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Axonal Common Peroneal Nerve Palsy and Delayed Proximal Motor Radial Conduction Block Following Infliximab Treatment

To the Editor:

A 38-year-old female, treated with infliximab (3 mg/kg) for a two-year history of psoriatic arthritis, was referred with a sudden onset of left foot drop. At referral, eight courses of infliximab (anti-tumor necrosis factor [anti-TNF] monoclonal antibody) had already been infused. Her past medical history was otherwise unremarkable. No familial history of hereditary neuropathies, that is, hereditary neuropathy with liability to pressure palsy, was reported.

Examination revealed paresis of the left tibialis anterior, peroneus longus and extensor hallucis longus (Medical Research Council [MRC] Scale for Muscle Strength:4/5). Sensory function, tendon reflexes, and also a lumbar spine magnetic resonance imaging (MRI) scan were normal. The findings of the nerve conduction study (stimulation sites at the ankle, at distal, and proximal to fibular head) were consistent with left axonal common peroneal nerve palsy, characterized by small peroneal compound motor action potentials (CMAPs) from the extensor digitorum brevis and tibialis anterior. Peroneal CMAPs and the superficial peroneal response were <50% compared to the contralateral side. There was no evidence of conduction block around the fibular head. Sural and saphenous nerve sensory conduction study was normal. Needle electromyography (EMG) showed mildly reduced recruitment of motor units in the affected peroneal nerve-innervated muscles and in the short head of the biceps femoris. Overall, and considering that, according to the patient’s statement, there was no evidence of peroneal nerve mechanical irritation from prolonged leg crossing or squatting, the

neurophysiological findings were considered to be nonlocalizing.¹

Blood counts, general biochemistry, protein electrophoresis, tumor markers, rheumatoid factor, serum cryoglobulin levels, and antinuclear antibodies (ANA) were either normal or negative. Erythrocyte sedimentation rate was 28 mm/hour. Use of the Naranjo adverse drug reaction probability score² revealed a probable relationship between infliximab and neurotoxicity. Therefore, infliximab was replaced by methotrexate, resulting in a progressive resolution of symptoms.

Three months after infliximab dechallenge, she was again referred with right hand drop. Examination revealed paresis of the right extensor carpi radialis, extensor digitorum communis (MRC:2+/5), and triceps (MRC:3+/5). Nerve conduction study revealed a partial motor conduction block of the right radial nerve at the Erb's point. The radial sensory study was normal. EMG in right radial nerve-innervating muscles showed decreased recruitment and early motor unit potential remodeling. Residual left axonal common peroneal nerve palsy also was evident. Laboratory analyses were similar as before, apart from an increased titer of ANA (1:320). Cerebrospinal fluid assay, and a brain and cervical spine MRI were unremarkable.

Three months afterward, and while the patient had been left untreated with observation alone, a spontaneous improvement was observed. The left peroneal nerve function was normal and the radial nerve conduction block significantly decreased. EMG in radial nerve-innervated muscles showed a mildly decreased recruitment.

She was then treated with intravenous immunoglobulin G (IVIG) (24 mg/day) for three days. A month afterward, there was a marked increase in the muscle strength of the right hand. The nerve conduction study was normal.

The literature contains several cases of complex regional pain syndrome³ and immune-mediated neuropathies secondary to anti-TNF- α therapy, including multifocal motor neuropathy,⁴⁻⁶ sensorimotor axonopathies,⁴⁻⁶ chronic inflammatory demyelinating polyneuropathies,⁷ mononeuritis multiplex,⁸ and Lewis-Sumner syndrome.⁹ In our case, the clinical, laboratory and electrophysiological findings rule out these diagnoses.

The onset of manifestation of neurotoxicity after infliximab administration (16 months)

corresponds to that previously reported.¹⁰ However, our case differs in that the radial nerve conduction block occurred three months after infliximab cessation and while the peroneal nerve function started to resolve. Bearing in mind the elevated ANA titers at that time, the delayed genesis of conduction block could be explained by the delay in anti-TNF-related induction of autoantibodies. Induction of autoantibodies, usually appears six weeks following infliximab administration and peaks as early as three to six months afterward.¹¹ To our knowledge, our case is the first to describe delayed manifestation of conduction block after infliximab discontinuation.

Our patient experienced a gradual improvement with observation alone, and a marked recovery after the IVIG administration. However, this improvement over a short time is consistent with a mechanism of ischemia reversed from infliximab withdrawal rather than with IVIG.⁸

Sequential EMG studies failed to document evolution of axonal changes, thereby supporting the demyelinating background of the radial nerve conduction block. This is further supported by the relatively rapid improvement, an unlikely event in axonopathies. Overall, this lesion is attributed to infliximab-triggered autoimmune or ischemic mechanism. Considering the rapid recovery of peroneal nerve function after dechallenge, the pathogenesis of this lesion is difficult to explain. Nevertheless, electrophysiological features were consistent with an axonal lesion of the peroneal branch of the sciatic nerve, possibly because of infliximab-induced inhibition of signaling support of axons.¹⁰ It seems that this lesion represents a separate entity than the subsequent manifestation of radial nerve conduction block.

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Attitudes of Patients with Advanced Cancer Toward Research

To the Editor:

There is a great need for an improved evidence base to guide clinical practice and service provision in palliative care, yet research in palliative care has been notoriously difficult, with poor trial accrual and high attrition rates.^{1–3} It is therefore of vital importance to design “patient-friendly” studies that will encourage participation and improve accrual and retention. To design such trials, the views of potential participants need to be known. The systematic review by Todd et al.,⁴ recently

published in this journal, includes studies published up to 2007 and highlights some of the views of advanced cancer patients toward research participation, including altruism, the desire for personal benefit, and the potential for hope. It also points to some of the potential deterrents, for example, concern about placebo arms and the possibility of increased hospital admissions.

In 2008, we published the results of a questionnaire that was designed to determine the views of 101 patients with advanced cancer toward research in palliative care, and particularly toward randomized controlled trials (RCT). We believe the findings of our study⁵ add significantly to this systematic review. It supports the finding reported by Todd et al. that patients are altruistic; 82% of our participants stated that they would participate in studies that might help others and not themselves. We also identified several other major factors that influenced the willingness of patients to participate that were not discussed in this systematic review.

First, our study demonstrated that patients were interested in palliative care trials, in that 88% of participants were interested in studies of symptom control that would have no impact on their cancer. However, patients were greatly influenced by the perceived invasiveness of a trial, with approximately 80% willing to participate in trials of pain education, aromatherapy, or a new mattress, compared with less than a quarter willing to participate in trials that would involve an epidural or placement of a spinal stimulator under a general anesthetic. Potential side effects were also a deterrent, with less than one-third willing to participate in trials of drugs that might have side effects.

Inconvenience associated with trial participation was a deterrent to some but not all in this study. When asked for a weekly commitment, about one-half of all participants were prepared to make extra visits to the hospital, and more than one-third an extra night in hospital. Two-thirds were prepared to answer questions (either by telephone or face-to-face) and more than half were prepared to complete a short questionnaire, with approximately 40% prepared for a detailed questionnaire just as frequently. Many were prepared to have extra blood tests and 33%, extra radiographs or scans at least weekly. Approximately two-thirds