MESENCEPHALIC FORM OF MENINGOENCEPHALITIS IN A PATIENT WITH HLA-B51 BEHÇET’S DISEASE: CASE REPORT

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SUMMARY – This case report is a detailed description of the clinical, laboratory, imaging and therapeutic characteristics of the sixth patient with neuro-Behçet’s disease reported by Bulgarian authors. The diagnosis was made in accordance with the international diagnostic criteria for Behçet’s disease and was verified by skin biopsy. Therapeutic response was followed up by clinical and magnetic resonance imaging data for 6 months. Discussed are differences in the classical Behçet’s disease presentation and other neuro-Behçet’s disease cases found in Bulgaria. The current case supports the wide clinical heterogeneity of the disorder and the variety of therapeutic options.

Key words: Behçet syndrome; Neuro-Behçet’s disease

Introduction

Behçet’s disease (BD) is a multi-system recurrent inflammatory disorder, a vasculitis of unknown etiology that affects most frequently oral and genitital mucosa and skin, eyes, joints and vessels. Genetic, autoimmune, infectious and environmental factors contribute to the development of BD. Males are affected more often and more severely by BD, with onset of the disease in the third or fourth decade. Neurological manifestations or syndromes, also named neuro-Behçet disease (NBD), are relatively rare. NBD involves the central nervous system (CNS) as well as peripheral nervous system (PNS) and could be affected in case of BD. NBD was found in 2%-49% of BD cases. Central nervous system (CNS) involvement has been classified into two main groups: (1) parenchymal form, causing meningoencephalitis with lesions in the brainstem, hemispheres and spinal cord; and (2) non-parenchymal form including dural sinus thrombosis, arterial occlusions and/or hemorrhagic ruptures of cerebral aneurysms. There were cases of optic neuritis, aseptic meningitis, neuro-psycho-Behçet, depression and headache (migraine or tension type), and manifestations that had no direct connection to symptoms or treatment of BD.

The aim of this case report is to describe and discuss the clinical, laboratory and therapeutic characteristics of a patient with BD, who had human leukocyte antigen HLA-B51, as well as to present magnetic resonance imaging (MRI) findings of predominantly...
mesencephalic parenchymal involvement of the CNS.

Case Report

A 19-year-old girl complained of numbness on the left side of the face, tongue and left extremities. A few days before the occurrence of these symptoms, the patient had an episode of headache and mild temperature elevation up to 37.5 °C, redness and blurred vision of the left eye. On examination at our Department, the patient reported headache, diplopia when looking straight ahead, non-systemic vertigo, and mild irritation from light.

For 18 months, the patient had had relapsing-recurrent aphthous ulcers in the mouth and genital mucosa. Three months before and in the past two weeks, she had been treated with antibiotics and local antimycotics for genital ulcers. The patient also described periodic occurrence of skin lesions, similar to acne, distributed on the skin of the extremities and the head.

On somatic examination, the patient had asthenic body structure, temperature of 37.4 °C, pale skin and blood pressure of 110/60 mm Hg. Cardio-circulatory disorder was not discovered on cardiologic examination and electrocardiography (ECG). On ophthalmoscopy, a few small hemorrhages were seen in the posterior part of the vitreous body. Arteries were intact. There was no evidence of uveitis. Examining the patient, the ENT specialist described deviation of nasal septum without active infections.

Dermatologic status was characterized by papulopustular and acneiform lesions distributed on the skin of the sternum, anterior thorax, upper limbs and the face. The aphthae on buccal mucosa bilaterally and on the lower lip were few in number, small and superficial (Fig. 1).

On neurologic examination, the patient had mild diplopia to the left, left-sided facial hypoesthesia, including the left side of the tongue. Muscle strength was preserved in four limbs with no signs of latent paresis. Deep tendon reflexes were diminished but symmetric. Pathologic reflexes or any coordination disorders were not found. Sensory disturbance was manifested on the left side of the body with hemihypesthesia and hypalgnesia. Higher cortical functions and control over the pelvis organs were intact.

Examinations

The values of complete blood count (CBC) and extended biochemistry panel were within the reference limits. The erythrocyte sedimentation rate (ESR) was 30 mm after the 1 hour. The C-reactive protein (CRP) value was 0.5 mg/dL. Differential blood count, erythrocyte morphology, urinalysis, chest x-ray and computed tomography (CT) of the head did not demonstrate any abnormal findings. Cerebrospinal fluid (CSF) was clear and colorless, with mildly elevated pressure. CSF total protein was 0.46 g/L, and the number of leukocytes was 61x10^6/L. Blood glucose was 1.9 mmol/L and chlorides 83 mmol/L. The CSF differential cell count was as follows: lymphocytes 0.85, monocytes 0.11, and plasma cells 0.02. Serum and CSF sample electrophoresis did not reveal oligoclinal bands or M-gradient. MRI of the brain showed five nodular lesions surrounded by edema (Fig. 2A). The biggest lesion was in the right thalamus, enhanced by the gadolinium under the form of a ring 9.5 mm in diameter. There was a similar 3-mm lesion in the right parahippocampal gyrus. Two similar lesions sized 2-3 mm were also found in the tectum of the midbrain. There was a 5-mm lesion in the left temporal lobe.

Fig. 1. Aphthous ulcerations on the lips and buccal mucosa in a different stage of resolution.
medially from the hippocampus. Electroencephalography (EEG) was within the normal limits with no paroxysmal activity. Extra- and transcranial Doppler and duplex scanning showed normal cerebral vessels and hemodynamic parameters. Visual evoked potentials (VEPs) were not delayed or changed on either side. Auditory afferent conduction was disturbed bi-laterally at the middle and high brainstem level under examination of brainstem auditory evoked potentials (BAEPs). Delayed latent times and abnormal configurations of BAEPs were more pronounced on the left side.

Serum samples tested for human immunodeficiency virus (HIV I/II), syphilis, tuberculosis, cryptococ-
cosis, Lyme disease, toxoplasmosis, hepatitis B and C, and cysticercosis were all negative. Values of serum and CSF IgG and IgM titters toward some of the most commonly encountered viruses were unremarkable (Epstein-Barr virus, herpes simplex virus 1 and 2, varicella zoster virus, cytomegalovirus) and not relevant to comment. Antinuclear, anti-DNA, anti-proteinase 3, antineutrophil cytoplasmic antibodies, lupus erythematosus (LE) cells and antiphospholipid antibodies were not detected. On testing the HLA system, it was found that the patient was HLA-B51 antigen positive and HLA-B27 antigen negative.

A skin biopsy was taken from the papular lesion under the left clavicle. Histologic picture demonstrated mild expression of epidermal acanthocytosis and perivascular round-cell infiltrations in the upper and middle dermal part. The vessel walls were hyalinized and showed endothelium proliferation. At sites, the vessel walls were partially involved by cell infiltrates. This type of histology finding was consistent with lymphocytic vasculitis (Fig. 3A).

Course of the disease and treatment

Sensory symptoms and headache in our patient began to decrease during her hospital stay, but before the final diagnosis was made. The treatment with 6-methyl-prednisolone, 60 mg daily IV, was carried out for 7 days along with infusions, Isoprinosine and analgesics. The patient was discharged with significant improvement of the aphthous ulcers, dermal lesions and neurological manifestations. Treatment with prednisolone starting with 40 mg daily by mouth (gradually decreasing) was suggested for a period of three months.

The patient was evaluated six months later for the occurrence of NBD or NB syndrome. Neurological deficit was not found. During the follow-up period, the patient experienced aphthous ulcers in the mouth twice (lasting for 5 days) without other systemic manifestations. On follow up MRI examination, the previously described lesions were completely resolved (Fig. 2B).

Discussion

Despite the geographic vicinity to Turkey as the country with the highest incidence of BD (approximately 80-370 cases per 100 000), a relatively small number of patients have been diagnosed with this disorder in Bulgaria. The present report is the sixth case of NBD published by Bulgarian authors. In 1998, Bogdanova, Milanov and Georgiev published for the first time a rare case of Parkinson-like manifestations of BD17. Previous reports of isolated NBD cases were...

The girl in this report had HLA-B51 antigen, with dermatologic and mucosal manifestations occurring at the end of the second decade of her life. These symptoms are in accordance with the international diagnostic criteria for BD; her complications were due to moderate involvement of the CNS. The acute presentation of sensory disturbance (preceded by headache, temperature, and visual symptoms) was the reason to discuss the following differential diagnostic possibilities: inflammatory or demyelinating episode in the CNS (in first place MS), ischemic stroke in young adulthood, primary angiitis of CNS, neuroinfection, parasitosis, or tumor-induced illness.

MRI is the examination of choice in cases of BD with CNS involvement.3,5,12,21,24,30 The lesions identified by MRI in the mesodiencephalic junction and in the hemispheres were small, ring-like, and surrounded by edema. Their intensity was enhanced by applying contrast media. They were not typical for MS, stroke or tumor disorder.31,32 In MS patients, the lesions are variable but usually oval, periventricular, supraval or infratentorial, in accordance with McDonald criteria.33 The type of MRI findings in our case, at first, directed us to search for parasitosis (e.g., toxoplasmosis), an inflammatory or a metastatic process of unknown etiology. Complex work-up performed to elucidate the case included blood, serologic, microbiologic, immunologic and CSF examinations. However, they did not reveal the cause of the presented symptoms. All tests mentioned above, i.e. HIV, syphilis, tuberculosis, cryptococcosis, borreliosis, toxoplasmosis, cysticercosis, and common viruses, were negative. There was neither clinical nor laboratory evidence of gastrointestinal disease, systemic lupus, antiphospholipid syndrome or another collagenosis. Of laboratory findings, our patient only showed elevated ESR.5,10.

Despite numerous investigations during the last 30 years, specific biomarkers for the diagnosis and prognosis of BD are still missing, as well as for the degree of severity or type of evolution of NBD.7,12 The key to the diagnosis in our case was the history of not elucidated recurrent oral and genital aphthae together with skin exanthema. In this particular case, one dermatologic manifestation very important to the diagnosis was observed. After scarification or puncture of the skin (e.g., 10-18 hours after performing lumbar puncture), locally or nearby on the skin of the patient, a non-itching small macular papule occurred. This is the so-called positive pathergy phenomenon (Fig. 3B). According to the International Study Group for BD,4 our patient had four of five diagnostic criteria: recurrent oral and genital aphthous ulcers, typical skin lesions, and a positive pathergy test. Ocular involvement with anterior or posterior uveitis was the only missing criterion. MRI lesions were located in the typical intra-axial sites of the midbrain and thalamic region. The disturbances in BAEPs, which were found in 10%-65% of other patients with NBD, were typical for our case too.14

CSF examination in our patient showed mild to moderate pleocytosis, with no total protein elevation or intrathecal IgG synthesis. This finding could be interpreted as a manifestation of aseptic leptomeningitis or meningoencephalitis. According to Siva et al.24,35, aseptic meningitis was seen extremely rarely in cases of NBD. Atypical CSF results in our case were normal protein content, lack of oligoclonal IgG-fractions, and low glucose and chloride levels.

Several regimens of corticosteroids, colchicine, dapsone, cyclosporine, azathioprine, methotrexate, cyclophosphamide and chlorambucil are used as a traditional or current therapy for BD.5,6,10. Based on current scientific research, some cases of BD were treated with thalidomide, tacrolimus, interferon alpha, and monoclonal antibodies blocking tumor necrosis factor-alpha (TNF-alpha, infliximab) or TNF-receptor (etanercept).15,16,36 Such approaches were not used in our patient. Due to the rapid improvement of her symptoms, pulse corticosteroid therapy (0.5-1.0 g IV, for 5-7 days) was not considered as a usual recommendation.6,12,21 We think this therapy should be used in the future only in case of a severe relapse, such as meningoencephalitis.

Conclusion

The case presented was different from the classical constellation described in 1937 by the Turkish dermatologist Halusi Behçet because of the absence of ophthalmologic symptoms.3 The current case also differed from many other NBD cases found in Bulgarian
literature, which presented with severe encephalitis and meningitis. It was similar to the cases of Yordanov et al., where CNS involvement was not associated with uveitis. The current case gave evidence supporting the wide clinical heterogeneity of the disorder and the variety of therapeutic options. Vascular involvement in our patient was verified by biopsy and histology examination of the skin. After a course of corticosteroid treatment, complete resolution of the dermatologic and MRI findings suggested a vasculitis as the etiology. NBD in this patient was relatively benign; however, the presence of HLA-B51 allele could increase the risk of future relapses, thus necessitating long-term careful observation of similar patients.

References


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Sažetak

MEZENCEFALNI OBLIK MENINGOENCEFALITISA U BOLESNICE S HLA-B51 BEHÇETOVOBOM BOLESĆU: PRIKAZ SLUČAJA

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U ovom prikazu slučaja daje se iscrpan opis kliničkih, laboratorijskih, slikovno prikaznih i terapijskih značajki šestog bolesnika s neuro-Behçetovom bolešću o kojem izvješćuju bugarski autori. Diagnoza je postavljena na osnovi medunarodnih dijagnostičkih kriterija za Behçetovu bolest i potvrđena biopsijom kože. Odgovor na terapiju pratio se kliničkim podacima i nalazima magnetske rezonancije kroz 6 mjeseci. Raspravlja se o razlikama u manifestiranju klasične Behçetove bolesti i drugim slučajevima neuro-Behçetove bolesti u Bugarskoj. Prikazani slučaj govori u prilog velike heterogenosti ove bolesti te o potrebi vrlo raznovrsnih terapijskih pristupa.

Ključne riječi: Behçetov sindrom; Neuro-Behçetova bolest