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CASPR2 antibody-associated peripheral nerve hyperexcitability presenting with neuropathic pain and insomnia

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Abstract

Contactin-Associated Protein-like 2 (CASPR2) antibody-associated disorders present with a wide range of clinical features, including peripheral nerve hyperexcitability (PNH), neuropathic pain, autonomic dysfunction, and central nervous system involvement such as insomnia or encephalopathy. While immunotherapy is frequently required, spontaneous clinical improvement has been reported in a small subset of patients. The clinical presentation may vary considerably, and electrophysiological findings often play a key role in diagnosis.

A 49-year-old man presented with burning pain and paresthesia affecting the hands and forearms, followed by similar symptoms in the lower extremities and deep aching pain in the thighs. Severe insomnia and mild autonomic symptoms, including diarrhea and hyperhidrosis, were also present. Neurological examination revealed distal paresthesia in a glove-and-stocking distribution. Routine laboratory investigations were unremarkable. Nerve conduction studies were within normal limits; however, low-amplitude after-discharges were observed following tibial M-wave responses. F-wave recordings demonstrated prominent after-discharges, particularly in the tibial and median nerves. Similar abnormalities were detected during low-frequency repetitive nerve stimulation. Needle electromyography revealed fasciculations, rare myokymic discharges, and increased insertional activity limited to the paraspinal muscles. Serum testing confirmed CASPR2 antibody positivity. Brain MRI, sleep EEG, and malignancy screening showed no abnormalities. By day 40, the patient experienced near-complete clinical recovery without immunotherapy, although electrophysiological abnormalities remained detectable. Oral prednisolone was subsequently initiated to reduce the risk of relapse. This case emphasizes the clinical heterogeneity of CASPR2-associated syndromes and suggests that spontaneous clinical improvement may occur even when electrophysiological findings have not fully normalized.

Keywords: After-discharges, CASPR2, insomnia, neuropathic pain, peripheral nerve hyperexcitability syndrome

INTRODUCTION

Contactin-Associated Protein-like 2 (CASPR2) antibody-associated syndromes present with an extended spectrum of clinical manifestations, including peripheral nerve hyperexcitability (PNH), neuropathic pain, autonomic symptoms, and central nervous system involvement including insomnia or encephalopathy, most prominently described in Morvan syndrome.[1-3] Although most patients require immunotherapy, spontaneous clinical remission has occasionally been reported.[1] In this report, a patient is described who experienced significant clinical improvement without any treatment with persistent electrophysiological findings of PNH.

CASE REPORT

A 49-year-old man presented with burning pain and paresthesia initially affecting his hands and forearms, followed by more severe burning

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sensations in both feet and calves. Within a week, he developed sharp, deep aching pain in both thighs, which worsened with walking. At that time, he also experienced diarrhea and mild hyperhidrosis. He described the pain as intense enough to cause significant insomnia, limiting his sleep to 1.5–2 hours per night. His personal and family history was unremarkable.

He first consulted a primary care physician. Empirical antibiotics, vitamin B12, and magnesium were prescribed. Although the diarrhea improved, his pain remained severe and disabling. As symptoms progressed, he was referred to a neurology clinic approximately two weeks after onset. Neurological examination revealed distal paresthesia in a glove-and-stocking distribution. Initial laboratory tests showed mild vitamin D deficiency and hyperlipidemia. Other biochemical and infectious markers were within normal limits.

Electroneuromyography (ENMG) was performed in the fourth week. Sensory and motor nerve conduction studies were within normal limits; however, low-amplitude after-discharges were noted following the M-wave response of the tibial nerve. F-wave recordings revealed prominent after-discharges especially in the tibial and median nerves. Additionally, after-discharges were also observed following low-frequency repetitive nerve stimulation (LF-RNS) recorded from the abductor digiti minimi muscle. Needle EMG showed increased insertional activity, fasciculations, and rare myokymic discharges (duplets and triplets) only in the paraspinal L3–L4 muscles. Motor unit morphology and recruitment were otherwise normal. Autonomic testing demonstrated normal heart rate variability, but the sympathetic skin response (SSR) was mildly abnormal, with reduced habituation to repeated stimuli (Figure 1).

Due to work-related constraints, the patient declined hospitalization, and further diagnostic work-up was completed on an outpatient basis. Brain MRI and sleep EEG were normal. Serum testing confirmed CASPR2 antibody positivity (1:10) using a cell-based assay. Screening for malignancy, including thoracic CT and whole-body PET, revealed no abnormalities.

By day 40, the patient reported near-recovery of pain and insomnia without any treatment. A follow-up EMG on day 60 still demonstrated after-discharges in F-wave recordings; though with slightly reduced intensity, alongside fasciculations, myokymic discharges, and occasional denervation potentials in the bilateral paraspinal L3–L4 muscles (Figure 1). Despite a marked reduction in symptom severity, minimal symptoms persisted alongside ongoing electrophysiological abnormalities; therefore, oral prednisolone was initiated based on shared decision-making, with a plan for gradual tapering. At six-month follow-up, he remained symptom-free.

DISCUSSION

CASPR2 antibody-associated disorders have traditionally been categorized into three main phenotypes; acquired neuromyotonia, Morvan syndrome, and limbic encephalitis. However, recent studies suggest that this classification may not fully reflect the clinical spectrum, as manifestations tend to cluster into predominant patterns rather than fully overlap. PNH may range from mild isolated forms to more complex presentations with insomnia and autonomic symptoms. In this context, this case shows a PNH-dominant presentation with additional neuropathic pain, insomnia, and mild transient autonomic symptoms, without fulfilling a complete Morvan phenotype.[4]

Neuropathic pain may be the initial symptom in up to 45% of these patients, and multiple pain patterns often coexist[5,6] as in this patient who had two distinct types of pain: distal burning and tingling in a glove-and-stocking distribution, and deep aching in the thighs. This combination suggests involvement of both small fibers and proximal motor roots, as previously described in CASPR2-positive patients.[6,7]

Sleep disturbances are also commonly observed, reported in up to 45% of cases. Lin *et al.* reported insomnia in 100% of CASPR2-positive patients evaluated with polysomnography or actigraphy, even without central nervous system findings.[8] In this case, severe insomnia was present without encephalopathy, seizures, or MRI abnormalities. It remains unclear whether the insomnia represented a primary manifestation of CASPR2-related central involvement or developed secondary to severe neuropathic pain, as described by the patient. Additionally, transient autonomic symptoms -diarrhea and hyperhidrosis- were also observed early in the disease. While both insomnia and dysautonomia are frequently associated with Morvan syndrome, their occurrence without objective CNS involvement, as in our patient, is increasingly recognized.[1,3]

Electrophysiological findings in PNH typically

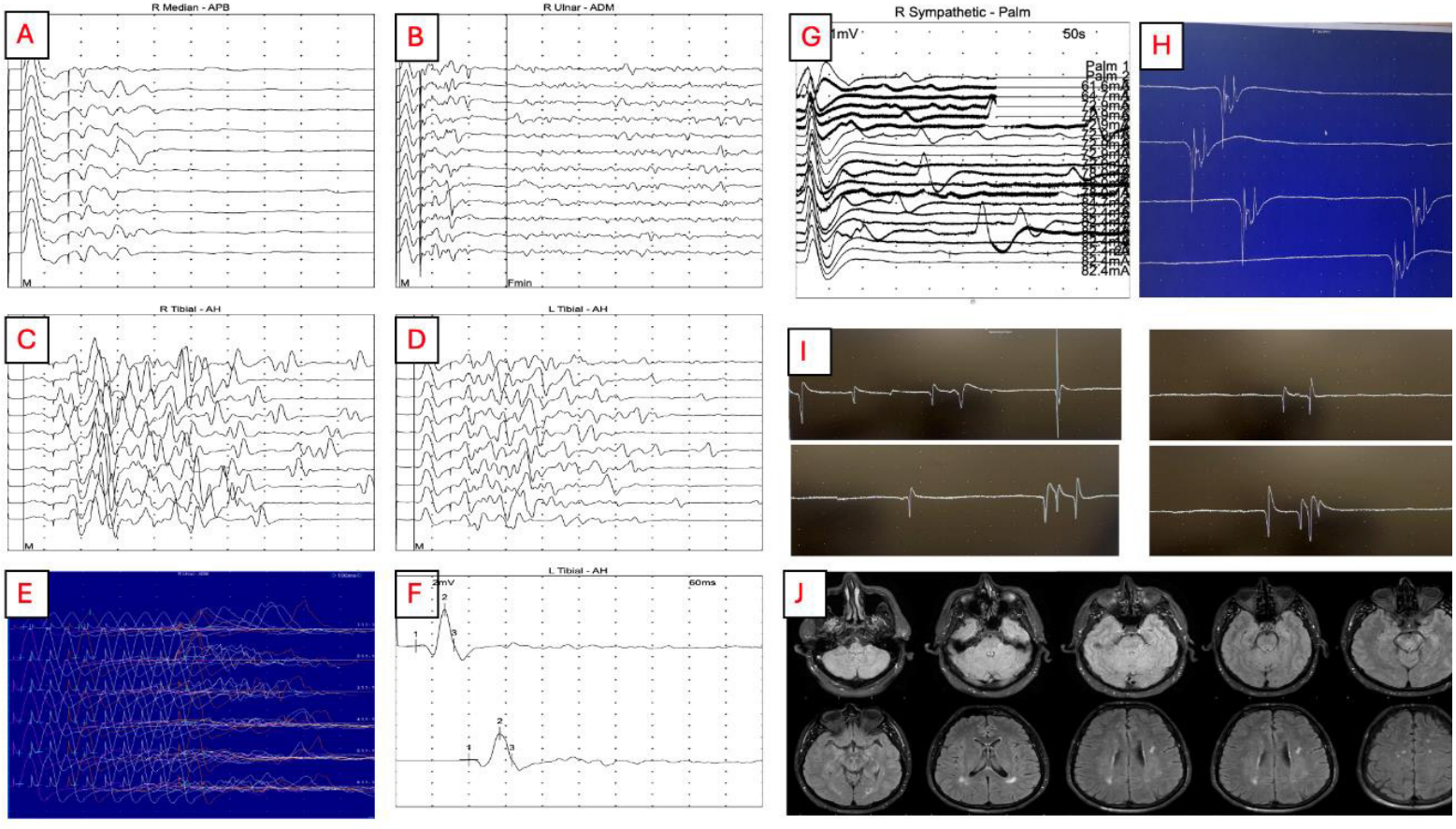

Figure 1. Electrophysiological and neuroimaging findings of the patient.
In the F-wave studies, repetitive after-discharges following CMAPs obscured the F waves, making them unrecognizable in the right median nerve and both tibial nerves (A-C-D). However, after-discharges following both CMAPs and F-waves were recognizable in the ulnar nerve (B). Low-frequency (3 Hz) repetitive nerve stimulation (RNS) did not show significant decremental response but demonstrated after-discharges following each CMAP (E). Low-amplitude after-discharges following M-response in tibial motor nerve conduction study (F). In the sympathetic skin response, habituation was absent, and spontaneous SSRs appeared even without stimulation when the sweep duration was extended (G). Needle EMG examinations showed irregular duplets with 4–6 Hz interburst frequency and 143 Hz intraburst frequency in the paraspinal L3–L4 muscles at rest (H). After 2 months, needle EMG still showed spontaneous duplets and triplets in the same muscles (I). Brain MRI, axial T2-weighted sequences, showed only non-specific Fazekas grade 1 small white matter lesions (J).

include after-discharges following CMAP or F-wave responses, and spontaneous motor unit discharges ranging from fasciculations, myokymia, neuromyotonia or cramps.[9,10] These findings reflect increased motor axon excitability, likely due to CASPR2-related disruption of Kv1 channel function, leading to impaired action potential termination and re-entrant excitation.[7] After-discharges are commonly observed in tibial nerves and may appear following M-waves, either recognizable or unrecognizable F waves or it may appear following F waves. A recent study suggested that after-discharges occurring after M-waves with unrecognizable F-waves are most frequently seen in Morvan syndrome and rarely observed in non-Morvan PNH syndromes. However, in the present case, there was no objective CNS involvement consistent with Morvan syndrome, despite the presence of this electrophysiological pattern[11]; specifically, the tibial and median nerves demonstrated after-discharges that obscured the F-waves, as illustrated in Figure 1.

Spontaneous remission without immunotherapy is rare but has been documented in a small subset of cases.[6] In this patient, symptoms improved markedly but did not completely resolve without treatment; therefore, oral prednisolone was initiated to reduce the risk of relapse.[3] Persistent electrophysiological abnormalities were still detectable as seen in this case, indicating a lack of concordance between clinical and neurophysiological recovery.

Finally, the antibody titer was low-positive (1:10, cell-based assay); follow-up serology was not performed. Serum CASPR2 titers have been shown to be significantly lower in mild or isolated peripheral nerve hyperexcitability compared with limbic encephalitis[4], though its contribution to the self-limited course in our patient remains uncertain**.**

DISCLOSURE

Ethics: Written informed consent for publication of the patient's clinical details and/or clinical images was obtained from the patient.

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Conflict of interest: None

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