Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4705-20
Intern Med 59: 2359-2367, 2020
http://internmed.jp

【 ORIGINAL ARTICLE 】

# Recommendations for the Management of Neuro-Behçet's Disease by the Japanese National Research Committee for Behçet's Disease

Shunsei Hirohata[1-3], Hirotoshi Kikuchi[3], Tetsuji Sawada[4], Masato Okada[5], Mitsuhiro Takeno[6], Masataka Kuwana[7], Izumi Kawachi[8,9], Hideki Mochizuki[10], Susumu Kusunoki[11] and Yoshiaki Ishigatsubo[12]

**Abstract:**

**Objective** Brain parenchymal involvement in Behçet's disease (BD) (neuro-Behçet's disease, NB) can be classified into acute type (ANB) and chronic progressive type (CPNB) based on differences in the clinical course and responses to corticosteroid treatment. The present study developed evidence-based recommendations for the management of NB.

**Methods** The task force of the research subcommittee consisted of seven board-certified rheumatologists (one was also a board-certified neurologist) and three board-certified neurologists. First, several clinical questions (CQs) were established. A systematic literature search was performed by The Japan Medical Library Association in order to develop recommendations. The final recommendations for each CQ developed from three blind Delphi rounds, for which the rate of agreement scores [range 1(strongly disagree)-5(strongly agree)] was determined through voting by the task force.

**Results** A flow chart of the algorithm was established for the management of ANB and CPNB. Thirteen recommendations were developed for NB (general 1, ANB 7, CPNB 5). The strength of each recommendation was established based on the evidence level as well as the rate of agreement.

**Conclusion** The recommendations generated in this study are based on the results of uncontrolled evidence from open trials, retrospective cohort studies and expert opinions, due to the lack of randomized clinical trials. Nevertheless, these recommendations can be used for international studies, although verification by further properly designed controlled clinical trials is required.

**Key words:** Behçet's disease, neurological involvement, management, guideline

**(Intern Med 59: 2359-2367, 2020)**
**(DOI: 10.2169/internalmedicine.4705-20)**

## Introduction

Behçet's disease (BD) is characterized by recurrent attacks of aphthous stomatitis, uveitis, genital ulcers, and skin lesions, including folliculitis, erythema nodosum like lesions, and superficial thrombophlebitis (1). Central nervous system (CNS) involvement is one of the most serious com-

[1]Department of Rheumatology, Nobuhara Hospital, Japan, [2]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Japan, [3]Department of Internal Medicine, Teikyo University School of Medicine, Japan, [4]Department of Rheumatology, Tokyo Medical University, Japan, [5]Immuno-Rheumatology Center, St. Luke's International Hospital, Japan, [6]Department of Allergy and Rheumatology, Nippon Medical University Musashi-Kosugi Hospital, Japan, [7]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Japan, [8]Comprehensive Medical Education Center, Niigata University School of Medicine, Japan, [9]Department of Neurology, Brain Research Institute, Niigata University, Japan, [10]Department of Neurology, Osaka University Graduate School of Medicine, Japan, [11]Department of Neurology, Kindai University School of Medicine, Japan and [12]Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Japan
Received: February 24, 2020; Accepted: May 11, 2020; Advance Publication by J-STAGE: June 30, 2020
Correspondence to Dr. Shunsei Hirohata, shunsei@med.kitasato-u.ac.jp

plications in BD and is called neuro-Behçet's disease (NB) (1, 2). There has been accumulating evidence that NB can be classified into acute type (ANB) and chronic progressive type (CPNB) based on differences in the clinical courses as well as in responses to corticosteroid treatment (3, 4), as ANB responds well to corticosteroids and usually runs a self-limiting course, while CPNB is characterized by intractable neuro-behavior changes and cerebellar ataxia that progress despite high doses of corticosteroids or immunosuppressive drugs, including azathioprine and cyclophosphamide (5-7).

Recently, the first systematic review and meta-analysis was performed with 10 studies to discriminate the clinical presentation of ANB and CPNB, including 205 ANB cases and 111 CPNB cases (8). The study revealed that a fever and elevated cerebrospinal fluid (CSF) cell count were characteristic of ANB, whereas CPNB was characterized by sphincter disturbances, ataxia, dementia, confusions, brain stem atrophy and abnormal magnetic resonance imaging (MRI) findings in the cerebellum (8). Thus, the study has confirmed the importance of recognizing ANB and CPNB separately for the appropriate management of NB patients (8).

The diagnostic criteria for ANB and CPNB were generated in 2013 based on the results of a multicenter clinical survey performed by the Behçet's Disease Research Committee of the Ministry of Health, Labor and Welfare of the Japanese Government (Supplementary material) (3). However, in the 2018 update of the EULAR recommendations for the management of Behçet's syndrome (Behçet's disease), recommendation 9 referred to the treatment of acute attacks of parenchymal involvement of CNS, corresponding to ANB (9), with no recommendation for CPNB included (9). Notably, the clinical entity of CPNB has been confirmed by the above-mentioned meta-analysis (8). Furthermore, there have been several related publications with new data on treatment of CPNB (7, 10-13). It is therefore necessary to update recommendations for NB with addition of CPNB.

The present study developed evidence-based recommendations for the management of NB in light of recent findings from new studies.

## Materials and Methods

### Study overview and patient and public involvement.

The operating process for developing recommendations followed the procedure proposed by the Medical Information Network Distribution Service (Minds) (14). Institutional review board approval and patient consent were not required because of the review nature of this study. Thus, patients and the public were not involved in this study. The study was carried out as a part of the development of 2020 Japanese Society for BD (JSBD) Clinical Practice Guidelines for BD.

### Organization of a task force

Within the Behçet's Disease Research Committee of the Research Program for Intractable Disease of the Ministry of Health, Labor and Welfare of the Japanese Government, a task force of the research subcommittee for NB was organized. The task force consisted of seven Japanese board-certified rheumatologists (one was also a Japanese board-certified neurologist) and three Japanese board-certified neurologists.

### Clinical questions (CQs)

The task force set 15 CQs on NB-related clinical issues, including 1 general question on the definition of NB in the Japanese diagnostic criteria and 14 questions on the management of ANB and CPNB, along with the generation of the algorithm for the management of NB. The questions were formulated into Population, Intervention, Comparison and Outcome (PICO) questions for the literature review.

### Systematic review

A literature search was performed by The Japan Medical Library Association (JMLA) using the following medical databases; Cochrane Database of Systematic Reviews, PubMed/Medline, The Cochrane Library and Igaku Chuo Zasshi (ICHUSHI) of the Japan Medical Abstracts Society (JAMAS), based on English or Japanese keywords listed from each PICO formatted CQ. Two researchers (SH, HK) screened the articles for possible inclusion independently. The final inclusion was decided after discussion between the two researchers. The strength of body of evidence for each clinical outcome was evaluated according to the methods proposed by Minds (14), such as A (strong), B (moderate), C (weak) and D (very weak).

### Generation of recommendations

Draft recommendations for each CQ proposed by the two researchers through their systematic review were presented to the task force members during a half-day consensus development conference. During the conference, these draft recommendations were discussed and modified accordingly. The modified recommendations were then further refined through three blind Delphi rounds. Consensus was obtained explicitly through voting with the level of agreement, such as 1 (strongly disagree), 2 (disagree), 3 (agree with conditions attached), 4 (agree) and 5 (strongly agree) for each recommendation (Table 1). It had been decided in advance that such recommendation that obtained the averaged level of agreement of less than 4.0 was declined. As a result, two CQs were dropped due to poor agreement scores.

For each surviving CQ, recommendations made by the committee were presented, followed by the evidence level, the agreement level of the 10 task force members and the strength of each recommendation according to Minds (Table 1) (14). The strength of each recommendation was established based on the evidence level as well as on the rate

**Table 1. Criteria of Evidence Level, Agreement Level and Recommendation Level.**

| Evidence level | | |
|---|---|---|
| 1 | 1a | High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) |
| | 1b | At least one RCT |
| 2 | 2a | Cohort studies with simultaneous controls |
| | 2b | Cohort studies with past controls |
| 3 | | Case-control studies (retrospective) |
| 4 | | Studies without before and after comparison or comparison with controls |
| 5 | | Single case reports or reports of case series |
| 6 | | Experts' opinions or reports of expert committees |

| | Agreement level | Frequency to follow recommendations at 10 clinical opportunities |
|---|---|---|
| 5 | Strongly agree | 9≤ |
| 4 | Agree | 7≤, 9< |
| 3 | Agree with conditions attached | 5≤, 7< |
| 2 | Disagree | 2≤, 5< |
| 1 | Strongly disagree | ≤1 |

| | Recommendation level | Evidence level | Agreement level |
|---|---|---|---|
| A | Strongly recommended | Mainly 1 | >4.8 |
| B | Recommended | Mainly 2,3 | >4.5 |
| C1 | Maybe considered, but no evidence | Mainly 4, 5, 6 | >4.0 |
| C2 | Not recommended due to the lack of evidence | No evidence | - |
| D | Recommended not to do | Not useful/ harmful | - |

The criteria are established based on the guidance for development of clinical practice guideline 2014 by Medical Information Network Distribution Service (Minds), Japan Council for Quality Health Care (14). The strength of each recommendation was established based on the evidence level as well as rate of agreement.

of agreement.

### The external evaluation and public comments

Public comments on the draft of recommendations were collected from the external evaluation by the Japan College of Rheumatology and JSBD. Revised recommendations were prepared with consideration of the public comments.

## Results

In Figure, the flow chart of the algorithm for the clinical practice for ANB and CPNB is presented. In the flow chart, various points of emerging CQs requiring answers are indicated. As summarized in Table 2, 13 CQs related to the diagnosis and management of NB were generated (general 1, ANB 7, CPNB 5).

### General aspect

**CQ1. What is the definition of "moderate or severe" CNS manifestations described in the Japanese diagnostic criteria for BD?**

*All cases that meet the diagnostic criteria for ANB or CPNB should be included in the category of "moderate or severe" CNS manifestations.*

ANB is characterized by attacks of inflammatory lesions in brain parenchyma and/or meninges, detected as high-intensity areas in T2-weighted images or fluid attenuated inversion recovery (FLAIR) images on MRI (3). Approximately 40% of patients with ANB have been shown to relapse without adequate treatment (15, 16). Furthermore, severe attacks can sometimes result in permanent damage or disability despite extensive treatment (2, 4, 6). By contrast, CPNB is characterized by slowly progressive dementia and/or cerebellar ataxia with persistent elevation of CSF interleukin-6 (IL-6), leading to permanent bed-ridden disability or death without appropriate treatment (3, 12). While corticosteroids, cyclophosphamide and azathioprine are not effective at all, low-dose methotrexate (MTX) and infliximab have been shown to be effective in preventing the progression of the neuropsychological manifestations (7, 11-13).

Therefore, those patients who meet the diagnostic criteria for ANB or CPNB (3) should be defined as patients with "moderate or severe" CNS manifestations and should be treated with appropriate immunosuppressive reagents.

### ANB

**CQ2. How should the dose of corticosteroids be determined in acute-phase treatment of ANB?**

*If administration of prednisolone at a dose ≥20 mg/day (oral or intravenous) has an insufficient effect, high-dose therapy, including steroid pulse therapy, should be considered.*

Corticosteroids are the gold standard for treating acute-phase attacks, although they do not prevent recurrence of attacks (1, 3, 15, 16). For acute attacks of ANB, prednisolone at a dose ≥20 mg/day should be given first (3, 16). Higher-dose corticosteroids, including pulse therapy, need to be

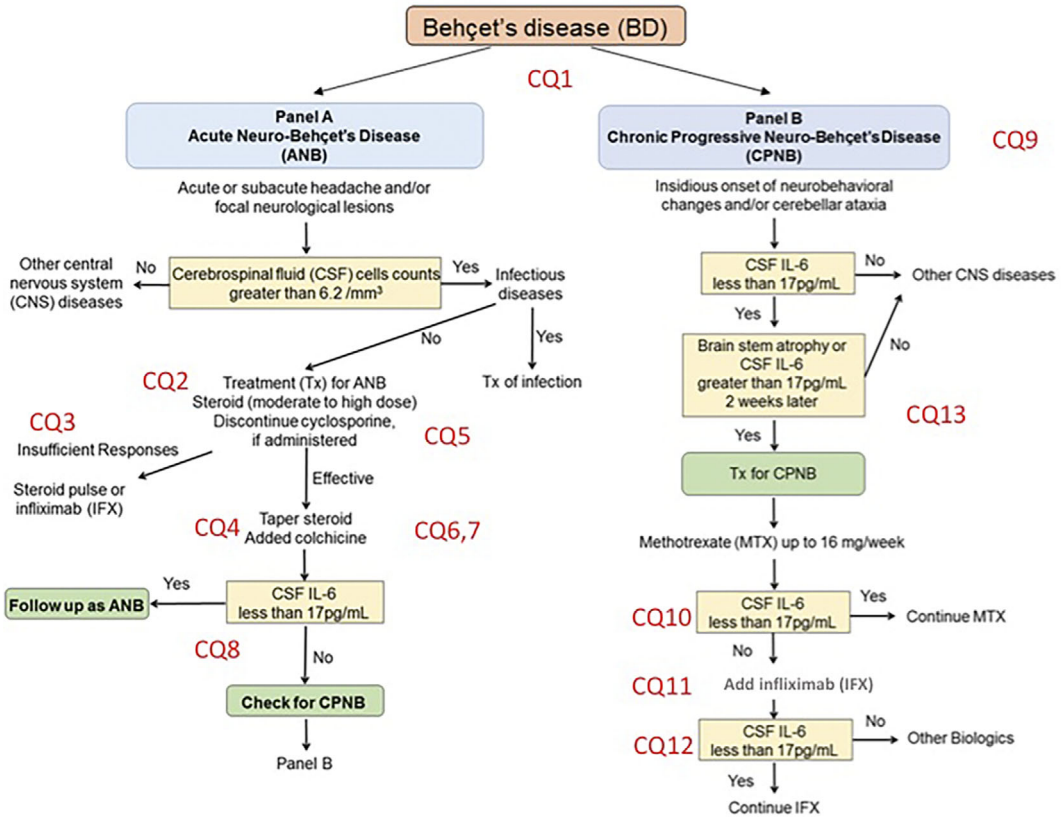


**Figure.** **The presentation of the recommendations for the management of neuro-Behçet's disease by the Japanese national research committee for Behçet's disease (BD) in the form of an algorithm. The position of each clinical question (CQ) is indicated. Panel A concerns BD patients with the acute or subacute onset of neurological symptoms, such as a headache, fever and/or any focal signs. Panel B concerns BD patients with insidious onset of neuropsychological symptoms, such as neurobehavioral changes and/or cerebellar ataxia.**

considered in patients with inadequate responses. However, it should be remembered that higher doses of corticosteroids may increase the frequency of side effects, such as aseptic necrosis of the femoral head. After the attacks subside, the doses of corticosteroids should be decreased gradually over two to three months in order to prevent relapses of ANB as well as ocular attacks (17).

After the acute phase of ANB, while the dose of corticosteroids is decreasing, colchicine should be started, since the efficacy of colchicine in preventing relapses of further attacks of ANB has been noted (15). However, the drug should be given under careful consideration of its risk and benefit for patients.

**CQ3. Should infliximab be used in acute-phase treatment of ANB?**

*If the effects of corticosteroids at a moderate or higher dose are insufficient, concomitant use of infliximab should be considered.*

There have been no reports indicating that infliximab is effective in the acute phase of ANB without corticosteroids. Corticosteroid pulse therapy or addition of infliximab should be considered when moderate or higher doses of corticosteroids show inadequate effects. However, it should be noted that no controlled study has assessed the effects of the addition of infliximab to corticosteroids in ANB, although there are some reports of single cases, case series or uncontrolled prospective studies (18-21). Furthermore, since the safety of infliximab in ANB is not established, the risks and benefits should be carefully evaluated in each patient before introducing infliximab.

**CQ4. When and how long should colchicine be used to prevent attack in ANB?**

*Administration of colchicine (1.0-2.0 mg/day) should start immediately after the first attack and continue for 5 years.*

Previous studies have shown that, in patients receiving colchicine, relapse was very rare after 5 years from the initial ANB attack (15). Therefore, it is recommended that colchicine (1.0-2.0 mg/day) be continued for 5 years (15). However, the drug should be given under careful consideration of its risks and benefits for each patient, as mentioned in CQ2.

**CQ5. What kind of treatment should be provided to patients with ANB in whom cyclosporine is used?**

*Cyclosporine should be discontinued. For ocular involvement, the use of infliximab should be considered.*

Cyclosporine is effective in preventing uveitis attacks (22). However, cyclosporine is often associated with the development of acute neurological attacks, which should

**Table 2. Recommendation for Management of NB.**

| CQ | Clinical Question | Recommendation | LoE | LoA | SoR |
|---|---|---|---|---|---|
| | 1. General aspect | | | | |
| 1 | What is the definition of "moderate or severe" CNS manifestations" described in the Japanese diagnostic criteria for BD? | All cases that meet diagnostic criteria* for ANB and CPNB should be included in the category of "moderate or severe" CNS manifestations. | 3 | 4.80 | A |
| | 2. ANB | | | | |
| 2 | How should the dose of corticosteroids be determined in acute-phase treatment of ANB disease? | If administration of prednisolone at a dose ≥20 mg/day (oral or intravenous) has an insufficient effect, high-dose therapy, including steroid pulse therapy, should be considered. | 3 | 4.50 | B |
| 3 | Should infliximab be used in acute-phase treatment of ANB? | If the effects of corticosteroids at a moderate or higher dose are insufficient, concomitant use of infliximab should be considered. | 5 | 4.40 | C1 |
| 4 | When and how long should colchicine be used to prevent attack in ANB? | Administration of colchicine (1.0-2.0 mg/day) should start immediately after the first attack and continue for 5 years. | 3 | 4.50 | B |
| 5 | What kind of treatment should be provided to patients with ANB in whom cyclosporine is used? | Cyclosporine should be discontinued. For ocular involvement, the use of infliximab should be considered | 3 | 4.90 | A |
| 6 | Are MTX, cyclophosphamide, and azathioprine effective for treatment and prevention of attacks in patients with ANB? | Since effects of these drugs for prevention of relapse are thought to be lower than those of colchicine, active use of these drugs is not recommended. | 3 | 4.20 | C1 |
| 7 | Is infliximab effective for prevention of attacks in patients with ANB? | When an attack relapses, even after the use of colchicine, treatment with infliximab should be considered. | 5 | 4.20 | C1 |
| 8 | How is the transition from ANB to CPNB confirmed? | Careful evaluation of neurological findings and brain MRI with CSF IL-6 is required after patients with ANB improve on withdrawal or reduced doses of corticosteroids. | 3 | 4.60 | B |
| | 3. CPNB | | | | |
| 9 | Are patients with CPNB always accompanied by precedent ANB? | Symptoms of ANB do not necessarily precede CPNB. | 3 | 4.80 | A |
| 10 | How much should be CSF IL-6 decreased in treatment of CPNB? | CSF IL-6 should be decreased under 17 pg/mL as soon as possible. | 3 | 4.60 | B |
| 11 | When should infliximab be introduced in treatment of CPNB? | Infliximab should be introduced immediately when there is no improvement of neurological manifestations and CSF IL-6 is not decreased below 17 pg/mL with administration of MTX at possible maximal doses. | 2b | 4.60 | B |
| 12 | How should the therapeutic goals be determined for patients with CPNB? | The goals should be the control of CSF IL-6 at a low level, no progression of symptoms, and no progression in atrophy of the brainstem on MRI. | 2b | 4.70 | B |
| 13 | How frequently should brain MRI and measurement of CSF IL-6 be performed in treatment of CPNB? | These examinations should be performed as needed until the therapeutic regimen is firmly established. Thereafter, brain MRI should be performed at least once a year, while CSF IL-6 should be examined once a year or more frequently if possible. | 3 | 4.70 | B |

*Diagnostic Criteria of Neuro-Behçet's Disease by Behçet's Disease Research Committee of the Ministry of Health, Labor and Welfare of the Japanese Government

ANB: acute neuro-Behçet's disease, BD: Behçet's disease, CNS: cetnral nervous system, CSF: cerebrospinal fluid, CPNB: chronic progressive neuro-Behçet's disease, IL-6: interleukin-6, LoE: levels of evidence, LoA: levels of agreement, MRI: magnetic resonance imaging, MTX: methotrexate, NB: neuro-Behçet's disease, SoR: strength of recommendation

be regarded as ANB (5, 15, 23). In fact, there were no significant differences in the demographic features, clinical symptoms, MRI findings, treatment regimens or outcomes between patients with cyclosporine-related ANB and cyclosporine-unrelated ANB (15).

It has been recently demonstrated that patients with cyclosporine-related ANB showed almost no relapse by the discontinuation of cyclosporine, whereas approximately 40% of patients with cyclosporine-unrelated ANB experienced recurrent ANB attacks (15). Therefore, the discontinuation of cyclosporine is strongly recommended for patients with cyclosporine-related ANB (9, 15). Tacrolimus, another calcineurine inhibitor, might have similar neurotoxic effects (15). Infliximab should be considered for patients who are at risk of recurrence of uveitis attacks after the discontinuation of cyclosporine. However, since the safety of infliximab in ANB has been established, the risks and benefits should be carefully evaluated in each patient before its introduction.

**CQ6. Are MTX, cyclophosphamide and azathioprine effective for treating and preventing attacks in patients with ANB?**

*Since the effects of these drugs for the prevention of relapse are thought to be lower than those of colchicine, the active use of these drugs is not recommended.*

There has been no evidence for the efficacy of MTX, cyclophosphamide or azathioprine for preventing ANB attacks. It has been shown that the effects of colchicine in preventing relapses of ANB were significantly better than those of MTX and azathioprine (15). Indeed, colchicine was found to decrease the relapse rates in patients with cyclosporine-unrelated ANB [hazard ratio (HR): 0.1672, 95% confidence interval (CI): 0.0089-0.9138], whereas the effects of MTX or azathioprine were not significant (15). In another report, a trend toward a shorter event-free survival was observed in patients treated with intravenous cyclophosphamide compared to those treated with azathioprine (16). However, the event-free survival rate in patients with cyclophosphamide was 56% at 5 years as well as at 10 years (16), whereas that in patients receiving colchicine was 90% at 5 years as well as at 10 years (15). Thus, it appears that cyclophosphamide might not be as effective as colchicine in preventing relapse of ANB, although differences in the background characteristics of the patient population between the two studies might have affected the results (15, 16).

However, the prolonged use of cyclophosphamide is now discouraged due to its carcinogenicity (24). Collectively, colchicine is the best choice for preventing relapses in patients with ANB. Of course, colchicine should be given under careful consideration of its risks and benefits for each patient, since the safety of colchicine is not established in ANB.

**CQ7. Is infliximab effective for prevention of attacks in patients with ANB?**

*When an attack relapses, even after the use of colchicine, treatment with infliximab should be considered.*

Infliximab has been demonstrated to prevent the development of uveitis attacks in BD by a randomized control trial (RCT) (25). It makes sense to expect infliximab to exert similar effects to prevent ANB attacks. Therefore, infliximab should be considered in patients who have relapses of ANB attacks, even when using colchicine. In fact, a recent prospective study showed the efficacy of infliximab in preventing attacks of ANB (26). However, the effect of infliximab on the prevention of ANB attacks needs to be examined through RCTs in the future.

Again, since the safety of infliximab in ANB is not established, the risks and benefits should be carefully evaluated in each patient with ANB before its introduction.

**CQ8. How is the transition from ANB to CPNB confirmed?**

*The careful evaluation of the neurological and brain MRI findings with the measurement of CSF IL-6 is required after patients with ANB improve and corticosteroids are reduced to <10 mg/day.*

Following acute attacks of ANB, corticosteroids should be gradually tapered with a careful evaluation of the neurological, brain MRI and CSF findings. In patients with CPNB, high doses of corticosteroids can reduce the levels of CSF IL-6 transiently. Thus, it is possible that prednisolone ≥10 mg/day might result in a false negative for CSF IL-6. Therefore, after patients with ANB improve and corticosteroids are reduced to <10 mg/day, the CSF IL-6 level should be examined. If it exceeds 17 pg/mL at this point, the CSF IL-6 level should be examined again in ≥2 weeks (3, 5). If CSF IL-6 still exceeds 17 pg/mL at the second examination, a diagnosis of CPNB should be made (3). If there is apparent brainstem atrophy with CSF IL-6 ≥17 pg/mL at the first examination, a diagnosis of CPNB can be made without waiting for the results of the second CSF evaluation (Figure) (3).

### CPNB

**CQ9. Are patients with CPNB always accompanied by precedent ANB?**

*Symptoms of ANB do not necessarily precede CPNB.*

Approximately 90% of patients with CPNB had a history of ANB (3, 5). Preceding symptoms of ANB might be mild headache alone, although some patients with CPNB show progressive neuropsychiatric manifestations without evident subjective symptoms of ANB (3, 4).

Whether or not preceding symptoms are evident, the CSF IL-6 levels in addition to the MRI findings should be examined for patients who present with slowly progressive neuropsychiatric changes, cognitive dysfunction or cerebellar ataxia (3).

For patients with brainstem atrophy on MRI, spinocerebellar degeneration needs to be ruled out. Since this condition does not show persistent elevation of CSF IL-6 levels, the repeated determination of the CSF IL-6 level with a ≥2-week interval is helpful for the differential diagnosis of CPNB (3, 5).

**CQ10. How much should CSF IL-6 be decreased under treatment for CPNB?**

*CSF IL-6 should be decreased to <17 pg/mL as soon as possible.*

On comparing patients with ANB in the convalescent phase to those with CPNB, the CSF IL-6 levels were significantly higher in the CPNB patients. A receiver operating characteristics (ROC) analysis indicated that CSF IL-6 can discriminate the CPNB from ANB in the convalescent phase with a sensitivity of 92.0% and specificity of 94.7% at a cut-off value 17.0 pg/mL (3). Based on this evidence, it is recommended that treatment be performed to reduce the CSF IL-6 level to <17 pg/mL as soon as possible (3). However, even in cases with a CSF IL-6 level ≥17 pg/mL, careful observation without changes in the treatment regimen may be sufficient, provided neurological manifestations and brainstem atrophy on MRI do not progress. In such cases, the CSF IL-6 levels should be examined at least once every six months to one year.

**CQ11. When should infliximab be introduced for the treatment of CPNB?**

*Infliximab should be introduced immediately when there is no improvement in the neurological manifestations and the CSF IL-6 levels has not been decreased to <17 pg/mL with the administration of MTX at the maximum feasible dose.*

MTX should be started immediately when the diagnosis of CPNB is made (7, 12). The dose of MTX should be increased until therapeutic effects can be confirmed (i.e. until CSF IL-6 is reduced below 17 pg/mL), as is the case with treatment of rheumatoid arthritis.

If there is no improvement in the neurological manifestations with CSF IL-6 levels still exceeding 17 pg/mL after the administration of MTX at 16 mg/week, or if the dose of MTX cannot be increased to the level needed to achieve an adequate response due to side effects, the immediate use of infliximab should be considered (Figure) (11). It should be remembered that CPNB progresses most extensively in an irreversible manner shortly after the onset (27).

**CQ12. How should the therapeutic goals be determined for patients with CPNB?**

*The goals should be no progression of symptoms, control of CSF IL-6 at a low level and no progression of atrophy of the brain stem on brain MRI.*

Treatment to target for CPNB should include a lack of progression of neurological manifestations (neuropsychiatric changes, cognitive dysfunction or cerebellar ataxia) as well as a lack of progression of brainstem atrophy on MRI (11, 27). A previous report found no progression of brainstem atrophy as long as CSF IL-6 levels were kept low (27). Therefore, CSF IL-6 might be a surrogate marker for 'treat to target'. In patients with advanced CPNB who have severe dysphagia and/or heavy cognitive dysfunction, infectious disease measures are necessary.

**CQ13. How frequently should brain MRI and CSF IL-6 measurements be performed for the treatment of CPNB?**

*These examinations should be performed as needed until the therapeutic regimen is firmly established. Thereafter, brain MRI should be performed at least once a year, while CSF IL-6 should be examined once a year or more frequently if possible.*

In order to establish the treatment regimen to achieve the treat to target goal, brain MRI and CSF IL-6 measurements need to be performed as frequently as required (3, 11). In rheumatoid arthritis, effect attenuation and second failure of MTX and infliximab have been noted. Therefore, in CPNB, the lack of progression of neurological manifestations (neuropsychiatric changes, cognitive dysfunction or cerebellar ataxia) as well as the lack of progression of brainstem atrophy on MRI should be checked regularly (at least once a year) after the treatment regimen is firmly established. Again, CSF IL-6 might be a useful surrogate marker for this purpose and should be examined once a year or more frequently if possible (27).

## Discussion

The current studies have provided a guideline for the management of NB, including ANB and CPNB. It should be noted that the 2018 update of the EULAR recommendations for the management of Behçet's syndrome (Behçet's disease) described the recommended treatment of acute attacks of parenchymal involvement, which correspond to ANB attacks (9). This recommendation was basically the same as that in the present study, except for the effectiveness of colchicine in preventing the relapse of ANB attacks (15). However, while the EULAR recommendation supported the use of azathioprine for ANB (9), the present review did not recommend this. There have been no RCTs regarding colchicine or azathioprine for ANB. However, in a study with a retrospective analysis of 61 patients with ANB, the results demonstrated the efficacy of colchicine, but not azathioprine, in preventing relapse of ANB (15). Furthermore, in one study, azathioprine was less effective than cyclophosphamide in preventing relapse (16). Cyclophosphamide should not be given over a long period of time because of its carcinogenicity (24). Therefore, our recommendation appeared to be more convincing than the EULAR recommendation, although further studies are required to confirm this point.

The most important message in the current recommendations is the overarching algorithm for the clinical practice of NB, incorporating ANB and CPNB as independent clinical entities and clarifying their relationship. Although CPNB was described as chronic progressive nervous system involvement in the 2018 EULAR recommendation, no details were mentioned (9). The presence of the progressive subtype of NB has been noted for more than 20 years, not only in Japan (5) but also in Turkey (4, 28). Furthermore, the first systematic review and meta-analysis confirmed the discrimination of ANB and CPNB as separate clinical entities (8). Although the frequency of CPNB is much lower than that of ANB, the recognition of CPNB is extremely important, since its treatment is totally different from that of ANB (3, 7), with corticosteroids and conventional immunosuppressive drugs, such as azathioprine and cyclophosphamide, not being effective (7) while MTX and infliximab exert favorable effects (7, 10).

It should be also noted that the diagnostic criteria for ANB and CPNB have been established based on the results of a retrospective survey of 144 patients (3). Special attention should be paid to the persistent elevation of CSF IL-6 over 17 pg/mL. Thus, a treat-to-target approach for CPNB also involves keeping the CSF IL-6 level below 17 pg/mL (3). Although the measurement of CSF IL-6 is not yet covered by health insurance in most countries, it can be now performed easily using enzyme-linked immunosorbent assay kits at the lab bench for a relatively low cost. Therefore, as much effort as possible should be made to measure the CSF IL-6 level in clinical practice when encountering patients with possible or definite CPNB, as there are no alternative

approaches available at present.

The limitation of these recommendations is that they were generated based on the results of uncontrolled evidence from open trials, retrospective cohort studies and expert opinions, thus resulting in relatively poor evidence levels for each CQ. In fact, there were no RCT results available, even for ANB (29). In addition, the current studies were not able to show how early CSF IL-6 levels should be reduced in patients with CPNB. Further studies are needed to address this point. By contrast, one strength of this study is that the task force in the present study included seven rheumatologists (one also with neurology board certification) and three neurologists. There was excellent concordance between the levels of agreement of the rheumatologists and those of the neurologists in all of the CQs, thus enhancing the reliability of the agreement levels on which recommendation levels were based in the present study.

In conclusion, we established 13 recommendations for ANB and CPNB. Although the frequency of CPNB is much lower than that of ANB, its recognition is very important due to its poor prognosis and differing treatment regimens from ANB. The international dissemination of these guidelines will facilitate the improvement of the management of patients with ANB and CPNB.

**Author's disclosure of potential Conflicts of Interest (COI).**
Masataka Kuwana: Honoraria, Tanabe-Mitsubishi Pharma.

**Financial Support**

Supported by a grant for the Behçet's Disease Research Committee, the Ministry of Health, Labor and Welfare of the Japanese Government.

**Acknowledgement**

The authors wish to thank Professor Nobuhisa Mizuki, Chairman of the board of directors, and Dr. Masaki Takeuchi, Director of the Japanese Society for Behçet's Disease, for their support.

Shunsei Hirohata and Hirotoshi Kikuchi contributed equally to this work.

## *References*

1. Hirohata S, Kikuchi H. Behçet's disease. Arthritis Res Ther **5**: 139-146, 2003.
2. Al-Araji A, Kidd D. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol **8**: 192-204, 2009.
3. Hirohata S, Kikuchi H, Sawada T, et al. Clinical characteristics of neuro-Behcet's disease in Japan: a multicenter retrospective analysis. Mod Rheumatol **22**: 405-413, 2012.
4. Akman-Demir G, Serdaroglu P, Tasci B; The Neuro-Behçet Study Group. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. Brain **122**: 2171-2182, 1999.
5. Hirohata S, Isshi K, Oguchi H, et al. Cerebrospinal fluid interleukin-6 in progressive neuro-Behcet's syndrome. Clin Immunol Immunopathol **82**: 12-17, 1997.
6. Hirohata S. Potential new therapeutic options for involvement of central nervous system in Behçet's disease (neuro-Behçet's syndrome). Curr Rheumatol Rev **3**: 297-303, 2007.
7. Hirohata S, Suda H, Hashimoto T. Low-dose weekly methotrexate for progressive neuropsychiatric manifestations in Behçet's disease. J Neurol Sci **159**: 181-185, 1998.
8. Ishido M, Horita N, Takeuchi M, et al. Distinct clinical features between acute and chronic progressive parenchymal neuro-Behçet disease: meta-analysis. Sci Rep **7**: 10196, 2017.
9. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis **77**: 808-818, 2018.
10. Kikuchi H, Aramaki K, Hirohata S. Low dose MTX for progressive neuro-Behçet's disease. A follow-up study for 4 years. Adv Exp Med Biol **528**: 575-578, 2003.
11. Kikuchi H, Aramaki K, Hirohata S. Effect of infliximab in progressive neuro-Behçet's syndrome. J Neurol Sci **272**: 99-105, 2008.
12. Hirohata S, Kikuchi H, Sawada T, et al. Retrospective analysis of long-term outcome of chronic progressive neurological manifestations in Behçet's disease. J Neurol Sci **349**: 143-148, 2015.
13. Hibi T, Hirohata S, Kikuchi H, et al. Infliximab therapy for intestinal, neurological, and vascular involvement in Behçet disease: Efficacy, safety, and pharmacokinetics in a multicenter, prospective, open-label, single-arm phase 3 study. Medicine (Baltimore) **95**: e3863, 2016.
14. Fukui T, Yamaguchi N, Morizane T, et al. [Medical Information Network Distribution Service (Minds) guidance for development of clinical practice guideline 2014]. Igakushoin, Tokyo, 2014 (in Japanese).
15. Hirohata S, Kikuchi H, Sawada T, et al. Analysis of various factors on the relapse of acute neurological attacks in Behçet's disease. Mod Rheumatol **24**: 961-965, 2014.
16. Noel N, Bernard R, Wechsler B, et al. Long-term outcome of neuro-behcet's disease. Arthritis Rheumatol **66**: 1306-1314, 2014.
17. Siva A, Fresko I. Behçet's disease. Curr Treat Options Neurol **2**: 435-448, 2000.
18. Fujikawa K, Aratake K, Kawakami A, et al. Successful treatment of refractory neuro-Behçet's disease with infliximab: a case report to show its efficacy by magnetic resonance imaging, transcranial magnetic stimulation and cytokine profile. Ann Rheum Dis **66**: 136-137, 2007.
19. Di Filippo M, Gregorio MD, Nannini C, et al. Infliximab monotherapy for neuro-Behçet's disease: a case report. J Neurol Sci **347**: 389-390, 2014.
20. Pipitone N, Olivieri I, Padula A, et al. Infliximab for the treatment of neuro-Behcet's disease: a case series and review of the literature. Arthritis Rheum **59**: 285-290, 2008.
21. Desbois AC, Addimanda O, Bertrand A, et al. Efficacy of anti-TNFα in severe and refractory neuro-Behçet disease: An observational study. Medicine (Baltimore) **95**: e3550, 2016.
22. Masuda K, Nakajima A, Urayama A, et al. Double-masked trial of cyclosporine versus colchicine and long-term open study of cyclosporine in Behçet's disease. Lancet **1**: 1093-1096, 1989.
23. Kotake S, Higashi K, Yoshikawa K, et al. Central nervous system symptoms in patients with Behçet's disease receiving cyclosporine therapy. Ophthalmology **106**: 586-589, 1999.
24. Philibert D, Cattran D. Remission of proteinuria in primary glomerulonephritis: we know the goal but do we know the price? Nat Clin Pract Nephrol **4**: 550-559, 2008.
25. Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol **31**: 1362-1368, 2004.
26. Zeydan B, Uygunoglu U, Saip S, et al. Infliximab is a plausible alternative for neurologic complications of Behçet disease. Neurol Neuroimmunol Neuroinflamm **3**: e258, 2016.

**27.** Kikuchi H, Takayama M, Hirohata S. Quantitative analysis of brainstem atrophy on magnetic resonance imaging in chronic progressive neuro-Behçet's disease. J Neurol Sci **337**: 80-85, 2014.
**28.** Akman-Demir G, Tüzün E, Içöz S, et al. Interleukin-6 in neuro-Behcet's disease: Association with disease subsets and long-term outcome. Cytokine **44**: 373-376, 2008.
**29.** Nava F, Ghilotti F, Maggi L, et al. Biologics, colchicine, corticosteroids, immunosuppressants and interferon-alpha for Neuro-Behçet's Syndrome. Cochrane Database Syst Rev CD010729, 2014.