Refractory Primary Central Nervous System Vasculitis of Childhood: Successful Treatment with Infliximab

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To the Editor:

Childhood primary angiitis of the central nervous system (cPACNS) is an increasingly recognized inflammatory brain disease causing devastating brain injury in previously healthy children. Early recognition and initiation of treatment may reverse the severe deficits caused by inflammation and lead to complete neurological recovery. cPACNS has a broad clinical spectrum including acute ischemic stroke, intractable seizures, and severe cognitive decline. cPACNS is classified into angiography-positive vasculitis and angiography-negative small-vessel vasculitis (SV-cPACNS).

We reported the efficacy and safety of a treatment protocol for SV-cPACNS. This immunosuppressive regimen led to complete neurological recovery in the majority of children. There is limited knowledge of the approach to children who fail standard therapy. Tumor necrosis factor (TNF) inhibition has been considered in the treatment of refractory systemic vasculitis. In addition, histological studies of SV-cPACNS brain biopsies demonstrated primary lymphocytic vessel wall infiltrates.

We describe 2 children with refractory SV-cPACNS who failed standard treatment with cyclophosphamide and high-dose corticosteroids. Treatment with anti-TNF therapy with infliximab (IFX) controlled disease activity and resolved neurologic symptoms.

In Case 1, a 7-year-old previously healthy girl presented with fever and headaches. She was admitted to hospital and developed a generalized tonic-clonic seizure. Her magnetic resonance imaging revealed multifocal lesions. Conventional angiography was normal. A lumbar puncture revealed pleiocytosis (Table 1). On fundoscopy, bilateral papilledema was documented. She started treatment with acyclovir and dexamethasone. A repeat MRI demonstrated multifocal gray and white matter lesions. Upon tapering of dexamethasone, she developed ataxia, dysarthria, and a fluctuating level of consciousness. She was admitted to the intensive care unit and given intravenous immunoglobulin (IVIG) and pulses of IV methylprednisolone. A presumed diagnosis of acute disseminated encephalomyelitis was made. Treatment was commenced with monthly IVIG and prednisone. Two months after the last dose of prednisone, she developed headaches and vomiting. A repeat MRI showed significant worsening of the multifocal lesions. Conventional angiography was normal. A presumed diagnosis of SV-cPACNS was given and she was started on the institutional immunosuppressive protocol. After 6 courses of IV cyclophosphamide, she developed new neurological symptoms (tremor and urinary retention). A repeat MRI showed new lesions in the deep white matter. Because of the distribution and depth of her lesions, she had a nonlesional brain biopsy. The histology was consistent with but not diagnostic of longstanding, previously treated vasculitis (periavascular lymphocytic and macrophage infiltrate). She again started to take high-dose prednisone and a decision was made to treat her with IFX (5 mg/kg/dose at 0, 2, and 6 weeks, followed by monthly infusions) and methotrexate. She continued to receive regular IVIG infusions. Significant improvement in her CNS lesions was seen on repeat imaging (Figure 1). Four years after diagnosis, she was symptom-free and taking no medications. Unfortunately, she suffered a flare of her disease the next year requiring regular IVIG infusions.

In Case 2, a 17-year-old previously healthy girl presented with bilateral visual loss along with headache and fever. Her MRI showed diffuse increased signal in bifrontal gray matter. With a diagnosis of bilateraloptic neuritis, she started pulse IV methylprednisolone therapy followed by oral prednisone. Every time her steroids were tapered, she relapsed. The bilateral visual loss (central scotomas) recurred twice and improved dramatically with IV methylprednisolone. One month after presentation, she developed a 7-hour seizure requiring a propofol-induced coma. Despite high-dose prednisone, she continued to experience headache and altered behavior. Three months later, her bilateral visual loss returned along with irritability and fever. Once again she was treated with methylprednisolone and IVIG. Conventional angiography was normal. A brain biopsy revealed...
lymphocytic angiitis. There was a vasocentric inflammatory process showing lymphocytes and macrophages associated with vessels, including through the wall. She was diagnosed with SV-cPACNS and started on the institutional immunosuppressive protocol. During her prednisone taper, she developed left-sided weakness, and a repeat MRI reported new multifocal lesions in both cerebral hemispheres and spinal cord. Cyclophosphamide was discontinued and she was started on IFX (5 mg/kg/dose), monthly IVIG for 6 months, and methotrexate. Six years following diagnosis, she still takes prednisone (10 mg daily), methotrexate, and IFX. She has permanent stable visual loss with no further seizures. Her last MRI showed no new cerebral lesions.

Anti-TNF therapy with IFX controlled the devastating vascular inflammation, resolved previously refractory seizures, and prevented permanent brain injury in 2 children with refractory SV-cPACNS. Both patients had persistent disease activity prior to IFX, despite prolonged, high-dose immunosuppressive treatment. In a case series of 2 adult patients with PACNS, TNF blockade was used in an attempt to control severe refractory disease. Prompt resolution of symptoms was seen. The efficacy of anti-TNF therapy was also demonstrated in case series of adult vasculitides including Takayasu arteritis and Wegener granulomatosis. Similarly, IFX led to cessation of fever in 81% of children with refractory Kawasaki disease. In addition to anti-TNF therapy, rituximab has also been used in a case of refractory cPACNS. Once again, the patient responded promptly with a prolonged relapse-free period.

The risks and benefits of IFX therapy must be considered. In our patients, IFX allowed tapering of glucocorticoid therapy. We avoided re-treatment with cyclophosphamide, which has its own well described dose-dependent toxicities. However, anti-TNF agents carry safety risks including infusion reactions, opportunistic infections, and reactivation of latent tuberculosis. One must also consider the black box warning on anti-TNF therapies in children and their potentially increased risk of malignancies. This concern was also raised in the Wegener’s Granulomatosis Etanercept Trial.

Anti-TNF therapy with IFX should be considered a rescue therapy for children with refractory SV-cPACNS. However, the efficacy and safety of
anti-TNF therapy in combination with methotrexate and IVIG in cPACNS has to be explored in larger prospective studies.

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