Distal Acquired Demyelinating Symmetric Neuropathy Associated with Decreased Electrical Excitability of the Femoral Nerves

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ABSTRACT

Introduction: There are many phenotypic variants of chronic inflammatory demyelinating polyneuropathy.

Case report: We report a rare case of the distal phenotype of chronic inflammatory demyelinating polyneuropathy with a subacute onset and rapidly progressive course. A 58-year-old male had distal, symmetric, predominantly motor impairment without ataxia and tremor. After a three-month duration of the disease, the patient had already complete paresis of the feet with absence of compound muscle action potentials (CMAPs) over the feet and lower leg muscles, but preserved proprioception and sural sensory nerve action potential. Cerebrospinal fluid protein level was elevated to 3.4 g/L. Demyelinating neuropathy was predominantly in the proximal segment of the nerves. Low amplitude of CMAPs was recorded hardly over the vastus medialis and rectus femoris muscles, while weakness and atrophy in these muscles were not. The patient was refractory to treatment. He died three years after disease onset.

Conclusion: We described a new clinical-electrophysiological phenomenon, which was characterized as a decrease in the evoked electrical excitability at the femoral nerve stimulation site (decreased CMAP), while the natural physiological conduction of the impulse from the motor neuron to the muscle was not blocked (preserved muscle strength).

Keywords: chronic inflammatory demyelinating polyneuropathy, nerve conduction studies, unexcitability, femoral nerve, nodo-paranodopathy.

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Abbreviations:

Casp1=Contactin-associated protein-1

CB=Conduction block

CIDP=Chronic inflammatory demyelinating polyneuropathy

CMAP=Compound muscle action potentials

CSF=Cerebrospinal fluid

CV=Conduction velocity

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a heterogeneous disorder having a wide clinical range and is characterized by demyelination that can involve the distal nerve terminals, intermediate and proximal nerve segments, and nerve roots (1, 2). There are many phenotypic variants of CIDP (1, 3, 4). While typical CIDP is characterized by proximal and distal involvement, the distal acquired demyelinating symmetric neuropathy phenotype is restricted to a distal, symmetrical distribution with predominantly sensory symptoms and slowly progressive course (5, 6). In addition, in the last two decades, the nodal region has been recognized as a possible site of the specific autoimmune attack in peripheral neuropathies (7-10).

Here we report a rare case from a clinical and neurophysiological point of view when the distal phenotype of CIDP had a subacute onset and rapidly progressive course. Predominantly distal motor axonal involvement was accompanied by reduced conduction predominantly at the proximal segment of the peripheral nerves and was associated with a decrease in the electrical excitability of the femoral nerves. Similar findings have not been reported in the medical literature. □

CASE REPORT

A 58-year-old male had a subacute onset (three-month duration), rapidly progressive, predominantly distal, symmetric, mainly motor impairment without ataxia and tremor. Complaints about the sensation of cold feet and pain in his legs as well as difficulty walking appeared after a respiratory infection. He did not have a family history of peripheral neuropathy or other neuromuscular disorders. He had a history of

duodenal ulcer disease. Clinical examination did not reveal any pathological findings. Mental status and cranial nerve examinations were normal. The patient walked with crutches (steppage gait). Neurological examination revealed complete paralysis of the feet and muscle atrophy in the lower legs. The proximal muscles of the lower extremities and all muscles of the upper extremities were spared. Pinprick hyperalgesia was presented on the lower third of the legs, intensifying distally. Hyperpathia as radiating sensation (spreading pain to the sides) after the pinprick was not present. Tendon reflexes at the ankles and knees were absent. Proprioception was spared. There were no symptoms or signs of autonomic dysfunction.

No recordable compound muscle action potentials (CMAPs) could be obtained with stimulation of the fibular and tibial nerves on both sides (recording muscles: extensor digitorum brevis, abductor hallucis, tibialis anterior, and gastrocnemius), but sensory nerve action potential (SNAP) was obtained from the left sural nerve (Table 1). Attention should be paid to a pronounced decrease in CMAP amplitude in the femoral nerves and a significant prolongation of the conduction time. However, there was no weakness and atrophy in the quadriceps femoris muscles, and the electric current power and pulse duration were the maximum possible (100 mA and 1.0 ms). The median nerve conduction velocity (CV) was decreased predominantly in the upper arm segment (elbow – Erb's point). The distal/proximal CVs ratio was 1.4 (reference mean±SD: 0.91 ± 0.07 , $n=35$). Neither conduction block (CB) nor temporal dispersion was observed. Routine laboratory studies showed no abnormalities. Cerebrospinal fluid (CSF) protein level was elevated to 3.4 g/L (range 0.15–0.45 g/L), whereas cell count was normal. M-protein was not identified by serum protein electrophoresis. Plasma protein fractions were normal. Brain MRI and skeletal survey showed no abnormalities.

Six months after the onset of neurological symptoms, weakness appeared in the hand muscles, and 58.2% CMAP area decay between elbow and Erb's point stimulation sites in the median nerve was determined. The patient's condition worsened despite the administered treatment (plasma exchange, prednisolone, methylprednisolone, azathioprine, or cyclophosphamide). On the 10th month, mild muscle atrophy in both hand

Nerve (muscle) Parameters	Three months	Six months	10 months	Normal			
Motor study							
Median (APB)	Right	Left	Right	Left	Right	Left	
DML (ms)	5.1	ND	5.1	ND	6.2	ND	< 3.8
Dur (ms)	7.4/7.7/9.0	ND	7.3/7.9/6.7	ND	10.0/8.5/11.2	ND	< 7.3
Amp (mV)	7.7/6.8/5.1	ND	5.5/5.2/2.4	ND	1.9/2.9/0.4	ND	> 9.3
CV (m/s)*	35.7/26.2	ND	35.0/27.0	ND	34.3/26.2	ND	> 50.4
F-wave min (ms)	49.0	ND	49.0	ND	53.0	ND	<30.6
Ulnar (ADM)							
DML (ms)	ND	ND	3.2	ND	ND	ND	< 3.4
Dur (ms)	ND	ND	6.4/7.7	ND	ND	ND	< 8.0
Amp (mV)	ND	ND	9.7/6.6	ND	ND	ND	> 11.0
CV (m/s)	ND	ND	39.0	ND	ND	ND	> 49.3
F-wave min (ms)	ND	ND	44.4	ND	ND	ND	<31.9
Femoral (VM)							
CT (ms)	14.4	15.2	ND	17.0	11.2	ND	<6.3
Dur (ms)	16.4	15.0	ND	19.0	12.5	ND	<15.7
Amp (mV)	0.5	1.0	ND	0.4	0.07	ND	>4.9
CV on the latency (m/s)*	19.7	16.0	ND	16.5	22.0	ND	>44.0
Femoral (RF)							
CT (ms)	10.7	9.7	10.5	9.0	9.7	ND	<4.0
Dur (ms)	11.8	16.1	12.7	14.8	12.2	ND	<11.8
Amp (mV)	1.0	1.7	0.3	0.4	0.05	ND	>14.3
CV on the latency (m/s)*	9.0	23.0	16.0	16.0	15.5	ND	>37.5
Sensory study							
Median							
Amp (μV)	8.6	ND	ND	ND	7.7/6.7	ND	> 15.0
CV (m/s)	44.6	ND	ND	ND	42.0/34.0‡	ND	> 50.0
Ulnar							
Amp (μV)	ND	ND	6.0	ND	ND	ND	> 15.0
CV (m/s)	ND	ND	42.2	ND	ND	ND	> 50.0
Sural							
Amp (μV)	3.6	NR	NR	NR	NR	NR	> 12.0
CV (m/s)	37.0	NR	NR	NR	NR	NR	> 44.0

*CV on segments of the forearm/elbow – Ebs's point.

†CV on the latency (CV was calculated by dividing the distance by the onset latency).

‡CV on segments of the wrist – second digit/forearm.

Amp=amplitude peak-to-peak; APB=the abductor pollicis brevis; ADM=the abductor digiti minimi; CT=conduction time; CV=conduction velocity; DML=distal motor latency; Dur=duration; F-wave min=minimal F-wave latency; ms=milliseconds; mV=millivolts; m/s=meters per second; ND=not done; NR=no response; RF=rectus femoris; VM=vastus medialis.

TABLE 1. Results of serial nerve conduction studies at different times in relation to symptom onset

muscles was noticed. CSF protein content decreased to 2.7 g/L. Femoral nerve CMAP amplitude was gradually reduced (Table 1), but neither weakness nor muscle atrophy of quadriceps femoris muscles was detected, and the amplitude of surface electromyogram over the rectus femoris muscle was normal during maximal volitional effort (Figure 1). Subsequently, the patient refused NCSs due to painful stimulation of the femoral nerve. Comparison between the CVs in the distal (wrist to the second digit) and more proximal segments (forearm) of the median sensory nerve showed significantly slower conduction in the fore-

arm segment. The distal/proximal CVs ratio was 1.24 (reference mean±SD: 0.91±0.08, n=29).

On the 15th month, bilateral muscle atrophy of the forearms was detected. Muscle strength was grade 2 in the flexor muscles and grade 1 in the hand extensor muscles and his steppage gait persisted. Pinprick sensation was decreased below the elbows and low shins. After administration of intravenous immunoglobulin, there was a slight improvement in strength by 0.5 points. Three months after that, he moved with crutches or a wheelchair. However, proximal strength in his leg remained relatively normal (grade 4-4.5). CSF protein con-

FIGURE 1. Compound muscle action potentials (1) recorded over vastus medialis (A, B) and rectus femoris (C, D) obtained by electric stimulation femoral nerves in the 58-year-old patient (A, C) and a 58-year-old healthy male (B, D). Note calibration is 0.1 mV per division for the patient and 5.0 mV for the healthy subject. Bottom recording (2) is surface electromyogram. Note calibration is 0.5 mV per division for the patient and healthy subject.

tent was decreased to 2.02 g/L. CSF pheresis was performed. The patient's condition worsened despite the administered treatment. Regrettably, he was lost to follow-up. Retrospectively, information was obtained by telephone contact by his wife. He died unexpectedly in his sleep three years later after symptom presentation. An autopsy was not performed. □

DISCUSSION

Our patient's disease was initially considered as subacute form Guillain-Barré syndrome due to an aggressive onset, but the follow-up established a diagnosis of the distal phenotype of

CIDP, and the clinical course was classified as rapidly progressive. Motor function impairment was the primary cause of clinical disability. Already after three-month duration of disease, the patient had complete paresis of the feet with absence of CMAP over the feet and lower leg muscles, but he had preserved proprioception and sural sensory nerve action potential. NCSs had shown a demyelinating neuropathy predominantly in the proximal segment of the nerves with axonal loss of fibers, innervating distal muscles (the absent CMAPs of the fibular and tibial nerves). The absence of responses could be due to a combination of primary demyelination and secondary axonal loss or nodo-paranodopathy. Previous studies demonstrated that the acute-subacute progressive course was associated with the clinical features of a predominantly disabling motor polyneuropathy, electrophysiological evidence of denervation and axonal neuropathy, and with autoantibodies against paranodal proteins. In particular, patients with anti-CNTN1 or anti-Caspr1 IgG4 antibodies showed the highest disability at onset (7-10).

The most unique finding was that low amplitude of CMAPs was recorded hardly over the vastus medialis and rectus femoris muscles in the absence of weakness and atrophy in these muscles. The cause of a decrease in the amplitude of CMAPs can be related to the CB below the site of stimulation, including the distal nerve terminals or axonal loss. However, CB reflects focal demyelination of motor fibers or disorganization of sodium channels and myelin detachment (nodo-paranodopathy), resulting in muscle weakness. The axonal loss reflects axonal degeneration of motor fibers, resulting in muscle weakness and atrophy. Another reason for the decrease in CMAP can be insufficient electrical stimulation of the femoral nerve. However, we used the greatest possible stimulation and repeated femoral NCSs many times at each hospital admission. Thus, a technical explanation of reduced electrical excitability can be ruled out. Therefore, this unusual phenomenon can be interpreted as a decrease in the electrical excitability of the femoral nerves. It was characterized as a decrease in the evoked electrical excitability at the nerve stimulation site (decreased CMAP), while the natural physiological conduction of the impulse from the motor neuron to the muscle was not blocked (preserved muscle strength). The mechanism of impaired excitability is not clear, but it dif-

fers from the reversible conduction failure which has been described in several subtypes of Guillain-Barré neuropathy. It is now well established that mammalian Na⁺ currents display striking diversity, suggesting the presence of numerous types of Na⁺ channels and may provide a basis for selective pathology of peripheral nerves. In addition, Na⁺ channels are present in both axons and associated glial cells and may constitute "shared epitopes" (11). It was shown that partial inactivation of the Na⁺ channels by intravenous infusion of lidocaine in humans reduced the CV without CB, possibly by increasing the rise time of the action potential and the internodal conduction time (12).

Reduced peripheral nerve excitability has been described in many chronic polyneuropathies using nerve excitability techniques (13). As a rule, there was a weakness of the muscles innervated by the damaged nerves in this condition. However, subclinical motor nerve excitability was reported in typical Miller Fisher syndrome with preserved limb strength and CV using CMAP scanning technique (14). The authors suggested that reduced motor nerve excitability might represent an initial step in nerve dysfunction, a process that results in muscle weakness only when a critical proportion of nerve fibers become inexcitable, as it was found in patients with Guillain-Barré syndrome. It is known that the excitability of motor axons is physiologically lower than the same one of sensory axons (15). We have recently described a patient with monoclonal gammopathy of undetermined significance who had a decrease in evoked electrical excitability in the distal segments of the peripheral nerves with severe demyelination (prolongation of tibial distal motor latency up to 86.5 ms) (16). The distal CMAP areas were considerably lower compared to the proximal CMAP areas. In this condition, the proximal impulse was not blocked at the distal segment. In addition, a dissociation between the pronounced degree of neurophysiological changes and preserved muscle strength was noticed (16, 17).

Another characteristic feature of this case was the "predominantly proximal" pattern of demyelinating peripheral nerve damage. CVs along the motor and sensory fibers of the median nerve in the more proximal segments were always lower than in the distal ones. F-wave latencies were significantly prolonged, but the distal motor latencies were marginally abnormal. In addition, six months after the onset of neurological symptoms, CMAP decay on

the "elbow – Erb's point" segment was revealed. In connection with the non-excitability of the femoral nerve, the question arises whether this is CB due to focal demyelination or CMAP decay due to a decrease in the electrical excitability of the median nerve. It has been previously shown that CV and amplitude decay were not consistently related to muscle strength (2). It was revealed that the "intermediate" patients (terminal latency index was 0.41; similar to our patient) whose conduction slowing was predominant in the forearm segments were relatively refractory to treatment with steroids or plasmapheresis and tended to have chronic progressive or stable courses (1). In contrast, patients with the "distal" motor pattern had a better response to corticosteroid treatment and showed a monophasic remitting course.

Thus, on the one hand there was a primary demyelinating proximal nerve damage pattern with preservation of the proximal muscle strength, and on the other hand there was a pronounced axonal damage to the fibers innervating the distal muscles. Such selective damage to individual fibers was probably possible at the proximal level of peripheral nerves and spinal roots. A combination of the autopsy, MRI and ultrasound studies have demonstrated that lesions in CIDP occurred predominantly in the spinal roots, proximal nerve trunks, and major plexuses (8). Exclusive binding to ventral but not dorsal roots has recently been described in a passive transfer rat model with autoantibodies against contactin-1 (18).

Overall, the clinical picture of our patient very much resembled the symptoms described in patients with autoantibodies against paranodal proteins especially against contactin-associated protein-1 (Casp1): acute onset of the severe motor more than sensory neuropathy; distal damage more than proximal (proximal muscle strength was spared during the observation period); poor response to intravenous immunoglobulin and corticosteroids; demyelinating features with early axonal involvement (7-10). Pain has been identified in patients with antibodies to Casp1 (8), but it was not the predominant finding in our patient. So far, information on this rare condition is limited, as only a few patients have been identified with autoantibodies against Caspr in CIDP (8-10). Patients with antibodies to neurofascin 155 had a severe, predominantly distal, motor neuropathy with ataxia and low-frequency postural and intention tremor (9). The absence of nodal/paranodal proteins de-

terminated potassium channel disorganization, myelin detachment at the paranode, and a decrease in nerve CVs due to an increase in paranodal capacitance secondary to misplacement of a potassium channel in knockout mice (19, 20). Patients with antibodies targeting the contactin-1, Caspr1, and neurofascin 155 generally had a poor response to intravenous immunoglobulin, but a very good one to rituximab (9, 10). However, this treatment was not used in our case.

CONCLUSION

This case study presented a new, not previously described in the literature, clinical-electrophysiological phenomenon which was charac-

terized as a decrease in the evoked electrical excitability at the femoral nerve stimulation site (decreased CMAP), while the natural physiological conduction of the impulse from the motor neuron to the muscle was not blocked (preserved muscle strength). The present study broadens current knowledge about the phenotypic spectrum of CIDP and provides important novel insights regarding its pathophysiology. Further investigation is needed to confirm our observations.

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