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CASE REPORT

An attack of acute neuro-Behçet's disease during the course of chronic progressive neuro-Behçet's disease: report of two cases

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Abstract A 29-year-old man and a 36-year-old man developed attacks of acute neuro-Behçet's disease (NB) (right Horner's syndrome and right hemiplegia and dysarthria, respectively) during the course of chronic progressive NB (acute on chronic). Although both patients recovered from acute NB after treatment with infliximab or corticosteroids, they continued to show manifestations of chronic progressive NB. It is suggested that acute NB and chronic progressive NB are different in their pathogenesis.

Keywords Infliximab · IL-6 · Cerebrospinal fluid · Magnetic resonance imaging

Introduction

Behçet's disease is a chronic, relapsing, inflammatory disorder of unknown etiology characterized by recurrent oral ulcers, skin lesions, genital ulcers, and uveitis [1]. Central nervous system (CNS) involvement in Behçet's disease is a serious complication [neuro-Behçet's disease (NB)]. Recent reports indicate that NB can be classified into acute type and chronic progressive type [2, 3]. Thus, acute NB is characterized by acute meningoencephalitis with or without focal lesions in the brainstem, cerebellum, or basal ganglia, presenting high-intensity areas in T2-weighted images or fluid-attenuated inversion recovery (FLAIR) images on magnetic resonance image (MRI) scans [2]. Acute NB responds well to corticosteroid and is usually self-limiting, although recurrence of attacks sometimes occurs [2]. By contrast, chronic progressive NB is characterized by intractable, slowly progressive neurobehavioral changes, ataxia, and dysarthria [2], along with persistent marked elevation of cerebrospinal fluid (CSF) interleukin-6 (IL-6) >20 pg/ml [2, 4, 5]. MRI findings usually show only atrophy of brainstem and cerebellum without T2 high-intensity lesions [2, 3]. Therefore, it is suggested that the pathogenesis of acute NB might be different from that of chronic progressive NB.

In this study, we report two patients who presented an attack of acute NB during the course of chronic progressive NB, suggesting the presence of different pathogenetic mechanisms between these two types of NB.

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Case reports

Case 1

A 29-year-old man first consulted his primary care physician for the sudden onset of melena in December 1999. He had had recurrent oral aphthous stomatitis for several years. He was diagnosed as having ileocecum ulcer of unknown origin and treated with mesalazine. In 2001, he presented with blurred vision due to posterior uveitis and was diagnosed as having Behçet's disease. He had a uveitis attack again in 2003. In June 2006, he presented with paresis on his right arm and bilateral legs and was admitted to our hospital. MRI scans revealed high-intensity lesions in pons on T2-weighted images (Fig. 1). He was diagnosed as NB, but he recovered from the manifestations without

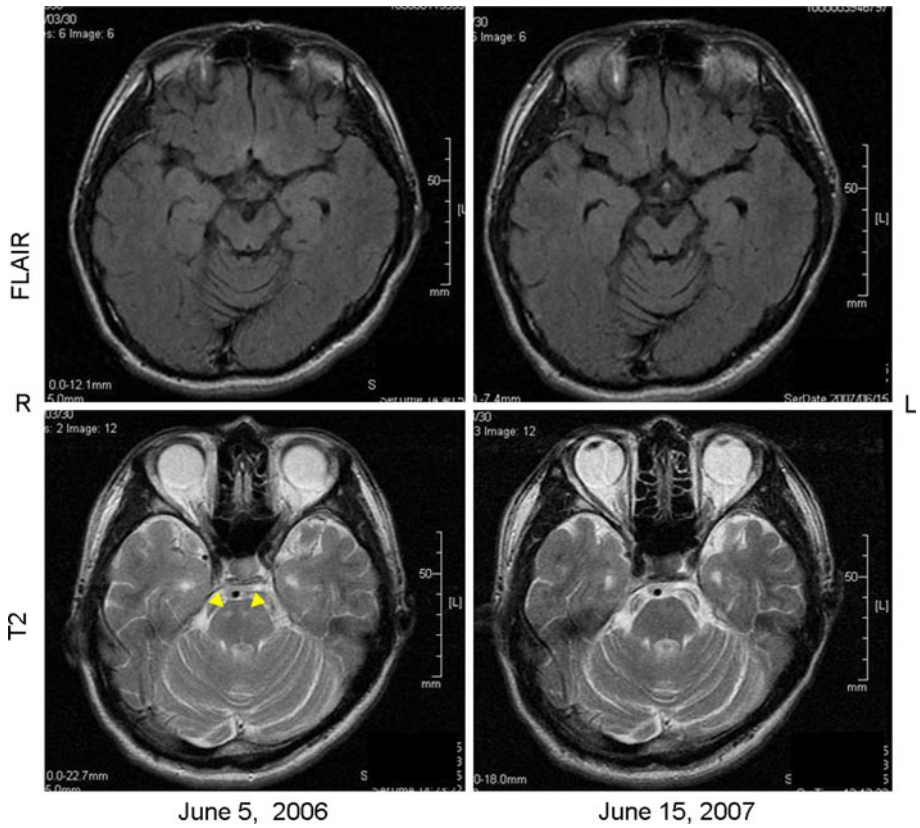

Fig. 1 Changes in brain magnetic resonance imaging (MRI) scans of case 1 between June 2006 and June 2007. Progression of brainstem atrophy was remarkable. *Arrowheads* indicate high-intensity lesions

corticosteroids in 2 weeks. However, he began to present urinary incontinence in July 2006 (Fig. 2), which slowly progressed despite steroid pulse therapy (methyl prednisolone 1 g/day for 3 consecutive days). In June 2007, he began to complain of difficulty in walking and was admitted to our hospital. Human leukocyte antigen (HLA)-B51 was positive, and CSF IL-6 was markedly elevated (460 pg/ml). In addition, brain MRI scans showed progression of an atrophy of brainstem despite disappearance of high-intensity lesions in the pons compared with the brain MRI scans in June 2006 (Fig. 1). He was diagnosed with chronic progressive NB, and treatment with methotrexate (MTX) 10 mg/week was started. Although CSF IL-6 slightly decreased to 118 pg/ml, gait disturbance slowly progressed. Therefore, administration of infliximab was considered. In the meantime, he suddenly developed diplopia and palpebral ptosis of the right eye on 12 December 2007 and was admitted to our hospital.

On admission, the patient was conscious, and his blood pressure was 137/76 mmHg with pulse rate of 82 bpm. Neurological examination disclosed right Horner's syndrome with right palpebral ptosis and miosis. He continued to show cerebellar signs in his lower extremities, with ataxic gait, urine incontinence, and bilateral hyperreflexia with bilateral Babinski's sign. Laboratory studies showed CSF cell counts 8.1/mm^3 and CSF IL-6 103 pg/ml. MRI scans revealed high-intensity areas in the right basal ganglia and midbrain on FLAIR images (Fig. 2). He was diagnosed with acute NB, and infliximab was given at 5 mg/kg body weight immediately, along with the increased dose of MTX (15 mg/week). He recovered from right Horner's syndrome completely, the high-intensity lesions disappeared after three shots of infliximab (0, 2, and 6 weeks) (Fig. 2), and CSF IL-6 declined to <20 pg/ml (19 pg/ml). However, CSF IL-6 was found to be elevated to 123 pg/ml 6 months later and continued to be >100 pg/ml thereafter despite repeated injection of infliximab (5 mg/kg body weight every 8 weeks until March 2010) (Fig. 3). Accordingly, ataxia and urinary incontinence persisted, although the recurrence of attacks of acute NB, including right Horner's syndrome, was not observed until March 2010.

Case 2

A 36-year-old man first consulted his primary care physician for the sudden onset of headache, dizziness, weakness of the right leg, and ataxia in September 2004. He had had recurrent oral aphthous stomatitis, genital ulcers, and folliculitis for several years. MRI scans revealed high-intensity lesions in the left thalamus on FLAIR images (Fig. 4). He was diagnosed as NB, and the neurological manifestations subsided spontaneously. However, he began to present

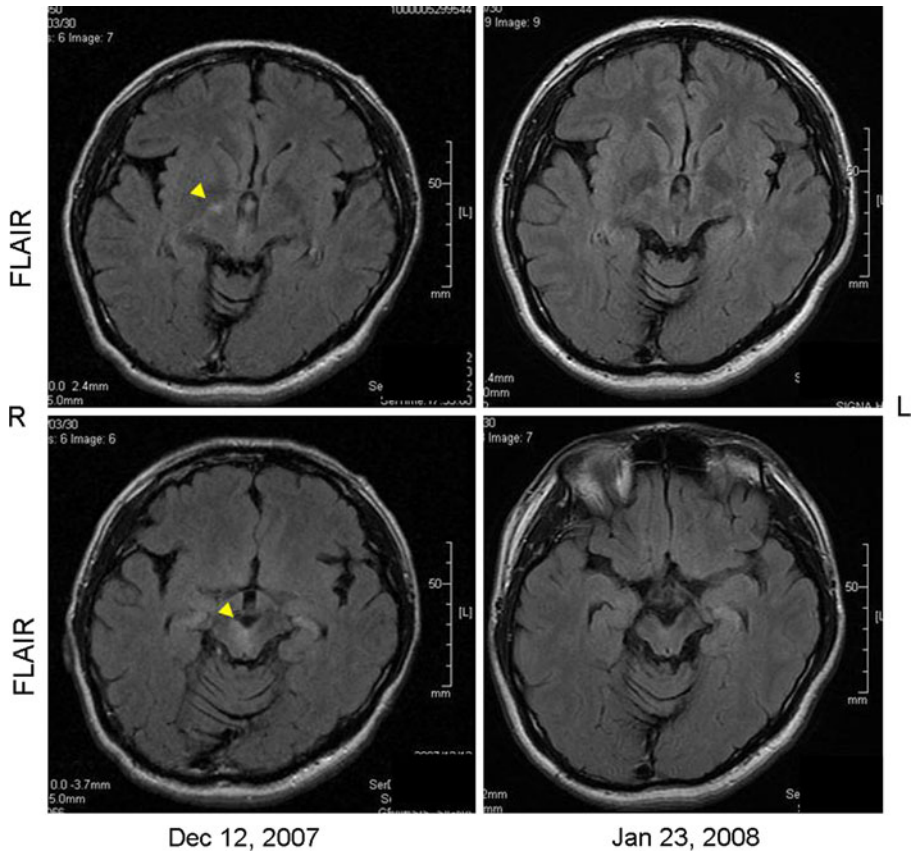

Fig. 2 Onset and recovery of acute neuro-Behçet's disease (NB) attack in case 1. Changes of brain magnetic resonance imaging (MRI) scan fluid-attenuated inversion recovery (FLAIR) images. *Arrowheads* indicate high-intensity lesions

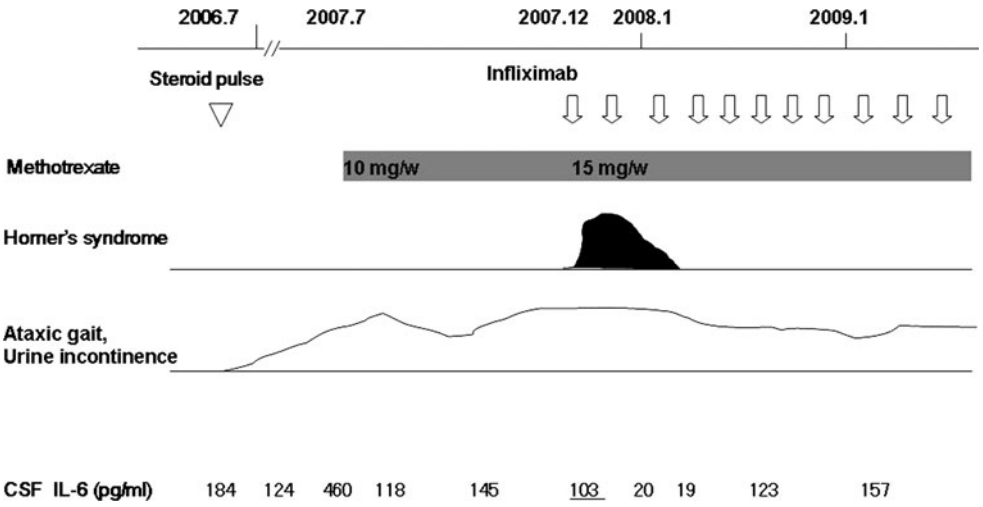

Fig. 3 Clinical course of case 1. Cerebrospinal fluid (CSF) interleukin-6 (IL-6) value at onset of acute neuro-Behçet's disease (NB) is shown by *underline*

myoclonus of the legs, ataxic gait, urinary incontinence, and dementia, which progressed slowly, and was admitted in January 2005. HLA-B51 was positive. CSF IL-6 was markedly elevated (353 pg/ml) (Fig. 5). In addition, brain MRI scans showed a slightly atrophy of the brainstem on T1-weighted images but no high-intensity lesions on FLAIR images (Fig. 4). High doses of corticosteroid [one course of methylprednisolone pulse (1 g/day for 3 consecutive days) followed by orally administered prednisolone 30 mg/day] was administered but was not effective in preventing progression of the manifestations. He was thus diagnosed with chronic progressive NB, and treatment with MTX 6 mg/week was started. CSF IL-6 decreased to 62 pg/ml, and he was discharged. However, dementia progressed slowly with continuing elevation of CSF IL-6 after discharge (Fig. 5). In the meantime, he suddenly developed

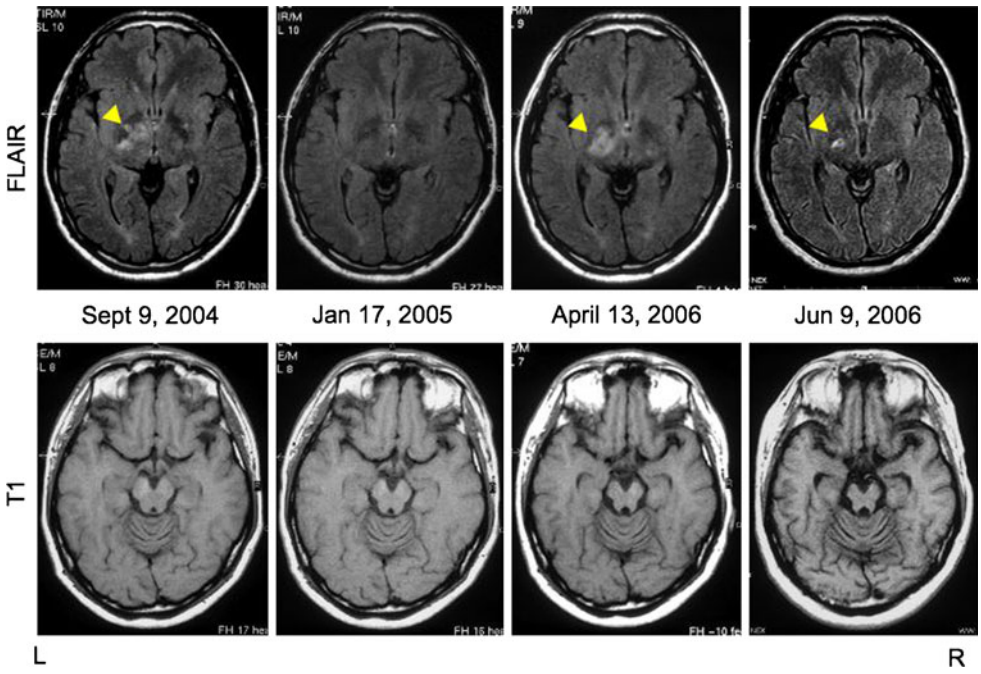

Fig. 4 Serial changes in brain magnetic resonance imaging (MRI) scans in case 2. Brainstem atrophy markedly progressed despite reduction of high-intensity lesions in the left internal capsule between 13 April 2006 and 9 June 2006. *Arrowheads* indicate high-intensity lesions

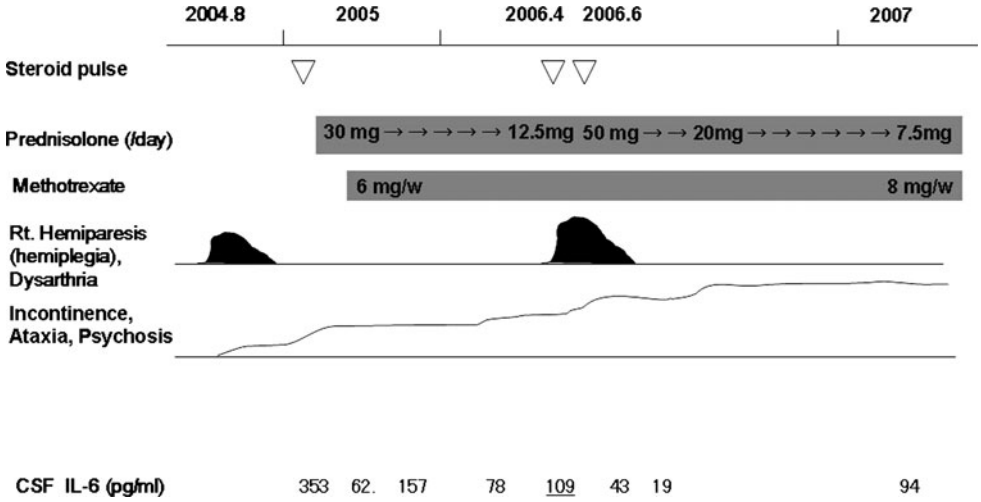

Fig. 5 Clinical course of case 2. Cerebrospinal fluid (CSF) interleukin-6 (IL-6) value at onset of acute neuro-Behçet's disease (NB) is shown by *underline*

hemiplegia with dysarthria on 9 April 2006 and was admitted again.

On admission, the patient was conscious, and his blood pressure was 130/70 mmHg with pulse rate of 66 bpm. Neurological examination disclosed right hemiplegia, dysarthria, and bilateral hyperreflexia with right Babinski's sign. He also showed cerebellar ataxia and urinary incontinence. Laboratory studies showed CSF cell counts 5/mm^3 and CSF IL-6 109 pg/ml. MRI scans revealed high-intensity areas in the left internal capsule on FLAIR images (Fig. 4). In addition, brain MRI scans showed a remarkable progression of brainstem atrophy on T1-weighted images (Fig. 4). He was diagnosed with acute NB, and two courses of methylprednisolone pulse (1 g/day for 3 consecutive days) were given, followed by orally administered prednisolone 50 mg/day. He recovered from right hemiplegia and dysarthria and had a reduction in high-intensity lesions in the internal capsule within 2 months, and prednisolone was tapered to 20 mg/day. However, brainstem atrophy on T1-weighted images further progressed despite the reduction of high-intensity lesions on FLAIR images (Fig. 4). Accordingly, he continued to show dementia, urinary incontinence, ataxia, and myoclonus, which slowly worsened, with continuing elevation of CSF IL-6 (94 pg/ml in March 2007) thereafter (Fig. 5).

Discussion

We report two patients who showed CNS events of sudden onset during the course of slowly progressive neurological manifestations. It is clear that case 1 suffered from chronic

progressive NB after the episode of acute NB of hemiparesis in June 2006. Thus, he showed slowly progressive ataxia and urinary incontinence, along with persistent elevation of CSF. In addition, MRI scans revealed the progression of brainstem atrophy between 2006 and 2007. Although he received MTX and infliximab, CSF IL-6 remained >20 pg/ml—which has been shown to be the critical threshold for progression of neurological manifestations in chronic progressive NB [4, 5]—as of March 2010. He suffered an attack of right Horner's syndrome in December 2007 during the course of chronic progressive NB. Previous studies showed that infliximab is beneficial for acute NB and is also expected to prevent the recurrence of attacks of acute NB [6, 7]. Consistently, he almost completely recovered from right Horner's syndrome, along with the disappearance of the high-intensity lesions in the right basal ganglia and midbrain after 2 weeks of treatment with infliximab. In addition, he thereafter showed no attack of acute NB under continuing treatment with infliximab. These results indicate that infliximab is beneficial for treatment as well as prevention of acute NB, although control studies with a larger numbers of patients are required for confirmation.

Of note is that chronic progressive NB in case 1 did not respond satisfactorily to treatment with MTX and infliximab. Thus, CSF IL-6 was not satisfactorily decreased to <20 pg/ml, even after treatment with increased MTX and infliximab. It is therefore suggested that some patients are still resistant to MTX and infliximab, although both treatments have been shown to be beneficial for chronic progressive NB [5, 7, 8]. Further strategies, including the increase in dosages of infliximab, would be necessary for such intractable cases.

However, it appears that treatment with increased MTX and infliximab might have some effect in preventing progression of neurological manifestations despite the high levels of CSF IL-6. Recent studies have shown that CSF IL-6 was markedly decreased on the day after infliximab infusion and gradually increased thereafter [8]. Since IL-6 was measured just before each infusion of infliximab in case 1, it is likely that there might be some periods during which CSF IL-6 decreased to <20 pg/ml. Since infliximab was started at the same time as increased MTX dosage, it is difficult to evaluate separately the effect of the increased MTX dosage. Both might have some beneficial effect.

Case 2 suffered from chronic progressive NB after the self-limiting episode of acute NB with right leg weakness and ataxia in September 2004. Brainstem atrophy progressed before the second episode of acute NB (right hemiplegia and dysarthria) on 9 April 2006. Moreover, although his manifestation of acute NB improved and high-intensity lesions showed reduction on MRI FLAIR images upon treatment with high doses of corticosteroids, brainstem atrophy further progressed in June 2006. These results confirm that the pathogenesis of chronic progressive NB is different from that of acute NB. Thus, in case 2, acute NB improved with corticosteroid administration, whereas chronic progressive NB did not respond, as is consistent with previous reports [2–5].

Previous studies show that CSF cell counts and IL-6 are usually markedly elevated in acute NB [2]. Interestingly, however, both of our patients showed no marked elevation of CSF cell counts and IL-6 when they presented with acute attacks, and the reason for this remains unclear. It is suggested that the presence of persistent inflammation of chronic progressive NB might contribute to such CSF findings. Further studies are required to delineate this point.

The pathogenesis of NB remains unclear. Although elevation of several cytokines in CSF has been reported, two recent reports have emphasized that CSF IL-6 plays a crucial role in the immunopathogenesis of NB [9, 10]. Although elevation of polymorphonuclear neutrophils in CSF is frequently observed in NB, it has been shown that CSF IL-17 was not elevated in NB [11]; however, CXCL8 (IL-8) has been shown to be elevated [11]. It is therefore likely that CXCL8 might play a role in recruiting inflammatory cells, including neutrophils, into CNS in NB. Characteristic histopathological features of CNS in NB are perivascular infiltration of CD45RO+ T cells and CD68+ monocytes, but very few CD20+ B cells [12]. Since infliximab decreases CSF IL-6 in NB [8], it is suggested that infiltrating CD68+ monocytes might produce high amounts of IL-6. Further studies would be required to confirm this point.

In summary, our patients presented attacks of acute NB during the course of chronic progressive NB, which may be called acute on chronic. The sequence of events indicates that acute NB and chronic progressive NB have distinct pathogenetic backgrounds [12]. First, neurological manifestations of acute NB were accompanied by high-intensity lesions on MRI FLAIR images, whereas those of chronic progressive NB were not. Second, neurological manifestations of acute NB disappeared after administration of infliximab, whereas those of chronic progressive NB were sustained despite that treatment in case 1. Finally, neurological manifestations of acute NB were improved by corticosteroids, although those of chronic progressive NB were rather worsened, and brainstem atrophy progressed during the same periods of corticosteroid therapy in case 2. Further studies to delineate the mechanism for the acute-onset inflammation in acute NB as well as the mechanism for persistent inflammation in chronic NB are important for a complete understanding of the pathogenesis of NB.

Conflict of interest statement None.

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