NEURO-BEHÇET:
A CLINICAL EXERCISE

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ABSTRACT

Behçet disease is a recurrent systemic vasculitis of unknown etiology, that involves vessels of nearly all sizes and types. Because of this, disease manifestations can occur at many sites throughout the body. Central nervous system (CNS) involvement may be parenchymal or nonparenchymal and has a global prevalence that ranges from 3% to 10%. Main signs of CNS involvement are pyramidal and those resulting from brain stem lesions. Aseptic meningitis, mental changes, sphincter disturbances, pseudobulbar syndrome, and deep sensory abnormalities may be seen. Analysis of cerebrospinal fluid, computed tomography (CT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and brain angiography offer assistance in the diagnosis. The course of disease can be primary progressive, secondary progressive or have a relapsing-remitting profile.
Boluses of methylprednisolone for three days followed by cyclophosphamide are the treatment of choice.
This papers discusses these aspects of neuro-Behcet on the basis of complex clinical case.

Key-words: Behcet`s disease; Neuro-Behçet.

RESUMO

A Doença de Behcet consiste numa vasculite sistémica recorrente de etiologia desconhecida que envolve vasos de quase todos os tamanhos e tipos. Por este motivo, as manifestações da doença podem afectar múltiplos órgãos e sistemas. O envolvimento do sistema nervoso central pode ser parenquimatoso ou não-parenquimatoso e tem uma prevalência de 3 a 10%. Os principais sintomas são de tipo piramidal e ainda os que resultam do atingimento do tronco cerebral. Meningite asséptica, alterações mentais, distúrbios dos enfincteres, síndrome pseudo-bulbar e anormalidades sensoriais profundas podem também ocorrer. A análise do líquido cefalo-raquídeo, ressonância magnética nuclear, o SPECT (single-photon emission computed tomography) e a angiografia cerebral são instrumentos úteis no diagnóstico. O curso da doença pode ser progressivo (primário e secundário) ou assumir um padrão com remissões e agravamentos.
Bólus de metilprednisolona por 3 dias, seguidos de ciclofosfamida constituem, actualmente, o tratamento de escolha.
Este trabalho aborda estes e outros problemas de Neuro-Behcet, tomando como base a discussão de um caso clínico complexo.

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Introduction

Behcet's disease, first described in 1937 by Hulusi Behcet, a Turkish dermatologist, is a multisystemic vasculitis, of unknown etiology, which involves blood vessels of different types and sizes, with a recurrent course. Prevalence is higher in Mediterranean countries, the Middle East and Eastern Asia, particularly Japan (along the ancient «silk road»). Males are more frequently affected. The mean age of onset ranges from 20-35 years, although cases have been described with an onset from 1 to 80 years of age[1,2,3]. The role of the HLA B51 in this disease has been extensively studied in the last few years, and it has been reported that the allele HLA-B5101 was found in 72% of the patients in which it seems to predispose to a more severe prognosis, particularly in males[4]. Despite the predisposition to Behçet`s disease conferred by HLA-B51, familial cases are not the role, consisting only about 5% of cases. Studies by Yazici et al[5] show that an earlier onset is associated with a worse prognosis. Males develop severe ocular disease more frequently whereas females present more commonly with erythema nodosum.

The International Study Group Criteria (ISG criteria) for Behcet's Disease, are presented in Table 1[6]. They have a sensitivity of 91% and a specificity of 96%[7].

– **Oral ulcerations** are usually painful, of variable size, affecting the lips, tongue, gingiva and cheeks. They usually heal after 2 to 10 days, without scarring, but are typically recurrent.

– **Genital ulcerations** are more specific of the condition and leave a scar upon healing.

Table 1. International Study Group Criteria for Behçet´s Disease[1,2,6].

1. Recurrent oral ulceration: minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, wich recurred at least 3 times in one 12-month period

Plus 2 of:

2. Recurrent genital ulceration: aphthous ulceration or scaring, observed by physician or patient
3. Eye lesions: anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination; or retinal vasculitis observed by an ophthalmologist
4. Skin lesions: erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by physician in postadolescent patients not on corticosteroid therapy.
5. Positive pathergy test: read by physician at 24-48 hr

– **Ocular involvement** represents one of the most serious manifestations as it is frequently associated with severe sequelae including blindness. Ophthalmologic manifestations include acute iridocyclitis, cataracts, glaucoma and posterior segment involvement with retinal vasculitis, vitritis, panuveitis, retinal edema and retinal detachment, arterial and venous occlusion and cytoid macular degeneration.

Ocular involvement is bilateral in about 80% of the cases and occurs more frequently in males. It is usually associated with disease flares but seldomly occurs as presenting feature.

– Regarding cutaneous manifestations, the most frequent ones are papulopustular lesions, and erythema nadosum like lesions, superficial thrombphlebitis (usually clinically difficult to tell

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from erythema nodosum like lesions) as well as macular eruptions and dermographism. Less frequently, purpura, bullae and digital necrotizing vasculitis can be observed.

– The **pathergy test** elicits a nonspecific cutaneous hyperreactivity: a sterile 20 gauge needle is inserted to 1cm depth in the anterior surface of the forearm, then is revolved and taken back. The procedure can be repeated at three different sites and the result is read at 24 to 48 hours: the test is considered positive if an aseptic papule or pustule has been produced[1,2]. Yazici et al. proposed the utilization of a solution of monosodium urate to precipitate the pathergy reaction (2,8).

The result of this test depends on the population studied and the size of the needle. Only 40 to 50% of Behcet's patients will present with a positive pathergy test. False positives can be observed in seronegative spondylarthropaties and in chronic myelogenous leukemia after IFN a treatment[1].

– **Arthralgia and arthritis** affect preferentially large joints of lower extremities, but any joint can be involved including the sacroiliac. The pattern is usually subacute, intermittent and not deforming. Erosions are rarely seen, but radiological evidence of bone proliferation is relatively common at tendon and ligament insertions.

– **Vascular inflammation** is commonly heralded by venous and arterial thrombosis. A recent review of the literature by Bartlett et al[2,9] shows that venous manifestations occur in about 33% of the patients. Arterial aneurysms are seen in about 7% of the cases. The abdominal aorta is the most common site of arterial inflammation, followed by the femoral and pulmonary arteries.

– **Gastrointestinal symptoms** are present in up to 50% of the patients. They include diarrhea, abdominal pain, and hemorrhage. The most frequent lesions are ulcers, affecting any section of the GI tract. They are frequently large and deep with a considerable tendency to perforation[1,2,10]. Differential diagnosis with inflammatory bowel diseases is mandatory.

– **Lung manifestations** are mainly due to vasculitis, leading to thrombosis or aneurysm formation. Multiple pulmonary aneurysms can cause massive hemoptysis, a medical emergency, that can be fatal in 40 to 80% of the cases. Hemoptysis, recurrent dry cough, fever, dyspnea and pleuritic chest pain, are the cardinal signs of pulmonary involvement. Radiological findings include pleural effusions, diffuse infiltrates and nodular opacities[1,2,10,11].

– **Heart involvement** may consist of granulomatous endocarditis, recurring ventricular arrhythmias. myocarditis and pericarditis, valvular regurgitation and coronary arteritis. The heart is affected in 5 to 10% of the patients[1,11-14].

– **Less common manifestations** includes epididymitis, (with a prevalence of 4 to 11%, in different series), acute glomerulonephritis, IgA nephropathy, renal vein thrombosis, and secondary amiloidosis, described in 2% of the patients. Sometimes lymph nodules enlargement can be the presenting sign, suggesting lymphoproliferative disease[1,2,10].

Neurologic involvement: Neuro-Bechet's.

Central nervous system (CNS) involvement has a prevalence that ranges from 3 to 10%, and represent the first manifestation of the disease in about 5% of the patients. Males are more commonly affected than females[1,2], and typically have more severe manifestations[15]. CNS disease is associated with considerable mortality[2].

Symptoms have a subacute onset in about 50% of the cases.

Pyramidal signs are the most common[4]; they usually cause spastic paralysis or paresia, Babinski sign, clonus and speech disturbance. Other clinical manifestations consist of cranial nerves paresis (paresis of the III and VI cranial nerves is not uncommon), aseptic meningitis, cerebellar and sensory signs and symptoms, headaches, increased intracranial pressure and focal motor deficits, that may progress to hemi or paraparesia. Peripheral neuropathy and isolated cerebellar involvement are distinctly rare in Behçet's[15]. Some authors refer that up to 30% of these patients present psychiatric manifestations including confusion, hallucinations and agitation[1].

A recent review of 200 patients (155 men, 45 women) with CNS involvement found that parenchymal involvement was more frequent than nonparenchymal (19%). 51% of the patients within parenchymal involvement group had brainstem involvement, 19% isolated pyramidal signs, 15% hemispheric involvement, and 14% spinal cord involvement[16,17].

Poor prognosis was found in patients with parenchymal involvement, especially brainstem involvement, in those with abnormal cerebrospinal fluid (CSF) analysis (elevated protein levels,

and/or pleocytosis), and in those who have two or more attacks, who were dependent at admittance, who relapse during steroid tapering and in those who have a progressive course (primary or secondary).

In another series of 50 patients[18] adverse prognostic factors include: young age of onset, brainstem involvement, high frequency of relapses and the presence of CSF abnormalities.

As it was referred before in Behçet`s disease there is a systemic vasculopathy and a tendency to venous thrombus formation. Increased levels of factor VIII-related antigen are found in patients with major vessel involvement. It has been also described defects in prostacyclin production in the vessel wall, antiendothelial cell antibodies and increased endothelin levels in serum[3].

Despite this knowledge the pathogenesis of CNS involvement in Behcet's disease is still not clear; according to some authors, ischemia secondary to vasculitis, especially venulitis has a primordial role, whereas others underline the importance of autoimmune demyelization (2). According to Powell et al. a non-specific inflammatory reaction with mononuclear and/or neutrophilic predominance seems to occur in common[19]. The earliest lesions in the CNS may involve a perivascular infiltration of lymphocytes and histiocytes followed by a perivascular fibrosis and nerve fiber degeneration[3].

In postmortem examination of the brain, demyelization is the most common finding, followed by multifocal encephalomalacia accompanied by perivascular cell infiltration. Other lesions include meningoencephalitis, cerebral atrophy, and vascular thrombosis[1,20].

Computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and brain angiography are indicated to help in the diagnosis of CNS involvement. Analysis of cerebrospinal fluid usually shows pleocytosis, with a predominance of PMN cells in the acute phase, and lymphocytes after a few days, elevated protein content and occasionally low glucose[3]. Intrathecal synthesis of immunoglobulin is not or very rarely seen.

CT scans and MRI images may show anatomic correlates; CT scan show hypodense areas and MRI images, in acute phase, reveals areas of increased signal. Brain angiography or digital subtraction angiography are used to identify the site of venous occlusions, but they are seldom indicated because the vessels involved are usually too small to show abnormalities.

In the group of 200 patients with neuro-Behçet, referred above, 88 performed a CT scan, 101 a cranial MRI, 12 a spinal MRI and 28 a cerebral angiography; the attempt to make a radiologic diagnosis was successful in all BD patients having an acute attack and in only 40% of BD patients during the chronic phase[17].

In this group of patients 41% of cases had at least one attack and remission, 28% showed secondary progression (slowly evolving and worsening neurological symptoms and signs after at least one previous attack, or step-wise progression if there was more than one), 10% had primary progression (slowly worsening neurological symptoms and signs over months or years with no preceding attacks), and 21% had silent neurological involvement (abnormal findings in neurological examination in cases who did not have any neurological complaints).

The following clinical case will highlight several clinical and therapeutical difficulties in neuro-Behect's

Clinical case

Male patient, 25 years old, Caucasian, single.

He was admitted to our rheumatology department to investigate increasing difficulties in moving about due to proximal muscle weakness in the lower limbs, associated with urinary and anal incontinence as well as sexual impotence. These symptoms had evolved over six months in a context of Behcet's disease diagnosed 6 years earlier.

The patient describes recurrent oral aphtosis since the age of 8. After a few years he began recurrent episodes of skin lesions diagnosed as folliculitis and pseudofolliculitis, still present, affecting trunk and limbs; when he was 18 he had associated erythema nodosum of the lower limbs.

At age 20 he was diagnosed of posterior uveitis of the right eye that progressively evolved despite therapy to complete loss of vision. He was observed by an ophthalmologist and was prescribed cyclosporine (2 mg/kg/day) that he maintained until now, and glucocorticoids (in a dose that he couldn't remember) in descending doses, until the age of 22. He has also taken colchicine (1 mg/day) during flares of oral aphtosis, and tried a variety of natural medicines.

On admission he presented no signs of confusion or emotional disturbance.

The right eye was blind and atrophic. Multiple oral painful aphtae were present and typical papulopustular lesions could be found in lower limbs and dorsal area of the trunk. A systolic murmur could be heard over the mitral focus; he has normal blood pressure and pulses, and no organ enlargement was observed in abdominal examination.

He had an ataxic, asymmetrical and widened gait. Neurological examination revealed paraparesis, with a proximal predominance: muscle power grade 4, in hip flexion and extension, on the right side and 4- in hip flexion and extension, on the left. Muscle reflexes were increased in the lower limbs with a distal clonus and enlarged reflex area. Babinski`s sign was bilaterally positive. Primitive reflexes were present, including palmo-mental, and snout reflexes.

Pin-prick sensation was enhanced over lower limb, lower sacral roots and discrete areas of the lower abdomen. No sensitivity level could be defined. There was an abnormal vibration sense in lower limbs.

Full blood count revealed sideropenic anemia (Hg: 11,7 gr/dl) with normal platelet and leukocyte counts. Coagulation test were within the normal range. Liver and muscle enzymes were normal, as well as kidney function. Serum protein and immunoelectrophoresis showed no abnormality.

The E.S.R was raised at 31 mm Hg at the first hour, and CRP was below 0,5 mg/dl.

Antinuclear antibodies, ANCA and anticardiolipin antibodies were negative.

Serological tests for Hepatitis virus B and C, as well as HIV 1 and 2 were negative.

Echocardiogram revealed mild mitral insufficiency, with no other changes.

The cerebrospinal fluid had normal appearance but a high leukocyte count (38/mm3) and increased protein (81mg/dl). Microbial cultures were negative.

An electromyogram of the lower limbs excluded any signs of neurological or muscular lesion.

Cranial, dorsal and lumbar MRI failed to show any significant abnormality (Figs 1 and 2).

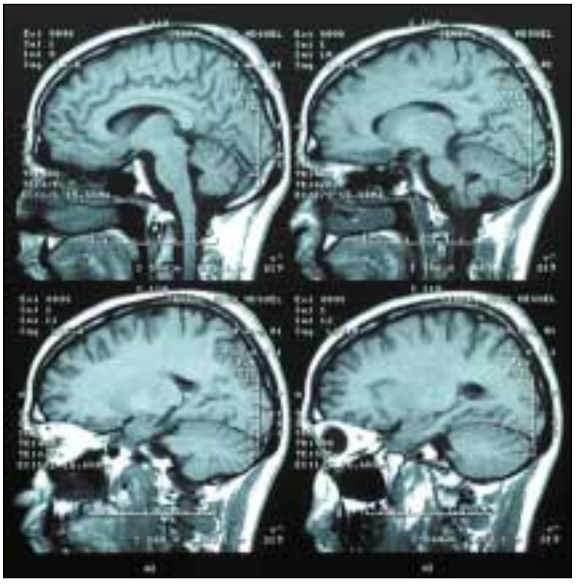
Cerebral SPECT revealed scarcely defined areas of abnormal perfusion, more pronounced in the anterior and inferior area of the right frontal lobe, as well as the right parietal and left temporal lobes and the basal ganglion region (Fig. 3).

Magnetic cortical stimulation studies identified the presence of dorsal medulla dysfunction, of axonal type, moderately severe.

Urodynamic investigation concluded for «neurogenic bladder».

Following these investigations the patient was treated with intravenous boluses of methylprednisolone (1gr/day, in three consecutive days), followed by oral prednisolone (1mg/kg/d, in divided doses) and oral cyclophosphamide (2,5 mg/Kg/ /day).

Two months later the patient described a slight improvement of sphincter function. Neurological examination showed no change in comparison to



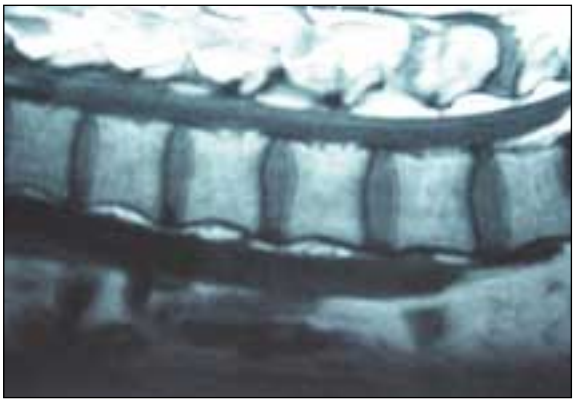


Figure 1 and 2. Cranial, dorsal and lumbar MRI failed to show any significant abnormality.

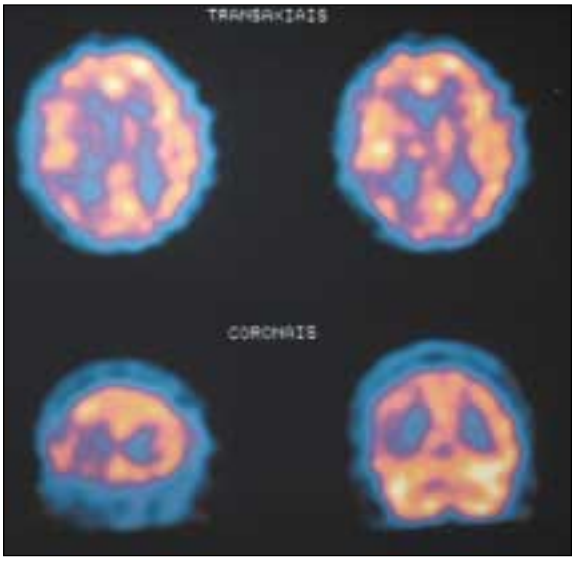


Figure 3. Cerebral SPECT. Scarcely defined areas of abnormal perfusion, more pronounced in the anterior and inferior area of the right frontal lobe, as well as the right parietal and left temporal lobes and the basal ganglion region.

the initial status.

Lumbar puncture was repeated and revealed a normal leukocyte count (4/mm3) with slight increased protein concentration.

He was kept on oral cyclophosphamide (150 mg/day equivalent to 2.3 mg/kg/day), methylprednisolone (24 mg/day, 0.5 mg/Kg/day prednisolone equivalent) and omeprazole (20 mg/od). He was started on rehabilitation therapy.

At the last observation, with 6 months of therapy, the patient described subjective improvement of muscle power, sphincter control and erection. Neurological examination still showed no objective improvement.

Discussion

Prof. Hasan Yazici and Prof. Aksel Siva

Question 1: The study and interpretation of this case was complicated by the negative results of MRI. How do you interpret this and how can we overcome these difficulties?
Answer 1: About 10% of all patients with Neuro-Behçet's have negative MRI's as was the case with this patient. Unfortunately other laboratory investigations are of little help. Perhaps the uncertainty about the precise pathology of the neurologic involvement in Behçet's is also contributory to the existence of these MRI negative patients with neurological disease.

Question 2: How do you value SPECT in these circumstances?
Answer 2: SPECT, as is applied to Behçet's is a very sensitive tool, as also has been formally demonstrated[21]. On the other hand its lack of specificity limits its routine use as a diagnostic technique.

Question 3: Some authors suggest that cyclosporine may be, itself, the cause of complications similar to those of Neuro-Behçet`s[17,22]. How do you see this problem? How can we distinguish both conditions?
Answer 3: The bulk of evidence related to cyclosporine associated neurologic toxicity comes from transplantation data. The usual clinical picture is that of headache, tremors, cortical blindness and seizure acitivity. Headache is also common. MRI shows a leukonecephalopathy with focal lesions. Tremors and seizure activity, on the other hand are rather uncommon in Behçet's. Even though formal studies are lacking about the frequency of such toxicity among the Behçet patients, common wisdom holds that cyclosporine be better avoided in Behçet's as in other systemic diseases with nerologic findings.

Question 4: Is it appropriate and useful to keep patients under long term cyclosporine, as in this case?
Answer 4: At our hands the only indication to keep a patient on long term cyclosporine therapy is continuing attacks of eye disease. We must however very closely monitor renal toxicity in such patients.

Question 5: Do you agree with our therapeutic options? For how long should we keep these and other measures?
Answer 5: We would basically do the same in this patient. Our first choice of cytotoxic agent would be azathioprine instead of cylophosphamide and if those cases we used cylcophosphamide we would add oral MESNA to combat bladder toxicity.

Unfortunately there is no rule of the thumb one could use to ascertain the duration of treatment. What we usually do is to try to stop the steroids within a course of months and continue

the cytotoxics for at least two years.

Question 6: Are there any further investigations and treatments we should perform?
Answer 6: Not really.

Question 7: Can you comment on the prognosis?
Answer 7: Unfortunately this patient has a rather poor prognosis. It is sobering to note that male patients in this age bracket may have up to 10 times increased mortality when compared to what we observe in the general population. On the other hand the positive changes at the end of 6 months of treatment are encouraging indeed.

Question 8: Do you have any other comments?
Answer 8: It is rather interesting that this patient had a neurogenic bladder without any changes demonstrable in the MRI of the medulla spinalis. On the other hand, as was the case with what was happening in his brain, the patient had objective evidence of a medulla pathology.

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