CASE REPORT

Open Access

Infliximab-induced seizures in a patient with Crohn's disease: a case report



Zhijie Lv¹, Xiaoqi Zhang² and Li Wu^{3*}

Abstract

Background: Infliximab-induced seizures in patients with Crohn's disease are extremely rare and the mechanism of infliximab-induced seizures is unclear.

Case presentation: A 60-year-old woman with Crohn's disease experienced infliximab-induced seizures, diagnosed on normal magnetic resonance imaging of the brain. Moreover, the rechallenge with infliximab was positive.

Conclusions: Neurological assessment and tight clinical monitoring before and during therapy with infliximab should be performed in patients with pre-existing seizure disorders.

Keywords: Infliximab, Seizures, Crohn's disease, Case report

Background

Infliximab is currently used as the first-line treatment for Crohn's disease(CD). During the 20 years since its first approval in 1998, infliximab has revolutionized the treatment of inflammatory bowel disease(IBD). Over half a million patients have been treated with tumor necrosis factor (TNF)- α antagonists, but concerns regarding their safety have been raised worldwide [1]. The most commonly reported adverse reactions to infliximab include acute or delayed hypersensitivity reactions; serious infections including reactivation of tuberculosis and hepatitis B virus; malignancy, especially lymphoma and hematologic reactions [2, 3]. However, new and rare sideeffects have been increasingly reported in post-marketing reports. Here, we have reported a rare case of a patient with CD who experienced infliximab-induced seizures, diagnosed on normal magnetic resonance imaging (MRI) of the brain. Moreover, the rechallenge with infliximab was positive.

³ Center of Clinical Evaluation, The First Affiliated Hospital of Zhejiang Chinese Medical University, 54 Youdian Road, Hangzhou 310006, Zhejiang, China

Full list of author information is available at the end of the article



Case presentation

A 60-year-old female presented to our hospital with a 10-day history of small intestinal stenosis due to CD. The patient was diagnosed with CD in 2015 due to chief complaints of abdominal pain and watery diarrhea (3-4 times per day). The patient's medical history was unremarkable. She was treated with mesalazine (3 g/day), which partially alleviated the symptoms of abdominal pain and diarrhea (2-3 times per day). Ten days before admission, she underwent colonoscopy, but it was difficult to advance the colonoscope due to secondary intestinal stenosis. Biopsy and three-dimensional computed tomography of the small intestine confirmed the diagnosis of CD. Following admission to the hospital, a series of related examinations were performed. Electrocardiography revealed a normalized rhythm. Further evaluation revealed the following: slight leukopenia (leukocytes count, 3.2×10^9 / L); serum albumin level, 36.1 g/L (normal range,40–55 g/L); platelet count, 123×10^9 / L (normal range, $125-350 \times 10^9$ /L); serum calcium level, 2.18 mmol/L (normal range, 2.25-2.75 mmol/L); fecal calprotectin level, 827.162 μ g/g (normal range 0–50 μ g/g) and serum magnesium level, 0.82 mmol/L (normal range, 0.7-1 mmol/L). T cell spot test for tuberculosis (T-SPOT. TB) revealed negative findings. She also had no history of

© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

^{*}Correspondence: wulily525@126.com

alcohol use or drug abuse. Subsequently, treatment with infliximab was initiated at a dosage of 5 mg/kg. She did not experience any side effects after the first infliximab infusion. Two weeks later, she received the second infliximab infusion (5 mg/kg), but after 5 days, she suddenly developed short episodes of impairment of consciousness at home along with limbs twitches and the extroversion of eyeball. During the episode, her tongue was bitten, and her head was hurt. The episodes lasted for approximately 3 min, and she was taken to a local hospital for treatment by her family. However, she was not treated after observation at the hospital (details unspecified). According to the schedule, the patient received the third infliximab infusion at a loading dose of 5 mg/kg. She experienced repeated episodes after 5 days of the third infusion. She was taken to the local hospital, and craniocerebral CT showed no obvious abnormalities. She was then admitted to the Department of Neurology for further evaluation. Laboratory data showed normal findings, except a high L-cholesterol level (3.35 mmol/L; normal range, 1.89-3.1 mmol/L) and low lencocyte count (2.7 \times 10⁹/L; normal range, $3.5-9.5 \times 10^9$ /L). All physical examination findings were unremarkable. On the third day of admission, she experienced another similar seizure episode. Therefore, diazepam (5 mg) and sodium valproate(800 mg) were administered intravenously to control the seizures. No recurrence was observed after treatment during hospitalization. She underwent a brain 3.0 T magnetic resonance angiography (MRA), which showed no apparent abnormality. Video electroencephalography revealed background activity in the alpha range with an amplitude reduction but a good waveform. On both sides of the forehead and temporal area, scattered sharp waves were observed; the waves were more obvious on the right side. During the monitoring period, the patient was cooperative and did not show any behavioural abnormalities. The Electroencephalogram (EEG) confirmed the diagnosis of seizures and so far we highly suspected that the occurrence of the seizures may be associated with the use of infliximab. The patient started maintenance therapy with valproic acid (500 mg/day) and was discharged after 6 days. Although there was a clear response to infliximab with a reduction of diarrhoea and abdominal pain, the infliximab treatment was ceased and no seizures occurred after discharge. Now thalidomide (25 mg/d) was used to maintain remission of CD. The patient was following up for the moment.

Discussion and conclusions

Infliximab is a chimeric monoclonal antibody against the soluble and the membrane tumour necrosis factor (TNF)- α [4]. It is effective in inducing and maintaining remission in patients with moderate-to-severe CD refractory to conventional therapy [5]. However, administration of infliximab is associated with a well-recognized risk of infusion-related adverse events, such as infusion reactions, autoimmune disorders, malignancies, opportunistic infections, and serious infections [6]. The neurological effects of infliximab have also been reported. Headache is the most commonly reported, occurring in 12–18% of patients studied in the clinical trial setting [7]. The other commonly reported events include peripheral neuropathy [8] and central nervous system and/or spinal cord demyelination. Most patients have good tolerance to infliximab; however, with its wide use in various autoinflammatory and immune diseases, it is expected that more adverse drug reactions will be reported in the future.

A literature review revealed that infliximab-related seizures have been rarely reported (Table 1). In 2008, a 14-year-old boy with active CD experienced probable occipital lobe seizures, followed by several episodes of generalized tonic clonic seizures, 5 days after the first infliximab administration [9]. In 2011, Francesco Brigo et al. [10] reported a case of a 74-year-old man with CD who developed a sudden seizures 2 days after the second infliximab administration. His medical history was notable for hepatitis C virus cirrhosis with normal liver function and for an ischemic right temporo-occipital stroke, but he did not have a history of previous seizures. Electroencephalography showed any paroxysmal activity. In 2011, Rosemary Haddock et al. [11] reported a case of posterior reversible encephalopathy syndrome in an 8-year-old girl with CD after infliximab administration and colectomy. In 2016, Chow et al. [12] reported a similar case of a 24-year-old woman who developed posterior reversible encephalopathy syndrome(PRES) after the second treatment with infliximab. Among the abovementioned, two cases occurred after the second injection of infliximab, and two occurred after the first injection of infliximab. There seemed to be no apparent consistency in the time of the occurrence of the adverse reaction and definitely none of the patients had a history of previous seizures.

In our case, there was a direct correlation between seizures and infliximab administration. To the best of our knowledge, this is one of few case reports of infliximabinduced seizures. In contrast to the previous cases, our patient experienced the rechallenge events. Five days after the second infusion, the patient experienced actually a seizure, just failing to give enough attention. She again experienced seizures after the third infusion. This positive rechallenge was the strongest proof of side effects of infliximab. In the absence of infective, metabolic encephalopathy and other known etiologies, symptoms regressed quickly and completely. We also ruled out the possibility of seizures caused by other drugs because no

Patients	Age at presentation, gender	Inflammatory disorder	TNF-alpha inhibitor onset to seizures	Features of seizures	EEG	CSF	Other	Treatment for the seizures	Seizures outcome	Inflammatory disorder outcome	Study author and year of publication
-	14, male	Crohn's disease	5 days after the first infliximab administration	Repeated episodes each lasting about 1 min by several by several by several periods of generalized tonic clonic seizures lasting more than 6 min	Mild excess slow wave activity	Normal	MRI revealed abnormal T2 and fluid- attenuated inversion recovery signal hyper- signal hyper- signal hyper- intensities in a broadly symmetrical distribution affecting the cerebellar hemispheres, poccipital parietal lobes, and peripheral frontal lobes	inhibitor stopped, phenytoin	No more seizures occurred	Remission for 6 months and finally relapse, culminating in colectomy and ileos- tomy.	Zamvar,2009 ⁽⁹⁾
2	74, male	Crohn's disease	2 days after the second infliximab administra- tion	Impairment of conscious- ness, amnesia and arrest of volitional movements, confusion and diso- rientation, aggressive- ness	Focal paroxys- mal activity	Not recorded	MRI showed encepha- lopathy involving mainly corti- cal regions	TNF-alpha inhibitor stopped	No more seizures occurred	Not recorded	Brigo,2011 ^[10]
m	24, female	Crohn's disease	3 days fol- lowing the second infliximab infusion	Experienced 2 episodes of generalized tonic clonic seizures	Diffuse nonspecific cerebral dysfunction	Not recorded	MRI showed scattered T2/ FLAIR signal abnormalities in the sub- cortical white matter pre- dominantly in the frontal and posterior parietal lobes	TNF-alpha inhibitor stopped	No more seizures occurred	Not recorded	Chow,2016 ^[12]

Table 1 Summary of patient characteristics, seizures, and outcome

Patients	Age at presentation, gender	Inflammatory disorder	TNF-alpha inhibitor onset to seizures	Features of seizures	EEG	CSF	Other	Treatment for the seizures	Seizures outcome	Inflammatory disorder outcome	Study author and year of publication
4	8, female	Crohn's disease	13 days after the first infliximab infusion	Nausea, visual disturbance, unresponsive dilated reac- tive pupils, bradycardic and hyper- tensive.	Right temporal lobe dysfunc- tion	Normal	MRI showed abnormal high signal in the subcorti- cal region, bilateral occipital occipital lobes, and on the right side with extension to involve the right tempo- ral region	TNF-alpha inhibitor stopped, benzodi- azepine, phenytoin	Three focal seizures post discharge	Well controlled, and no fur- ther seizures at two year follow up.	Haddock,2011 ^[11]
TNF, tumor r	necrosis factor; EEG	i, electroencephalo	gram; CSF, cerebro	spinal fluid; MRI: m	agnetic resonance i	maging					

Table 1 (continued)

special drugs were administered before the first three seizures except infliximab. MRA revealed no abnormalities. Based on the video electroencephalography findings, we speculated that the seizures were clearly associated with infliximab-related neurotoxicity. In previously reported cases, Posterior Reversible Encephalopathy Syndrome (PRES) has been reported, but in our case, both clinical symptoms and neuroradiological results were incompatible with the diagnosis of PRES. Therefore, this case was different from the other previously reported cases.

The mechanism of infliximab-induced seizures is unclear. However, it may be due to the systemic proinflammatory effects of α -TNF agents that cause an inflammatory response in the nerves [13]. Therefore, infliximab should be cautiously administered to patients to minimize possible morbidity for patients. Medication withdrawal is the first step in managing patients with suspected drug-induced neuropathy [14], The adverse events can occur in the initial stage of infliximab treatment during induction phase. Moreover, all cases reported thus date had no history of previous seizures and no other plausible cause of the seizures. Consequently,we must underline the possibility of serious and unexpected adverse reactions to infliximab, which are rare and unpredictable. Considering the elimination half-life of infliximab (10 days), we should pay particular attention to the adverse reactions after infliximab injection, especially before and after the second injection. Various neurological complications such as demyelination and peripheral neuropathy after treatment with TNF- α inhibitors have been reported [14, 15]. For patients with a history of demyelination, seizures or other serious neurological disorders, the use of TNF- α inhibitors may increase the risk of exacerbation of neurological symptoms. Neurological assessment and tight clinical monitoring before and during therapy with infliximab should be performed in patients with pre-existing seizure disorders. If absolutely necessary, prior assessment and appropriate measures should be still taken before initiating therapy. Further studies are still needed to evaluate the exact relationship between infliximab and seizures.

Abbreviations

CD: Crohn's disease; IBD: inflammatory bowel disease; TNF-a: Tumor necrosis factor-alpha; MRI: Magnetic resonance imaging; MRA: Magnetic Resonance Angiography; EEG: Electroencephalogram; CT: Computed tomography; PRES: Posterior Reversible Encephalopathy Syndrome.

Acknowledgements

All authors thank the patient for her support.

Authors' contributions

LZJ performed the literature review. ZXQ collected the clinical data. WL prepared the first version of the manuscript. All authors participated in further drafting and revision of the manuscript. All authors read and approved the final manuscript.

Funding

This research was funded by Health Commission of Zhejiang Province (No.2020KY201) and Zhejiang Chinese Medical University (No.KC201936). The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

This case report contains clinical data from the electronic medical record in the Nanjing Drum Tower Hospital. The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Authors' institution does not require ethical approval for publication of a single case report. Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Pharmacy, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 3 Qingchun Road, Hangzhou 310006, Zhejiang, China. ²Department of gastroenterology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, Jiangsu, China. ³Center of Clinical Evaluation, The First Affiliated Hospital of Zhejiang Chinese Medical University, 54 Youdian Road, Hangzhou 310006, Zhejiang, China.

Received: 30 November 2020 Accepted: 20 April 2021 Published online: 27 April 2021

References

- Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. Drug Saf. 2004;27(5):307–24.
- Melsheimer R, Geldhof A, Apaolaza I, Schaible T. Remicade[®] (infliximab): 20 years of contributions to science and medicine. Biologics. 2019;13:139 – 78.
- Aubin F, Carbonnel F, Wendling D. The complexity of adverse side-effects to biological agents. J Crohns Colitis. 2013;7(4):257–62.
- Bramuzzo M, Arrigo S, Romano C, et al. Efficacy and safety of infliximab in very early onset inflammatory bowel disease: a national comparative retrospective study. Unit Eur Gastroenterol J. 2019;7(6):759–66.
- Zaltman C, Amarante H, Brenner MM, et al. Crohn's disease-treatment with biological medication. Rev Assoc Med Bras. 2019;65(4):554–67.
- Wang X, Cao J, Wang H. Risk factors associated with Infusion Reactions to Infliximab in Chinese Patients with Inflammatory Bowel Disease: A Large Single- Center Study. Med Sci Monit. 2019;25:2257–64.
- Gill C, Rouse S, Jacobson RD. Neurological complications of therapeutic monoclonal antibodies: trends from oncology to rheumatology. Curr Neurol Neurosci Rep. 2017;17(10):75.
- Shivaji UN, Sharratt CL, Thomas T, et al. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2019;49(6):664–80.
- Zamvar V, Sugarman ID, Tawfik RF, Macmullen-Price J, Puntis JW. Posterior reversible encephalopathy syndrome following infliximab infusion. J Pediatr Gastroenterol Nut. 2009;48(1):102–5.
- Francesco Brigo 1, Luigi Giuseppe Bongiovanni. et al. Infliximab-related seizures: a first case study. Epileptic Disord. 2011;13(2):214–7.
- Haddock R, Garrick V, Horrocks I, Russell RK. A case of posterior reversible encephalopathy syndrome in a child with Crohn's disease treated with infliximab. J Crohns Colitis. 2011;5(6):623–7.

- Chow S, Patnana S, Gupta NK. Posterior reversible encephalopathy syndrome in a patient with Crohn's disease on infliximab. J Clin Gastroenterol. 2016;50(8):687.
- Tsouni P, Bill O, Truffert A, Liaudat C, Ochsner F, Steck AJ, et al. Anti-TNF alpha medications and neuropathy. J Peripher Nerv Syst. 2015;20(4):397–402.
- 14. Stübgen JP. Tumor necrosis factor-alpha antagonists and neuropathy. Muscle Nerve. 2008;37(3):281–92.
- 15. Deepak P, Stobaugh DJ, Sherid M, Sifuentes H, Ehrenpreis ED. Neurological events with tumour necrosis factor alpha inhibitors reported to the

Food and Drug Administration A dverse Event Reporting System. Aliment Pharmacol Ther. 2013;38(4):388–96.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

