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

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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-existence 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

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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/mm³ (normal, <13 leukocytes/mm³) 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 (1 g/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/mm³ (normal, <13 leukocytes/mm³), 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 polynuropathy, 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

| Parameter/age | RL | 41y 10m | 43y 8m | 44y 3m | 44y 3m | 45y 3m | 45y 10m | 46y 2m | 46y 4m | 47y 2m |
|---------------|----|---------|--------|--------|--------|--------|--------|--------|--------|--------|
| CK            | RL | 38–174  | 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) |
polynervopathy (GALOP); distal acquired demyelinating sym-
metric (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 prox-
imal and distal weakness and sensory dysfunction of all ex-
 tremities, developing over at least 2 months. Cranial nerves
may be occasionally affected. Tendon reflexes need to be ab-
sent or reduced in all 4 extremities [2]. Supportive criteria in-
clude: elevated CSF protein and a leukocyte count <10/mm³;
gadolinium enhancement or hypertrophy of cervical or lum-
bar nerve roots on MRI; demyelination on nerve conduction
studies; improvement upon immune-modulatory treatment;
and nerve biopsy confirming demyelination or re-myelina-
tion [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 ap-
lication of different diagnostic criteria and inclusion of dif-
ferent variants [5]. First-line treatment of CIDP relies on immu-
oglobulins [11] but steroids and plasma exchange can be also
given with level 1 evidence. If ineffective, rituximab is an al-
ternative [12]. Treatment of MADSAM, CISP, and DADS is not
at variance from classical CIDP [5]. DADS responds particular-
ly poorly to standard therapy [13]. MMN mainly responds to
immunoglobulins. In some CIDP and MMN patients, the ef-
ect of immunoglobulins decline over time, necessitating an
increase in the immunoglobulin dosage [14–16]. Rituximab
has been particularly applied to MMN patients and was inef-
fective 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 predomi-
nantly distal weakness on the lower limbs, and tendon reflexes
were only distally reduced. Sensory disturbances predominantly
involved the lower legs. Furthermore, CSF investigations re-
vealed mild pleocytosis 2 times (15 leukocytes/mm³ and 54
leukocytes/mm³). Nerve conduction studies revealed an axo-
nal and demyelinating polynervopathy with partial conduc-
tion 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 perone-
al and tibial nerves (Table 2), and the delayed occurrence of
sensory disturbances, manifesting not earlier than 1 year af-
after onset of muscle weakness. Recurrent CK elevation present
before diagnosing CIDP does not exclude CIDP. The initial, uni-
lateral, distal weakness of the left lower leg may also be com-
patible with the diagnosis of a length-dependent asymmet-
ric polynervopathy 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 im-
munoglobulin dosage. MADSAM was excluded because nerve
conduction studies also revealed an axonal lesion and senso-
dy dysfunction developed 1 year after onset. CISP was exclud-
ated 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 dis-
turbances. Myopathy was excluded by the neurogenic electro-
myography, but the patient did not consent to muscle biopsy.

Since CK elevation is not a typical feature of CIDP, it is rare-
ly reported in CIDP patients and does not seem to be rele-
vant for the diagnostic work-up or follow-up. Few patients
with CIDP have been reported in whom CK-values were mea-
sured 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].

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.
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 hyper excitability 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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