steroid treatment, however, did not improve visual acuity.

Patient 3 was a 74-year old man who presented with progressive gait difficulties and progressive memory deficits. Clinical examination revealed absent Achilles tendon reflexes and pallhypesthesia with consecutive gait instability. He had insulin-dependent diabetes for 10 years and suffered already from diabetic retinopathy. He did not report any pain (0/10). CSF examination revealed increased protein levels (1,150 mg/L) with intrathecal immunoglobulin synthesis and positive oligoclonal bands. MRI revealed a non-active,

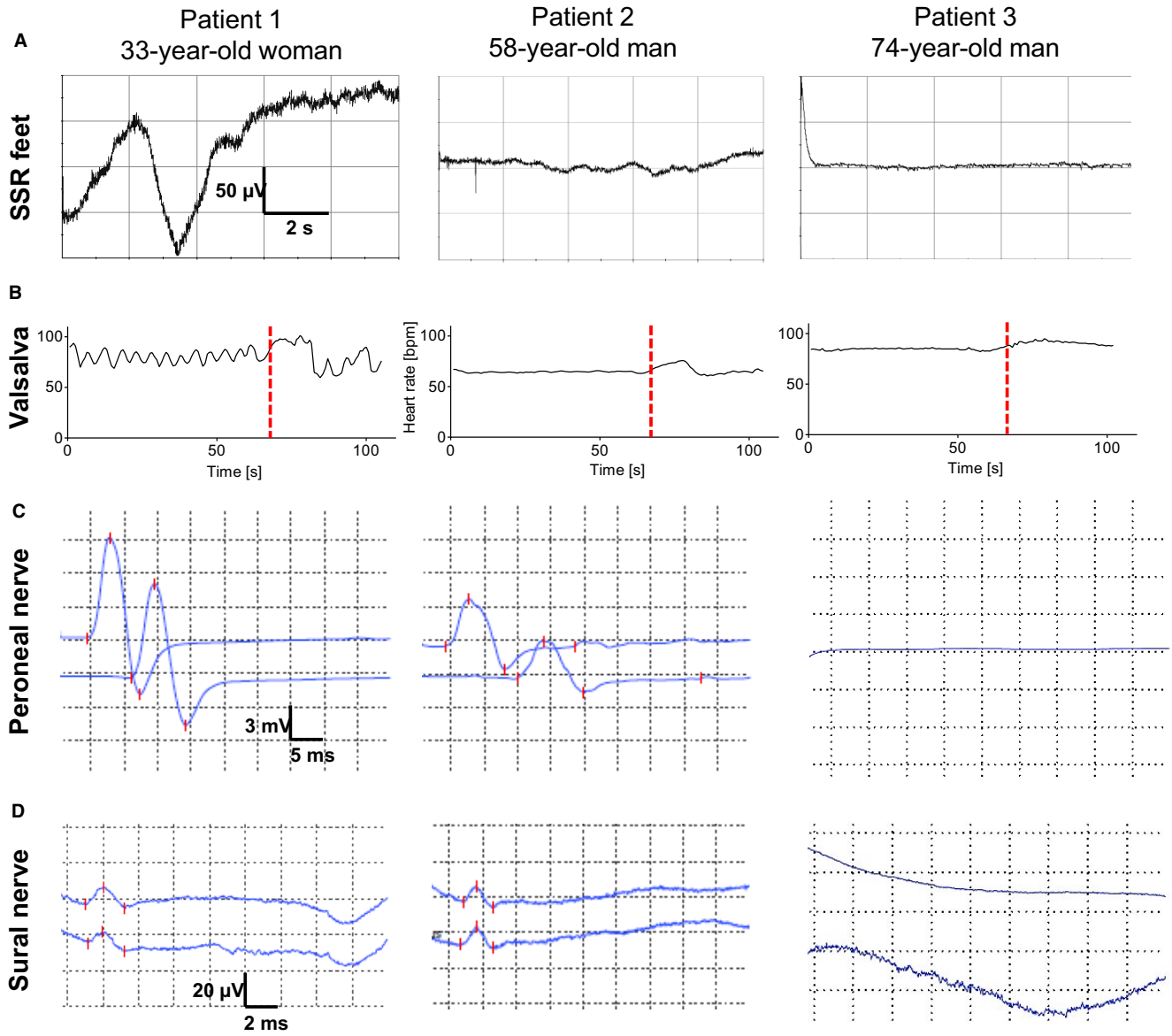

FIGURE 3 Autonomous testing and nerve conduction. Sympathetic skin response (SSR; mean traces of four recordings) of the feet could not be recorded in patients 2 and 3 (a), also impaired heart rate variability in patients 2 and 3 at valsalva (b). Nerve conduction showed normal results for patient 1 (peroneal nerve NCV 48.6 m/s; MSAP 14 mV and sural nerve NCV 48 m/s; SNAP 22.2 µV), slight motor neuropathy for patient 2 (peroneal nerve NCV 39 m/s; MSAP 9.8 mV and sural nerve NCV 41.9 m/s; SNAP 10 µV) but a severe axonal neuropathy in patient 3 (c and d)

possibly inflammatory lesion in the cervical spinal cord at C4, but showed no signs of cerebral microangiopathy. Neurography demonstrated an axonal neuropathy (no MSAP for sural or peroneal nerve, Figure 3d right panel). QST showed a sensory loss pattern and autonomic testing was pathological (Figures 2 and 3). Caspr2 antibodies were positive in serum (titre 1:100). We finally diagnosed sensorimotor and autonomic polyneuropathy that could be explained either by the diabetes or inflammatory reasons (positive caspr2 antibodies and inflammatory CSF). Despite this aetiological uncertainty, the remarkable finding is that in this case the caspr2 autoantibodies did not cause any neuropathic pain but instead probably contributed to the encephalomyelopathy with memory decline.

4 | DISCUSSION

This small case series describes different types and extents of peripheral neuropathic pain in three patients with anti-caspr2 autoantibodies. The first patient presented with the typical findings of erythromelalgia with pain often occurring spontaneously (Parker et al., 2017), the second with symptoms of motor nerve hyperexcitability (i.e. fasciculation–crampus syndrome; painful legs moving toes) and pain predominantly while walking (Vincent et al., 2018), and the third patient had no pain at all. It is important for clinicians to be aware of the wide clinical spectrum of anti-caspr2 autoantibody-mediated diseases in order to recognize the autoimmune pathophysiology of neuropathic pain and to choose the right treatment.

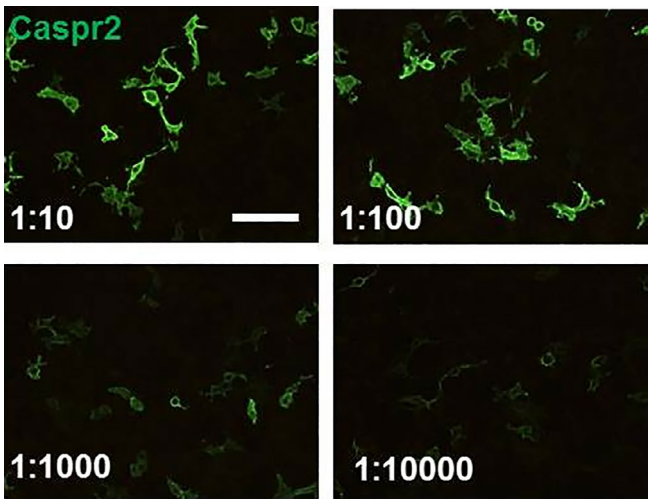

FIGURE 4 Contactin-associated protein 2 (caspr2) expression by Hek293 cells. Incubation of serum from *patient 2* and immunostaining with fluorescent antibodies for caspr2. Clear positive staining up to a titre of 1:10,000. Scale bar = 50 µm. For *patient 3* a similar staining pattern could be observed with positive staining up to a titre of 1:100 (not shown). Serum of *patient 1* was investigated in two external laboratories; therefore, we do not possess images

Caspr2 (contactin-associated protein—like 2) is located in the juxtaparanodal region of myelinated axons and is associated with different potassium channel subunits such as Kv1.1 or Kv1.2. Anti-caspr2 autoantibodies were first described in 1999 (Poliak et al., 1999). While the association of the less specific anti-voltage–gated potassium channel complex (VGKC) autoantibodies with encephalitis and neuromyotonia has been described for some time (Vincent et al., 2004), such an association with caspr2 was discovered later on (Irani et al., 2010). Since then several patients with very different symptoms, such as seizures, encephalopathy, psychiatric symptoms, peripheral nerve hyperexcitability and pain, have been described (Gadoth et al., 2017; van Sonderen et al., 2016). Anti-caspr2 antibodies can coincide with anti-leucine–rich glioma-inactivated 1 (LGI1) antibodies (LGI1 is another extracellular component of potassium channels), which are, however, mainly responsible for CNS symptoms. The association with cancer, especially thymoma, is significant and demands extensive tumour screening (van Sonderen et al., 2016). This was negative in our patients but has to be followed-up for several years.

Immune mechanisms of neuropathic pain have received increasing attention in recent years. Most investigations, however, have concentrated on innate immunity mechanisms (e.g., cytokines, Langerhans cells, mast cells) for nociceptor activation or sensitization. Such innate immune mechanisms have been shown for peripheral neuropathies including small-fibre neuropathy (Uceyler et al., 2010), peripheral nerve lesion (Held et al., 2019) and complex regional pain syndromes (CRPS) (Kramer et al., 2011). However, it has been known for some time that erythromelalgia might not only be primary due to sodium channel mutations, but also secondary, coinciding with autoimmune diseases like lupus (Alarcon-Segovia, Babb & Fairbairn, 1963). This suggests that not only the innate but also the adaptive immune system (B- and T-cells) could be involved in the generation of pain.

Autoantibodies directed against neural antigens cause different neurological diseases (e.g. neuromyelitis optica or stiff person syndrome), which are mainly characterized by neurological deficits, but also include pain as a symptom. Caspr2 antibodies seem to be particularly important for pain. Pain occurs in 50% of caspr2-positive patients (Klein, Lennon, Aston, McKeon, & Pittock, 2012). The antibody itself appears to cause the pain directly because transfer of serum from patients to healthy animals resulted in mechanically related hypersensitivity in these animals (Dawes et al., 2018). The pain characteristics associated with caspr2 antibodies are not specific; they range from phenotypically neuropathic to rather diffuse pain symptoms. There is a clear involvement of caspr2 in neuromyotonia (patient 2) which should always prompt serum antibody testing (Gadoth et al., 2017). However, it is important to recognize that pain might occur as the only symptom without any other clinical signs, e.g. for peripheral neuropathy (28% of patients with caspr2-associated pain [Klein et al., 2012]), as in patient 1. It is not known why 50% of the caspr2-positive patients remain pain free. Presumably, the antibodies in these cases do not lead to sufficient blocking of the potassium channels to cause pain. In such cases, CNS symptoms like amnesia might be clinically predominant (Binks, Klein, Waters, Pittock, & Irani, 2018) (patient 3). Further insight into the interaction of immunity and pain arises from very recent findings from chronic CRPS patients. IgG transfer from CRPS patients into previously injured mice led to pain-like behaviour and sustained microglia and astrocyte activation in the dorsal horn of the spinal cord and pain-related brain regions, indicating central pain sensitization (Helyes et al., 2019). The effect was mediated via the interleukin-1ß (IL-1β) and conditional knockout of IL-1β or blockade with the antagonist anakinra reversed the effect.

However, apart from immunomodulatory treatment, effective symptomatic treatment in some caspr2 patients can be achieved with sodium channel blockers such as carbamazepine or lacosamide (see patients 1 and 2). The pain causing nerve hypersensitivity is at least partially due to impaired VGKCs triggered by caspr2 antibodies and a resulting preponderance of VGSC; this can be blocked with these drugs. Randomized clinical trials regarding the immune treatment are lacking so far, but IV immunoglobulin (IVIg), IV or oral steroids, plasma exchange or cyclophosphamide have been successfully used so far (Gadoth et al., 2017; van Sonderen et al., 2016). Some patients require a long-lasting therapy and some do not respond at all.

All three patients in our report had other symptoms in addition to pain. While dizziness, weight loss, tachycardia, headache (patient 1) and memory loss (patient 3) have been described several times in caspr2-positive patients (Gadoth et al., 2017; van Sonderen et al., 2016), optic neuritis (patient two) has not. It is speculative, but inflammation of the optic nerve could be an as-yet unrecognized sign of restricted anti-caspr2 encephalitis. A limitation is that we cannot distinguish whether these caspr2 antibodies are accounting for all described clinical features in this study or whether they are just co-incidental. Whether high antibody titres correlate with a more severe disease outcome is not yet clear, although one retrospective analysis found that higher titres associate with an increased risk of developing autoimmune encephalitis (Bien et al., 2017). Although the symptomatology of our patients is quite different, a plethora of symptoms, including encephalitis with cognitive deficits, peripheral nerve hyperexcitability and pain have been reported in larger-scale studies (van Sonderen et al., 2016).

In summary, our observations suggest that serum analysis for caspr2 (plus LGI1 and VGKC) antibodies is justified in patients presenting with neuropathic pain of unclear origin in combination with a variety of peripheral neuropathic or central encephalopathic symptoms. Awareness of these immune mechanisms of pain offers the possibility for a causal immune treatment or the targeted selection of symptomatic drugs.

ACKNOWLEDGEMENTS

We thank Rosalind Gilchrist for proofreading the manuscript. We thank Aneka Müller and Christian Dresel for coordinating the clinical investigations.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

EE, CG and JL designed the figures. EE, CG, JL and FB wrote and commented on the manuscript.

SIGNIFICANCE

This article describes and characterizes three patients with caspr2 – antibodies and different characteristics of pain or no pain.

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How to cite this article: Ellwardt E, Geber C, Lotz J, Birklein F. Heterogeneous presentation of caspr2 antibody-associated peripheral neuropathy – A case series. *Eur J Pain*. 2020;24:1411–1418. https://doi.org/10.1002/ejp.1572