ORIGINAL ARTICLE

Clinical characteristics of neuro-Behçet's disease in Japan: a multicenter retrospective analysis

Shunsei Hirohata · Hirotoshi Kikuchi · Tetsuji Sawada · Hiroko Nagafuchi · Masataka Kuwana · Mitsuhiro Takeno · Yoshiaki Ishigatsubo

Abstract To delineate the clinical characteristics of neuro-Behçet's disease (NBD), a multicenter retrospective survey was performed in BD patients who had presented any neurological manifestations between 1988 and 2008. The diagnosis of acute NBD, chronic progressive (CP) NBD, and non-NBD was confirmed by retrospective review of clinical records. Data on a total of 144 patients were collected; 76 with acute NBD, 35 with CP NBD, and 33 with non-NBD. High-intensity lesions on T2-weighted magnetic resonance imaging (MRI) were found in 60.5% of the patients with acute NBD, 54.2% with CP NBD, and 42.4% with non-NBD, whereas brainstem atrophy was observed in 7.5% with acute NBD, 71.4% with CP NBD, and 9.0% with non-NBD. The cerebrospinal fluid (CSF) cell count was prominently elevated in patients with acute NBD, but was normal in about 15% of those with CP NBD. The sensitivity and specificity of the CSF cell count for the diagnosis of acute NBD versus non-NBD were 97.4 and 97.0%, respectively (cut-off 6.2/mm^3). The sensitivity and specificity of CSF interleukin (IL)-6 for the diagnosis of CP NBD versus the recovery phase of acute NBD were 86.7 and 94.7%, respectively (cut-off 16.55 pg/ml). The results indicate that elevation of the CSF cell count and CSF IL-6 and the presence of brainstem atrophy on MRI are useful for the diagnosis of NBD.

Keywords Behçet's disease · Central nervous system · Cerebrospinal fluid · Diagnostic criteria · Magnetic resonance imaging

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Introduction

Behçet's disease (BD) is a chronic relapsing inflammatory disease of unknown etiology, presenting with recurrent aphthous stomatitis, uveitis, genital ulcers, and skin lesions. The disease is characterized by recurrent episodes of remission and exacerbation of various symptoms, whereas chronic sustained inflammation in certain tissues is rare [1]. Central nervous system (CNS) involvement in BD is caused either by primary neural parenchymal lesions [neuro-Behçet's disease (NBD)] or is secondary to major vascular involvement [2–4]. The latter type should be called vasculo-BD [2]. Several recent studies have disclosed that the parenchymal lesions (NBD) can be classified as acute NBD and chronic progressive (CP) NBD depending on their differential clinical courses, especially on their differential responses to steroids [3, 5–8].

Because factors other than BD can cause neurological manifestations, the diagnosis of NBD is often difficult and its treatment is challenging. The present study was therefore designed to delineate the clinical characteristics of acute NBD and CP NBD and to determine reliable diagnostic parameters.

Patients and methods

Study design

This study was performed as a project by the Behçet's Disease Research Committee (hereafter, the Research Committee) guided by the Ministry of Health, Labor and Welfare of the Japanese Government in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. This study was approved by the ethics committees of the 6 institutions with which each of the authors is affiliated. We performed an exhaustive questionnaire survey on BD patients who had been hospitalized due to neuropsychiatric manifestations between 1988 and 2008. The contents of the questionnaire included age, gender, HLA-B51, history of smoking, date of diagnosis of BD (fulfillment of the International Study Group for BD criteria), date and details of presentation of neuropsychiatric manifestations, cerebrospinal fluid (CSF) findings, magnetic resonance imaging (MRI) findings, treatment and outcome, and final diagnosis assigned retrospectively.

Eligibility criteria

Patients had to fulfill the diagnostic criteria of the International Study Group for BD [9] and had to present with neurological manifestations. Data on patients eligible for the study were collected by exhaustive checking of medical records.

Diagnosis

The original diagnosis of the neuropsychiatric manifestation, which had been made with the aid of neurologists and radiologists at each institution and recorded on the clinical charts, was checked by members of the Research Committee at each institution by retrospective review of the entire clinical records including those in the follow-up period until 2008. NBD was defined as neurological manifestations in the absence of an alternative condition that better explained the neurological manifestations. After this maneuver, the final diagnosis of either NBD or neurological manifestations due to causes other than BD (non-NBD) was assigned and reported on a questionnaire form. At this stage, NBD was further classified as acute NBD or CP NBD based on the patients' clinical courses [3, 5–8]. Thus, acute NBD was defined as acute meningoencephalitis with or without focal lesions,

which was attenuated by corticosteroids or resolved spontaneously, although there might have been recurrence of the attacks or residual permanent damage or disability without progression [7, 8]. CP NBD was defined as intractable, slowly progressive neurological manifestations leading to severe disability and deterioration in spite of empirical immunotherapy [7, 8]. The diagnosis was reconfirmed by the chief members of the NBD Study Group of the Research Committee (S. H. and M. T.) through a careful retrospective review of the clinical records, and was finally approved by all the members of the Research Committee.

CSF interleukin 6 (IL-6)

On admission, when the patients showed active neurological manifestations, routine CSF analysis, including cell count, total protein, and glucose, as well as CSF IL-6 testing, was done. CSF IL-6 was measured by an enzyme-linked immunosorbent assay (ELISA) or a bioassay using an IL-6-dependent cell line, MH60.BSF2 [6] at each institution without knowledge of the clinical condition of the patients. The values of CSF IL-6 determined by ELISA have been shown to be identical with those determined by bioassay using MH60.BSF2 [6].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) scans with T1-weighted images, T2-weighted images, and fluid attenuated inversion recovery (FLAIR) images without contrast enhancement were recorded in 140 of the 144 patients. Judgment of MRI findings was performed by expert radiologists at each institution. Detailed findings and judgments by the radiologists were reported on a questionnaire form.

Statistical analysis

Comparison of the frequencies of various findings or parameters among the groups was carried out using the χ^2 test or Kruskal-Wallis test with multiple comparison, where appropriate. Receiver operating characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of various parameters, using the software, GraphPad Prism Version 4.0 (GraphPad Software, San Diego, CA, USA). All the statistical analysis was done by S.H.

Results

Summary of the review of cases in the questionnaire

A total of 159 BD patients were hospitalized due to neurological manifestations during the 20-year surveillance

period, of whom 144 patients underwent CSF examination. The neurological manifestations in 111 of the 144 patients were judged to have been caused by BD (76 acute NBD and 35 CP NBD), whereas those in 33 patients were judged as non-NBD, including 9 with atherosclerotic cerebrovascular diseases, 6 with intrinsic psychiatric disorders, 5 with systemic metabolic disorders, 4 with peripheral neuropathy of various causes, 3 with spinal spondylosis, 3 with epilepsy, and 2 with brain tumors; there was only 1 patient with cerebral vein thrombosis (CVT), who was classified as non-NBD. There was some overlapping in 18 patients with NBD. Thus, 6 patients with acute NBD had another attack of acute NBD, 9 patients with acute NBD subsequently developed CP NBD, so called "secondary progression" [5], and 3 patients with non-NBD had another episode of non-NBD. Thus, strictly speaking, 126 patients presented 144 occasions of neurological manifestations.

As summarized in Table 1, there were no significant differences in age or gender distribution among the 3 groups, although there was a tendency for male predominance in all the 3 groups. The interval between the diagnosis of BD and the presentation of neurological manifestations was significantly shorter in acute NBD compared with CP NBD and non-NBD. Of note, the prevalences of cigarette smoking and HLA-B51 were significantly higher in CP NBD ($P = 0.0024$ and 0.0106, respectively), whereas significantly higher numbers of acute NBD patients had been taking cyclosporin ($P < 0.0001$).

Clinical neurological manifestations (Table 2)

Among a variety of neurological manifestations, headache and fever were more common in acute NBD, whereas ataxia, dysarthria, urinary incontinence, and neurobehavioral/cognitive symptoms were more frequently observed

in CP NBD. Headache and ataxia were also commonly observed in non-NBD. Focal neurological deficit was less frequent in CP NBD, although the difference in frequency compared with that in acute NBD or non-NBD was not statistically significant. Vertigo was more frequent in acute NBD, although it also occurred in non-NBD.

MRI findings

MRI was done in all patients, except for 4 with acute NBD, who showed only fever and/or headache. High-intensity lesions on FLAIR images or T2-weighted images were observed in 60.5, 54.2, and 42.4% of patients with acute NBD, CP NBD, and non-NBD, respectively ($P = 0.1149$), indicating that these high-intensity lesions were not specific for NBD. These high-intensity lesions were most frequently observed in the pons, midbrain, and basal ganglia (Table 3). By contrast, brainstem atrophy was observed in 7.5, 71.4, and 9.0% of the patients with acute NBD, CP NBD, and non-NBD, respectively ($P < 0.0001$), indicating that it was specific for CP NBD.

CSF findings

Routine CSF analysis was performed in all the 144 patients. CSF cell counts were significantly elevated in acute NBD compared with non-NBD and CP NBD (Fig. 1a). CSF cell counts were also significantly elevated in CP NBD compared with non-NBD, but they were within normal limits in approximately 15% of the CP NBD patients. Significant increases in CSF total protein, as well as decreases in CSF glucose level, were observed in acute NBD and CP NBD compared with non-NBD, although most patients showed normal CSF total protein and glucose (Fig. 1b, c).

Table 1 Demographic features in 144 patients with Behçet's disease (BD)

	Acute NBD (%)	Chronic progressive NBD (%)	Non-NBD (%)	P value
n	76	35	33	
Age at onset of BD (years)	39.5 ± 11.8 (mean ± SD)	42.2 ± 11.4	44.6 ± 14.6	0.1578*
Interval between onset of BD and onset of neurological symptoms (years)	5.0 ± 5.2 (mean ± SD)	8.2 ± 5.5	10.9 ± 12.0	0.0040*
Follow-up period (years)	7.9 ± 6.2 (mean ± SD)	8.9 ± 6.3	4.9 ± 4.4	0.0233*
Gender (M:F)	49:27	27:8	20:13	0.2955[a]
HLA-B51	23/44 (52.3)	24/28 (85.7)	9/17 (52.9)	0.0106[a]
Smoking	47/68 (69.1)	31/34 (91.2)	15/29 (51.7)	0.0024[a]
Cyclosporin use[b]	26/76 (34.2)	1/35 (11.1)	1/33 (3.0)	<0.0001[a]

NBD Neuro-Behçet's disease

* Statistical significance was evaluated by the Kruskal-Wallis test with multiple comparison

[a] Statistical significance was evaluated by the χ^2 test

[b] One patient received tacrolimus instead of cyclosporin

Table 2 Clinical symptoms in 144 patients with Behçet's disease

	Acute NBD (%)	Chronic progressive NBD (%)	Non-NBD (%)	P value*
n	76	35	33	
Headache	41 (53.9)	2 (5.7)	14 (42.4)	<0.0001
Fever	43 (56.6)	1 (2.9)	3 (9.1)	<0.0001
Neurobehavior/cognitive symptoms	7 (9.2)	18 (51.4)	3 (9.1)	<0.0001
Alteration of consciousness	7 (9.2)	1 (2.9)	5 (15.1)	0.2088
Ataxia	9 (11.8)	17 (48.6)	10 (30.3)	0.0001
Dysarthria	14 (18.4)	15 (42.9)	3 (9.1)	0.0019
Focal symptoms (motor, sensory, etc.)	20 (26.3)	7 (20.0)	10 (30.3)	0.6136
Bladder/bowel disturbances	2 (2.6)	6 (17.1)	2 (6.1)	0.0208
Dizziness	0	2 (5.7)	4 (12.1)	0.0123
Vertigo	8 (10.5)	0	3 (9.1)	0.1429

* Statistical significance was evaluated by the χ^2 test

Table 3 Location of high-intensity lesions on T2-weighted magnetic resonance imaging (MRI) scans or FLAIR images in patients with Behçet's disease

	Acute NBD (%)	Chronic progressive NBD (%)	Non-NBD (%)	P value*
n	72[a]	35	33	
Cerebral white matter	12 (16.7)	5 (14.3)	8 (24.2)	0.5244
Basal ganglia	17 (9.7)	4 (11.4)	1 (3.0)	0.0194
Internal capsule	10 (13.9)	6 (17.1)	3 (9.1)	0.6214
Midbrain	18 (25.0)	4 (11.4)	2 (6.1)	0.0336
Pons	23 (31.9)[b]	9 (25.7)	2 (6.1)	0.0158
Bulb	4 (5.6)	2 (5.7)	0	0.3801
Cerebellum	3 (4.2)	1 (2.9)	1 (3.0)	0.9259

FLAIR fluid attenuated inversion recovery

* Statistical significance was evaluated by the χ^2 test

[a] MRI was not done in 4 of 76 patients with acute NBD

[b] Including 1 patient with hemorrhage

Comparison of clinical characteristics between patients with cyclosporin and those without cyclosporin in the acute NBD group

It is unclear and still under debate whether cyclosporin-induced neurological manifestations might be different from those of acute NBD. We therefore compared the clinical characteristics of patients with cyclosporin with the characteristics of those without cyclosporin. All the 26 patients with cyclosporin had eye involvement, whereas 43 of the 50 patients without cyclosporin also had eye involvement. As shown in Table 4, there were no significant differences in demographic features, clinical symptoms, MRI findings, or laboratory findings between patients with cyclosporin and those without cyclosporin. There were no significant differences in the distribution of high-intensity lesions on MRI between the 2 groups, either (data not shown). These results therefore suggest that cyclosporin-induced neurological manifestations might be almost identical with those of acute NBD.

ROC analysis of various parameters

The sensitivity and specificity of the CSF cell count for the diagnosis of acute NBD versus non-NBD were 97.4 and 97.0%, respectively, at the cut-off value of $6.2/mm^3$ ($P < 0.0001$) (Fig. 2a), whereas the sensitivity and specificity of the CSF cell count for the diagnosis of CP NBD versus non-NBD were 68.6 and 97.0%, respectively, at the cut-off value of $6.0/mm^3$ ($P < 0.0001$) (Fig. 2b).

The sensitivity and specificity of CSF IL-6 for the diagnosis of CP NBD versus non-NBD were 96.0 and 100%, respectively, at the cut-off value of 5.5 pg/ml ($P < 0.0001$) (Fig. 2c). It should be noted, however, that CP NBD often follows episodes of acute NBD [5, 6]. It is therefore very important to discriminate CP NBD from the recovery phase of acute NBD. ROC curve analysis was performed for the 19 patients with acute NBD in the recovery phase (2–8 weeks after the attacks) and for the 25 patients with CP NBD. As shown in Fig. 2d, the sensitivity and specificity of CSF IL-6 for the differential diagnosis of
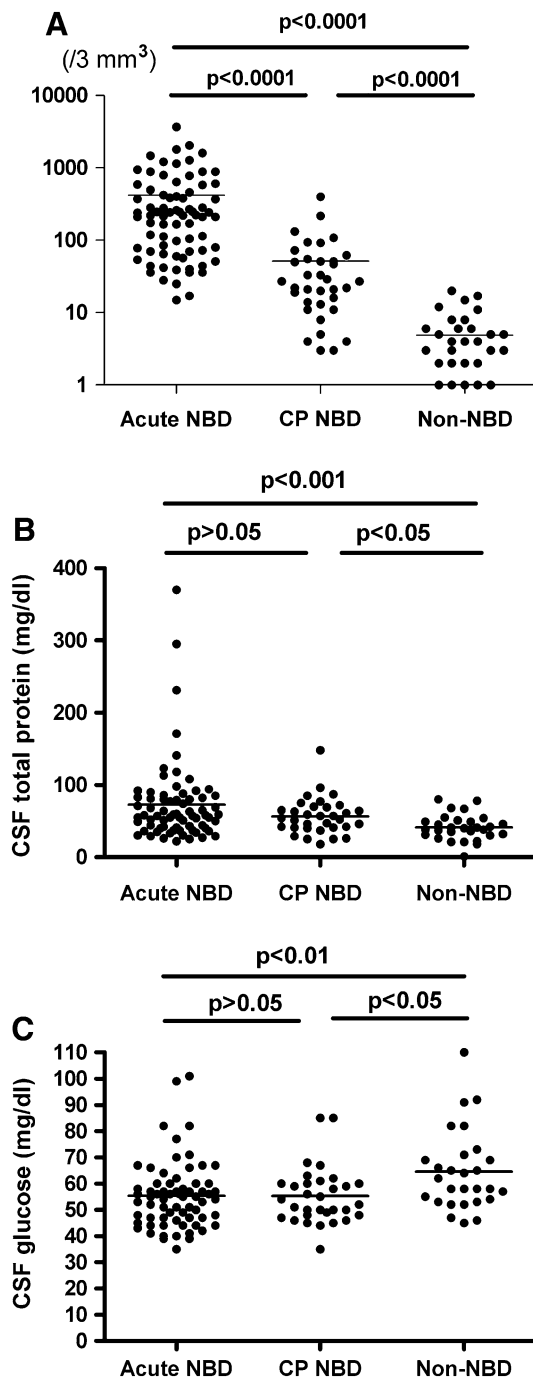
Fig. 1 Cerebrospinal fluid (*CSF*) in neuro-Behçet's disease (*NBD*). CSF cell count (**a**), total protein (**b**), and glucose (**c**), in patients with acute NBD, chronic progressive (*CP*) NBD, and non-NBD. Statistical significance was analyzed by the Kruskal-Wallis test with multiple comparison

CP NBD from the recovery phase of acute NBD were 92.0 and 94.7%, respectively, at the cut-off value of 16.55 pg/ml ($P < 0.0001$). These results indicate that CSF IL-6 was a useful tool for the diagnosis of CP NBD in BD patients who showed neurological manifestations of insidious

onset, whereas the CSF cell count was a sensitive and reliable marker for the diagnosis of acute NBD in BD patients who showed neurological manifestations of acute or subacute onset. Because CSF IL-6 and the CSF cell count have been found to be elevated in CNS infections, it is necessary to rule out such conditions, especially in acute NBD. Based on these findings, diagnostic criteria for acute NBD and CP NBD are proposed, as shown in Table 5.

Treatment

Precise evaluation of the efficacy of treatment choices is beyond the scope of this paper. It should be noted, however, that more than 80% of the patients with acute NBD were treated with corticosteroid, whereas approximately 75% of the patients with non-NBD received immunosuppressive treatment including corticosteroid. Approximately half of the patients with CP NBD received methotrexate (MTX) and/or corticosteroid. Only 1 patient with CP NBD was given infliximab.

Discussion

We have summarized the clinical data of BD patients who showed neurological manifestations between 1988 and 2008. Only 1 of the 144 patients showed cerebral vein thrombosis (CVT), and this patient was classified as having non-NBD, confirming that the incidence of CVT in BD in Japan is much lower than that in Middle-Eastern or European counties [2–5]. The reason for the paucity of CVT in BD patients in Japan remains unclear. It is suggested that some ethnic differences in genetic factors might be involved, as in the case of intestinal involvement, which is much more common in the Japanese population [1]. Another possible reason for the low frequency of CVT in our study was that our sample size was relatively small. Further studies with a larger number of patients would be necessary to evaluate the frequency of CVT in BD patients in Japan.

The results in the present study have confirmed that HLA-B51 and cigarette smoking are associated with CP NBD, as was reported previously [10]. The role of HLA-B51 and smoking in the progression of CNS inflammation might involve immune responses that need to be further clarified. On the other hand, it has been found that cyclosporin is frequently associated with acute NBD, at least in Japanese patients [11]. Consistently, in our series of patients, 34.2% of patients with acute NBD had been taking cyclosporin (including 1 patient with tacrolimus) when they developed neurological manifestations [11]. In contrast with the neurotoxicity of cyclosporin in patients with organ transplantation, such as posterior reversible

Table 4 Comparison of clinical characteristics between patients with cyclosporin and those without cyclosporin in the acute NBD group

	With cyclosporin (%)	Without cyclosporin (%)	P value*
n	26	50	
Interval between onset of BD and onset of NBD (years)[a]	5.5 ± 4.7	4.7 ± 5.6	0.5197
Gender (M:F)	19:7	30:20	0.3802
HLA-B51	8/15 (53.3)	15/29 (51.7)	1.0000
Smoking	16/19 (84.2)	31/49 (63.3)	0.1661
Headache	11 (42.3)	30 (60.0)	0.2204
Fever	15 (57.7)	28 (56.0)	1.0000
High-intensity lesions (FLAIR or T2) on MRI	18 (69.2)	28/46 (60.9)	0.6498
Serum CRP (mg/dl)[a]	2.24 ± 3.00	4.25 ± 5.83	0.0584[‡]
CSF cell counts (/3 mm^3)[a]	391.2 ± 419.2	432.9 ± 652.9	0.7366[‡]
CSF IL-6 (pg/ml)[a]	442.9 ± 786.2	1035.1 ± 1072.8	0.1652[‡]

MRI magnetic resonance imaging, *CRP* C-reactive protein, *CSF* cerebrospinal fluid, *IL* interleukin

* Statistical significance was evaluated by the χ^2 test or [‡] by Student's *t*-test

[a] Data are expressed as means ± SD

encephalopathy syndrome (PRES), the neurological manifestations induced by cyclosporin in the BD patients in our series were always accompanied by an elevation of CSF cell counts and IL-6. Of note, a previous report disclosed that patients with cyclosporin-induced PRES showed normal CSF findings [12], suggesting that the pathogenesis of cyclosporin-induced PRES is different from that of acute NBD induced by cyclosporin. There were no significant differences in demographic features, clinical symptoms, or laboratory findings between patients with cyclosporin and those without cyclosporin in the acute NBD group in the present study. It is therefore very likely that cyclosporin might induce acute NBD. A recent report from Turkey also confirmed the association of cyclosporin with NBD [13].

Based upon the differences in clinical courses and responses to corticosteroid treatment, NBD can be classified as acute NBD or CP NBD [7, 8]. Acute NBD is characterized by acute meningoencephalitis with or without focal lesions, presenting high-intensity areas on T2-weighted MRI scans or FLAIR images [7, 8]. Acute NBD responds to corticosteroid therapy, and is usually self-limiting, although recurrence of attacks is sometimes seen [7]. By contrast, CP NBD is characterized by intractable, slowly progressive neurobehavioral changes, ataxia, and dysarthria, leading to severe disability and deterioration [6–8]. Of note, CP NBD is resistant to conventional treatments with corticosteroid, cyclophosphamide, or azathioprine [7, 14], although the efficacy of low-dose weekly MTX in CP NBD has been suggested [14]. Akman-Demir et al. [5] proposed subsets of NBD, including attack(s) and remission, secondary progression, primary progression, and silent neurological involvement. Attack(s) and remission in their series are considered to correspond to acute NBD, whereas primary and secondary progression would be the

same as CP NBD. Similarly, Kidd et al. [3] reported 50 patients with NBD, the majority with only single attacks, one-third with further attacks, and 4 with progressive deterioration leading to disability. In their series of patients, one or repeated attacks correspond to acute NBD, and progressive deterioration would be the same as CP NBD. Our present study has shown that the frequency of CP NBD was 31.5% of NBD patients, a finding which was comparable to that in the previous report of Akman-Demir et al. [5]. Because of the different responses to treatment of CP NBD and acute NBD, especially the response to corticosteroid, and because of differences in outcome, it is quite important to discriminate CP NBD from acute NBD.

Headache is the most common neurological symptom seen in BD [4, 15]. Consistently, in the present study, headache and fever were observed in the majority of patients with acute NBD, whereas these symptoms were rare in patients with CP NBD. However, it should be pointed out that headache was present in 53.9% of the patients with acute NBD and 42.4% of the patients with non-NBD, consistent with previous findings that headache is also a common symptom in BD independent of neurological involvement [4, 15]. Therefore, it is difficult to delineate acute NBD versus non-NBD by the presence of headache alone. On the other hand, ataxia, dysarthria, and neuropsychiatric symptoms were frequently observed in CP NBD [7]. These neuropsychiatric symptoms were consistent with the neurobehavioral changes previously reported by Siva et al. [4]; these changes included cognitive dysfunction, euphoria, loss of insight, disinhibition, indifference to their disease, psychomotor agitation or retardation, and paranoid attitudes and obsessive concerns.

High-intensity lesions on FLAIR images or T2-weighted MRI scans have been shown to be frequently observed in
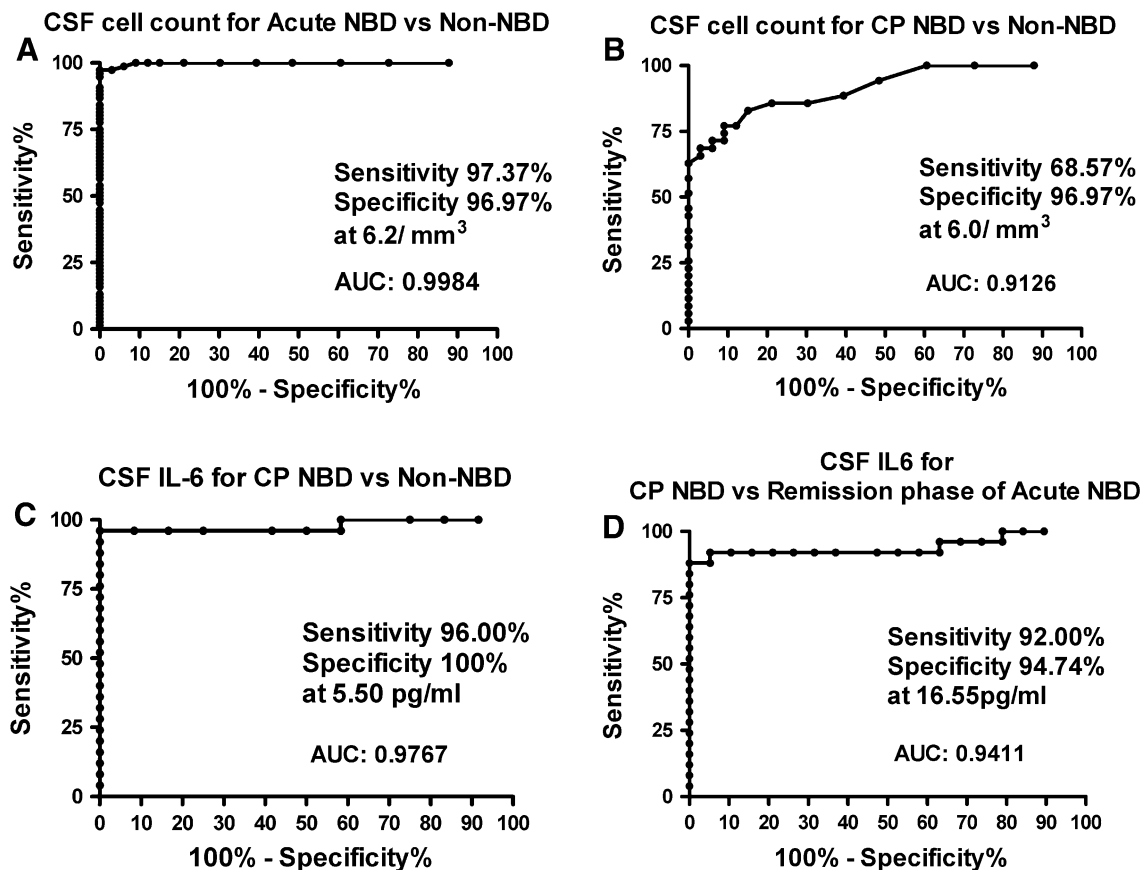
Fig. 2 Receiver operating characteristic (ROC) analysis of the CSF cell count and CSF interleukin-6 (*IL-6*) for the differential diagnosis of NBD. **a, b** ROC analysis of the CSF cell count for the differential diagnosis of acute NBD and CP NBD from non-NBD. The sensitivity and specificity of CSF cell counts for the diagnosis of acute NBD versus non-NBD were 97.4 and 97.0%, respectively, at the cut-off value of 6.2/mm^3 (**a**) [area under the curve (AUC): 0.9984 (95% confidence interval; CI, = 0.9951–1.002), $P < 0.0001$], whereas the sensitivity and specificity of the CSF cell count for the diagnosis of CP NBD versus non-NBD were 68.6 and 97.0%, respectively, at the cut-off value of 6.0/mm^3 [AUC: 0.9126 (95% CI = 0.8473–0.9778), $P < 0.0001$] (**b**). **c, d** ROC analysis of CSF IL-6 for the diagnosis of CP NBD. The sensitivity and specificity of CSF IL-6 for the differential diagnosis of CP NBD ($n = 25$) versus non-NBD ($n = 12$) were 96.0 and 100%, respectively, at the cut-off value of 5.5 pg/ml [AUC: 0.9767 (95% CI = 0.9292–1.024), $P < 0.0001$] (**c**), whereas the sensitivity and specificity of CSF IL-6 for the diagnosis of CP NBD ($n = 25$) versus acute NBD in the recovery phase ($n = 19$) were 92.0 and 94.7%, respectively, at the cut-off value of 16.55 pg/ml [AUC: 0.9411 (95% CI = 0.8626–1.020), $P < 0.0001$] (**d**)

Table 5 Proposed preliminary diagnostic criteria for classification of NBD

Acute NBD

  1. Fulfilling the International Study Group (ISD) criteria for BD

  2. Acute or subacute onset of neurological symptoms, including headache, fever, or any focal signs

  3. Increase in the CSF cell count of more than 6.2/mm^3

  *The diagnosis of acute NBD requires all the above items 1–3

  Exclusion: infections of the central nervous system

Chronic progressive NBD

  1. Fulfilling the ISD criteria for BD

  2. Insidious onset of neuropsychiatric symptoms, including dementia/neurobehavior changes, ataxia, and dysarthria, with or without other manifestations

  3. Presence of one of the following:

    a. Increase in CSF IL-6 of more than 17.0 pg/ml on 2 different occasions at intervals of at least 2 weeks

    b. Increase in CSF IL-6 of more than 17.0 pg/ml and the presence of brainstem atrophy on MRI

  *The diagnosis of chronic progressive NBD requires all the above items 1–3

NBD, especially in the brainstem-diencephalon and pontobulbar regions [16]. In accordance with these findings, high-intensity lesions were frequently seen in the pons, midbrain, and basal ganglia in acute NBD as well as CP NBD in the present study. However, there were no significant differences in the frequencies of FLAIR or T2-weighted high-intensity lesions among acute NBD, CP NBD, and non-NBD. These high-intensity lesions were observed in as many as 42.4% of our non-NBD patients, but in as few as 54.2% of the acute NBD patients. Therefore, it is evident that the inclusion of abnormal MRI findings in the diagnostic criteria of acute NBD results in reduced sensitivity and specificity. By contrast, brainstem atrophy was observed significantly more frequently in CP NBD (71.4%) than in acute NBD (7.5%) or non-NBD (9.0%), indicating that brainstem atrophy is a frequent and specific finding in CP NBD and therefore can be included in the diagnostic criteria. Determination of the presence of brainstem atrophy in the present study depended on the anecdotal judgment of expert radiologists, and thus, a more objective definition of brainstem atrophy could be required.

The efficacy of CSF analysis in the diagnosis of NBD has been poorly explored in the literature [3, 5]. In a study with a limited number of patients, CSF constituents were shown to be altered in only around 70–80% of patients with parenchymal NBD [17]. In fact, in the present study, elevation of the CSF cell count was not observed in 9 of 35 patients with CP NBD. However, almost all of the 76 patients with acute NBD showed elevation of the CSF cell count, whereas the CSF cell count was within normal ranges in all the 33 patients with non-NBD. Thus, the sensitivity and specificity of the CSF cell count for the diagnosis of acute NBD versus non-NBD were as high as 97.4 and 97.0%, respectively, at the cut-off value of $6.2/mm^3$, providing strong evidence for the rationale of inclusion of the CSF cell count in the proposed diagnostic criteria for acute NBD; however, the sensitivity of CSF cell counts for the diagnosis of CP NBD was unsatisfactory.

It should be pointed out that infectious meningoencephalitis is accompanied by an elevation of the CSF cell count. Therefore, it is mandatory to exclude the possibility of infectious meningoencephalitis in the diagnosis of acute NBD (Table 5). In addition, multiple sclerosis might show similar lesions, including those of the brainstem, along with an elevation of the CSF cell count. However, it has been very rare that multiple sclerosis occurs in patients who have fulfilled the diagnostic criteria of BD, although careful differential diagnosis from acute NBD is important.

Recently, increasing attention has been paid to CSF cytokines, especially IL-6, in NBD. Thus, CSF IL-6 has been shown to be increased in patients with relapsing-remitting NBD (acute NBD), as well as in those with progressive NBD (CP NBD) [6, 18–21]. Consistently, in the present study, CSF IL-6 was elevated in acute NBD as well as in CP NBD, but not in non-NBD. Previous studies demonstrated that CSF IL-6 was not elevated in patients with multiple sclerosis [22, 23]. Therefore, the determination of CSF IL-6 might be useful for the differential diagnosis of NBD and multiple sclerosis. CSF IL-6 has been found to be decreased after successful treatment of acute NBD [19]. It should be noted that a number of patients with CP NBD have a preceding history of attacks of acute NBD [6, 7]. It is therefore possible that those patients with acute NBD whose CSF IL-6 levels do not return to normal ranges might develop CP NBD. It is thus important to discriminate patients with acute NBD who continue to have persistent inflammation leading to CP NBD from those who completely recover from acute NBD without further progression. In this regard, we have demonstrated that the sensitivity and specificity of CSF IL-6 for the differential diagnosis of CP NBD from non-progressive acute NBD in the recovery phase were 92.0 and 94.7%, respectively, at the cut-off value of 16.55 pg/ml.

We previously disclosed that patients with CP NBD presented with persistent marked elevation of CSF IL-6 (>20 pg/ml), lasting more than 3 months, with a modest increase in CSF cell numbers and total protein [6]. It is therefore essential to show this sustained elevation of IL-6 for the diagnosis of CP NBD, requiring the examination of CSF IL-6 on at least 2 occasions. Because most patients with acute NBD showed lower levels of CSF IL-6 2–8 weeks after the initial diagnosis than those with CP NBD, the interval of time between the two occasions of CSF IL-6 examination might well be at least 2 weeks, although further studies are required to determine the precise interval. Alternatively, brainstem atrophy, which was found to be specific for CP NBD, might be a result of prolonged inflammation. Therefore, its presence with elevation of CSF IL-6 on a single occasion is considered to provide strong evidence for CP NBD.

In summary, the results in the present multicenter retrospective study have disclosed the characteristic features of acute NBD as well as those of CP NBD, leading to the proposed diagnostic criteria for each. It should be pointed out that CSF IL-6 was examined in only 40% of patients in the present study. Because the sample size of the present study was relatively small, the paucity of CSF IL-6 data might be a limitation of our study results. Accumulating data on CSF IL-6 would be needed to confirm the results of our study. In this regard, a prospective study for validation of the preliminary diagnostic criteria, especially those for CP NBD, would be very important.

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