Case of elderly onset possible neuro-Behçet’s disease with HLA-B51 homozygosity

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SUMMARY
Behçet’s disease commonly affects 20–40-year-old men and shows ophthalmo-dermatological manifestations. Here, we report a man in his 70s with acute onset of dysarthria, dysphagia and hemiplegia showing brainstem and subcortical lesions, which responded to steroid and colchicine therapy. He had a history of uveitis and was homozygous for the human leukocyte antigen-B51 allele, and we clinically diagnosed him with acute neuro-Behçet’s disease. Old-age onset neuro-Behçet’s disease is uncommon, and as far as we know, this is the oldest case of the first attack of neuro-Behçet’s disease. Clinicians should consider Behçet’s disease even for elderly patients.

BACKGROUND
Behçet’s disease is a multisystemic, recurrent inflammatory disorder that affects the eyes, skin, mucosa, joints, vascular system, lungs, gastrointestinal tract and nervous system. Among these systematic symptoms, neuro-Behçet’s disease refers to neurological manifestations, and in a strict definition, it is a disorder of the brain parenchyma. Behçet’s disease commonly affects young adults with a typical age of onset between 20 and 40 years; onset after the age of 50 years is rare. It has also been reported that less than 10% of all Behçet’s patients develop neuro-Behçet’s disease. Hence, elderly onset neuro-Behçet’s disease may be a diagnostic challenge. Here, we describe an elderly case of first-attack neuro-Behçet’s disease who was homozygous for the human leucocyte antigen (HLA)-B51 allele and who presented with dysarthria, gait disturbance and a brainstem lesion, and responded to corticosteroid and colchicine therapy.

CASE PRESENTATION
A man in his 70s was referred to our hospital on suspicion of a brain tumour on MRI. The patient first presented to a local doctor due to a 3-day history of gait disturbance, left hemiparaesthesia, dysarthria and dysphagia. MRI of the brain showed high-intensity lesions in the brainstem and left caudate nucleus. He had a history of uveitis and retinitis pigmentosa in his 30s and was blind. He also had a medical history of hypertension and bronchial asthma and was being treated with esaxerenone (2.5 mg/day), azilsartan (20 mg/day), amlodipine (5 mg/day) and tuloberutol patch (2 mg/day).

On physical examination, he had a mild fever of 37.2°C, without headache or consciousness disturbance. He showed no rash on the extremities or body trunk. No vulvar ulcers or stomatitis were noted. The pathergy test was negative. Vulvar ulcers were absent.

On neurological examination, he showed dysarthria and dysphagia. He displayed mild paraesthesia and hypoesthesia on the left half of the body, including the face. The deep tendon reflexes in the extremities showed hyper-reflexia, and his gait was spastic. Areflexia was detected for the plantar reflexes.

INVESTIGATIONS
The history was not remarkable except for the history of uveitis and retinitis pigmentosa. He had not been previously noted to have Behçet’s disease. Also, he had no family history of Behçet’s disease. Blood examination revealed no elevation of white cell count (5.4 x 10^3/μL; normal 3000–8900/μL), liver enzymes, normal kidney function and no increased levels of cancer markers (carcinoembryonic antigen, carbohydrate antigen 19-9 and soluble interleukin (IL)−2 receptor). Autoimmune antibodies (rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-aquaporin-4 antibody and antimiylcin oligodendrocyte glycoprotein antibody) were negative. Anti-aquaporin-4 antibody and antimiylcin oligodendroglial antibody were negative. Cerebrospinal fluid (CSF) analysis showed normal results without elevation of IL-6 (11.0 pg/mL; normal <17 pg/mL); CSF oligoclonal IgG bands and CSF cytopathology were negative. HLA analysis revealed homozygosity for the B51 alleles.

MRI of the brain showed hyperintense lesions in the brainstem and left caudate nucleus. These lesions were hyperintense in diffusion-weighted and apparent diffusion coefficient images. Gadolinium enhancement was absent, and MR spectroscopy showed an elevation of the choline peak and preserved N-acetyl aspartate (NAA) peak, suggesting neuroinflammation (figure 1).

DIFFERENTIAL DIAGNOSIS
Based on the history of uveitis and HLA-B51 homozygous allele, neuro-Behçet’s disease is the most likely diagnosis. According to the diagnostic criteria, the patient did not meet the criteria of the International Study Group Criteria but had a steroid-responsive brainstem lesion that improved on colchicine alone. The patient meets the criteria for probable neuro-Behçet’s disease according to the International consensus recommendation criteria for neuro-Behçet’s disease diagnosis. It is a brainstem lesion in an elderly person and possibly a
brain tumour. Other possibilities include demyelinating diseases such as multiple sclerosis and neuromyelitis optica spectrum disorders.

**TREATMENT**
According to the acute onset of a brainstem lesion, MRI findings and HLA-B51 positivity, we started oral corticosteroid and colchicine therapy after intravenous methylprednisolone administration (1000 mg/day for 3 days) on suspicion of neuro-Behçet’s disease.

**OUTCOME AND FOLLOW-UP**
After administration, his symptoms gradually ameliorated, and 2 months later, he returned home with minor sequelae of mild.

![MRI images of the patient's brain](image)

**Figure 1** MRI of the patient's brain. (A and B) Fluid-attenuated inversion recovery imaging of the brain showed hyperintense lesions in the frontal lobe and brainstem (arrowhead). The brainstem lesion was hyperintense in (C) diffusion-weighted imaging and (D) apparent diffusion coefficient imaging (arrowhead). (E) The brainstem lesion was negative for gadolinium enhancement (arrowhead). (F) MR spectroscopy showed a choline (Cho) peak and preserved N-acetyl aspartate (NAA) peak.

**Figure 2** Clinical course. After steroid therapy and oral colchicine induction, the patient's symptoms and MRI of the brain lesions were improved (arrowheads). mPSL, methylprednisolone; PSL, prednisolone.
left hemiparesis and gait disturbance. At that time, we diagnosed him as neuro-Beçhet’s disease. Follow-up MRI showed a reduction of the brain lesions. Therefore, we ceased oral corticosteroid administration for 2 months and continued with colchicine treatment alone, and he has not had a relapse to date (figure 2).

**DISCUSSION**

Beçhet’s disease was first described by the Turkish dermatologist Hulusi Beçhet in 1937.7 Beçhet’s disease is a systemic inflammatory disease with an unknown cause that is common in the Far East, Middle East and Mediterranean regions along the Silk Road, and a genetic predisposition has been shown.8 Beçhet’s disease commonly affects men between the ages of 20 and 40 years, and the clinical features and course of the disease are reportedly closely related to sex and age.9 Our patient may have had Beçhet’s disease in his 30s when he had uveitis but was not diagnosed at the time. Beçhet’s disease with an onset over 60 years of age is rare, but there are a few reports of cases with an age of onset over 70 years with ophthalmic and dermatological manifestations.10 With the recent ageing of the world’s population, the number of elderly patients with Beçhet’s disease is likely to increase. In addition, there is reportedly a higher rate of neurological symptoms as the age of onset increases.11 However, to the best of our knowledge, there are no previous reports of new-onset neuro-Beçhet’s disease in patients aged over 70 years. Therefore, our case has the oldest onset age of neuro-Beçhet’s disease.

Considering the diagnosis of our patient, he presented with a brainstem lesion, which is frequently a diagnostic challenge because there is considerable risk associated with biopsy, and there are many differential diagnoses including primary brain tumour, metastatic cancer, malignant lymphoma, cerebrovascular stroke and autoimmune inflammatory diseases (such as multiple sclerosis, neuromyelitis optica spectrum disorder, neuro-Beçhet’s disease and neurosarcoïdosis). Our case showed poor gadolinium enhancement on MRI, and malignancy was unlikely. On MR spectroscopy, he showed an elevated choline peak and preserved NAA peak, which suggest demyelination or inflammation. Choline in the brain is usually in an insoluble form, so a high choline peak may represent abnormal choline mobility, suggesting inflammation, demyelination and remyelination.12 In addition, a decrease in NAA reflects axonal injury or loss. Meanwhile, a preserved NAA peak indicates that axonal damage is mild.13 The location of the brainstem lesion in our case also supports the diagnosis of neuro-Beçhet’s disease.12

Regarding CSF examination, our case showed normal CSF test results. More than 30% of patients with neuro-Beçhet’s disease reportedly do not have CSF pleocytosis,3 so normal CSF findings cannot be used to rule out a diagnosis of neuro-Beçhet’s disease. In our case, the fact that the patient was homozygous for the HLA-B51 allele also contributed to the diagnosis. Menthon et al reported that the risk of developing Beçhet’s disease is 5.78 times higher in HLA-B51 carriers than in non-carriers. Especially, in a Japanese cohort, the risk ratio was found to be 7.48 times higher in HLA-B51 carriers.13 Also, previous report showed that in various types, neuro-Beçhet’s disease have the highest rate of HLA-B51 positivity.14

For the treatment of neuro-Beçhet’s disease, steroid therapy is effective in the acute phase, but it may increase the rate of side effects and should be administered for a short period of time.15 For this reason, colchicine (1.0–2.0 mg/day) administration immediately after the first attack and continued for 5 years is recommended to prevent relapse.15 In addition, the administration of cyclosporine to suppress ocular Beçhet’s disease is known to induce neuro-Beçhet’s disease.16 Therefore, if a patient is taking cyclosporine, it is best to discontinue it. Our patient had a good outcome with the use of steroids and colchicine.

**Learning points**

- Beçhet’s disease over the age of 70s is considered to be rare.
- Treatable brain lesions, including neuro-Beçhet’s disease, should be listed in the differential diagnosis of brain lesions of the elderly.
- Clinicians should consider human leucocyte antigen tests for diagnosing neuro-Beçhet’s disease even if the patients are over their 70s.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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**REFERENCES**

Case report