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ASYMPTOMATIC CNS DEMYELINATION RELATED TO TNF- α INHIBITOR THERAPY

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Tumor necrosis factor (TNF)- α inhibitors are a subtype of disease-modifying antirheumatic drugs that have revolutionized the treatment of rheumatologic and gastrointestinal disorders. TNF- α is a cytokine with a complex role in immune system regulation and maintenance of self-tolerance. Despite their clinical benefit in rheumatologic conditions, TNF- α inhibitors have been implicated in the development of CNS and peripheral nervous system disorders.^{1,2} We describe an asymptomatic patient with radiologic and CSF analysis suggestive of CNS demyelination in the setting of TNF- α therapy.

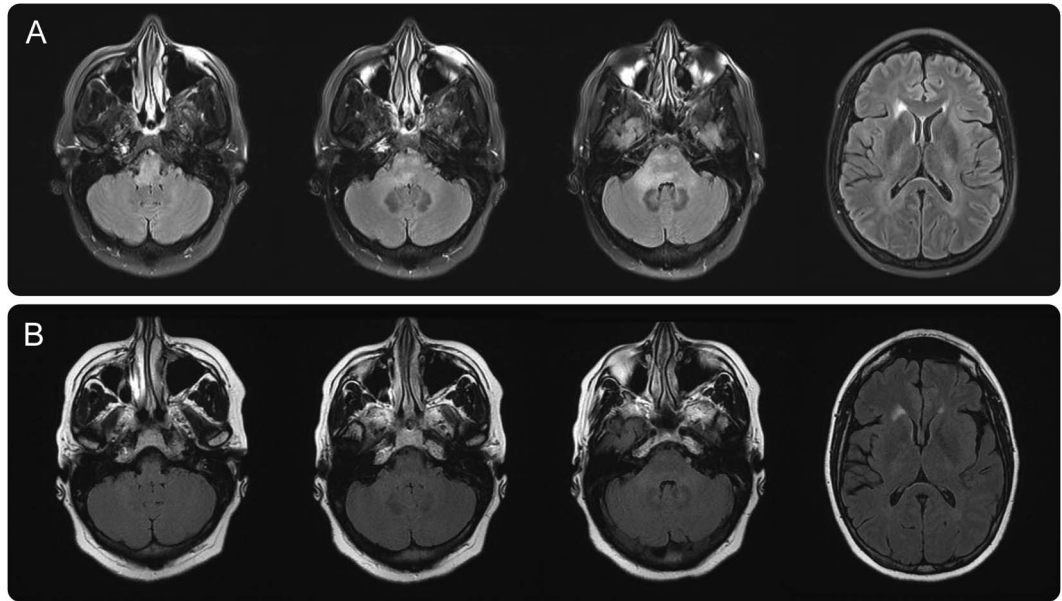
Case report. A 42-year-old right-handed woman presented for neurologic evaluation regarding 3 prior episodes of right face and arm numbness and lightheadedness lasting seconds to minutes. She was asymptomatic at the time of her clinical evaluation and her neurologic examination was normal. Her medical history was notable for rheumatoid arthritis treated with etanercept for the previous 2 years. MRI brain at presentation showed nonenhancing T2 hyperintensities in the ventral pons, right middle cerebellar peduncle, and bilateral parietal, occipital, and right frontal periventricular white matter concerning for demyelinating disease (figure, A). MRI of the spinal cord and visual evoked potentials were normal. Serologic evaluation revealed an elevated C-reactive protein of 17.3 and anticyclic citrullinated peptide >250 units consistent with her known diagnosis of rheumatoid arthritis. Lyme serology was negative. CSF analysis demonstrated elevated immunoglobulin G (IgG) index 0.95, IgG synthesis rate 35.19 mg/24 h, 11 oligoclonal bands, elevated protein at 94 mg/dL, and 17 nucleated cells with lymphocytic predominance. JC virus serology and neuromyelitis optica aquaporin-4 IgG cell-based assay performed on the CSF were negative. Although the patient was clinically asymptomatic with no examination findings localizable to areas of MRI lesions, due to the possibility of this representing an early demyelinating process and the potential risk of progression, etanercept was discontinued. No other intervention was undertaken.

At 6 months, the patient remained neurologically asymptomatic. Repeat MRI brain performed at 1 year showed near complete resolution of her lesions. The asymptomatic area of right frontal white matter hyperintensity remained stable (figure, B). Telephone follow-up was conducted 24 months after initial presentation and the patient denied subsequent neurologic symptoms.

Discussion. TNF- α inhibitors have been associated with central and peripheral demyelination. In a reported series of 75 patients, 3 patients developed demyelinating disease at 18 months follow-up. Clinical presentations of CNS demyelination included transverse myelitis, optic neuritis, and brainstem syndromes. TNF- α -associated leukoencephalopathy, small and large fiber neuropathy, and multiple cranial neuropathies have also been reported.^{1,2} In these previously reported cases, CSF analysis usually demonstrated elevated protein, oligoclonal bands, and increased IgG synthesis index.³ Discontinuation of TNF- α inhibitors led to variable resolution of symptoms and only occasional need for additional immunotherapy.

The mechanism by which TNF- α inhibitors induce demyelination is not completely understood. TNF- α is an endogenous cytokine that exerts its effects by binding TNF receptor 1 (TNFR1) or 2 (TNFR2). TNFR1 has an intracellular death domain and mediates the inflammatory effects of TNF. TNFR2 is involved in maintenance of immune tolerance, remyelination, and oligodendrocyte regeneration.^{4,5} Disrupting the balance between effector and regulatory T cells via inhibition of TNF can lead to excessive autoreactive T cells that escape immune surveillance. This process in turn might stimulate humoral immunity and lead to an autoimmune disease of the nervous system.^{6,7} Despite these theories, the exact mechanism by which TNF- α inhibition causes demyelination is unknown.

CNS demyelination has been described in association with TNF inhibitors. Our case introduces the concerning possibility that undetected CNS demyelination may be occurring in some patients. Our patient was clinically asymptomatic at the time of presentation but had an inflammatory CSF study and demyelinating lesions on MRI. The imaging findings almost resolved after withholding etanercept for 12 months. Such patients may be at risk for permanent



(A) Axial fluid-attenuated inversion recovery images show hyperintense lesions in the right and left middle cerebellar peduncle, pons, right frontal periventricular white matter, and mild hyperintensity bilaterally in the parietal and occipital lobe white matter. No enhancement was present. (B) Significant improvement of lesions 1 year post discontinuation of etanercept. Mild asymptomatic right frontal periventricular hyperintense lesion is seen.

neurologic deficits. There are no recommendations to obtain baseline neuroimaging in patients before starting therapy with TNF- α inhibitors but our patient prompts the question regarding such screening. Prescribers should be aware of potentially devastating consequences of CNS demyelination, and consider whether screening neuroimaging might be appropriate in select patients. This case also highlights that early detection of demyelination and prompt discontinuation of these agents may prevent the need for immunotherapy unless there is neurologic and radiologic progression despite discontinuation. Despite our presentation of a single patient without long-term imaging and ongoing CSF parameters, this case emphasizes important concerns in using and evaluating patients with TNF- α inhibitors, highlighting those who may be clinically asymptomatic.

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