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Research paper

Afterdischarges following M waves in patients with voltage-gated potassium channels antibodies

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ABSTRACT

Objective: To explore the correlation between afterdischarges in motor nerve conduction studies and clinical motor hyperexcitability in patients with voltage-gated potassium channels (VGKC) antibodies.
Methods: Six patients with positive serum antibodies to contactin-associated protein-like 2 (CASPR2) or/and leucine-rich glioma-inactivated protein 1 (LGI1) were recruited, including 5 with autoimmune encephalitis, and 1 with cramp-fasciculation syndrome. Electromyography (EMG), nerve conduction studies (NCS) and F waves were performed, and afterdischarges were assessed. One patient was followed up.
Results: Five patients had clinical evidence of peripheral motor nerve hyperexcitability (myokymia or cramp), and four of them had abnormal spontaneous firing in concentric needle electromyography (EMG). Prolonged afterdischarges following normal M waves were present in all six patients, including the two patients who had no EMG evidence of peripheral nerve hyperexcitability (PNH). Afterdischarges disappeared after treatment with intravenous immunoglobulin (IVIG).
Conclusion: The afterdischarges in motor nerve conduction study might be a sensitive indicator of peripheral motor nerve hyperexcitability in patients with VGKC antibodies.
Significance: Afterdischarges in motor nerve conduction study might be more sensitive than needle electromyography for detecting peripheral motor nerve hyperexcitability, and could disappear gradually in accordance with clinical improvement and reduction of antibodies.

1. Introduction

Contactin-associated protein-like 2 (CASPR2) and leucine-rich glioma-inactivated protein 1 (LGI1) are auto-antigens related to voltage-gated potassium channels (VGKC). The antibody to CASPR2 could cause both encephalitis and peripheral nerve hyperexcitability (PNH), while the antibody to LGI1 could cause encephalitis (Lancaster et al., 2011). Acquired neuromyotonia, Morvan's syndrome and cramp-fasciculation syndrome are the common manifestations of PNH in patients with CASPR2 antibodies (Sunwoo et al., 2015). Prolonged afterdischarges were also described as a sign of PNH (Harrison and Benatar, 2007). We report a small case series of six patients, in which VGKC antibody associated peripheral nerve hyperexcitability indicated by afterdischarges was no longer evident after IV immunoglobulin (IVIG) therapy.

2. Materials and methods

2.1. Patients

Six patients were recruited in Peking Union Medical College hospital from 2014 to 2016. All patients had positive serum antibodies to CASPR2 or/and LGI1, and clinically presented with PNH with or without autoimmune encephalitis. Symptoms and signs of PNH included myokymia, cramp, and pain (as a sign of hyperexcitability of nociceptive pathways). All patients underwent a neurological examination , neoplastic screening, and a cerebrospinal fluid evaluation that also included VGKC antibody titers. The study was approved by the local ethics committee, and complied with the 2013 update of the Declaration of Helsinki.

2.2. Electrophysiology

Electromyography (EMG), nerve conduction studies (NCS) and F waves were performed with a CareFusion Nicolet EMG machine. The filter settings were 20 Hz to 10 kHz for needle EMG, 2 Hz to 10 kHz for motor NCS (including F waves), and 2 Hz to 2 kHz for

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sensory NCS. Motor NCS and F waves were followed up in one patient after IVIG treatment. Assessment of afterdischarges was performed by an investigator who was blinded to the clinical history.

Orthodromic sensory NCSs were performed on median, ulnar and tibial nerves. Conventional needle EMG was performed in tibialis anterior, vastus medialis, vastus lateralis, gastrocnemius, extensor digitorum communis, abductor digiti minimi, deltoid, and biceps femoris. The room temperature was maintained to ensure that the patients' skin temperature remained above 31 °C.

Motor NCS were performed in all subjects on the median, ulnar, fibular, and tibial nerves with percutaneous supramaximal nerve stimulation while recording the CMAPs with 10-mm disk electrodes. F waves of median, ulnar and tibial nerves were performed on all subjects with repetitive supramaximal stimulations at the rate of 1 Hz. The sweep was 5 ms/division when performing the procedure. Bilateral nerves were studied in some cases with the patient's permission. The median nerve was stimulated at the wrist and elbow, with recording from the abductor pollicis brevis; the ulnar nerve was stimulated at the wrist and distal elbow, with recording from the abductor digiti minimi; the fibular nerve was stimulated at ankle and below fibular head, with recording from the extensor digitorum brevis; the tibial nerve was stimulated at ankle and popliteal fossa, with recording from the abductor hallucis. Measurements included distal motor latency (DML), MCV, CMAP amplitude (baseline to negative peak), area and duration of negative wave.

Afterdischarges were assessed at gains of 5 mV/div and 200 μV/div, respectively. Afterdischarges were defined as repetitive late potentials following initial compound muscle action potential (Loukaides et al., 2012; Lukas et al., 2013).

3. Results

3.1. Clinical features

There were 3 females and 3 males. The median age at onset was 50 years (range 30–70 years). The median duration of illness was 2.5 months (range 1–24 months). All of the five patients with anti-CASPR2 antibodies had central nervous system symptoms, including hallucination, confusion, insomnia, seizures, or dysphasia, and were diagnosed autoimmune encephalitis. The patient with anti-LGI1 antibody who didn't have any central nervous system symptom was diagnosed cramp-fasciculation syndrome. Five patients had myokymia or cramp clinically, the other claimed limb pain only. Symptoms of autonomic nervous system were present in 4 patients. 2 patients had hyperhidrosis and difficulty in defecating, and 2 had hyperhidrosis. After being treated with IVIG, five patients had clinical recovery.

3.2. Electrophysiology

Motor and sensory nerve conduction displayed normal amplitude and conduction velocity in all patients. EMG showed normal motor unit action potential (MUAP) and recruitment in all patients. Fasciculation was detected in two patients (Patients C and D), multiplets in two (Patient D and F), and myokymic discharges in one (Patient E). No abnormal spontaneous firing was detected in Patients A and B (Table 1). Motor nerve conduction recording showed prolonged afterdischarges following normal M waves in all six patients. The prolonged afterdischarges were first noticed during F-wave recording because of the high gain setting (200 μV/d) for F wave studies.

3.3. The comparison of clinical symptoms and electrophysiology

Table 1 shows the correlation between clinical PNH symptoms and electrophysiological findings. Five patients (B, C, D, E and F) had clinical evidence of PNH (myokymia or cramp), while needle EMG showed evidence of PNH (fasciculation, multiplets, or myokymic discharges) only in 4 patients (C, D, E and F). Patient A had no clinical signs of peripheral motor nerve hyperexcitability and no abnormal spontaneous firing on EMG. However, prolonged afterdischarges following normal M waves were present in all six patients.

3.4. The following up of one patient

In Patient A, the duration of afterdischarges decreased on the 10th day after IVIG treatment in accordance with symptom relief, then decreased gradually and finally disappeared during follow-up of 4 months (Fig. 1).

Table 1
Clinical and laboratory information of patients.

Patient number	Gender	Age at onset, y/o	Duration, months	Tumor	Clinically myokymia or cramps	CNS symptoms	CMAP Amp and MCV	SNAP Amp and SCV	Needle EMG	Serum Abs	CSF Abs	Treatment
A	F	70	3	–	–	+	–	–	No aSF	CASPR2, LGI1	–	IVIG, prednisone
B	F	40	3	–	+	+	–	–	No aSF	CASPR2, LGI1	LGI1	IVIG, MP, CBZ
C	M	30	24	–	+	+	–	–	Fasciculation	CASPR2	–	IVIG , prednisone, VPA, LD
D	F	39	1	–	+	+	–	–	Fasciculation, Doublets, triplets, and multiplets	CASPR2, LGI1	–	IVIG, prednisone, CBZ, MM
E	M	66	2	–	+	–	–	–	Myokymic discharges	LGI1	–	CBZ
F	M	60	2	–	+	+	–	–	Doublets, triplets, and multiplets	CASPR2, LGI1	CASPR2, LGI1	IVIG, MP, PE

Abbreviations: CNS = central nervous system; MCV = motor conduction velocity; SCV = sensory conduction velocity; CMAP = compound motor action potential; SNAP = sensory nerve action potential; Amp = amplitude; EMG = electromyography; aSF = abnormal spontaneous firing; CSF = cerebral spinal fluid; CASPR2 = contactin-associated protein-like 2; LGI1 = leucine-rich glioma-inactivated protein 1; Ab = antibody; IVIG = intravenous immunoglobulin; MP = methylprednisolone; CBZ = carbamazepine; VPA = valproate; LD = levodopa; MM = mycophenolate mofetil; PE = plasma exchange.

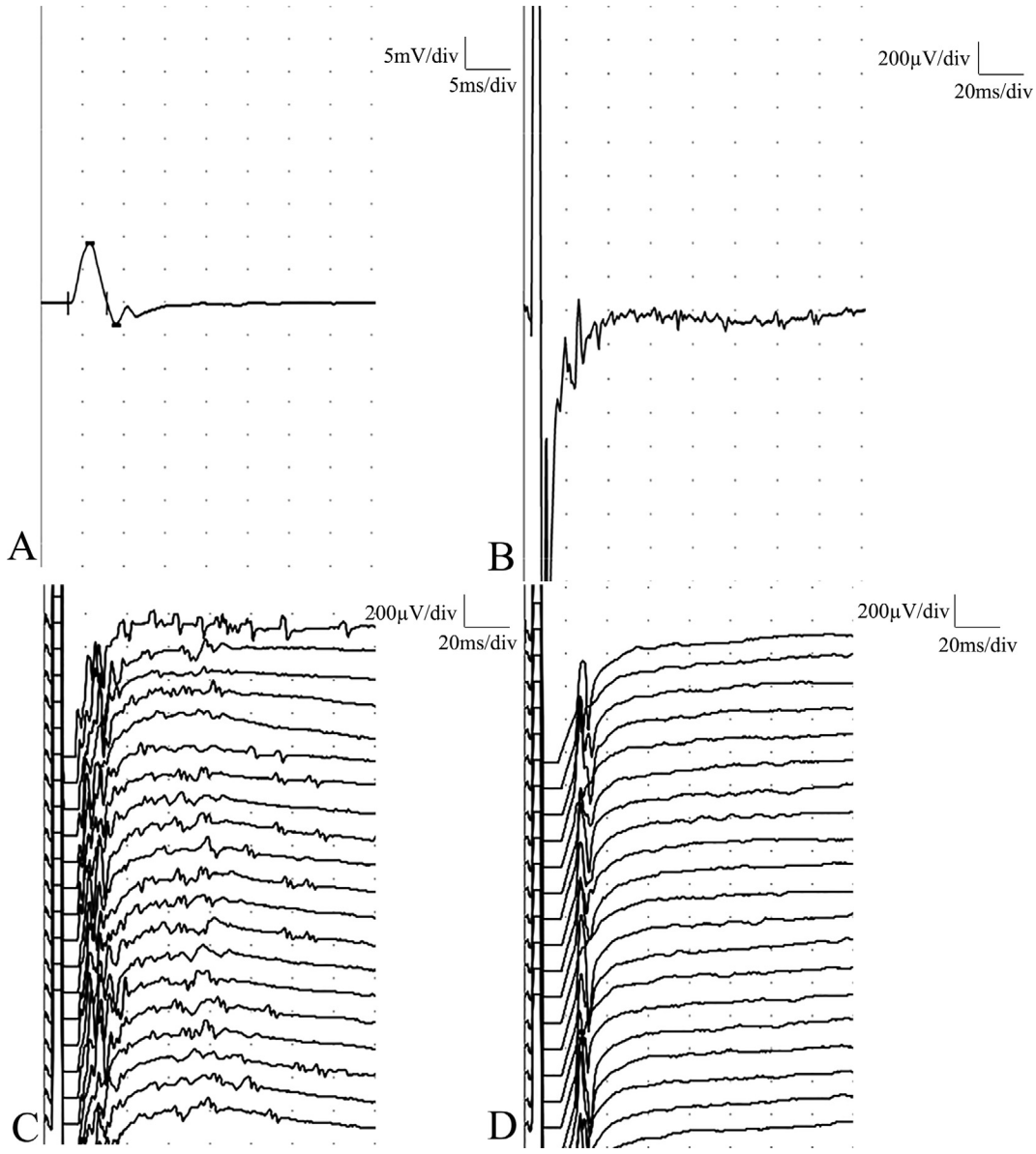

Fig. 1. Afterdischarges recorded in median nerve of Patient A. A and B, Median nerve motor conduction recording. C and D, F wave recording. A. Afterdischarges were hardly visible with normal gain of 5 mV. B. Prolonged afterdischarges were easily seen with a gain of 200 μV. C. Prolonged afterdischarges obscured the median F waves. Afterdischarges precede the normal F-waves and overlap it. D. 4 months after treatment, the afterdischarges disappeared. (In figure C and D, the sweep of F wave recording was adjusted from 5 ms/division to 20 ms/division, in order to display all afterdischarges.)

4. Discussion

Afterdischarge was defined as repetitive late potentials following initial compound muscle action potential after stimulus (Loukaides et al., 2012; Lukas et al., 2013). The presence of afterdischarges reflects the presence of hyperexcitability of the nerve membrane (Bodkin et al., 2009). PNH could be divided into primary and secondary mechanisms. Primary PNH is due to hereditary or acquired disorders of neuronal potassium channels (Liewluck et al., 2014).

VGKCs play an important role in signal transduction and membrane stabilization within both the central and peripheral nervous system. VGKCs are closely associated with other proteins including LGI1, CASPR2, ADMA23 and others (Liebenthal et al., 2015). Antibodies to the VGKC complex, including CASPR2 and LGI1 protein, may decrease number of functioning VGKC, suppress voltage-gated outward K(+) current, thus prevent the repolarization and termination of neuronal action potential (Liebenthal et al., 2015) (Arimura et al., 2002). CASPR2 is strongly expressed at neural juxtaparanodes of the nodes of Ranvier, and is essential for clustering of VGKC (Vincent et al., 2011). It was found to be expressed both in peripheral nerve and in hippocampus (Lancaster et al., 2011). On contrary, LGI1 is a major central nervous system (hippocampus) target of VGKC complex-binding autoantibodies (Lancaster et al., 2011). In peripheral nerves, the binding of CASPR2 antibodies may lead to down-regulation of the CASPR2/VGKC complexes on axons, resulting in PNH (Liebenthal et al., 2015). Acquired neuromyotonia, Morvan's syndrome and cramp-fasciculation syndrome are the common manifestations of PNH in patients with CASPR2 antibodies (Sunwoo et al., 2015). Liewluck et al. and Lukas et al. described prolonged afterdischarges in patients of cramp-fasciculation syndrome and Morvan syndrome, who had positive serum antibodies to VGKC (Lukas et al., 2013; Liewluck et al., 2014). The appearance of afterdischarges, if accompanied by clinical symptoms of encephalopathy or cramp-fasciculation syndrome, might suggest the clinician to test for CASPR2 antibodies.

According to the results, we found that afterdischarges in motor NCS might be more sensitive than clinical symptoms and needle EMG in detecting peripheral motor nerve hyperexcitability. In patient A, there were no clinical signs of peripheral motor nerve hyperexcitability or abnormal spontaneous discharges on needle EMG studies, but afterdischarges were detected after M waves. Prolonged afterdischarges in patients of VGKC encephalitis with no clinical signs of peripheral motor nerve hyperexcitability have not been reported. PNH includes a spectrum of disorders with varying degrees of nerve hyperexcitability. In patients with high degree of PNH, as patient E, hyperexcitability of motor nerve membrane was continuous, and myokymic discharges were detected on routine needle EMG. While in those with less hyperexcitability, there is lower rate and non-continuous manner of firing, manifesting as the fasciculation or multiplet potentials in patients C, D and F. In those with even less hyperexcitability, as patients A and B, no spontaneous firing was detected on routine EMG. However, afterdischarges after M waves were detected in all patients. The mechanism for this phenomenon might be as following. Spontaneous firing on needle EMG was recorded at rest, and couldn't be easily detected when the motor hyperexcitability was not high enough. On the other hand, afterdischarges were sustained firing of an induced action potential following stimulation, which could induce and facilitate motor nerve membrane hyperexcitability (Benatar et al., 2004). The electric stimulation might be the reason why afterdischarges were more sensitive. Afterdischarges could disappear gradually in accordance with the improvement of encephalitis or PNH, and reduction of antibodies. Thus, the afterdischarges might be a sensitive monitoring indicator of peripheral motor nerve hyperexcitability. Afterdischarges may first be noted during F-wave recording because the gain setting is higher (100–200 μV/d). Due to lower gain in normal motor conduction studies, the presence of afterdischarges might be overlooked.

In our study, patient B had her electrophysiological tests performed after IVIG treatment, by when her symptoms of cramp and myokymia had partly resolved. This might be the reason why her needle EMG showed no abnormal spontaneous firing.

In conclusion, afterdischarge is a more sensitive and non-invasive monitoring indicator of peripheral motor nerve hyperexcitability in patients with VGKC antibodies, who present with signs of PNH with or without autoimmune encephalitis. Afterdischarge may be overlooked in motor NCS, but revealed easily during F-wave recording due to different gain settings.

Conflict of interest

None.

Acknowledgments

None.

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