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Case Report

Chronic inflammatory demyelinating neuropathy after etanercept therapy in the course of juvenile idiopathic arthritis

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ABSTRACT

Background. Chronic inflammatory demyelinating neuropathy has been reported after the use of tumor necrosis factor inhibitors. The mechanisms of nerve injury caused by tumor necrosis factor inhibitors are not yet well understood.

Case. In this paper, we report a 12 year and nine month old girl who developed chronic inflammatory demyelinating neuropathy in the course of juvenile idiopathic arthritis after etanercept withdrawal. She became non-ambulant with four-limb involvement. She received intravenous immunoglobulins, steroids, and plasma exchange, but had a limited response. Finally, rituximab was given and a slow, but progressive clinical improvement was seen. She was ambulant four months after rituximab treatment. We considered chronic inflammatory demyelinating neuropathy as a probable adverse effect of etanercept.

Conclusions. Tumor necrosis factor inhibitors could elicit the demyelinating process, and chronic inflammatory demyelinating neuropathy might persist despite treatment discontinuation. First-line immunotherapy may be inefficient as in our case, and aggressive treatment may be necessary.

Key words: tumor necrosis factor inhibitors, etanercept, chronic inflammatory demyelinating neuropathy, adverse drug reaction.

Juvenile idiopathic arthritis (JIA) is an autoimmune disease affecting joints. Treatment is directed at suppressing inflammation that causes joint damage. First-line agents for the treatment of JIA are non-steroidal anti-inflammatory drugs and non-biologic disease-modifying anti-rheumatic drugs, such as methotrexate. In severe cases, biological agents are used as second-line drugs, with the most common being tumor necrosis factor (TNF) inhibitors, including infliximab, etanercept, and adalimumab.[1] However, demyelinating inflammatory disorders have been reported after the use of anti-TNF agents in post-marketing surveillance and case reports.[2] Demyelinating central nervous system disorders, including optic neuritis and multiple sclerosis, are the major reported events elicited by anti-TNF agents. Relatively less frequently, anti-TNF-associated neuropathies such as Guillain-Barré syndrome (GBS) and its variants, chronic inflammatory demyelinating neuropathy (CIDP) and its variants, multifocal motor neuropathy, and axonopathies have also been described.[3-6]

In this paper, we report a child, who developed CIDP in the course of JIA after etanercept

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withdrawal and discuss the causal relationship of TNF inhibitors with CIDP in view of the literature.

Case Report

A 12-year-and-nine-month old girl presented to our clinic with difficulty walking for the previous two weeks. She had a five-year history of arthritis and was followed up at our pediatric rheumatology department for the last year with a diagnosis of rheumatoid factor negative polyarticular JIA. The main affected joints at admission were the temporomandibular joints, wrists, elbows, knees ankles, and neck. She had joint contractures in the bilateral proximal interphalangeal joints. Her initial laboratory results showed a slightly elevated erythrocyte sedimentation rate (36 mm/hr). Antinuclear antibodies and rheumatoid factor were negative. The radiography of the affected joints showed chronic arthritic changes, periarticular osteoporosis, and narrowing of joint spaces. Initially, she was treated with a short course of prednisone (1 mg/kg/day methyl-prednisolone, followed by 0.2 mg/kg/day for two months) in addition to methotrexate (15 mg/week) and etanercept (0.8 mg/kg/week). She showed a good clinical response, and prednisone was stopped early in the course. She received etanercept for 10 months. However, one month after the withdrawal of etanercept, she presented with difficulty walking and gait instability. She had no history of a recent infection or vaccination. Her family history was also unremarkable. The physical examination revealed active synovitis in both knees and ankles. She had a wide-based waddling gait and weakness in the proximal and distal lower limbs [4/5 on the Medical Research Council (MRC) scale]. The patellar and achilles deep tendon reflexes were absent. Her upper extremity muscle strength was normal. According to the cerebrospinal fluid (CSF) analysis, her protein level was 205 mg/dl, glucose level was 66 mg/dl, white blood cell count was 0/ul, and red blood cell count was 0/ul. There was no oligoclonal band in the CSF analysis. The lumbosacral magnetic resonance imaging showed an increased thickness in the fibers of the cauda equina and diffuse contrast enhancement in the nerve roots. The electromyography (EMG) findings were compatible with acute-subacute sensorimotor demyelinating polyneuropathy. In the nerve conduction studies, there was no sensory nerve action potential in the upper and lower extremity. Other findings included absent F waves, prolonged distal latency of the median and ulnar motor nerves, temporal dispersion, slower motor conduction velocity, and absence of tibial and peroneal motor nerve action potentials. The patient received daily intravenous immunoglobulin (IVIG) (0.4 g/kg) for five days with the diagnosis of GBS. Clinical improvement was observed after the IVIG treatment. Three weeks later, her neurological symptoms worsened, she was unable to walk and the upper extremities were also involved. She was treated with plasma exchange. Although her weakness improved after the plasma exchange, she had relapses that gradually worsened during the follow-up, and she was eventually diagnosed with CIDP. EMG was repeated and showed chronic demyelinating sensorimotor polyneuropathy. In the third month, when she had a maximum disability, her MRC scale score was 3/5 for the upper extremity and 1/5 for the lower extremity. She had mild exotropia and diplopia, but no bulbar involvement. She was treated with monthly IVIG, steroid treatment (1 g methylprednisolone for 5 days, followed by 1 mg/kg methylprednisolone for 3 months, and monthly pulse steroid for 6 months) with minimal response, and plasma exchange with partial response. She also had findings of active arthritis of the wrists and small joints of her hands under methotrexate and hydroxychloroquine treatment. For both refractory CIDP and JIA, rituximab treatment was started at a dose of 375 mg/m^2 weekly for two weeks at the sixth month of symptom onset. She started to improve after three months and began to walk independently after four months of rituximab therapy. For 9 months she was completely immobile. Rituximab was repeated six months after the first dose, followed by monthly IVIG for one year. At the last follow-up, when she was 14

years old, she was walking independently and her muscle strength was normal, except for slight weakness in the bilateral knee extensor and foot dorsiflexor muscles (MRC scale score +4/5). Her biceps reflexes were hypoactive, and patellar and Achilles reflexes were absent. She had no arthralgia or arthritis. She was receiving methotrexate and hydroxychloroquine for JIA.

Informed consent was obtained from the family.

Discussion

Peripheral neuropathies may be seen in the course of autoimmune diseases due to vasculitis, nerve entrapment, nutritional imbalances, or drug toxicity.[4] Autoimmune diseases may coexist in a patient; however, JIA and rheumatoid arthritis are not typically associated with peripheral neuropathy. In the literature, all reported CIDP cases among patients with rheumatoid arthritis or JIA are associated with the use of TNF inhibitors. When we applied the Naranjo algorithm, also known as the Adverse Drug Reaction Probability Scale (definite, over 9; probable, 5-8; possible, 1-4; and doubtful, below 0) to investigate the relationship between CIDP and etanercept treatment in our patient, we determined the score as 7, indicating probable adverse drug reaction.[7]

TNF-α inhibitors are used in several advanced inflammatory diseases, including JIA, rheumatoid arthritis, psoriasis, and inflammatory bowel diseases.[8] TNF inhibitors are known to cause demyelinating disorders both in the central nervous system and peripheral nervous system. In a French national survey, 33 patients developed demyelinating disorders in a period of three years after a median of 10.2 months of treatment, and 22 patients had central nervous system involvement and 11 had peripheral nervous system involvement. In that series, there was only one child, a 13-year old girl diagnosed with JIA, who developed optic neuritis after etanercept treatment.[9] In Switzerland, of the 2,017 patients treated with TNF inhibitors, 12 developed associated neuropathy, with the prevalence being calculated as 0.60%.[10] Peripheral neuropathies reported secondary to the use of TNF inhibitors include GBS, Miller Fisher syndrome, multifocal motor neuropathy, CIDP, Lewis-Sumner syndrome (a variant of CIDP), and axonopathies.[3,9,10] Yagita et al.[3] reviewed 60 patients with peripheral neuropathies, who were receiving biological therapy. The duration of therapy prior to the onset of neuropathy ranged from eight hours to five years. The majority of the patients (47/60) had demyelinating neuropathy. The outcome was favorable in most patients, and the discontinuation of the agent resulted in spontaneous resolution in most reported patients. In the literature, nearly all the published data belong to adult patients. We found only one case report in the pediatric age group, in which Alqurashi et al.[11] described an eight-year-old girl with polyarticular JIA, who developed demyelinating peripheral neuropathy a few months after etanercept withdrawal. She was treated with IVIG and abatacept. This is similar to our patient whose symptoms also started after the withdrawal of etanercept. To our knowledge, this is the second pediatric case that developed CIDP after TNF inhibitor treatment.

The underlying mechanism of demyelinating neurologic diseases in patients treated with TNF inhibitors needs to be elucidated. Both humoral and cellular immune mechanisms are implicated in the pathogenesis. TNF-α is a cytokine with both pro-inflammatory and immunoregulatory properties. In the peripheral immune system, TNF-α plays important roles as antigen-presenting cells and in the regulation of the apoptosis of auto-reactive T cells. Paradoxically, TNF-α is also involved in the pathogenesis of inflammatory demyelinating neuropathies. Serum TNF- α levels are increased in a subgroup of GBS and CIDP cases during the active disease and decreased after immunotherapy with clinical recovery.[8,12] Bosch et al.[2] reported that chronic TNF inhibition might increase the anti-myelin

immune response through the activated T lymphocytes. Nerve ischemia and inhibition of signaling support for axons have also been proposed as mechanisms for secondary axonal loss.[8] Demyelinating disorders may persist even after the withdrawal of the offending agent, suggesting that after TNF inhibitors trigger the demyelinating process, the disease progresses independently of the eliciting agent.[9]

In our case, the treatment plan was supposed to cover not only CIDP but also JIA. We preferred rituximab, a monoclonal anti-CD20 antibody, for refractory CIDP in our patient. Rituximab is an alternative treatment for both JIA and refractory CIDP disease.[13,14] It is shown to be effective in CIDP patients with hematological or autoimmune diseases.[15] Rituximab was effective for both CIDP and JIA in our patient, indicating that humoral mechanisms may be important in the pathogenesis of TNF inhibitor-associated neuropathy.

CIDP may be a rare adverse event in children treated with TNF inhibitors. Neuropathy symptoms may start after the withdrawal of the offending agent, and patients may be unresponsive to first-line therapy, including steroids and IVIG, necessitating further immunosuppressive treatment.

Ethical approval

Informed consent was obtained from the family.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HMG, BK, BS; data collection: HMG, BK, RS, HGS, BS; analysis and interpretation of results: HMG, BK, BS; draft manuscript preparation: HMG, BK, RS, HGS, BS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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