MedCrave
Step into the World of Research

Journal of Neurology & Stroke

Infliximab Induced Leukoencephalopathy and Peripheral Neuropathy: A Case Report and a Review of Literature

Abstract

Infliximab is an anti-tumor necrosis factor alpha (TNF-α) biological agent that has been used in the treatment of inflammatory bowel disease where conventional management deems ineffective. Well-recognized side effects of anti TNF-α agents include risk of infections, hypersensitivity reactions and malignancies. However, although rare, neurological side effects have been described in the literature. In this report we present a case of a seven-year-old patient with ulcerative colitis who developed demyelinating leukoencephalopathy with peripheral neuropathy as a side effect after receiving three doses of infliximab. The patient had an evidence of cerebral demyelination on magnetic resonance imaging and signs of axonal sensory and motor neuropathy on nerve conduction studies. The patient was managed with pulse corticosteroids, intravenous immunoglobulin and five sessions of plasmapheresis. He received extensive physiotherapy over three years until achieving full neurological recovery.

Keywords: Inflammatory bowel disease; Anti-tumor necrosis factor alpha; Infliximab; Leukoencephalopathy; Peripheral neuropathy

Case Report

Volume 8 Issue 1 - 2018

Hasan M Isa[1], Maryam F Ashoor[1]*, Ayman K Ali[2] and Hussain Mohamed[1]

[1]Department of Pediatrics, Salmaniya Medical Complex, Kingdom of Bahrain
[2]Department of Neuroscience, Salmaniya Medical Complex, Kingdom of Bahrain

***Corresponding author:** Maryam Fareed Ashoor, Pediatric Junior Resident, Pediatrics Department, Salmaniya Medical Complex, Kingdom of Bahrain, H: 2349B, R: 5718, B: 257, Amwaj Islands, Kingdom of Bahrain, Tel: 00973 38383071; Email: mariamfareed@hotmail.com

Received: October 28, 2017 | **Published:** January 12, 2018

Abbreviations: TNF-α: Tumor Necrosis Factor Alpha; IBD: Inflammatory Bowel Disease; IFX: Infliximab; CD: Crohn's Disease; UC: Ulcerative Colitis; CRP: C-Reactive Protein; ESR: Erythrocytes Sedimentation Rate; IV: Intravenous; MRI: Magnetic Resonance Imaging; IVIG: Intravenous Immunoglobulin

Introduction

Inflammatory bowel disease (IBD) is an idiopathic, chronic condition in which tumor necrosis factor alpha (TNF-α) is thought to play a role [1]. Infliximab (IFX) is a chimeric anti-tumor necrosis factor monoclonal antibody that has a potent anti-inflammatory effect [2]. IFX is currently used as a treatment for severe active cases of IBD in both Crohn's disease (CD) and ulcerative colitis (UC) that are unresponsive to conventional therapy [2]. The most common side effects of IFX are the increased risks of developing severe infections, hypersensitivity reactions and malignancies.3 Rare cases of neurological complications secondary to IFX use have been reported including Guillain-Barre syndrome, chronic inflammatory demyelinating poly-radiculo-neuropathy and neuropathy [3]. Here, we describe a rare case of demyelinating leukoencephalopathy in a patient with UC managed with IFX.

Case Presentation

A seven-year-old Bahraini male, who had no significant past medical history, presented to the pediatrics gastroenterology clinic with a history of abdominal pain, vomiting and blood in the stool of one month duration. Symptoms were associated with fatigue, unintentional weight loss and loss of appetite. The patient was a product of a full term delivery, vaccinated up to date with non-contributory family or social history. Physical examination was significant for anterior anal fissure. Laboratory investigations revealed a microcytic hypochromic anemia with a hemoglobin level of 9.4 g/dl (normal range 13-15.5), an elevated C-reactive protein (CRP) and erythrocytes sedimentation rate (ESR) at 33.8 (normal range 0-20) and 43 (normal range 0-3) mg/L respectively. Liver function tests showed an elevated serum globulin, 41 g/L (normal range 15 - 30), and reduced serum albumin levels, 31 g/L (normal range 35 - 50). Three stool cultures were negative. Viral screening for hepatitis A, B and C viruses, Epstein bar virus, cytomegalovirus and human immunodeficiency virus were negative. Purified protein derivative skin test and chest X ray were negative. Other imaging studies including abdominal ultrasound, barium studies and computed tomography of the abdomen were suggestive of UC. Esophagogastroduodenoscopy and colonoscopy confirmed the diagnosis by revealing diffuse severe ulcerations with friable and easy to bleed mucosa up to the transverse colon.

As per protocol, UC management was started. The patient received conventional therapy including intravenous (IV) antibiotics followed by IV methylprednisolone, oral mesalazine and azathioprine. However, the bleeding per rectum continued and the conventional therapy was considered ineffective. Biological therapy with Infliximab was initiated at a dose of 5 mg /Kg with infusion protocol at 0, 2, 6 and every 8 weeks thereafter. On admission for the 3rd dose of IFX, the patient had marked reduction in the episodes of bloody diarrhea, ESR dropped to 2 and CRP dropped to 0.6. He received the dose of IFX and a single albumin infusion and was discharged home.

Two weeks later, he presented with a significant fatigue and inability to move independently or do any physical activity. Examination revealed a wasted, sick looking with dry lips. Full neurological examination showed visual hallucinations, diplopia, roving eye movements, bilateral nystagmus and exophoria. Numbness at all four limbs with flaccid quadriplegia, hypotonia of

all limbs and absent deep tendon reflexes. The patient was admitted to the pediatric intensive care unit. Magnetic resonance imaging (MRI) of the brain showed signal intensities in the periventricular area with mild volume loss of the cerebral white matter involving the periventricular and subcortical white matter interpreted as demyelinating non-specific white matter abnormality likely to be related to either viral infection or medications (Figure 1). Cerebrospinal fluid sample showed elevated proteins with normal glucose and lactic acid, negative oligoclonal bands and negative viral serology. Nerve conduction study showed an axonal sensory motor neuropathy. A diagnosis of IFX induced demyelinating leukoencephalopathy with peripheral neuropathy was made. Management course started with IV pulse glucocorticosteroids, intravenous immunoglobulin (IVIG) infusions twice weekly at doses of 2 g/kg and five sessions of plasmapheresis at 250 ml/Kg. After three years of extensive physiotherapy sessions, a full neurological recovery was achieved.

Discussion

IFX use has been established in the treatment of UC in cases that prove to be resistant to conventional therapy [1]. Cury et al. [2] described a case of severe UC failing IV steroids and azathioprine entered remission with significant clinical and endoscopic response after initiating IFX.2 The mechanism of action for IFX in UC is less well studied than in CD, it is thought that IFX works through mediating apoptosis of inflammatory cells expressing TNF-α. Studies have shown that these cells are resistant to apoptosis in IBD [1].

Although rare, neurological side effects of TNF-α antagonists have been reported in the literature (Table 1). In a study of 77 patients treated with anti TNF-α was conducted to assess the rate of neurological adverse events associated with the medication, before and after initiation of therapy, three patients developed neurological side effects in the form of facial nerve paralysis with evidence of demyelination on MRI imaging, peripheral neuropathy and optic neuritis. The side effects resolved after withdrawal of therapy. A rate of 4% risk was estimated for neurological side effects [4].

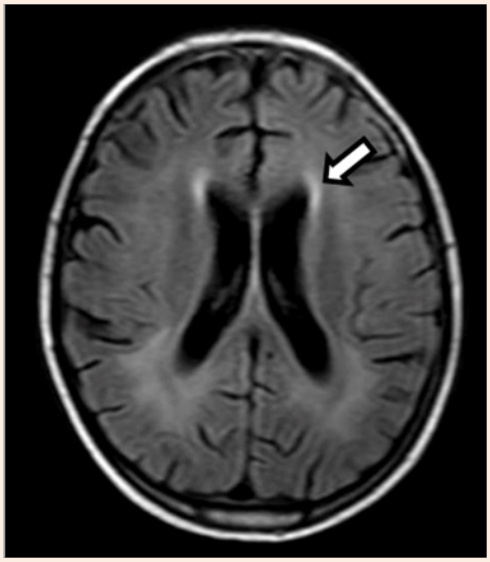

Figure 1: Flair magnetic resonance imaging (MRI) of the brain showing signal intensities in the periventricular area (arrow), mild volume loss of the cerebral white matter involving the periventricular and subcortical white matter.

Table 1: Reported cases of neurological side effects secondary to the use of TNF-α antagonists.

Author, Year	Age (Y)	Sex	Primary Diagnosis	Anti TNF* Alpha Dose	Side Effect	Management	Outcome
Brigo et al. [11]	7	Male	CD†	2nd	Seizure, encephalopathy	withdrawal	Recovered
Haddock et al. [12]	8	Female	CD†	1st	PRES‡	Withdrawal	Recovered
Kaltsonoudis et al. [4]	50	Female	AS§ and CD†	After 25 months	Peripheral neuropathy	Withdrawal	Recovered
Kaltsonoudis et al. [4]	35	Male	PsA ||	After 8 months	Paresis of the left facial nerve, demyelinating lesions brain MRI	Withdrawal, steroids	Recovered
Seo et al. [13]	58	Female	Rheumatoid arthritis	6th	Multifocal motor neuropathy	Withdrawal, IVIG	Stabilized
*Tumor necrosis factor, †Cronhs' disease, ‡ Posterior reversible encephalopathy syndrome, § ankylosing spondylitis, || psoriatic arthritis							

In this report, the patient developed combined peripheral neuropathy with demyelinating leukoencephalopathy. Kamel et al. [5] reported a case of a 29 years old male with crohn's disease who developed lower extremity weakness and dysesthesia after the 4th dose of infliximab. He was managed with corticosteroids, IVIG and three sessions plasmapheresis achieving resolution of symptoms. The patient presented three months later with recurrence of neurological symptoms, which was refractory to plasampheresis at the time. He was diagnosed with chronic inflammatory demyelinating neuropathy secondary to infliximab use [5].

El Aidli et al. [6] reported a 61 years old woman with rheumatoid arthritis who developed peripheral neuropathy after the ninth dose (at 17 months) of IFX therapy and showed complete recovery three months after IFX withdrawal and monthly IVIG infusions [6]. The pathogenesis of peripheral neuropathy is suggested to be due to T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons [7].

Ryu et al. [8] reported a case of Adalimumab induced leukoencephalopathy. A 66 year old male with rheumatoid arthritis who was admitted three months after initiation of therapy due to developing gait disturbances, postural instability, hand tremor, worsening writing ability and cognitive slowing. Investigations excluded infectious, autoimmune or malignant pathology. MRI Brain showed several T2 hyperintensities in the bilateral periventricular white matter, the posterior limb of the internal capsule, the temporal subcortical white matter and globus pallidus, all which did not enhance with gadolinium. These findings are similar to the findings in our patient. Adalimumab was stopped, methylprednisolone and meloxicam were continued and patient's condition improved [8].

Management of neurological side effects described in the literature were dependent on withdrawal of the therapy which usually leads to resolution of symptoms [4]. For our patient, we used IV glucocorticoids, IVIG and plasmapheresis for management. IVIG is a well-recognized therapy implicated in the treatment of immunodeficiency. It has recently been implicates in the treatment of many autoimmune disease and of those are autoimmune neuropathies such as Guillain-Barre syndrome, chronic idiopathic demyelinating polyneuropathy, multi-focal neuropathy with conduction block and acute myasthenia gravis [9]. Plasmapheresis has been established as a method of management for a number of substances in the toxicology field [10].

Conclusion

Although IFX is effective in the management of IBD, serious and unexpected side effects are still possible. Direct causal relationship between the medication and observed side effect might not be always easy to prove, however one must beware of the possibility of such complications. Counseling patients and their families regarding the known and unknown side effects of IFX is highly important.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

None.

References

1. Levin A, Shibolet O (2008) Infliximab in ulcerative colitis. Biologics 2(3): 379-388.
2. Cury D, Cury M, Elias G, Mizsputen S (2009) Infliximab to treat severe ulcerative colitis. World J Gastroenterol 15(14): 1771-1773.
3. Uyanikoglu A, Ermis F, Pinarbasi B, Baran B, Aydogan T, et al. (2014) Infliximab in inflammatory bowel disease: attention to adverse events. Eur Rev Med Pharmacol Sci 18(16): 2337-2342.
4. Kaltsonoudis E, Zikou A, Voulgari P, Konitsiotis S, Argyropoulou M, et al. (2014) Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study. Arthritis Res Ther 16(3): R125.
5. Kamel AY, Concepcion O, Schlachterman A, Glover S, Forsmark CY (2016) Chronic Inflammatory Demyelinating Polyneuropathy Following Anti-TNF-α Therapy With Infliximab for Crohn's Disease. ACG Case Rep J 3(3): 187-189.
6. El Aidli S, Gaïes E, Cherif F, Zaiem A, Daghfous R, et al. (2014) Peripheral neuropathy during infliximab therapy for rheumatoid arthritis. La Presse Médicale 43(9): 1012-1014.
7. Stübgen J (2008) Tumor necrosis factor-α antagonists and neuropathy. Muscle Nerve 37(3): 281-292.
8. Ryu Y, Park S, Kim J, Kim E, Lee J, et al. (2011) A case of leukoencephalopathy associated with adalimumab-treated rheumatoid arthritis and a review of literature. Rheumatol Int 32(11): 3481-3485.
9. Hartung H, Mouthon L, Ahmed R, Jordan S, Laupland K, et al. (2009) Clinical applications of intravenous immunoglobulins (IVIg) - beyond immune deficiencies and neurology. Clin Experi Immunol 158 suppl 1: 23-33.
10. Nenov V, Marinov P, Sabeva J, Nenov D (2003) Current applications of plasmapheresis in clinical toxicology. Nephrol Dial Transplant 18 Suppl 5: v56-v58.
11. Brigo F, Bongiovanni LG, Cerini R, Manganotti P, Storti M, et al. (2011) Infliximab-related seizures: a first case study. Epileptic Disord 13(2): 214-217.
12. Haddock R, Garrick V, Horrocks I, Russell RK (2011) A case of posterior reversible encephalopathy syndrome in a child with Crohn's disease treated with Infliximab. J Crohns Colitis 5(6): 623-627.
13. Seo B, Jeong Y, Hong S, Kim Y, Lee CK, et al. (2016) A Case of Infliximab-induced Multifocal Motor Neuropathy in a Patient with Rheumatoid Arthritis and Literature Review. J Rheum Dis 23(4): 250-255.