OPEN

Seizure During Infliximab Infusion in a Child With Crohn's Disease: An Illustration of a Neurologic Adverse Event Associated With Drug Antibodies

Shelly Joseph, MD, Anna W Reed, MD, MPH, and Carmen Cuffari, MD

Abstract: Antitumor necrosis factor (anti-TNF) therapy has proven efficacy in the induction and maintenance of remission in children with Crohn's disease (CD). With the increased use of these medications, several adverse events have been associated, including the emergence of neurologic side effects. While demyelinating conditions and neuropathy associated with anti-TNF therapy have been reported in adults, seizures have been anecdotally described in case reports. We describe a case of an adolescent boy who experienced an infliximab-associated seizure during an infusion and the potential role that medication antibody levels may have played in this adverse event.

Key Words: side effect, reaction, medication

INTRODUCTION

Although antitumor necrosis factor (anti-TNF) medications have proven efficacy in slowing the progression of Crohn's disease (CD), a number of drug-related side effects have been described in detail, ranging from mild reactions, such as rash and myalgia, to severe reactions, including anaphylaxis and reversible encephalopathy [1–3]. Acute infusion reactions occur in 4%–18% of pediatric patients who receive infliximab; among those, neurologic adverse events are uncommon and incompletely understood but are assumed to be mediated by the development of neutralizing antibodies to the medication[4]. We report the first pediatric case of an infliximab-associated seizure during an infusion of infliximab in a 17-year-old patient and consider how this might be related to circulating drug and infliximab antibody levels in this patient.

CASE REPORT

A 17-year-old boy diagnosed with moderate-to-severe ileocolonic CD at age 14 underwent successful induction followed by maintenance infliximab therapy with 10 mg/kg every 8 weeks. His course was complicated by a terminal ileum stricture and abscess that required an ileocecectomy 2 years after diagnosis. Following surgery, the patient was in a steroid-free remission with improvement in clinical symptoms and routine labs obtained with each infusion. Fecal calprotectin improved from >1000 to 258 μg/g. After 3 years on maintenance infliximab, the patient began to experience abdominal pain, vomiting, headache, and myalgia following each infusion that continued for approximately 24 hours afterward. Symptoms resolved within 72 hours, and he felt well during the weeks between infusions. After experiencing these symptoms with a few infusions, he informed his gastroenterologist who implemented premedication with acetaminophen and diphenhydramine before infusions. The patient tolerated 4 infliximab infusions with premedication without issue. Of note, he received infliximab and not a biosimilar medication.

The patient presented to an outpatient, hospital-based infusion center for a routine maintenance infusion of infliximab. Within 4 minutes of initiation, he became unresponsive with witnessed rhythmic jerking movements of all of his extremities for approximately 2–3 minutes. Following cessation of these movements, the patient was noted to be confused, analogous to a postictal state. The infusion was immediately discontinued, and he was transported to the emergency department. He had neither a prior history nor family history of convulsive or underlying neurologic disorder and no other significant medical history. In the emergency department, he was noted to have normal vital signs and a normal physical, including neurologic, examination. Evaluation included normal blood glucose, urine toxicology screen, complete blood count, comprehensive metabolic panel, urinalysis, electrocardiogram, and brain magnetic resonance imaging. He had headache and myalgia that resolved with ketorolac and acetaminophen.

Infliximab and anti-TNF antibody levels were obtained 2 days following the episode using a nonradio-labeled liquid phase mobility shift assay via Prometheus Anser laboratories. Before this, drug levels and antibody levels had not been obtained; however, laboratories with infusions demonstrated normalization of inflammatory markers and improvement in calprotectin. The patient had a persistent microcytic anemia that improved modestly on infliximab. Linear growth rate and weight gain were normal. Infliximab drug levels were undetectable (<0.1 μg/mL), and the patient had a moderate anti-TNF antibody level (15.2 U/mL). The patient demonstrated resolution of neurologic symptoms before leaving the emergency department and has since transitioned to adalimumab monotherapy without issue and with no further convulsive events. Neurology follow-up was recommended for additional evaluation, but was not pursued given resolution of symptoms. Moreover, he has not shown immunogenicity or symptoms associated with an underlying neurologic disorder while on adalimumab therapy.

DISCUSSION

Infliximab infusion-associated seizures have been reported in several case reports in adults, while other neurologic adverse events have been reported in children[3,5]. The Food and Drug Administration's drug monitoring program has cited adverse neurologic events associated with infliximab including vasculitis, seizures, neuropathy, optic neuritis, and exacerbation of demyelinating disorders[6]. The neurologic effects associated with anti-TNFs can involve both

Received December 29, 2020; accepted May 27, 2021.
From the Division of Pediatric Gastroenterology, Hepatology, and Nutrition, The Johns Hopkins University School of Medicine, Baltimore, MD.
The authors report no conflicts of interest.
Correspondence: Shelly Joseph, MD, 600 N Wolfe Street CMSC 2-124 Baltimore, MD 21287. E-mail: sjosep35@jhmi.edu

JPGN Reports (2021) 2:3(e101)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000101

the central and peripheral nervous system and have been cited largely among populations receiving treatment for rheumatologic conditions[7].

The cause of anti-TNF-associated adverse neurologic events is unknown, and it is unclear whether these events represent an unmasking of underlying conditions or an antibody-associated adverse event triggered by the medication. Nonetheless, several mechanisms have been suggested, including the reactivation of latent viral infections leading to increased systemic inflammation and autoantibody formation by way of molecular mimicry, and alteration of the inflammatory cytokine milieu resulting in upregulation of cytokines specific to demyelinating or other neurologic conditions[7].

Notably, anti-TNFs largely cannot traverse the blood brain barrier and are not detected in the cerebral spinal fluid, suggesting that while the effects of anti-TNFs are beneficial in tissues with a high degree of drug penetrance such as intestinal mucosa, the same cannot be said for the central nervous system[8].

Studies have described the development of anti-TNF-related neuropathy and demyelinating disease in patients with CD on either infliximab or adalimumab therapy without mention of drug levels, anti-TNF antibody levels, the use of biosimilars, or infliximab-related seizures in children[9]. Overall, it has been shown that patients with CD with detectable antibodies to infliximab are generally 2–3 times more likely to develop any type of infusion-related reaction[10]. While childhood seizure disorders have been reported in the pediatric patient population to occur in 5.3–8.8 per 1000 children, febrile and one-time seizures occur in approximately 3.5 per 1000 children[11]. It is important to note that our patient's seizure event may have been unrelated to infliximab infusion or drug antibody levels. However, the patient had normal MRI findings, a normal examination, no prior seizure history, and complete resolution of symptoms, which is evidence against an underlying neurologic condition. The patient also demonstrated moderate antibody levels and low drug levels indicating a higher risk for adverse drug reaction[10]. Little information is available regarding adverse neurologic reactions and how this might be related to drug antibody levels. Additional studies are needed on how to best identify pediatric patients who may be at risk in developing infliximab-related neurologic side effects and how that risk might be associated with either the drug itself or immunogenicity to infliximab.

ACKNOWLEDGMENTS

S.J. drafted and reviewed the manuscript. A.W.R. was involved in critical review and approval of final manuscript. C.C. was involved in conception, critical review, and final approval of the manuscript.

REFERENCES

1. Fumery M, Pariente B, Sarter H, et al; Epimad Group. Long-term outcome of pediatric-onset Crohn's disease: a population-based cohort study. *Dig Liver Dis*. 2019;51:496–502.
2. Vernier–Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008;135:1106–1113.
3. Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis*. 2015;9:806–815.
4. Miehsler W, Novacek G, Wenzl H, et al; Austrian Society of Gastroenterology and Hepatology. A decade of infliximab: the Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. *J Crohns Colitis*. 2010;4:221–256.
5. Haddock R, Garrick V, Horrocks I, et al. A case of posterior reversible encephalopathy syndrome in a child with Crohn's disease treated with Infliximab. *ecco-jcc*. 2011;5:623–627.
6. FDA. Full prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf. Accessed February 10, 2019.
7. Kaltsonoudis E, Voulgari PV, Konitsiotis S, et al. Demyelination and other neurological adverse events after anti-TNF therapy. *Autoimmun Rev*. 2014;13:54–58.
8. Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor α antagonism: by what mechanisms could tumor necrosis factor α antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? *Arthritis Rheum*. 2001;44:1977–1983.
9. Lees CW, Ali AI, Thompson AI, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther*. 2009;29:286–297.
10. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876–885.
11. Oka E, Ohtsuka Y, Yoshinaga H, et al. Prevalence of childhood epilepsy and distribution of epileptic syndromes: a population-based survey in Okayama, Japan. *Epilepsia*. 2006;47:626–630.