AN UNUSUAL NEUROPATHY IN A DIABETIC PATIENT: EVIDENCE FOR INTRAVENOUS IMMUNOGLOBIN-INDUCED EFFECTIVE THERAPY

P. ROMEDENNE (1), R. MUKENDI (2), P. STASSE (1), P. INDEKEU (2), M. BUYSSCHAERT (3), I.M. COLIN (1)

SUMMARY - We report the case of a 68-year old type-2 diabetic male patient who was admitted to hospital for progressive weakness in the right lower limb. Although his metabolic control was good, he lost more than 20 kg of weight. Despite intensive physio- and vitamino-therapy, his neurological condition kept on degrading with a severe amyotrophy and pain of the right thigh. He was unable to walk and to stand alone. Besides a yet known sensitive polyneuropathy, the electrophysiological study revealed an obvious motor involvement with signs of demyelination and axonal degeneration. Combined with the albuminocytologic dissociation observed in the cerebrospinal fluid, these specific clinical and electrophysiological features led us to postulate a diagnosis of inflammatory neuropathy. The patient underwent a treatment by methylprednisolone and immunoglobins that rapidly induced a striking improvement of his neurological condition.

This case report illustrates that rare forms of neuropathy such as inflammatory neuropathies close to chronic inflammatory demyelinating polyneuropathy (CIDP) can occur in diabetic patients and superimpose on the more commonly described forms of neuropathies. It recalls the importance of recognizing CIDP-like neuropathies because unlike other forms of neuropathy, inflammatory neuropathies are perfectly curable.

Key-words: diabetic neuropathy, Chronic Inflammatory Demyelinating, polyradiculoneuropathy (CIDP), immunoglobulins, corticosteroids.
Neuropathy is a common complication of diabetes that already affects 7% to 8% of patients at the time of diagnosis, but up to 50% of them after 25 years of evolution [1]. It can be roughly split into three major categories including symmetrical polyneuropathy, mononeuropathy and autonomic neuropathy [2]. Peripheral polyneuropathy is usually considered as the most common form of diabetic neuropathy. It is predominantly sensory with minor motor involvement and its distribution is usually symmetrical. Neuropathic symptoms (stabbing or burning pain, hyperpathia and hyperaesthesia) can be excruciating and distressing. The Diabetes Control and Complications (DCCT) trial clearly pointed out the benefit of improved blood glucose control on diabetic neuropathy [3]. Nevertheless, beside attempts to achieve tight regulation of blood glucose, there is no specific effective treatment for diabetic neuropathy. This can be highly frustrating for patients and physicians, because once set up, the distal polyneuropathy is irreversible.

In some cases though, diabetic patients can develop progressive disabling neuropathy characterized by a prominent motor involvement. Hence, as lately suggested by recent publications, when the course of neuropathy is asymmetrical, subacute rather than chronic and leads to muscular weakness, an inflammatory aetiology, for instance close to chronic inflammatory demyelinating polyneuropathy (CIDP), might be considered [4-9]. It is of cardinal importance to clearly identify this entity because unlike the common sensitive diabetic neuropathy, inflammatory neuropathies are often curable [4, 10-12].

**CASE REPORT**

A 68-year old male patient was hospitalized for progressive weakness in the right lower limb for 3 weeks, with reduced flexion from the leg to the thigh. The patient was not complaining of pain or paresthesia, there was no sign of any kind of trauma, but he could walk only on crutches. He lost more than 20 kg of weight during the last six months. This patient was diagnosed for type-2 diabetes six months earlier (HbA1c: 13%; nl.: 3.9-6.7%). He was at this time hospitalized for a surgical treatment of a right knee anthrax from which he completely recovered. The diabetes was complicated with macroangiopathy (myocardial infarction) and asymptomatic sensitive polyneuropathy. Blood glucose had been quickly controlled by intensive insulin therapy followed by two daily injections of mixed insulin (30/70) along with biguanides. Until his admission, this patient was re-

out help. His gait was unsteady and showed foot drop. Deep tendon reflexes were symmetrical in the upper limbs, weak in the lower left limb and absent in the right leg. There was no Babinski sign. Cranial nerves and finger to nose testing were normal. The nucha was supple.

Laboratory data showed HbA1c: 7.1%, C-reactive protein (CRP): 7.7 mg/dl (< 0.8 mg/dl) that normalized 5 days later, and microalbuminuria: 224.6 mg/g creatinine (< 20 mg/g). Other biological parameters were either normal or non relevant to the case.

Doppler ultrasound study of the neck vessels described severe carotid atheromatosis and cerebral CT-scan showed cortico-subcortical atrophy and leucoma-

lia but no picture suggestive of stroke. The electromyographic study confirmed a yet known sensitive neuropathy but also a significant reduction in motor nerve conduction velocity in peroneal and tibial nerves (< 40 m/s). At this stage of investigation, we concluded for a diabetic mononeuropathy. We challenged the patient to get a tighter control of blood glucose and we prescribed intensive physio- and vitamin therapy. The patient then left the hospital for a month.

He came back thereafter for control in the outpatient clinic. His general condition deeply worsened. He was confused. He kept loosing weight and couldn’t walk anymore. The previously observed crural amyotrophy aggravated with a painful tumescence on the right thigh.

Positive tendon reflexes were present on the left lower limb but absent on the right side. Ankle jerks were absent on both sides. There was a bilateral flexion plantar response. Laboratory tests showed an increased sedimentation rate value: 75 mm/h (< 8 mm/h), as well as CRP: 1.8 mg/dl (< 0.8) and creatine phosphokinase: 327 UI/l (55-170 UI/l). HbA1c was nearly in the normal range at 7%. Serological tests for cytomegalovirus, HIV, B and C hepatitis and rickettsia were negative, whereas we detected by ELISA antibodies of IgA class to Epstein Barr virus (EBV) consistent with a likely reactivation of the viral infection. A total abdominal CT-scan along with a echo-biopsy of the prostate ruled out a neoplasia. The ultrasound analysis of the swollen right thigh showed that the tumescence actually corresponded to a haematoma due to a torn muscle.

The patient underwent a new electromyographic study, as well as a lumbar puncture. The severe motor involvement was confirmed by the markedly slowed motor conduction velocity consistent with a demyeli-

nating process. There was also electrophysiological evidence for axonal degeneration as illustrated by the increased number of fibrillations with reduced recruitment and positive sharp waves. Cerebrospinal fluid showed an increased protein level: 1.06 g/l (0.19-0.4 g/l), without white blood cell count. Altogether, these data led us to postulate a diagnosis of inflamma-
Inflammatory neuropathy that required a treatment by corticosteroid and IV immunoglobins. The treatment started with intravenous (IV) methylprednisolone (3 doses of 1 gr. over 3 days) which already made the patient getting better. He thereafter received once an IV treatment of immunoglobins (0.4 g/Kg) over a 5 day period. Improvement was immediate. Less than two weeks after the onset of treatment, the patient was clearly autonomous and able to walk alone with crutches. He benefited from an intensive physiotherapy. He completely recovered and has been reported to be in good condition more than a year later.

**DISCUSSION**

As recently suggested by several authors, this diagnosis of inflammatory neuropathy might be evoked in a diabetic patient when motor symptoms are predominant and more severe than expected. It is essential to identify this entity which can superimpose on the common diabetic polyneuropathy, because unlike other causes of neuropathy, inflammatory neuropathy is quite often curable (Table I). Krendel et al. described two categories of progressive inflammatory neuropathy that respond to anti-inflammatory and/or anti-immune treatments [4]. As for our patient, the first one mostly occurs in type-2 diabetic patients along with pain, atrophy of one thigh and weight loss. In contrast to the non inflammatory vascular disease that accounts for acute mononeuropathy, it corresponds to a multifocal axonal neuropathy caused by inflammatory microvasculopathy with collections of lymphocytes around small vessels. The second category is related to chronic inflammatory demyelinating polyneuropathy (CIDP), an acquired autoimmune disorder of the peripheral nervous system characterized by a more symmetric and distal distribution of the lesions. It mostly occurs in type-1 diabetic patients without weight loss. Segmental demyelination and remyelination, onion bulb formations, and infiltration by mononuclear cells of the endoneurium are hallmarks of this CIDP-like neuropathy [4, 5, 7, 9].

Both forms of inflammatory neuropathies exhibit electrophysiological criteria for demyelination processes such as slow conduction velocity, prolonged distal latencies, conduction block, as well as for denervation activity (fibrillations and positive sharp waves) [7]. The CSF analysis reveals a typical profile with increased protein content without rise of cell counts [4, 5, 7]. Although nerve biopsy can be helpful to rule out other etiologies such as amyloidosis, vasculitis and toxic neuropathies, it is not fully required in cases of typical inflammatory neuropathy. Indeed, axonal loss, presence of onions bulbs, regenerative

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**Table I. Differential diagnosis of neuropathies in diabetic patients (see text for details).**

<table>
<thead>
<tr>
<th></th>
<th>Distal Polyneuropathy</th>
<th>Focal/Multifocal Neuropathies</th>
<th>Inflammatory Neuropathies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of Presentation</strong></td>
<td>Insidious/Chronic</td>
<td>Acute</td>
<td>Progressive onset/Subacute</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Symmetric/Distal</td>
<td>Cranial/Thoraco-abdominal/</td>
<td>Mostly asymmetrical and proximal</td>
</tr>
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<td></td>
<td></td>
<td>Limb nerves</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic Control</strong></td>
<td>Poor</td>
<td>Poor</td>
<td>can be good</td>
</tr>
<tr>
<td><strong>Accompanying Symptoms</strong></td>
<td>Autonomic neuropathy</td>
<td>Diabetic amyotrophy</td>
<td>Category 1: Weight loss (+)* IDDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Category 2: Weight loss (–) IDDM</td>
</tr>
<tr>
<td><strong>Electrophysiological Features</strong></td>
<td>Sensory involvement</td>
<td>Motor involvement</td>
<td>Motor involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impaired conduction velocity</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Signs of denervation</td>
</tr>
<tr>
<td><strong>Etiopathology</strong></td>
<td>Ischemic/Metabolic</td>
<td>Ischemic disease of vasa</td>
<td>Immunomediated inflammatory</td>
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<td></td>
<td>Distal axonopathy of</td>
<td>nervorum</td>
<td>disorder</td>
</tr>
<tr>
<td></td>
<td>dying-back type</td>
<td>Vascular occlusion</td>
<td>Category 1: Inflammatory vasculopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Category 2: Demyelinating neuropathy</td>
</tr>
<tr>
<td><strong>Treatment/Efficacy</strong></td>
<td>Vitamin and physiotherapy(–)</td>
<td>Tighter metabolic control and physiotherapy(+)</td>
<td>Immunotherapy(++++)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Definitive</td>
<td>Spontaneously reversible</td>
<td>Reversible if adequate treatment</td>
</tr>
</tbody>
</table>

* Krendel et al. 1996

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clusters and wallerian degeneration can also be observed in other forms of diabetic neuropathies [5, 7]. In contrast, clinical improvement after anti-inflammatory treatment or immunotherapy is considered as an important criterion to confirm the diagnosis of inflammatory neuropathy versus other forms of neuropathy. Uncini et al. even suggested that in doubtful cases, a therapeutic trial with one of the established treatments for CIDP (plasma exchange, IV immunoglobulins, steroids) should be used to help defining the diagnosis [7].

Idiopathic CIDP most often occurs alone but may accompany plasma cell dyscrasias, virus infection, connective tissue diseases, neoplasia and others diseases, such as diabetes [12, 13]. Of interest is the recent study by Gorson et al. who showed that diabetic patients with CIDP have clinical features similar to those with idiopathic CIDP [9]. However, their nerve conduction studies and nerve biopsies show more severe axonal loss and the degree of improvement following treatment is less favorable. In our case though, the clinical improvement after steroid and immunotherapy was immediate. Noteworthy was the observation of a reactivation of EBV infection. Although the link between EBV infection and CIDP has not yet been clearly established, EBV is a known precipitant for the acute form of demyelinating polyneuropathy (AIDP or Guillain-Barré syndrome) [14]. Although clear evidences are lacking, it is tempting in the present case to establish a link between the reactivation of the EBV infection and the onset of the inflammatory neuropathy.

In conclusion, through the presentation of the present case report, we aimed to draw the attention of the community of diabetologists on the importance of identifying inflammatory neuropathies. This diagnosis might be evoked in diabetic patients when the motor involvement is prominent and rapidly evolutive. Therapeutic trials with corticosteroid and/or immunoglobins can be useful to ascertain the diagnosis.

REFERENCES


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