American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 834-838
DOI: 10.12659/AJCR.903961

Received: 2017.02.22
Accepted: 2017.05.02
Published: 2017.07.27

Chronic Inflammatory Demyelinating Polyneuropathy Variant with Creatine-Kinase Elevation and Vanishing Effect of Immunoglobulins

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 46
Final Diagnosis: Cidp variant
Symptoms: Weakness
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Rare co-existance of disease or pathology

Background: Whether creatine-kinase (CK) is elevated or not in chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants is not comprehensively investigated.

Case Report: We report the case of a 47-year-old male who developed weakness of the left lower leg and the right index finger at age 42 years. At age 44 years, paresthesias and dysesthesias of both lower legs and mild right lower leg weakness additionally developed. CK was recurrently elevated since age 42 years but paraprotein and anti-myelin-associated glycoprotein (MAG)-antibodies were negative. Nerve conduction studies at age 43 years showed an axonal and demyelinating lesion with conduction blocks. Cerebrospinal fluid (CSF) investigations revealed mild pleocytosis and elevated protein, which is why CIDP variant was diagnosed. Immunoglobulins were administered with success. Because of recurrent relapses, immunoglobulins were increased at age 45 years, resulting in stabilization. Currently, the patient is infusing immunoglobulins subcutaneously himself.

Conclusions: CIDP variants may go along with CK elevation, an axonal lesion, pleocytosis, and asymmetry of the lesion. A vanishing effect of immunoglobulins over time may be characteristic of CIDP variants.

MeSH Keywords: Creatine Kinase • Electromyography • Guillain-Barre Syndrome

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903961

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Background

The significance of creatine-kinase (CK) elevation in chronic inflammatory demyelinating polyneuropathy (CIDP) or its variants is unclear. Among all 15 diagnostic criteria sets for CIDP available [1], including the EFNS criteria [2], CK does not serve as a supportive biomarker for diagnosing CIDP. Recent studies, however, have shown that CK can be elevated in up to one-quarter of the patients [3]. The following case report describes a patient with a CIDP variant associated with CK elevation.

Case Report

A 47-year-old, non-smoking, non-alcoholic, white male, height 192 cm, weight 110 kg, with a previous uneventful history and without regularly taking drugs, developed discrete, painless weakness of the left lower leg and the right index finger at age 42 years. CK elevation was found (Table 1). Nerve conduction studies showed an increased distal latency of the right tibial nerve, reduced conduction velocity in some of the lower-leg nerves, reduced amplitudes of nerve action potentials with partial conduction blocks in the right median and ulnar nerves, and complete conduction block in the left peroneal nerve; therefore, axonal and demyelinating polyneuropathy was diagnosed (Table 2). Needle electromyography of the left anterior tibial muscle showed no abnormal spontaneous activity but there was prolonged mean motor unit action potential duration, as well as a reduced interference pattern attributed to a neurogenic lesion. Lumbar MRI revealed a disc prolapse at L5/S1, which was mistakenly considered to be responsible for his complaints. Upon physical therapy, only incomplete recovery could be achieved. No other therapy was applied.

At age 44 years, the patient developed sudden-onset bilateral paresthesias and dysesthesias starting at both foot soles after previous infection, which ascended in a stocking-type distribution up to the thighs within a few days. Additionally, muscle weakness (Medical Research Council [MRC] grade 4) of the left lower leg deteriorated and mild distal weakness (MRC 5-) of the right lower leg developed. Patella and Achilles tendon reflexes were reduced. Blood tests showed CK elevation (Table 1). Ganglioside-GM1 and anti-myelin-associated glycoprotein (MAG) antibodies were normal. Immunofixation did not show paraprotein. Nerve conduction studies were unchanged from the previous investigation (Table 2). Cerebrospinal fluid (CSF) investigations revealed 15 leukocytes/mm^3 (normal, <13 leukocytes/mm^3) and a protein of 109.8 mg/dl (normal, 18–43 mg/dl). Based upon these findings, CIDP was diagnosed and immunoglobulins (2 g/kg body weight) were given for 5 days. Sensory disturbances resolved completely within a few days. Weakness resolved within a few days to the level recorded before age 44 years. Since then, he experienced recurrent relapses of lower-limb muscle weakness, which partially resolved under immunoglobulins (1g/kg body weight every 4 weeks) each time. Since age 45 years, the dosage had to be increased to 2 g/kg body weight every 3 weeks and the diagnosis was revised to CIDP variant.

At age 46 years, paresthesias recurred and ascended to the right knee. There was stiffness and myalgias of both calves, and distal weakness of the lower limbs (MRC 4 to 5-). CSF investigations revealed 54 leukocytes/mm^3 (normal, <13 leukocytes/mm^3), a protein of 137 mg/dl (normal, 18–43 mg/dl), and blood-brain barrier disturbance. Nerve conduction studies were unchanged from the 2 previous investigations (Table 2). Paraproteinemia, vasculitis, autoimmune disease, malignancy, sarcoidosis, diabetes, amyloidosis, thyrotoxicosis, borreliosis, myositis with polyneuropathy, and metabolic myopathy with neuropathy were excluded. Vasculitis was largely excluded based on the clinical presentation (no pain, long-term relatively stable course) and normal blood chemical investigations: anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and circulating immune complexes). Because the effect of immunoglobulins declined over time, rituximab was tried, without effect. Immunoglobulins were re-established, with a favorable response. Since age 47 years, the patient has been administering the immunoglobulins himself by subcutaneous infusions.

Discussion

CIDP is a rare, acquired, chronic, demyelinating, and frequently disabling sensorimotor neuropathy. CIDP is caused by an immune system attack against peripheral nerve myelin, which usually responds to immune-modulatory therapy [4,5]. In addition to classical CIDP, various subtypes have been defined: multifocal acquired, demyelinating sensory, and motor neuropathy (MADSAM), also known as Lewis-Sumner syndrome (asymmetric variant of CIDP); chronic inflammatory sensory polyneuropathy (CISP); gait disorder, antibody, late-age onset

Table 1. Results of blood chemical investigations over four years.

Parameter/age	RL	41y 10m	43y 8m	44y 3m	44y 3m	45y 3m	45y 10m	46y 2m	46y 4m	47y 2m
CK	38–174 U/l	363	nd	546	650	301	675	506	566	524

RL – reference limits; y – years; U – units; Nd – not done.

Table 2. Nerve conduction studies.

Nerve	DL	dCMAP/dSNAP	pCMAP/pSNAP	CB	NCV
Age 43y					
Right median, motor	4.8	1.9	0.3	Partial	45.3
Right median, sensory	na	5.7	na	No	53.4
Left median, motor	3.8	6.0	4.7	No	53.3
Left median, sensory	na	19	na	No	55.4
Right ulnar, motor	3.2	5.4	3.0	Partial	57.6
Right ulnar, sensory	na	21	na	No	54.3
Left ulnar, motor	3.0	5.9	5.5	No	54.8
Left ulnar, sensory	na	16	na	No	58.7
Right peroneal, motor	4.3	3.2	1.6	No	38.9
Left peroneal, motor	5.3	1.8	0.8	Complete	36.1
Right tibial, motor	7.8	2.8	1.6	No	47.9
Left tibial, motor	4.9	1.7	0.8	No	33.0
Age 44y					
Right median, motor	⊥	↓	↓	Partial	↓
Right median, sensory	na	⊥	⊥	No	⊥
Left median, motor	⊥	⊥	⊥	No	⊥
Left median, sensory	na	⊥	⊥	No	⊥
Right ulnar, motor	⊥	⊥	↓	Partial	⊥/↓ (sulcus)
Right ulnar, sensory	na	⊥	⊥	No	⊥
Left ulnar, motor	⊥	⊥	↓	Partial	⊥/↓ (sulcus)
Left ulnar, sensory	na	⊥	⊥	No	⊥
Right radial, sensory	na	⊥	na	No	⊥
Right peroneal, motor	⊥	↓	↓	No	↓ (mild)
Left peroneal, motor	⊥	↓	↓	Complete	↓ (distal)
Right tibial, motor	⊥	↓	↓	No	↓
Left tibial, motor	⊥	↓	↓	No	↓
Right sural	na	↓	na	No	⊥
Left sural	na	⊥	na	No	⊥
Age 46y					
Right median, motor	⊥	⊥	↓	Partial	↓
Left median, motor	⊥	⊥	⊥	No	⊥
Left median, sensory	na	⊥	⊥	No	⊥
Right ulnar, motor	⊥	⊥	↓	Partial	⊥/↓ (sulcus)

Table 2 continued. Nerve conduction studies.

Nerve	DL	dCMAP/dSNAP	pCMAP/pSNAP	CB	NCV
Left ulnar, motor	⊥	⊥	⊥	No	⊥
Left ulnar, sensory	na	⊥	⊥	No	⊥
Right peroneal, motor	⊥	↓	↓	No	⊥
Left peroneal, motor	⊥	↓	↓	Partial	↓ (distal)
Right tibial, motor	⊥	↓	↓	No	↓

DL – distal latency; dCMAP – distal compound muscle action potential; dSNAP – distal sensory nerve action potential; pCMAP – proximal compound muscle action potential; pSNAP – proximal sensory nerve action potential; CB – conduction block; NCV – nerve conduction velocity; na – not available, F-wave studies were normal on the left median nerve but revealed absent F-responses on the right tibial nerve; ⊥ – normal, ↓ – reduced.

polyneuropathy (GALOP); distal acquired demyelinating symmetric (DADS) neuropathy; and multifocal motor neuropathy (MMN) [6,7]. At least 15 different diagnostic criteria sets for CIDP are available [1]. Among these, the EFNS/PNS criteria have the highest sensitivity (73%) and specificity (90%) [2,5]. According to these criteria, classical CIDP is present if there is chronic, progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months. Cranial nerves may be occasionally affected. Tendon reflexes need to be absent or reduced in all 4 extremities [2]. Supportive criteria include: elevated CSF protein and a leukocyte count <10/mm^3; gadolinium enhancement or hypertrophy of cervical or lumbar nerve roots on MRI; demyelination on nerve conduction studies; improvement upon immune-modulatory treatment; and nerve biopsy confirming demyelination or re-myelination [8]. Respiratory insufficiency or autonomic involvement is rare. Applying any of the diagnostic criteria sets, prevalence and incidence of CIDP are highly variable [8–10] due to application of different diagnostic criteria and inclusion of different variants [5]. First-line treatment of CIDP relies on immunoglobulins [11] but steroids and plasma exchange can be also given with level 1 evidence. If ineffective, rituximab is an alternative [12]. Treatment of MADSAM, CISP, and DADS is not at variance from classical CIDP [5]. DADS responds particularly poorly to standard therapy [13]. MMN mainly responds to immunoglobulins. In some CIDP and MMN patients, the effect of immunoglobulins decline over time, necessitating an increase in the immunoglobulin dosage [14–16]. Rituximab has been particularly applied to MMN patients and was ineffective in some of them [17].

The presented patient was diagnosed as having CIDP variant since he did not fulfill the EFNS criteria for classical CIDP [2,5]. Initially, he presented with asymmetric weakness and predominantly distal weakness on the lower limbs, and tendon reflexes were only distally reduced. Sensory disturbances predominantly involved the lower legs. Furthermore, CSF investigations revealed mild pleocytosis 2 times (15 leukocytes/mm^3 and 54 leukocytes/mm^3). Nerve conduction studies revealed an axonal and demyelinating polyneuropathy with partial conduction blocks in the upper limbs and complete conduction block in the left lower limb. Arguments against classical CIDP are the asymmetry of weakness, the axonal lesion of the peroneal and tibial nerves (Table 2), and the delayed occurrence of sensory disturbances, manifesting not earlier than 1 year after onset of muscle weakness. Recurrent CK elevation present before diagnosing CIDP does not exclude CIDP. The initial, unilateral, distal weakness of the left lower leg may also be compatible with the diagnosis of a length-dependent asymmetric polyneuropathy with distal and lower limb predominance. The beneficial effect of immunoglobulins, however, is a strong argument in favor of an immune-neuropathy. The temporarily vanishing effect of immunoglobulins over time is not unusual and fits with the course of a CIDP variant [16]. There was no relationship between CK level and severity of symptoms. There was also no relationship between CK elevation and the effect of immunoglobulins. CK elevation was independent of the immunoglobulin dosage. MADSAM was excluded because nerve conduction studies also revealed an axonal lesion and sensory dysfunction developed 1 year after onset. CISP was excluded because motor nerves were affected. DADS was excluded upon the asymmetric distribution. GALOP was excluded upon the early onset. MMN was excluded because of the sensory disturbances. Myopathy was excluded by the neurogenic electromyography, but the patient did not consent to muscle biopsy.

Since CK elevation is not a typical feature of CIDP, it is rarely reported in CIDP patients and does not seem to be relevant for the diagnostic work-up or follow-up. Few patients with CIDP have been reported in whom CK-values were measured and recorded [3, 18]. In a 10-year-old girl with CIDP, CK was normal [19]. In a recent study of 79 patients with definite CIDP according to the EFNS criteria, 27% had CK elevation [3].

CK elevation has been also occasionally reported in patients with GBS and concomitant disease, such as myocardial infarction [18], rhabdomyolysis [20,21], *Campylobacter jejuni* enteritis [22], or myositis due to infection with mycoplasma pneumoniae [23]. CK elevation in these patients was explained by rapid and extensive denervation due to severe axonal degeneration of motor terminals. Denervation caused hyperexcitability of muscle cells and resulting in muscle cramps and CK-release [22]. CK elevation may also occur if CIDP patients experience unusual physical stress. In a case series of 4 patients with axonal GBS, marked CK elevation was reported in 2 [24]. In all these cases, CK elevation was transient.

Conclusions

The presented case shows that CIDP variants may go along with CK elevation, a mixture of an axonal and demyelinating lesion, mild pleocytosis, and asymmetry of the lesions. CK elevation may be mild but permanent and independent of the clinical manifestations and the immunoglobulin dosage. The vanishing effect of immunoglobulins over time may be another characteristic of CIDP variants. Rituximab does not seem to be effective in treating these conditions.

Conflicts of interest

None.

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