Journal of Neuroimmunology 357 (2021) 577631

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short Communication

Infliximab for reversible dementia in acute onset of neuro-Behçet's disease: A case report and cytokine analysis

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ARTICLE INFO

Keywords:
Neuro-Behçet's disease
Reversible dementia
Infliximab
Methotrexate
Cerebrospinal fluid
IP-10

ABSTRACT

We describe a 49-year-old female patient with neuro-Behçet's disease (NBD) with acute onset of fever and symptoms of dementia. High-dose glucocorticoid was partially effective for cognitive impairment, and infliximab, an anti-TNF-α antibody, gradually improved the symptoms. An analysis of cytokines showed that IP-10 in the cerebrospinal fluid was higher than that in the peripheral blood, and both decreased after treatment. This is the first known case of NBD wherein the patient with acute onset of dementia responded to a treatment with infliximab. In glucocorticoid-resistant patients, it is important to consider the introduction of infliximab to prevent irreversible brain dysfunction.

1. Introduction

Behçet's disease (BD) is characterized by aphthous stomatitis, uveitis, genital ulcers, and skin lesions. Central nervous system involvement, neuro-BD (NBD), is one of the most serious complications of the disease (Hatemi et al., 2018). It is known that there are two types of NBD: acute onset NBD (AONBD) and chronic progressive NBD (CPNBD) (Hirohata et al., 1997, 2012; Akman-Demir et al., 1999). Dementia and personality changes sometimes occur in CPNBD, but rarely in AONBD, which often takes the form of meningoencephalitis with fever. Here we report that a patient with AONBD, acute onset of fever, and cognitive impairment was successfully treated with infliximab (IFX), and the results of cytokine analysis of serum and cerebrospinal fluid (CSF) performed before and after treatment.

2. Case report

A 49-year-old female patient presented to our department with prolonged high fever, sudden memory disturbance, and attention deficit. One month before her arrival, she experienced high fever exceeding 38 °C. At approximately the same time, she developed attention disorder and cognitive impairment, although she had previously exhibited an animated personality and no memory loss. She had recurring oral ulcers from childhood. There was no family background of BD or a history of smoking or heavy drinking. On examination, the Mini Mental State Examination, a tool to assess cognitive disorder, was as low as 22 of 30 points. She had nuchal rigidity and did not show other neurological findings including dysarthria, dysphagia, ataxia, and abnormalities in tendon reflexes. She exhibited no arthritis, genital ulcers, or ocular abnormalities. Erythema nodosum was found on the left lower leg. Skin biopsy showed findings of panniculitis and thrombotic

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https://doi.org/10.1016/j.jneuroim.2021.577631
Received 12 February 2021; Received in revised form 19 May 2021; Accepted 5 June 2021
Available online 8 June 2021

phlebitis, results suggestive of BD.

The initial workup showed an elevated erythrocyte sedimentation rate of 46 mm/h and a C-reactive protein level of 3.5 mg/dL. There were no abnormalities of electrolytes and trace elements associated with cognitive disorders. Tests for autoantibodies including anti-nuclear antibody; anti-DNA antibody; anti-SS-A antibody; anti-neutrophil cytoplasmic antibody; and anti-*N*-methyl-D-aspartic acid receptor antibody were negative. Serology results for human immunodeficiency virus, syphilis, hepatitis B virus, and hepatitis C virus were also negative. Human leukocyte antigen (HLA)-A26 and B51 results were negative. CSF evaluation showed that total cell counts, total protein, and interleukin 6 (IL-6) were elevated at 51/μL, 46 mg/dL, and 280 pg/mL, respectively. Oligoclonal bands were absent. Polymerase chain reaction findings for herpes simplex virus, varicella zoster virus, Epstein-Barr virus, and *Mycobacterium tuberculosis* were negative. CSF cultures showed no bacterial or fungal growth. Magnetic resonance imaging (MRI) of the head showed T2-prolonged lesions in the left basal ganglia enhanced by gadolinium but no brain atrophy (Fig. 1a). Whole-body contrast-enhanced computed tomography, gastroscopy, colonoscopy, transvaginal echocardiography, and breast cancer screening showed no signs of malignancy, ruling out paraneoplastic syndrome.

After excluding infection etiology and other autoimmune diseases such as systemic lupus erythematosus and neuromyelitis optica, the diagnosis of NBD was made according to the international diagnostic criteria for BD (Davatchi et al., 2014) from findings of recurrent oral aphthae, erythema nodosum, thrombophlebitis, and neurological involvement (meningoencephalitis and cognitive disorder). Oral prednisolone (60 mg/day) was initiated and immediately lowered the patient's fever, although the treatment failed to improve her cognitive impairment. In addition, ^{123}I-IMP brain perfusion single-photon emission tomography (SPECT) performed after prednisolone administration showed diffuse decreased blood flow in the cerebral hemispheres and brain stem. We introduced methotrexate (MTX) and IFX as more intensive treatment for acute onset cognitive disorder to avoid irreversible brain damage. Oral MTX (8 mg/week) was started on the 22nd hospital day and was titrated up to 12 mg/week. Infliximab (5 mg/kg) was administered intravenously at 2 weeks, 6 weeks, and then every 8 weeks. The patient's cognitive disorder and attention deficit gradually improved after initiating MTX and IFX. Follow-up brain SPECT on the 34th hospital day showed increased cerebral blood flow in the cerebral hemispheres and brain stem. Retesting of the CSF on the 37th hospital day showed marked improvement of inflammation, with total cell counts, 4 /μL; total protein level, 33 mg/dL; and IL-6, 3.2 pg/mL. The patient's Mini Mental State Examination score on the 66th hospital day also showed an improvement in cognitive dysfunction, with 30 of 30 points. MRI of the head 8 months after therapy showed no T2-prolonged lesions in the left basal ganglia (Fig. 1b). The patient's clinical course is described in Fig. 2.

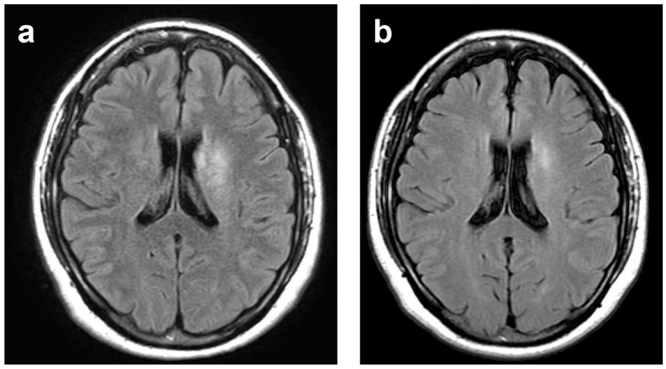

Fig. 1. MRI of the head: a) MRI showed T2-prolonged lesions in the left basal ganglia. There was no brain atrophy. b) MRI 8 months after therapy showed improvement of the T2-prolonged lesions in the left basal ganglia.

With the purpose of detecting cytokines that contributed to the clinical course in this patient other than IL-6, we compared cytokines in the peripheral blood and CSF before and after treatment (day 0 and day 50) (Table 1). Cytokines were analyzed using Bio-Plex Pro Cytokine Assays (Bio-Rad Laboratories, Hercules, CA), revealing that the level of IP-10 in the CSF was higher than in the peripheral blood.

3. Discussion

In this case report, we investigated three significant clinical issues. First, we found that acute onset cognitive dysfunction can occur in patients with AONBD. The patient reported here had acute onset meningoencephalitis, a known form of AONBD, but also exhibited cognitive impairment and behavioral changes. It is generally thought that cognitive impairment is rare in AONBD (Hirohata et al., 1997, 2012; Akman-Demir et al., 1999). However, in a recent meta-analysis of NBD that included 11 reports of 184 patients with AONBD and 114 patients with CPNBD, no less than 7% of patients with AONBD exhibited cognitive impairment compared with 61% of patients with CPNBD (Ishido et al., 2017). The patient reported here did not show characteristic findings of CPNBD, such as slowly progressive dementia, brain stem and cerebral atrophy, and persistent high CSF IL-6 levels (Akman-Demir et al., 1999); whereas she rather showed acute onset of the T2-prolonged lesions in the left basal ganglia on MRI. The basal ganglia cooperate with the cerebral cortex to form the cortico-basal ganglia loop, among which the motor and limbic loops play an integrative role in cognitive information processing (Middleton and Strick, 2000). Considering that this MRI finding disappeared after the treatment, the finding was consistent with the neurological symptom of reversible cognitive disorder. We concluded that the acute onset cognitive impairment was associated with AONBD.

Second, acute onset cognitive dysfunction associated with AONBD can be reversed with IFX treatment. To our knowledge, there is no previous report of a response to IFX for cognitive impairment in AONBD. Because IFX, an anti-TNF-α antibody, was first reported to be effective in the treatment of CPNBD (Kikuchi et al., 2008), its efficacy has been widely reported in AONBD as well (Vallet et al., 2015; Desbois et al., 2016; Watanabe et al., 2018). The recommendations of the International Society for BD (Hatemi et al., 2018) include the administration of high-dose glucocorticoids for AONBD first, considering IFX in patients with severe glucocorticoid-refractory disease. In our patient, the increased inflammatory response was rapidly improved by glucocorticoid administration, but cognitive dysfunction was refractory. SPECT taken after glucocorticoid induction also showed decreased blood flow throughout the cerebrum, including the brain stem. Considering that adequate treatment was required before cognitive dysfunction became irreversible, MTX and IFX were administered, resulting in an improvement in cognitive dysfunction. Previous reports of cognitive dysfunction associated with AONBD showed only partial response to glucocorticoids (Deniz et al., 2009; Mimura et al., 2009), with no reports of treatment with IFX. Treatment for cognitive dysfunction with IFX before it becomes irreversible should be considered in glucocorticoid-resistant patients.

Third, cytokine analysis suggested that IP-10 in the CSF may play some role in reversible cognitive impairment. The analysis of the peripheral blood showed that proinflammatory cytokines (TNF-α, IL1-β); chemokines (IL-8, IP-10, MCP-1, MIP1-α, MIP1-β, G-CSF); T helper 1 (Th1) type cytokines (IFN-γ, IL-2); and T helper 17 type cytokines (IL17-A) decreased after treatment, consistent with previous analyses of active NBD (Saruhan-Direskeneli et al., 2003; Zhou et al., 2012). The analysis of the CSF showed that the level of IP-10 in the CSF was higher than in the peripheral blood. This implies that IP-10 may be overproduced in the brain, especially glial cells (such as astrocytes and microglia) and T cells induced from the peripheral blood to the brain by the resulting gradient of IP-10. Because IP-10 has a chemotactic effect on T cells through the cell surface receptor CXCR3, which is generally expressed by activated

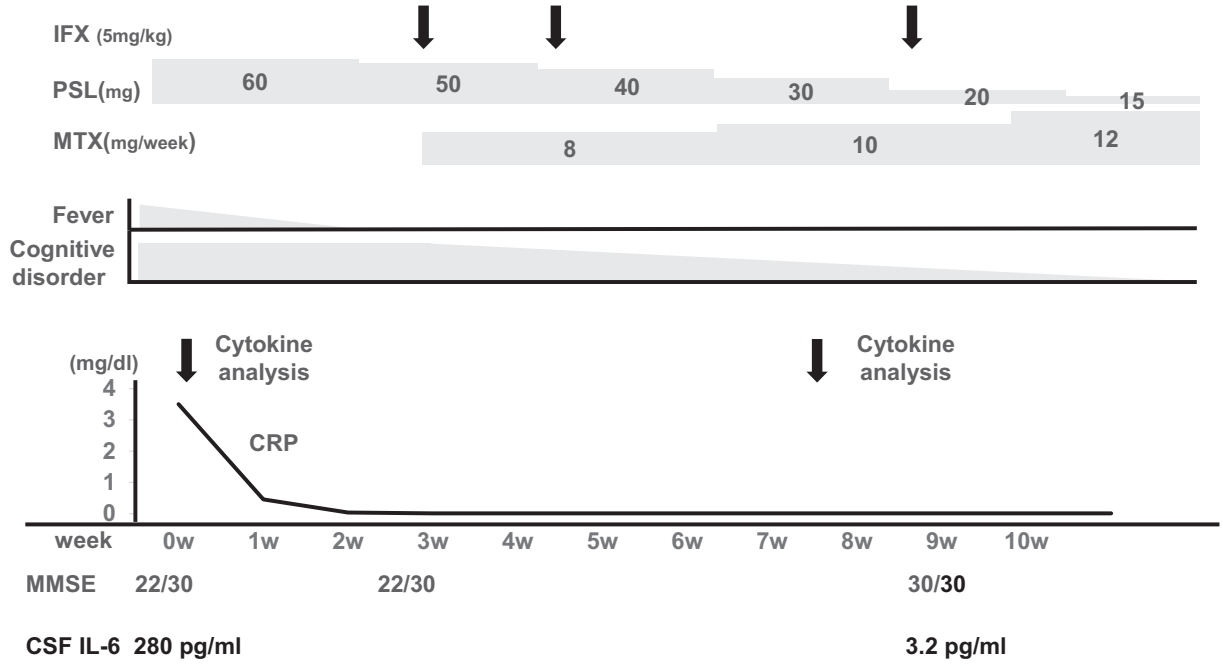

Fig. 2. Clinical course of the patient: IFX, infliximab; PSL, prednisolone; MTX, methotrexate; CRP, C-reactive protein; MMSE, Mini Mental State Examination; CSF, cerebrospinal fluid; IL-6, interleukin 6.

Table 1
Analysis of cytokine profile. Cytokines in peripheral blood serum and CSF before and after treatment were analyzed using Bio-Plex Pro Cytokine Assays, revealing that the level of IP-10 in the CSF was higher than in the peripheral blood. Unit of cytokine concentration was pg/mL.

	Serum		CSF	
	Before	After	Before	After
IL-1β	116.1	1.5	ND	ND
IL-2	116.1	1.4	ND	ND
IL-8	4160.0	1.9	59.9	38.6
IL-12	4.8	1.6	ND	ND
IL-17A	144.8	6.6	ND	ND
MIP-1α	512.9	0.80	0.4	ND
MIP-1β	1563.0	62.0	1.95	1.2
MCP-1	125.7	79.6	22.4	82.0
TNF-α	764.5	17.2	ND	ND
IFN-γ	28.0	5.1	0.30	1.0
G-CSF	1321.7	36.9	11.1	ND
IP-10	2932.4	565.5	4501.1	278.0

IL, Interleukin; MIP-1, Macrophage inflammatory protein-1; MCP-1, Monocyte chemoattractant protein 1; TNF-α, Tumor necrosis factor alpha; IFN-γ, Interferon-γ; G-CSF, Granulocyte colony stimulating factor; IP-10, Interferon-γ inducible protein 10; ND, Not detected.

Th1 and CD8 T cells, the enhanced IP-10 levels suggest type 1 immunity (Dufour, 2002), consistent with previous reports indicating the involvement of Th1 cells in the pathogenesis of NBD (Belghith et al., 2018; Saruhan-Direskeneli et al., 2003; Hamzaoui et al., 2011; Zhou et al., 2012). It has been reported previously that IP-10 concentrations were higher in the CNS of patients with NBD compared with healthy individuals (Saruhan-Direskeneli et al., 2003) and that BD monocytes were more likely to overexpress IP-10 protein upon stimulation with IFN-γ (Ambrose et al., 2015). In our patient, the level of IFN-γ in the CSF was not high and the cytokines that may contribute to the production of IP-10, such as IFN-α, were not measured. Therefore, the key stimuli responsible for IP-10 production in NBD need to be further examined. Furthermore, some studies have shown that IP-10 was directly involved in cognitive dysfunction in the brain in addition to T cell activation and migration (Bajetto et al., 2002). In patients with Alzheimer's disease, known to cause progressive cognitive impairment, it has been reported that IP-10 and CXCR3 were overexpressed in astrocytes and neurons, and that overexpression of IP-10 caused amyloid formation, which is the primary cause of Alzheimer's disease (Sui et al., 2006). These reports and our analysis indicate the involvement of IP-10 in cognitive impairment in AONBD. Additionally, IFX treatment may have reduced the level of IP-10 in the CSF and peripheral blood. IP-10 is induced by TNF-α as well as IFNs (Ohmori et al., 1993); thus, anti-TNF-α antibodies may decrease the level of IP-10, as shown in the peripheral blood of patients with rheumatoid arthritis (Han et al., 2016). Anti-TNF-α antibodies are also reported to have a direct inhibitory effect on TNF-α -producing cells (Horiuchi et al., 2010; Mitoma et al., 2008). It is possible that IFX acted directly on glial cells, which have been identified as TNF-α-producing cells in CNS inflammation (Olmos and Lladó, 2014), and subsequently reduced the production of IP-10 from the glial cells.

4. Conclusion

This is the first known case of a patient with AONBD presenting with acute onset dementia responding to IFX. In patients who show poor improvement with glucocorticoids, it is important to consider the introduction of IFX to prevent irreversible brain dysfunction. Cytokine analysis suggested that IP-10 is involved in reversible cognitive impairment in this patient with NBD.

Declaration of Competing Interest

The authors have no conflict of interest.

Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English language review.

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