Neuro-Behçet is a rare disease but should be considered in all kinds of neurological findings, even in childhood

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Abstract

Objective

Behçet's disease (BD) is a vasculitis characterised by eye, musculoskeletal, neurological and gastrointestinal involvement, in addition to recurrent oral ulcers. Neuro-Behçet is the term used to define the nervous system involvement in BD and is very rarely seen in childhood. This study aims to show that neuro-Behçet can manifest a clinical course involving all kinds of neurologic findings in the paediatric population.

Methods

The Clinic of Paediatric Neurology at Uludag University provides tertiary treatment for children up to eighteen years of age in Bursa, Turkey. Five patients who were clinically diagnosed with Neuro-Behçet in the last 5 years were included in the study.

Results

Seizure, myopathy, transverse myelitis, polyneuropathy, venous thrombosis and facial nerve paralysis were respectively seen in the patients.

Conclusion

Neuro-Behçet is rare in children, but it is important to know that it can cause various neurological findings, and also systemic findings should be taken into consideration in the diagnosis of neurological diseases. Studies on the neurological involvement of BD in children are inadequate. We believe that paediatric neurologists should be more aware of the neuro-Behçet condition.

Key words
Behçet's disease, neuro-Behçet, children

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Introduction

Behçet's disease (BD), which has an unknown aetiology and leads to systemic involvement, was first defined by a Turkish dermatologist, Hulusi Behçet. The diagnosis is made according to the clinical findings: recurrent oral ulcers, involvement of skin, ocular, vascular and neurologic systems are seen in BD (1). Heterogeneity is seen in BD patients in terms of demographic characteristics, organ symptoms, frequency and severity of relapses, course of the disease, response to treatment, and prognosis (2). Nervous system involvement can be seen with various clinical findings in BD. The term neuro-Behçet's disease (NBD) is used to address nervous system involvements in BD (1). Reports in the current medical literature are generally related to the adult patient population, since NBD is rarely diagnosed in childhood. It is not yet clearly understood which symptoms actually indicate the nervous system involvement of BD or whether it is a non-specific symptom (3). When the diagnosis of NBD should be considered with regard to clinical findings or symptoms frequently encountered in neurology practice is not yet known. In this article, we aimed to share the neurological symptoms, clinical findings and neuroimaging results of our cases, which we consider as NBD.

Materials and methods

The Clinic of Paediatric Neurology at Uludag University provides tertiary treatment for children up to eighteen years of age in Bursa, Turkey. Five patients who were clinically diagnosed with NBD in the last 5 years were included in the study. Data of demographic characteristics, clinical findings, HLA groups, pathergy test, cerebrospinal fluid (CSF) test, evoked potential values, treatments, neuro imaging, long-term follow-ups were retrospectively evaluated from their medical records. Ethics committee approval was given by the local Institutional Review Board on April 10, 2019.

Results

Five paediatric patients diagnosed with NBD were included in this study: three male and two female with a mean age of 15 years. Oral ulcers were present in all patients (Table I).

Case 1

This patient had been followed-up for 3 years with the diagnosis of BD and was hospitalised in the paediatric neurology clinic for focal seizure. Her neuromotor development was normal. There was no history of trauma, fever and drug intake, except colchicine. Electrolytes and neurological examination were normal, the electroencephalography showed sharp slow wave complexes arising in the right hemisphere, and visual evoked potentials (VEP) and somatosensory evoked potentials (SEP) were normal. There were no other aetiology factors found for seizure. The cranial magnetic resonance imaging (MRI) and cranial MRI angiography were also normal. Carbamazepine was added to the colchicine treatment. There was no occurrence of seizures during the one-year follow-up. It may be a question of coincidental association of BD and seizure, because there was no parenchymal or non-parenchymal involvement in this case.

Case 2

The patient was admitted complaining of the sudden inability to walk and bilateral leg pain. The right nasolabial fold was flat, and stocking-glove type of sensory loss was observed in the hands and distal parts of the legs. The muscle strength was found as 2–3/5 in the lower extremities, and the deep tendon reflexes were absent. There was no anal sphincter tonus, and urinary retention was present. The patient was hospitalised with the preliminary diagnoses of transverse myelitis and peripheral neuropathy. The detailed medical history of the patient revealed that he had been diagnosed with BD, and colchicine treatment had been initiated. However, the patient had not been compliant with the treatment and did not present at follow-up. Cranial MRI revealed hyperintense lesions in regions extending from the left thalamus and the posterior part of the internal capsule to the left cerebral peduncle (meso-diencephalic), the medial portion of the left thalamus, in

Table I. Paediatric patients diagnosed with NBD.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	female	male	male	male	female
Age (years)	12	16	15	17	16
Systemic involvement	arthritis, oral ulcers	oral ulcers, skin lesions	oral ulcers, skin lesions	oral ulcers, artritis	oral ulcers
Family history of BD	father	no	father	no	no
Pathergy test	negative	positive	positive	negative	positive
HLA groups	HLA B51	HLA B51	HLA B51 HLA B35	HLA B51 HLA B35	HLA B51 HLA B35
Neurological complaint and findings	seizure	myopathy, transverse myelitis, polyneuropathy	Headache, vertigo	Headache, papilledema	Headache, facial nerve paralysis
Neuroimaging	normal	hyperintense lesions	hyperintense lesions	thrombus	hyperintense lesions
Lumbar puncture	not performed	oligoclonal band is negative, 10 erythrocytes/ mm^3 630/mm^3 lymphocyte, CSF glucose: 45 mg/dL, concurrent blood glucose 97 mg/dL, CSF protein value was 275 mg/dL	oligoclonal band is negative, 8/mm^3 lymphocyte, CSF glucose: 65 mg/dL, concurrent blood glucose: 95 mg/dL, protein: 48 mg/dL	not performed	oligoclonal band is negative, 10/mm^3 lymphocyte, CSF glucose: 60 mg/dL, concurrent blood glucose 88 mg/dL, protein: 36 mg/dL
Treatment	colchicine carbamazepine	colchicine, IVIG, Steroid, azathioprine	colchicine	colchicine, steroid, enoxaparin	colchicine, steroid

both hippocampi, and the posterior part of the right centrum semiovale. Spinal MRI revealed hyperintense lesions in T2A images, segmentally located at the levels of T1 to T6 and from T8 to the conus, at the central part of a long segment of the medulla spinalis, particularly involving the grey matter, anterior and posterior horns, accompanied by severe swelling at the level of the conus (Fig. 1). The patient had diffuse muscle pain, and creatine kinase (CK) level was found to be increased (CK: 809 IU/L). The electroneuromyography performed on the first day revealed the absence of the F-response in the nerves of the lower extremities together with the reduction of F-response persistency in the upper extremity nerves. Lumbar puncture (LP) was performed. Erythrocyte sedimentation rate was found as 75 mm/hr. VEP and SEP were prolonged. Intravenous immunoglobulin (IVIG) treatment was firstly initiated due to the clinical findings of medulla spinalis and peripheral polyneuropathy. However, there was no response to treatment. The patient was started on pulsed-steroid (methylprednisolone) and colchicine treatments on the fifth day of admission. A physiotherapy programme was initiated, but response to treatment was insufficient, and so azathioprine was started. Two months later the patient was discharged from hospital, the physiotherapy programme was continued, and the patient was followed-up by outpatient clinical visits. It was observed that the patient started to walk independently during his outpatient clinical follow-up examinations nine months after the admission.

Case 3

This patient had been followed-up for 4 years with the diagnosis of BD and was admitted with the complaint of long-term headache and vertigo. Neurological examination was normal, no papilledema and no hypertension were detected. Both lateral ventricles are adjacent to the posterior horns, the right mid-centrum, the frontal hyperintense foci were detected in the subcortical location in the region. Corpus callosum and posterior fossa were preserved in the cranial MRI (Fig. 2). MRI angiog-

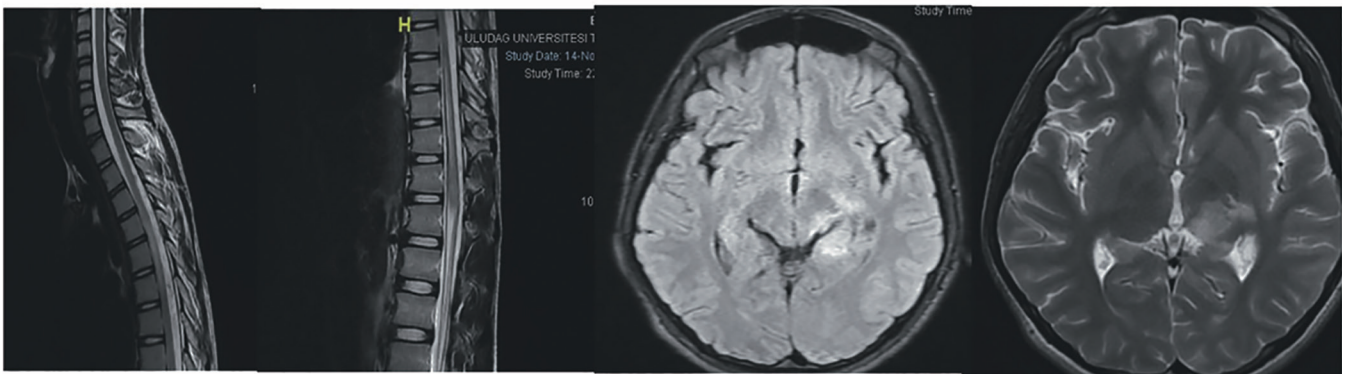

Fig. 1. Spinal MRI revealed hyperintense lesions in T2A images, segmentally located at the levels of T1 to T6 and from T8 to the conus.

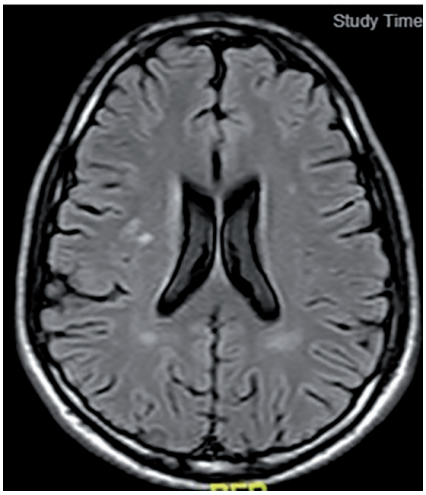

Fig. 2. Corpus callosum and posterior fossa were preserved in the cranial MRI.

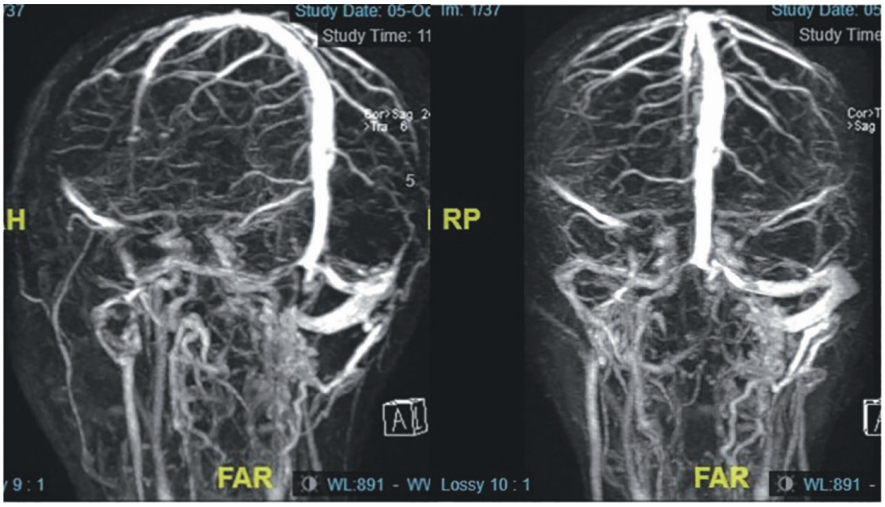

Fig. 3. The MRI angiography detected a thrombus that had completely occluded the internal cerebral veins, galena vein and sinus rectum, causing partial obstruction in the right transverse sinus and sigmoid sinuses.

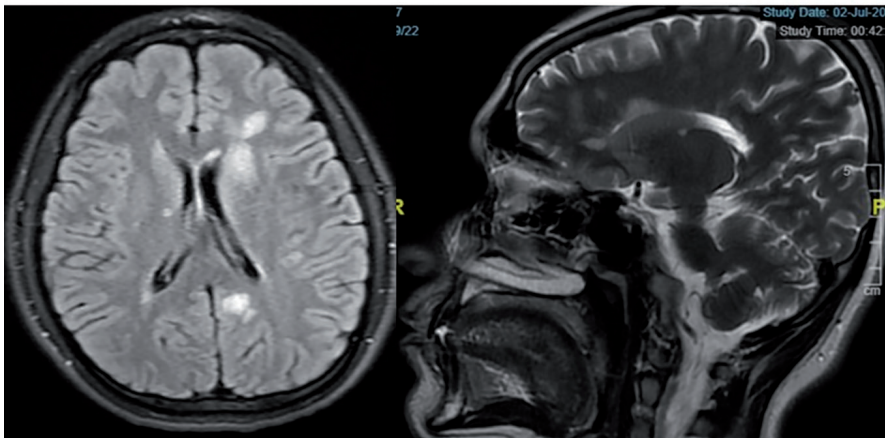

Fig. 4. Cranial MRI showed hyperintense lesions in the right lateral ventricle, right periventricular area and temporal region of the pons posterior to the atrium.

raphy was normal, as were VEP and SEP, and the oligoclonal band was negative. He was taught to manage the headache triggers and the colchicine treatment dose was increased.

Case 4

This patient had been followed-up for 6 years with the diagnosis of BD and was admitted with the complaint of acute headache. The neurological examination revealed papilledema. The MRI angiography detected a thrombus that had completely occluded the internal cerebral veins, galena vein and sinus rectum, causing partial obstruction in the right transverse sinus and sigmoid sinuses (Fig. 3). Steroid and enoxaparin were started and he soon recovered.

Case 5

The patient was admitted with the complaint of headache and facial nerve paralysis. Recurrent oral aphthosis was in her medical history, but did not have a diagnosis of BD. There was no family history of BD. The neurological examination was normal except for peripheric facial nerve paralysis. Viral markers, ANA and ANA profile were found to be negative, while the immunoglobulins had normal levels. Pathergy test was positive. MRI showed hyperintense lesions in the right lateral ventricle, right periventricular area and temporal region of the pons posterior to the atrium (Fig. 4). VEP and SEP were normal and the oligoclonal band was negative. The patient was diagnosed with BD and was started on colchicine and steroids.

Discussion

BD, which can cause systemic involvements, has an unknown aetiology. The diagnosis is made based on clinical findings (1). Rheumatologists and dermatologists are very familiar with BD and can diagnose it more easily. However, it can be difficult for paediatric neurologists to diagnose it when the patients only present with neurological findings before other systemic findings appear. The BD criteria for paediatric patients were revised in 2015 by the International Behçet's Disease Study Group, and having three of any of the six following recurrent symptoms: oral aphthous lesions, genital ulcers, skin involvement, eye involvement, neurological findings, and vascular findings, is the indication for the diagnosis of BD. The term neuro-Behçet is used to define the nervous system involvements in BD. The rate of neuro-Behçet in paediatric patients with BD was reported to be 15–30% (1), however, the studies related to children are inadequate and often in the form of case presentations. Neuro-Behçet is classified into two major categories: parenchymal and non-parenchymal (cerebral venous thrombosis, acute meningeal syndrome, intracranial hypertension syndrome) (4). In a study conducted in our country, dural sinus venous thrombosis was found to be the most common neurological involvement in paediatric-onset NBD (4). According to

this classification, one patient is in the non-parenchymal group and the others are in the non-parenchymal group in this study.

The most common neurological symptom in BD is headache, followed by meningoencephalitis, cranial nerve paralysis, ataxia, hemiplegia, benign intracranial hypertension, and seizures (1). In this study, patients presented with neurological findings that may be frequently encountered in neurology practice. Seizure, transverse myelitis, myopathy, polyneuropathy, headache, sinus venous thrombosis and facial nerve paralysis were seen in the patients, respectively. Three of the patients were already known to have BD before neurologic involvement, while the other two (patients 2 and 5) were diagnosed after neurological findings appeared. Systemic involvements such as collagen tissue disorders were suggested as the cause for such a clinical picture in Patient 2 since central nervous system, medulla spinalis, peripheral nerve, and muscle involvements occurred together, and he was considered as having neuro-Behçet. The rate of medulla spinalis involvement was reported to be 1.6–13% in the studies also including an adult neuro-Behçet patient population (6, 7). It would have been very difficult to diagnose neuro Behçet if patient 2 had only had spinal involvement.

Cranial MRI sections show hyperintense lesions in neuro-Behçet. This kind of lesion can be seen mostly in autoimmune diseases, such as multiple sclerosis (MS) in neurology practice. Lesions in neuro-Behçet are most frequently seen in the brainstem and diencephalic structures (9), while lesions are usually localised in the juxtacortical, periventricular and infratentorial areas in patients with MS (10). In the present study, hyperintense lesions were detected on MRI in three patients. The neurological findings in neuro-Behçet are treated with immunosuppressive agents. Corticosteroids are the first line of treatment, and the response is satisfactory in patients when well-tolerated. The other immunosuppressive treatment choices in patients who do not respond to corticosteroids are azathioprine, methotrexate, interferon-α and infliximab (4, 8, 11). In this study the patient with myopathy, transverse myelitis and polyneuropathy had a poor prognosis, so azathioprine was given because response to steroids was insufficient.

However, there are some limitations in this study. We evaluated patients diagnosed with neuro- Behçet in a Neurology Clinic, whereas we do not have information about neurological findings in patients with BD in other clinics, such as Dermatology, Rheumatology or Ophthalmology. Moreover, these clinics see more BD patients than we do. Further studies are certainly needed.

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