Motor neuropathy with multiple conduction blocks associated with TNF-alpha antagonist

Paulo Eduardo Mestrinelli Carrilho, Allan César Faria Araújo, Orival Alves, Paulo Gustavo Kotze

Infliximab, etanercept and adalimumab are tumour necrosis alpha factor (TNF-alpha) antagonists which recently became part of several auto-immune diseases therapeutic arsenal, mainly in rheumatoid arthritis, ankylosing spondilitis, psoriatic arthritis, as well as inflammatory bowel diseases. TNF-alpha plays a crucial role in many aspects of immune system development, immune-response regulation and T-cell-mediated tissue injury. It is a cytokine with both pro-inflammatory and immunoregulatory properties and is involved in normal inflammation and immune responses. TNF-alpha is an important growth factor for prothymocytes and thymocytes, and thereby influences the generation of the T-cell repertoire. In the peripheral immune system, TNF-alpha participates in antigen-presenting cell-function and in regulating apoptosis of potentially auto-reactive T-cells. So that, immunological complications with drugs that antagonize TNF-alpha receptors were expected to occur. Demyelinating peripheral motor neuropathy is one of them, but it is relatively uncommon.

We report a patient who had a severe form of Crohn’s disease, who developed a peripheral neuropathy with multiple motor conduction blocks at atypical sites, with axonal damage signs, probably associated with infliximab treatment.

CASE

The present report was written after patient information and with her agreement with the data publication. She is a 64-year-old woman with a severe histologically defined Crohn’s disease started to be treated with infliximab (5 mg/Kg) with improvement of all symptoms after the first infusion. Almost immediately after the overall fifth dose of infliximab, she developed right radial, right ulnar and left posterior tibial nerve palsies. Electroneuromyography (Figs 1 and 2) disclosed a predominant motor neuropathy in the nerves described above with multiple motor conduction blocks pattern, also associated with fibrillations and reduction of motor unit recruitment in the muscles innervated by those nerves. Non-significant amplitude decrease of sensory potentials was noticed. The rest of laboratory investigation was unremarkable, and included FAN, ANA, P-anca, C-anca, anti-DNA, anti-GM1, thyreoid hormones, blood glucosis, renal and hepatic functions, HIV1 and 2, HBV and HCV serology, vitamine B12. Infliximab infusions were interrupted and the patient obtained a gradual, but incomplete, recovery. After 6 months of follow-up, the patient still had a slight radial and ulnar nerves paresis, but an almost complete clinical improvement was observed in the left posterior tibial nerve.

DISCUSSION

The advent of TNF-alpha antagonists brought new horizons on treatment of several auto-immune disorders, mainly in rheumatoid arthritis and inflammatory bowel diseases. Two distinct receptors
for TNF-alpha (p55 and p75) exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF-alpha is dependent upon binding to either cell surface receptor. Nowadays, two different groups of anti-TNF-alpha are available: the eternectept group and monoclonal antibodies group. The former is a soluble, dimeric fusion protein of the human p75 TNF receptor linked to the Fc portion of human IgG1. The second group is composed by infliximab and adalimumab. Adverse events are commonly slight, generally injection site inflammatory reaction, flu-like symptoms and headache. Collateral effects secondary to inadequate immune system modulation are quite rare, but drug-induced lupus and demyelinating syndromes are described. Such reactions are expected to occur in about 233 subjects per million of treated patients. Central nervous system autoimmune demyelinating disorders include anterior and posterior optic neuritis and worsening of multiple sclerosis. Peripheral nervous disorders include Guillain-Barré and Miller-Fischer syndromes, chronic inflammatory demyelinating polyradiculoneuropathy, mononeuritis simplex and multiplex, axonal sensory-motor polineuropathy and even motor neuropathy with multiple conduction blocks. Two explanations about these anti-TNF-alpha collateral effects are discussed in the literature: a direct toxic drug aggression or a specific autoantibody production and T cell immune system derangement induced by this group of agents. The real cause of such undesirable events is obscure, but the second hypothesis is well accepted. It is logical to argue that pathogenesis of such type of neuropathy should include a myelin aggression both by inadequate T-cell dependent immune system activation and a humoral antibody production. Also, an ischemic damage from vasculitis and inhibition of axon support signals are suspected to be involved. It is important to know that TNF-alpha probably has a pro-inflammatory function in the pathogenesis of Guillain-Barré syndrome (serum levels correlate with disease activity and severity). TNF-alpha deficiency leads to failed regression of myelin-specific T-cell reac-

Fig 1. Right ulnar nerve motor conduction block at axilla and right radial nerve motor conduction block at the arm.
activity and prolonged survival of activated T cells. When endogenous TNF-alpha is blocked by repeated injections of a TNF-alpha antagonist, T-cell-proliferative responses and cytokine production are enhanced. The prolonged administration of TNF-alpha antagonists is thought to enhance autoimmune responses by altering antigen-presenting cell function, potentiating T-cell receptor signaling, and decreasing apoptosis of auto-reactive T cells.

According to proposed criteria, an illness, like neuropathy, can be considered as drug-induced or environmentally associated based on: [1] temporal closed association; [2] lack of likely alternative explanations; [3] stabilization or improvement by interrupting exposure to the presumed inciting agent; [4] rechallenge; [5] biological plausibility; [6] analogy; [7] dose responsiveness; [8] specificity. To report findings of a possible causal relationship between exposure and clinical syndrome, at least 4 of the 8 attribution elements should be present. Based on these criteria, the motor neuropathy described in the present article is probably very well correlated with infliximab.

Paradoxically, it is interesting to report that preliminary observations of a single retrospective uncontrolled study suggested possible efficacy of etanercept (Enbrel) treatment in selected patients with CIDP, or its variants, who were refractory to or intolerant of conventional therapies. In another case report, mononeuritis multiplex (demyelinating and axonal) complicated active Crohn’s disease and was treated with a series of infliximab infusions. The manifestations of neuropathy improved clinically after the first infusion, and after 22 weeks, the electrophysiological studies returned to normal. The present case differs from that, once the symptoms of intestinal disease improved markedly with infliximab and the neuropathy developed only after repeated series of infusions. Eventually, Crohn’s disease may predispose such type of complication with anti-TNF-alpha agents, once this entity is also rarely associated with mononeuritis multiplex by itself.

REFERENCES