Acute demyelination in childhood associated with TNF alpha-inhibitor therapy

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Introduction: Tumor necrosis factor-alpha inhibiting medications (TNFi) have revolutionized the treatment of autoimmunity. These are the most common medications used for conditions such as rheumatoid arthritis, juvenile idiopathic arthritis and for many other rheumatologic disorders (uveitis, vasculitides, granulomatous disorders). These drugs have made possible long-standing disease remission. Regarding the large number of people on active treatment with TNFi, their benefits must be balanced against concerns for side effects.

Case report: We report a case and discuss a rare, but serious adverse event associated with TNFi usage: central nervous system (CNS) demyelination.

Discussion: Possible side effects related to TNFi include CNS acquired demyelinating disorders. After starting any immune modulating therapy, such as TNFi, there should be close monitoring of side effects or new disease symptoms.

Keywords: Tumor necrosis factor (TNF), Monoclonal antibodies, Anti-TNF treatment, Acute demyelination, Multiple sclerosis, Optic neuritis.

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Introduction

Tumor necrosis factor (TNF)-alpha is synthesized as a monomeric Type-2 transmembrane precursor protein (tmTNF) and it is produced by many cell types, including macrophages, lymphocytes, dendritic cells, and Natural Killer cells in the periphery. In the CNS, it is produced by microglia and astrocytes [1]. TNF-alpha form trimers bind to one of two receptors: TNFR1 and TNFR2. TNFR1 is preferentially activated through soluble TNF-alpha, and triggers the production of pro-inflammatory mediators causing cell death. TNFR2, activated by transmembrane TNF-alpha, propagates the inflammatory cascade [2].

Tumor necrosis factor-alpha inhibiting (TNFi) medications would be expected to be effective by a balanced inhibition or activity biased against the pathologic effector T-cells. However, in some patients, the administration of TNFi medication appears to have a greater inhibiting effect on the regulatory cells over pathogenic effector T-cells, resulting in a paradoxical inflammatory response in the periphery. The inflammatory cytokines subsequently produced pass freely into the CNS, stimulating an inflammatory response in microglia and macrophages [3].

Our case series and literature review demonstrates an association between TNFi therapy and inflammatory neurological disease [4].

Case report

A 15-year-old girl with a six-year history of polyarticular juvenile idiopathic arthritis, on oral methotrexate (10 mg weekly) developed breakthrough activity and started intravenous infliximab (10 mg/kg every 6 weeks). After one year of starting infliximab, she woke up with blurred vision in her right eye. She had retro-orbital pain, worsened by eye movements. She had no previous history of demyelinating pathology or other neurological symptoms. She had no preceding illness or fever, and her arthritis was under good control. Her examination confirmed right optic neuritis with severely impaired visual acuity (20/200 -2), dyschromatopsia, and a right afferent pupillary defect. The rest of her neurological examination was unremarkable.

She was admitted to the hospital for further evaluation and management. Blood test results were within normal range), except for low levels of 25(OH) vitamin D (17 ng/mL, range 30–100 ng/mL). Extensive infectious work up and aquaporin-4 antibody were negative. A brain MRI performed one week after the onset of symptoms revealed asymmetric T2-hyperintensity and enlargement of the right prechiasmatic optic nerve, compatible with optic neuritis without gadolinium enhancement. The remainder of the brain parenchyma was unremarkable (Figure 1). She and her family declined to have a lumbar puncture, which had been proposed for routine studies (cell count, protein, glucose, cultures) and IgG-index and oligoclonal bands.

Patient began corticosteroids (methylprednisolone 1000 mg IV daily for three days followed by an oral prednisone taper) for one week and experienced rapid improvement. Infliximab was discontinued and oral methotrexate was increased to 25 mg weekly. She was also started on vitamin D3 supplementation. After three years of follow-up, her central acuity is 20/20 in the right eye. She has had no clinical or MRI evidence of additional demyelinating lesions.

Discussion

The causative role of TNFi medications in demyelinating disease remains unclear. While there does not appear to be a clear association, the data suggests a risk for the development of demyelinating disease with TNFi usage, whether the etiology is from the drug itself or from genetic predisposition for autoimmunity. The observed association could either be attributed to the unmasking of a latent demyelinating disease or to the emergence of a de novo demyelinating disease [5].

However, it is not completely clear whether TNFi antagonists increase the incidence of demyelinating diseases in patients with rheumatic diseases. Differences between
cases depending on the pharmacovigilance source could be explained by selective reporting bias outside registries [6]. In fact, some authors have hypothesized that optic neuritis is rare among those who initiate anti-TNF therapy and occurs with similar frequency among those with non-biological treatments exposure [7].

Consensus opinion seems to be that TNFi should not be used in patients with multiple sclerosis or other acquired demyelinating syndromes. Any patient under TNFi therapy should be well informed that the development of neurologic symptoms should not be taken lightly, and the medication should be stopped if such symptoms occur. Clinicians should evaluate the choice of medication and monitor all patients closely for the development of neurological symptoms [8].

We conclude that TNFi-associated neurological syndromes may be associated with significant disability and longer follow-up is needed to better determine natural history (monophasic or recurrent disorder) and evaluate appropriate treatment interventions [9].

Abbreviations

TNF: Tumor necrosis factor; tmTNF: Transmembrane Tumor necrosis factor; TNFi: Tumor necrosis factor-alpha inhibiting medication.

Competing interests

The authors declare no conflict of interest.

References


