Invited Review

Neurological Involvement in Behçet’s Disease: Clinical Characteristics, Diagnosis and Treatment

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Behçet’s disease was first defined as the triad of recurrent oral aphthous ulcers, genital ulcerations and uveitis observed in 3 cases by Professor Hulusi Behçet from the Dermatology Department of Istanbul University, and at the time was named as the tri-symptom complex (1). It is a recurrent systemic inflammation with unknown etiology. It is more prevalent among males and onset is usually in the third decade of life.

According to the diagnostic criteria proposed by the International Behçet Study Group in 1990, in addition to oral aphthous ulcerations recurring at least three times a year, two of the following four findings are required to make a diagnosis; these include genital ulcers or scarring, skin lesions (pseudofoliculitis, acneiform lesions, erythema nodosum, skin ulcers), anterior or posterior uveitis or retinal vasculitis diagnosed by an ophthalmologist and skin Pathergy test positivity (2). Skin Pathergy test is characterised by an erythematous papule formation following the puncture of the skin 5 mm deep obliquely at an unvascularized region with a sterile 20-22 gauge needle (3), although lacking high sensitivity for Behçet’s disease diagnosis, it is a highly specific diagnostic test.

Behçet’s disease may involve vessels (especially veins and pulmonary arteries), joints, gastrointestinal system and central nervous system besides the initially defined triad. Although liver, kidneys, heart and peripheral nerves are relatively less affected in Behçet’s disease course.

NEUROLOGICAL INVOLVEMENT

Although quite variable rates of neurological involvement in Behçet’s disease has been reported in different series, a study conducted at our clinic found 5.3 % neurological involvement in all of the Behçet’s disease patients evaluated in one year (5). Neurological involvement in Behçet’s disease manifests about five years after the onset of systemic findings, is seen 3-4 times more commonly in males compared to females and usually presents with central nervous system (CNS) involvement with extremely rare peripheral nerve and muscle involvement. In this review mainly CNS involvement will be discussed. Neurological involvement in Behçet’s disease may be evaluated in two main groups as parenchymal and non-parenchymal CNS involvement.

Parenchymal CNS Involvement

The most frequently encountered clinical picture is a brain stem syndrome evolving over days. Headache and fever may accompany this picture. Neurological examination often reveals ataxia, dysarthria, hemiparesis and bilateral pyramidal findings. Usually sphincter dysfunction and behavioral changes or cognitive impairment precedes or accompanies neurological involvement; this type of involvement can be designated as ‘brain stem+’ type. Despite brain stem involvement, cranial nerve involvement and sensory symptoms are encountered relatively less often. Occasionally a smaller brain stem
lesion may present with isolated hemiparesis or cranial nerve involvement with contra-lateral hemiparesis. In such instances, cognitive impairment or sphincter dysfunction does not concur. In addition to brain stem involvement spinal involvement can be seen in isolation or more often with brain stem involvement or cognitive dysfunction (‘spinal +’ type) and in this case clinical presentation is more severe since the onset. Hemispheric involvement may be predominant in a minority of the cases, and approximately 10% of the cases may present with a multiple sclerosis (MS) like clinical picture. Occasionally, coincidental ‘soft’ neurological signs (ie., reflex asymmetry, pyramidal signs, decreased vibration sense) can be found in neurological examination of some patients performed for complaints like headaches. We assume that these patients have “silent” neurological involvement. Although the clinical significance of this type of neurological involvement is not completely understood, cases with “silent” neurological involvement followed in our clinic for 8 years did not develop a significant neurological disability.

The preferred imaging method for investigating CNS involvement is cranial magnetic resonance imaging (MRI). Characteristically a uni-or bilateral large T2 hyperintense lesion with mild mass effect and small central contrast medium enhancement extending form the brain stem or the basal ganglia to the diencephalic structures is seen (Figure 1). With treatment, the lesion shrinks and remains as milimetric T2 hyperintensities. In late stages, especially after recurrent relapses, significant brain stem atrophy may develop. In patients with spinal involvement T2 hyperintensities at one or multiple levels or medullary atrophy may be seen with spinal MRI. Approximately 10% of the patients have white matter lesions in MRI and it might be very difficult to differentiate these lesions from MS lesions.

![Figure 1: Cranial MRI during an acute neuro-Behçet episode. Left image shows coronal T2 weighted image, right image shows coronal T1 weighted image acquired after gadolinium injection. On the right a large lesion extending from the putamen to the internal capsule, thalamus and the brain stem is evident. Only a small mesencephalic portion of this large lesion shows gadolinium enhancement.](image)

In parenchymal neuro-Behçet’s disease cerebrospinal fluid (CSF) examination is helpful in diagnosis. Even though in some instances it may be normal, usually a mild to moderate pleocytosis consisting of lymphocytes and polymorphonuclear cells and a mild elevation in protein levels is encountered. Usually oligoclonal IgG bands are not found in CSF but IgG index may be elevated. Besides supporting inflammatory neurological involvement abnormal CSF
findings indicate more severe prognosis and dictates more aggressive treatment (10).

Clinical course is usually with relapses and remissions and as the number of relapses increase prognosis worsens; some cases may develop a secondary progressive course (10,11). Less frequently especially in patients with spinal involvement an insidious progressive course may be seen. Unfavorable prognostic factors for neuro-Behçet’s disease are parenchymal CNS involvement, CSF pleocytosis and increased protein levels, involvement with an extensive lesion (ie. ‘brain stem+’), spinal involvement, primary progressive course and two or more relapses (10).

Non-parenchymal CNS involvement

Non-parenchymal involvement denotes cases where the primary insult is not directed to CNS parenchyma and the neurological findings evolve secondary to cerebral venous or arterial involvement. Furthermore, cases with exclusive meningeal involvement where the brain parenchyma remains unaffected may also be included in this group.

In this group intracranial hypertension due to dural sinus thrombosis is the most common clinical presentation. These patients may have a tendency towards other vascular involvement such as deep vein thrombosis or pulmonary artery aneurysms (12). Dural sinus thrombosis due to Behçet’s disease usually presents with a clinical picture similar to dural sinus thrombosis resulting from other causes. Patients experience a subacutely evolving severe headache which worsens in supine position and is frequently accompanied by nausea and vomiting. Papillaedema and uni-or bilateral sixth cranial nerve palsy may be found but the rest of the neurological examination and neuropsychological evaluation is unremarkable. However unlike dural sinus thrombosis caused by other etiologies, epileptic seizures and cortical venous infarction are rarely encountered (13).

Cranial MRI is usually unremarkable but may reveal flow void phenomena in the occluded dural sinus (14). MR venography or cerebral angiography is helpful in diagnosis. CSF is almost always normal except raised pressure. Parenchymal CNS involvement is practically never seen in these patients (10,11). Non-parenchymal CNS involvement’s prognosis is much better than parenchymal involvement (10,11).

Occasionally there may be arterial involvement of the CNS with a stroke like syndrome or arterial aneurysm.

DIFFERENTIAL DIAGNOSIS

In differential diagnosis two main situations should be considered. In the first scenario, a patient without Behçet’s disease diagnosis presents with a neurological complaint; in the second scenario the patient has Behçet’s disease and develops neurological symptoms. In this second case, it should be kept in mind that Behçet’s disease patients may have neurological symptoms due to other causes and not all neurological findings should be associated with neuro-Behçet’s disease. If the first scenario is met, in a case without a former diagnosis of Behçet’s disease, the following features should raise the suspicion that neuro-Behçet’s disease is responsible for the clinical presentation: the patient is a male, the neurological presentation is mainly a motor-cognitive involvement, a T2 hyperintense lesion extending from brainstem and/or basal ganglia to the diencephalic structures is detected with MRI, CSF protein levels are increased with a lymphocytic and/or polymorphonuclear pleocytosis. In this case, oral aphthous ulcers, genital ulcers and skin lesions should be sought in the medical history and with physical examination, ophthalmologic examination for uveitis and Pathergy test should be performed. MRI, CSF examination, neuropsychological testing should be performed in all patients evaluated for neuro-Behcet’s disease, evoked potentials, MR venography, spinal MRI or cerebral angiography should be performed when indicated. In the differential diagnosis of neuro-Behcet’s disease the following should be kept in mind: CNS infections, multiple sclerosis, stroke in the young, rarely CNS tumors. Furthermore, all kinds of neurological or psychiatric diseases ranging from vestibular neuritis to schizophrenia may coincidentally occur in Behçet’s patients. Neurological examination, MRI, CSF and
evoked potentials are helpful in excluding neuro-Behçet’s disease.

Headache in patients with Behçet’s disease merits special comment. Parenchymal CNS attack may present with severe headache but there are always associated neurological signs. Elevation of intracranial pressure in a young male should always raise the possibility of Behçet’s disease. However, most of the patients referred to our Neuro-Behçet outpatient clinic have common headache syndromes such as tension type headache or migraine. These patients do not greatly differ from the patients presenting to the headache outpatient clinic. However, in some patients systemic Behçet’s disease exacerbations such as oral aphteous ulcers, genital ulcers or uveitis might trigger these primary headache syndromes. Interestingly, approximately 5% of patients experience migraneous headaches only during systemic Behçet’s disease exacerbations and their headaches improve with treatment of the systemic Behçet’s disease exacerbations rather than analgesics (15).

TREATMENT

Randomised, double-blind, placebo controlled trials on the treatment of neuro-Behçet’s disease have not been performed (16). Therefore treatment approaches depend on anectodal reports and personal experience. However blind, placebo-controlled trials have been concluded in Behçet’s disease patients without neurological involvement (17,18). In most of these trials mucocutaneous symptoms have been studied and thalidomide and colchicine were found to be superior to placebo. However, mucocutaneous involvement is usually observed in cases with mild disease course. Therefore, studies done on patients with ocular involvement are more instructive in treating neurological complications. In a short-term study azatioprine was found to be effective in Behçet’s uveitis and long-term follow-up has proved its sustained efficacy (17). In another study where Cyclosporin A and intravenous high dose cyclophosphamide were compared, at the end of the first year both treatments were equally effective (19). However, cyclosporine A’s neurotoxicity may limit its use in patients with CNS involvement (20). Although there are studies suggesting that interferon alpha is effective in ocular disease further studies are required (17).

Therapeutic approach based on our personal experience and other reports on this subject is summarized below.

Parenchymal CNS Involvement

In acute episodes intravenous (IV) methylprednisolone is given 1000mg/day usually for 5 days, followed by once a week administration of 1000mg/day intravenous (IV) methylprednisolone for four weeks. In addition, 32mg/day oral methylprednisolone is given with weekly IV doses. After following the patient at the 32mg/day dose for a few months, methylprednisolone is tapered very slowly to 4-8mg/day and the patient is maintained at this basal dose. Other centers recommend higher doses of IV methylprednisolone for 5-7 days and tapering slowly with oral dosing (16). The crucial point is to avoid sudden discontinuation of steroids, since rapid tapering of steroid dose usually causes relapses and treatment of these relapses might be more difficult then the initial episodes.

If the patient has bad prognostic factors or if a second neurological episode has occurred an immunosuppressant agent should be added. Based on the evidence with ocular involvement (17) azatioprine may be given as the first choice (2.5mg/kg/day). If the patient had an episode while on azatioprine or if toxicity develops, IV cyclophosphamide 1000mg/day may be administered monthly or every 3 weeks or mycophenolate mophetyl may be given 2gr/day.

Non-parenchymal CNS involvement

The role of oral anticoagulants in dural sinus thrombosis is still debated and the same discussion is applicable for deep vein thrombosis seen in Behçet’s disease (17). In our unit a combination of oral or high dose intravenous methylprednisolone and acetylsaliclycic acid is used. However, some authors recommend short-term administration of subcutaneous low molecular weight heparin (16). In this case, pulmonary artery aneurysm should be excluded with a thorax
CT before initiating anticoagulant therapy, since bleeding from a pulmonary aneurysm can be fatal. Long-term anticoagulant therapy or CSF shunting is usually not required. Unless the sinus thrombosis recurs or is unresponsive to steroids alone, long-term anticoagulant therapy is not necessary.

In rare cases presenting with arterial involvement of the CNS, high dose IV methylprednisolone or IV cyclophosphamide can be given according to the regimes described above.

REFERENCES


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