NEURO-BEHÇET'S DISEASE ONSET – A DIAGNOSTIC CHALLENGE

Casandra Buzatu, Sanziana Daia, Ruxandra Ionescu
Internal Medicine and Rheumatology Department, Sf. Maria Clinical Hospital, Bucharest
Internal Medicine and Rheumatology Department, Carol Davila University of Medicine and Pharmacy, Bucharest

Abstract

We are presenting the case of a 51 years old female diagnosed with Neuro-Behçet's disease, undergoing immunosuppression and corticoid therapy in the present. The onset was with recurrent oral ulcerations. Neurological manifestations progressed rapidly from paresthesia in the upper and lower limbs to corset-like hypoesthesia of the abdominal wall and sphincterian incontinence. MRI of the spinal cord showed Transverse Myelitis.

Keywords: Neuro-Behçet's disease, immunosuppression, corticoid therapy

CASE PRESENTATION

B.L, female, 51 years, presents for the first time in the Internal Medicine and Rheumatology Department accusing low back pain with inflammatory characteristic and hypoesthesia of the upper abdominal wall with an insidious onset for 2 weeks.

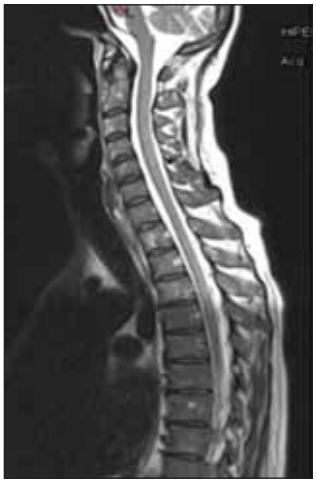
Physical examination revealed mouth sores, nasal crusts and fetid secretions, painful fibromyalgia trigger points, hypoesthesia of the upper abdominal wall and paresthesis in both upper and lower limbs. Laboratory examination showed anemia (Hb 8.5 mg/dl) and leucopenia (2700/ul), minimal inflammatory syndrome (ESR 31 mm/h, RCP 6.09 mg/dl). Electromyography examination of the nerves of the upper and lower limbs was within the normal range.

A careful medical history revealed the onset of the disease approximately 8 years before the actual episode with inflammatory low back pain that irradiated in the anterior lower right quadrant. At that time it was considered acute appendicitis and the appendix was removed surgically, with no clinical benefits. At that same time, patient related the presence of recurrent mouth sores. Seriate radiological examinations of the sacroiliac joints showed, repeatedly, bilateral osteocondensation.

Two weeks before presentation, patient was diagnosed with undifferentiated Spondiloarthritis in another service, based on the low back pain, negative HLAB27, positive anti Shigella antibodies and MRI osteocondensation of the sacroiliac joints, and received treatment with sulfasalazine.

During hospitalization appeared urinal and fecal incontinence, corset-like progression of hypoesthesia of the abdominal wall, muscular contraction in the lower limbs, intense occipital headache. The neurological examination revealed increased tendon reflexes, positive abdominal reflexes, positive Romberg test.

The MRI examination of the spinal cord reveals transverse myelitis lesions, small islands between C3-T9.



Correspondence address:
C. Buzatu, Sf. Maria Clinical Hospital, 37-39 Ion Mihalache Boulevard, Bucharest

Transverse Myelitis			
Primary			
Secondary	Autoimmune Disease	LES	• No clinical criteria • Negative ANA • Normal seric levels of complement C3,C4 • Negative direct and indirect Coombs test • Negative VDL
		Systemic sclerosis	Cerebral MRI – normal range
		Devic's Disease	• Cerebral MRI – normal range • Ophthalmological examination of the optic nerve – normal • Anti aquaporine antibodies – negative
	Hematologic pathology	Myelodisplazic process	• Bone marrow biopsy – normal
		Vitamin B12 deficit	• Bone marrow biopsy – normal • Upper gastrointestinal endoscopy – no atrophis gastritis • Biopsy of the gastric mucosae – normal
	Malignancy	• Abdominal and pelvic ultrasound – normal • Abdomen Computer Tomography – normal • Gynecological consult – normal • Bone marrow biopsy – normal • Upper gastrointestinal endoscopy – normal • Cerebral and Spinal MRI – no tumors • Tumor markers – negative	
	Infection	• Minimal inflammatory syndrome • Insidious onset • Lack of answer to antibiotic therapy	

Corticoids in pulse therapy are initiated promptly, continued with high doses of oral corticoid therapy.

The differential diagnosis took into consideration Transverse myelitis as a singular affliction or as a secondary manifestation of an autoimmune disease. Systemic lupus erythematous was the first taken into account, but the lack of clinical criteria, negative antinuclear antibodies, normal levels of seric complement, negative direct and indirect Coombs test didn't sustain the diagnosis. Systemic sclerosis and Devic's Disease were excluded after the ophthalmologic examination of the optic nerve infirmed the presence of demielinization lesions, and the cerebral MRI was within the normal range. Antiaquaporine antibodies were also tested, and they were negative. A hematologic pathology was taken into consideration. The bone marrow biopsy didn't show any mielodisplazic processes, but rose the question of vitamin B12 deficiency. Upper gastrointestinal endoscopy was performed and a biopsy was taken from the gastric mucosae. There was no evidence of atrophic gastritis. The levels of B12 vitamin and folic acid were also tested, the results were between the normal range. Infection hypothesis is not sustained by the insidious onset, the minimal inflammatory syndrome and the lack of response to antibiotics. A thorough screening for malignancy was also performed and it came back negative.

The patient was transferred into a Neurology Department. During the hospitalization, appeared pustular lesions at the puncture sites, interpreted as pathergy. Genetic tests HLAB 51/HLA B35 were performed and they were positive. Taking into consideration the recurrent mouth sores, positive pathergy, positive genetic tests HLA B51 and 35, and the insidious onset, it is considered the diagnosis: Behçet's disease with neurological manifestations – Neuro-Behçet.

It is considered opportune the initiation of immunosuppression with cyclophosphamide pulse therapy 600 mg a month. Clinical evolution was good with total remission of abdominal wall hypoesthesia, mouth sores and negative pathergy. Parenthesis in the lower limbs and muscular contraction at this level were persistent. After 5 courses of immunosuppression, spinal cord MRI showed no new lesions and sechelar lesions of transverse myelitis in spinal cord.

DISCUSSIONS

Behçet's disease usually presents with the triad of recurrent oral aphthous ulcers, genital ulcers and uveitis. It may have been described for the first time by Hippocrates in the fifth century B.C. later on, in 1930 a Greek ophthalmologist reported the presence inflammatory arthritis, oral and genital ulcers and

phlebitis in a patient with iritis. The disease was named after the Turkish dermatologist Hulusi Behçet who was the first physician to describe this affliction in modern times. (1)

The disease is most common along the "Old Silk Route", regions between Japan, China, the Far East and Mediterranean sea, including Turkey and Iran. Even so, it appears in persons who are not at risk because of their ethnic background. (1,2)

Behçet's disease is a chronic relapsing disease with multiple organ system involvement. It is a rare type of small vessel vasculitis, that affects persons generally between 25 and 35 years of age, with a higher prevalence in male population. Clinical manifestations are polymorphous and symptoms can develop in time, years even, that is why the diagnostic criteria cannot be completely met on a first evaluation in up to 75% of cases. (1,3,4)

A great deal of symptoms can be attributed to an abnormal reaction of neutrophils and lymphocytes, a hyper reactivity of neutrophils due to the change in CD4:CD8 distribution, a predominant lymphocyte T helper 1 response and production of TNFalpha, IL-6, IL-8. (1,5)

It is one of the few forms of vasculitis in which there is a known genetic predisposition. The presence of the HLA B51 antigen is considered a risk factor for developing the disease. Even so, it must be well understood that, the singular presence of the genetic marker is not enough to cause the disease. Many people have this gene, but only a small portion of them develop Behçet's disease. Despite this predisposition, familial cases represent only 5% of cases. The etiology of this disease is still unknown, and it is considered that there are other factors , environmental and infectious that play their part in the development. (1,2,4)

There is not a specific test to diagnose Behçet's Disease, the diagnosis is considered because of the signs and symptoms compatible with the diagnosis that are present at the time of the evaluation. The presence of features characteristic for Behçet's Disease (recurrent oral and genital ulcerations), elimination of possible causes for the patient symptoms and if possible, a biopsy of an affected organ that shows signs of vasculitis, would support the diagnosis. (2,6)

In 1990, The International Study Group for Behçet's Disease proposed a separate set of diagnostic criteria for Behçet's disease. A diagnosis of Behçet's disease requires recurrent oral ulceration and at least 2 additional criteria, including recurrent genital ulcers, ocular lesions, skin lesions, and a positive pathergy test (Table 1) (1,2,7)

TABLE 1. *Behçet's Disease – diagnostic criteria*

Recurrent oral ulceration	Major, minor or herpetiform, 3 ore more episodes in a 12 month period
+ 2 of the following manifestations	
Recurrent genital ulcers	Aphthous ulcerations or scarring observed by the physician
Eye lesions	Anterior uveitis, posterior uveitis, cells in the vitreous slit lamp examination or retinal vasculitis observed by the ophthalmologist
Cutaneous lesions	Erythema nodosum, pustular lesions, acneiform nodules in post-adolescent patients
Positive pathergy test	Read by physician at 24 and 48 hours

A pahergy test is simple, the forearm is pricked with a small, sterile needle. The appearance of a red bump or pustule at the site of the needle insertion represents a positive test. A positive test is helpful for the diagnosis, but only a small number of patients demonstrate the pahergy phenomenon. Also, there are other conditions that can occasionally result in a positive pathergy test, this is why the test is not 100% specific. (2). Differences in positive and negative pathergy and severity of the reaction at the puncture site depend on a lot of variables: disease activity, ethnicity, type of needle used for the prick test. The mechanisms underlying pathergy are unknown, the skin lesion triggers an inflammatory cutaneous response that is more prominent and extensive. It is believed that there is an increased and aberrant release of cytokines from the cells in the epidermis or dermis. (2,8,9)

Neuro-Behçet is a subtype of Behçet's Disease that involves the Central Nervous System. It appears more frequently in male patients between the ages of 20 and 40 years. The spectrum of neurological manifestations is wide. The evolution of the disease and the response to therapy are not easy to predict because of the heterogeneity and the wide spectrum of neurological manifestations (5,7,8)

Studies show that between 10-49% of patients diagnosed with Behcet disease, develop neurological symptoms, but the presence of neurological symptoms at the onset is rare, approximately 5-15% of cases.(3,8)

Central Nervous System involvement – Neuro-Behçet is sub-classified in two forms: parenchymal and no parenchymal. The two types rarely occur in the same individual. Parenchymal involvement is the most common presentation reported in Neuro-Behçet (82%) and is characterized by focal and multifocal involvement of the brain parenchyma. Usually this type of affection presents with hemiparesis, cognitive changes, sphinteric incontinence and fever. At the clinical examination, the most common findings are pyramidal tract signs and brain stem signs. IRM is the sensitive imaging modality of assessing this type of lesions and show focal and multifocal abnormalities. Lesions in parenchymal Neuro-Behçet are located in the brainstem, thalami, basal ganglia, cerebellum, spinal cord. The non-parenchymal type results from vascular involvement of major vessels or rarely aseptic meningitis. Often are affected major intracranial vessels with the frequent involvement of the venous sinuses, cerebral veins and intracranial arteries. Venous sinus thrombosis is the most frequent manifestation of this subtype of Neuro-Behçet's Disease. (3,8,10)

The differentiation between this two subtypes is very important for the course of treatment and prognostic. Vascular Neuro-Behçet's Disease, due to high intracranial pressure and venous sinus thrombosis has a better prognosis if diagnosed and treated immediately. The acute lesions that occur in parenchymal Neuro-Behçet's Disease can be reversible with the appropriate treatment.(8)

In Neuro-Behçet cases, the spinal cord involvement was discovered in 10-18% of cases, and after autopsy the rate increased up to 28% (3). Spinal cord lesions are often associated with cerebral or brainstem lesions. Isolated spinal cord involvement in Behçet's disease is very rare. When the spinal cord is involved the clinical signs present pyramidal syndrome, progressing hypoesthesia and paresthesias, and sphinteric disfunction. Isolated spinal involvement may be seen rarely in neuro-Behçet's syndrome and becomes a challenge in differential diagnosis.(8)

Cerebrospinal fluid (CSF) examination is an useful diagnostic tool. Sometimes this result come back normal, but often they reveal mild pleocytosis with lymphocytes and polymorphs and a slightly raised level of proteins. The study of the cerebrospinal fluid verifies the inflammatory etiology and, when abnormal, indicates a worst prognosis and justifies a more aggressive therapy. (8,11)

The MRI characteristics of spinal cord lesions in Behçet's disease are similar to those of cerebral lesions. They usually extend over two or more vertebral segments posterolaterally. (10,11)

An MRI is used not only for the diagnosis, but also in the follow up of progression and the response to treatment . Studies showed that even if there is improvement in imaging tests, the clinical symptoms are not always improved. (10,11)

The prognosis of Neuro-Behçet's Disease depends on the type of neurological involvement. The non-parenchymal type has a better prognosis if diagnosed and treated immediately. The parenchymal involvement, even though with the right treatment the lesions may be reversible, has a poor prognosis because of high risk of relapsing and a higher risk of mortality and disability. (1,5,6,8)

CASE PARTICULARITY

It was presented the case of a 51 years female, with a history of recurrent oral ulcerations and inflammatory low back pain for over 8 years. The neurological symptoms developed quickly, in a 2 week period, with paresthesis in both upper and lower limbs, corset-like progression of hypoesthesia of the abdominal wall and sfincterian incontinence. The diagnosis was transverse myelitis, confirmed by the IRM imaging. There were no other central nervous system involvement found and the results of the cerebrospinal fluid came back normal. Taking into consideration the history of recurrent mouth ulcerations, the genetic marker and the pathergy test the diagnosis was Behçet's Disease with Neurological manifestations, singular spinal cord involvement. Remission induction was started with corticoid therapy and immunosuppression, with a good clinical and imaging evolution.

REFERENCES

1. **Alnaimat F.A., Lisse J.R.** Behcet Disease http://emedicine.medscape.com/article/329099-overview
2. www.hopkinsvasculitis.org/types-vasculitis/behcets-disease/
3. **Murat Terzi, Hande Türker, Nilgün Cengiz, Musa K. Onar,** Isolated lesion of the cervical spine in a case of neuro-Behçet, Case reports

4. **Banu Turgut Ozturk*, Refik Oltulu, Hurkan Kerimoglu and Suleyman Okudan,** Behcet's disease presenting with cerebral vasculitis: a case report, *Cases Journal* 2009, 2:7528
5. **Sirbu A., Popoescu C., Antochi F., Mitulescu C.T., Predeteanu D.** Behcet Disease- at the crossroad of medical specialties – case report, reumato.medica.ro, nr. 3, 2013
6. **Tsuyoshi Sakane, Mitsuhiro Takeno, Noboru Suzuki, Goro Inaba,** Behçet's Disease, Current Concepts The New Eangland Journal Of Medicine
7. **Ioan Buraga, Roxana Martin, Adrian Dobrescu, Magda Buraga,** Behçet disease – Case presentation Romanian Journal of Neurology – Volume IX, No. 3, 2010
8. www.asn.org/neurographic/4/2/1/42.shtml
9. **Rios Scherrer M.A., Fonseca de Castro L., Barreto Rocha V., Pachenco L.** The dermatoscopy in the skin pathergy testing: case series in patients with suspected Behcet's Disease, Revista Brasiliera de Reumatologia 2014,5
10. **Kocer N., Islak C., Siva A., Saip S., Akman C., Kantarci O., Hmuryundan V.** CNS involvement in Neuro-Behcet Syndrome: an MRI study American Journal of Neuroradiology
11. **Gulsen Akmar-Demir, Piraye Serdaroglu,** Neuro-Behcet disease: a practical approach to diagnosis and treatment Practical Neurology, 2002.
12. **Kalra S., Silman A.,et co.** Diagnosis and management of Neuro-Behcet's Disease: international consensus recomandations Journal of Neurology, 2014