

Clinical characteristics of paediatric neuro-Behçet's disease: a single tertiary centre experience

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Received on January 9, 2014; accepted in revised form on February 11, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 84): S165-S170.

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EXPERIMENTAL RHEUMATOLOGY 2014.

Key words: neuro-Behçet's disease, children

ABSTRACT

Objective. To investigate the demographic and neurological features and treatment modalities of neuro-Behçet's disease (NBD) in children, to share our experiences and to summarise the literature.

Methods. We retrospectively reviewed the medical records of Behçet's disease (BD) patients who attended our paediatric rheumatology department between December 2005 and October 2013. Five patients had the diagnosis of NBD. Initial neurological presentation, clinical BD presentation, magnetic resonance imaging pictures of those five patients was recorded.

Results. A total of 18 patients were diagnosed with BD. Among BD patients five of them were identified with NBD (27.8%). The mean age of NBD patients at the time of diagnosis was 12.4 years (range 5.5–15 years). The mean follow-up time after the neurological involvement was 5.2 years (range 0.5–14). In two cases neurological involvement occurred at the same time with the onset of other clinical findings of BD (40%). Both of these patients had parenchymal involvement. Three patients were admitted with headache as the initial neurological symptom. They revealed benign intracranial hypertension. One of them had cerebral venous sinus thrombosis (CVST). The other two had normal cranial magnetic resonance images. All patients received colchicine and steroid, two of them who had parenchymal involvement received also cytotoxic drugs.

Conclusion. This study has shown that neurological symptoms can be the first manifestations of BD in children. Clinicians should be aware of this possibility and when a patient presents with neurological manifestations, it would

be valuable to query the patient for the clinical features of Behçet's disease.

Introduction

Behçet's disease (BD) was first described by a Turkish dermatologist Hulusi Behçet in 1937. It is a multisystemic vascular disease of unknown origin (1, 2). The international study group (ISG) described diagnostic criteria for BD in 1990. According to those criteria, a definite diagnosis requires recurrent oral ulcerations plus two of the following: recurrent genital ulcerations, skin lesions, eye lesions and a positive pathergy test (3, 4). However disease criteria do not involve neurological complaints and make no reference to nervous system involvement. The involvement of the central nervous system (CNS) in BD can be divided into two main groups: parenchymal and non-parenchymal. Non-parenchymal involvement usually presents with cerebral venous sinus thrombosis (CVST) and intracranial hypertension. Pseudotumor cerebri can either be secondary to CVST or due to the BD itself. Parenchymal involvement has a tendency to produce lesions in brain stem, basal ganglia, diencephalon and internal capsules (2, 5, 6).

The frequency and type of neurological involvement in paediatric population is not definite and there are limited information from case reports and small series (1, 4, 6–13). Most authors discuss neuro-Behçet's disease (NBD) when a patient meets the diagnostic criteria of BD and simultaneously has a documented neurological manifestation (11).

The present study aimed to describe the demographic and neurological features and treatment modalities of NBD in the paediatric age group, based on a retrospective series of five patients and review of the literature.

Competing interests: none declared.

Patients and methods

We retrospectively reviewed the medical records of BD attended to our paediatric rheumatology department between December 2005 and October 2013. All these patients fulfilled the ISG criteria for diagnosis of BD (14). Concomitant BD-related neurological involvement was considered eligible for the study. Five patients were diagnosed with NBD. We reviewed those patients' initial neurological presentation, clinical BD presentation, magnetic resonance imaging pictures and if performed cerebrospinal fluid (CSF) results. Patients with headache and clinical findings of pseudo tumour cerebri and high CSF pressure but with normal magnetic resonance imaging were accepted as NBD, thus we could not explain their pseudo tumour cerebri clinic with other etiological factors. Statistical analysis was performed. For continuous variables, the data were presented as mean $\pm$ standard deviation, and as frequency and percentage for categorical variables.

Results

A total of 18 patients were diagnosed with BD. The demographic and clinical characteristics of the patients are summarised in Table I. Among them, five were identified with NBD (27.8%). The mean age of BD at initial referral was 10.7 years (range 5.5–15 years). The mean follow-up time for BD was 6.9 years (range 1–15 years). Age at onset of neurological symptoms ranged from 5.5 to 15 years (mean 12.4 years). The mean follow-up time after the diagnosis of NBD was 5.2 years (range 0.5–14 years). All NBD patients were female. Consanguinity was found in three families. One patient had a family history of BD (20%).

In two cases, neurological involvement occurred at the same time with the onset of other clinical findings of BD (patient no. 1 and 2) (40%). Both of these patients had parenchymal involvement. Patient no. 1 who had recurrent oral and genital ulcerations and pustular lesions on her extremities, presented with fever, occult onset of blurry vision, which progressed to vision loss, and consciousness. Her ophthalmological

examination revealed uveitis, retinal haemorrhage, macular inflammatory infiltrates, retinal vasculitis and papilloedema. Visual evoked potentials were unresponsive. She had hippocampal and bulbar lesions on MRI presenting like vasculitic process. Contrast uptake and diffusion restriction was not detected. High protein level was obtained on CSF examination. Viral study, oligoclonal band were negative. According to imaging and BOS studies cranial involvement considered as meningoencephalitis. She was treated with a bolus of intravenous methylprednisolone (30 mg/kg/day, 3 consecutive days) followed with oral prednisolone (2 mg/kg/day for 1 month, gradually tapered to 0.25 mg/kg/day) daily. As she had a cranial parenchymal involvement, retinal vasculitis and also had an ongoing clinical severity, cyclophosphamide (600 mg/m², i.v. infusion, monthly for 6 months) was added to the therapy. Although, her MRI revealed normal findings after 6 months therapy, she was still having blurry vision and retinal findings and did not improve completely, methotrexate (10 mg/m²/week) was added to the therapy.

Patient no. 2 was admitted with a history of walking disability, aphthous and genital ulcerations and severe myalgia. She had parenchymal and spinal cord involvement at MR images compatible with BD. Pulse steroid therapy (30 mg/kg/day, 3 consecutive days) followed with oral prednisolone (2 mg/kg/day for 1 month, gradually tapered to 0.25 mg/kg/day) daily and colchicine was started. She refused to take oral azathioprine. Because of her severe spinal and cranial lesions on MRI and her disease activity refractory to steroid and colchicine therapy, cyclophosphamide (600 mg/m², i.v. infusion monthly, for six months period) was added to the treatment. Six months after the treatment her symptoms remain the same, her MR imaging findings did not improve and she was started on infliximab therapy.

Three patients who were diagnosed with BD and were receiving colchicine therapy (patient no 3, 4 and 5) (60%) were admitted with headache as the initial neurological symptom. They

Table I. Clinical and demographic characteristics of Behçet disease patients.

	Years
Mean age at diagnosis of BD	10.7 (5.5–15)
Mean age at diagnosis of NBD	12.4 (5.5–15)
Mean follow-up time of BD	6.9 (1–15)
Mean follow-up time of NBD	5.2 (0.5–14)
	Number of patients (%)
Female	12 (66.7)
Male	6 (33.3)
Uveitis	10 (55.6)
Oral ulcer	18 (100)
Genital ulcer	14 (77.8)
Joint involvement	7 (38.9)
Consanguinity	4 (22.2)
Family history	7 (38.9)
HLA B5	6 (33.3)
Pathergy	12 (66.7)

had papilloedema on ophthalmological examination. Also their CSF pressure were raised (>200 mmH₂O). A complete work-up were performed for benign intracranial hypertension. One of them had right cerebral venous sinus thrombosis (CVST) (patient no 5). This patient did not have a cortical infarct and also she had a work-up for hypercoagulability states and none of them were positive. The patient was treated with high dose oral steroid (2mg/kg/day) and enoxaparin sodium. Three months after the therapy her MR venography revealed no sinus thrombosis. The other two patients (patient no 3, 4) had normal cranial magnetic resonance imaging (MRI) and MR venography findings. Both patients were treated with bolus methylprednisolone (30 mg/kg/day for three consecutive days) and oral prednisolone, patient no 4 was continued with colchicine and azathioprine for her uveitis, the other patient with only colchicine.

All patients had an elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at the onset of symptoms and returned to normal there after the therapy. Human leukocyte antigen (HLA) was studied in all patients. Four of them displayed HLA-B5 (80%).

Demographic characteristics and neurological involvement of NBD patients were summarised on Table II-III and MRI findings of patients were presented in Figures 1-4.

Table II. Demographic and clinical characteristics of the paediatric NBD patients.

Patient no.	Sex	Oral ulcer	Genital ulcer	Skin lesions	Ocular involvement	Arthritis/artralgia	Pathergy test	HLA B5	Family history
1	F	(+)	(+)	Pustular lesions	Uveitis, retinal haemorrhage, vasculitis and papilloedema	(-)	Not done	(+)	(+)
2	F	(+)	(+)	(-)	(-)	(-)	(+)	(+)	(-)
3	F	(+)	(+)	(-)	Papilloedema	(+)	(+)	(-)	(-)
4	F	(+)	(+)	(-)	Papilloedema, uveitis	(+)	(+)	(+)	(-)
5	F	(+)	(+)	(-)	Retinal venous dilatation and tortuosity, vasculitis	(+)	(-)	(+)	(-)

M: Male; F: Female.

Table III. Neurological involvement data, imaging data, outcome and treatment of NBD patients.

Patient no.	Age at onset of BD (years)	Age at onset of NBD (years)	Neurological manifestation	Neurological involvement	MRI	Treatment	Outcome
1	5.5	5.5	Blurry vision, Loss of consciousness	Meningoencephalitis,	Mesencephalome and parahippocampal involvement	Pulse steroid Cyclophosphamide Methotrexate Colchicine	Decrease of vision Last MRI: normal
2	15	15	Walking disability, Myalgia	Parenchymal involvement	Bulbar and spinal lesions	Pulse steroid Cyclophosphamide Colchicine Infliximab	No deterioration
3	7	13	Headache, vomiting	Intracranial hypertension	Normal	Pulse steroid Colchicine	Improvement
4	13	14	Headache, vomiting	Intracranial hypertension	Normal	Pulse steroid Colchicine	Improvement
5	13	14,5	Headache, vomiting	Intracranial hypertension CVST	Thrombosis on left transverse sinus	Colchicine High dose steroid Enoxaparin	Improvement

Last MR venography: Normal.

Discussion

Neuro-Behçet's disease is rare among paediatric population. Therefore our report is important to identify the clinical and demographic features and also treatment modalities of paediatric onset NBD. In the literature with paediatric and adult patients frequency of NBD is variable and ranged from 15% and 30% (12). When isolated headaches were included, this frequency can increase up to 50% (15). Most studies did not include patients with isolated headache in their cohorts (12). Three of our patients had headache as the initial symptom. After investigation, their ophthalmological examination revealed papilloedema and they all had high opening CSF pressure. Furthermore, one had CVST on her MRI venography. Consequently they were included in our study

and also they were considered non-parenchymal NBD. Similarly, Uluduz *et al.* reported a large BD cohort and included the patients with headache in their study when they had an abnormal MRI, CSF analyses, or neurophysiologic studies (1). In 2010, Vastel *et al.* reported 12 paediatric NBD among 40 paediatric BD patients, with a ratio of 33% (12). Distinct from the literature Allali *et al.* identified six NBD children (50%) among 12 Moroccan BD cases. They explained this result by different expressions of BD in various ethnic groups and geographical areas (16). Supporting this comment an international study reported that patients from France and Saudi Arabia had significantly more frequent neurological and gastrointestinal involvement, whereas patients from Turkey had more cutaneous

complications (17). Indeed, Mosa-wi *et al.* reported nine cases of BD from Bahrain with a neurological involvement of 44% (18). In our series of 18 children with BD, we identified paediatric onset NBD in five patients with a ratio of 27.8% distinct from the Arabian and African reports but similar to the European and Turkish cohorts. In 2013 Talarico reported 117 adult BD from Italy, 32% of them (excluding peripheral neuropathy and isolated headache) diagnosed as NBD and only 2 of the patients had endocranial hypertension due to cerebral venous thrombosis (19). Diagnosis of NBD in children can sometimes be difficult since specific diagnostic criteria may not always be obvious at the same time with neurological findings. Therefore, most BD patients are diagnosed retrospectively.

When typical (uveitis, recurrent oral and genital ulcerations) or unexpected presentations (thrombosis) are seen, early detection could be done (12). Our two patients (patients no. 1, 2) with a severe course of neurological involvement also had major findings for BD, so that we had no suspicion regarding the diagnosis. Other three patients (patients no. 3, 4, 5) were already under control for BD in our clinic, and developed neurological symptoms on their routine follow-up period. For this reason they did have no difficulty at the stage of diagnosis.

Familial tendency of BD was found to be significantly higher in the paediatric population compared to the adult group (20-22). In our study of BD patients, 7 had a positive family history (38.9 %). Karıncaoglu *et al.* revealed no family history in BD patients (23). However the number of patients in our study was too small to make a decision.

In the literature some authors associated HLA B5 with a higher risk of cerebral thrombosis, uveitis or nervous system involvement (12, 24). In our BD patients, only 7% of them had positive HLA B5 results. In contradistinction to whole BD patients, four of the NB patients displayed HLA B5 (80%) similar to the literature, but this is an inadequate number of patients to produce a supportive statistical result.

Both BD and NBD have the same sex ratio with a male predominance (12, 15, 19, 25). In contrast, among all our BD patients 12 of them were female with a ratio of 66.7%. Also, our five patients with NBD were all female. Our result cannot be explained by the ethnicity and geographic variance as past studies in Turkey which showed a male predominance in paediatric BD and NBD (1, 10). However, our results could be coincidence.

In our study, mean age at onset of neurological symptoms was 12.4 years (range 5.5–15) compatible with the literature (4, 12, 15, 25). Two of our patients' initial referral reasons were their neurological symptoms (40%). When they were investigated, their other features supporting BD were identified. Therefore, if a patient presents with severe neurological symptoms, without a past

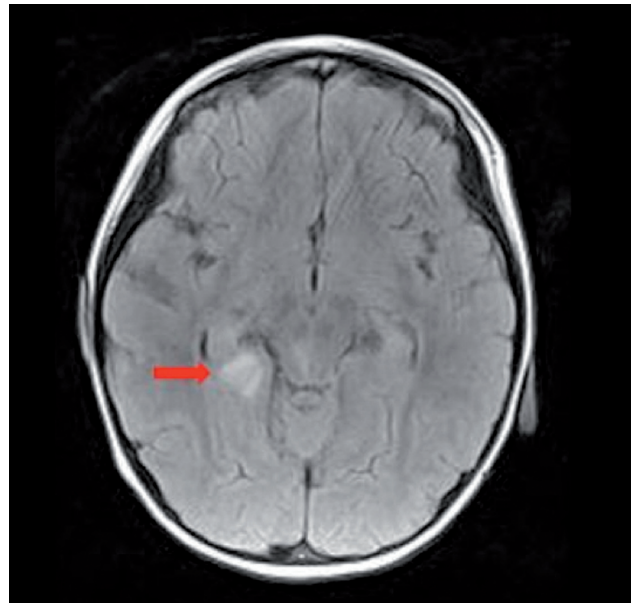


Fig. 1. Cranial axial flair MRI scan shows parahippocampal lesion (patient no. 1)

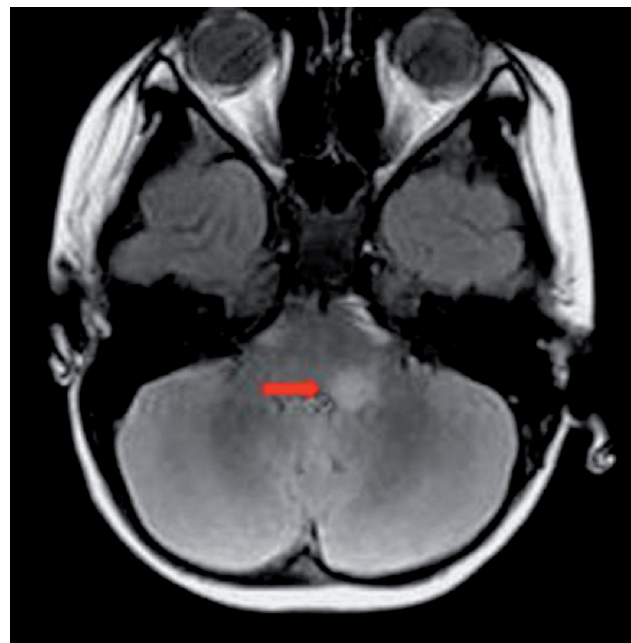
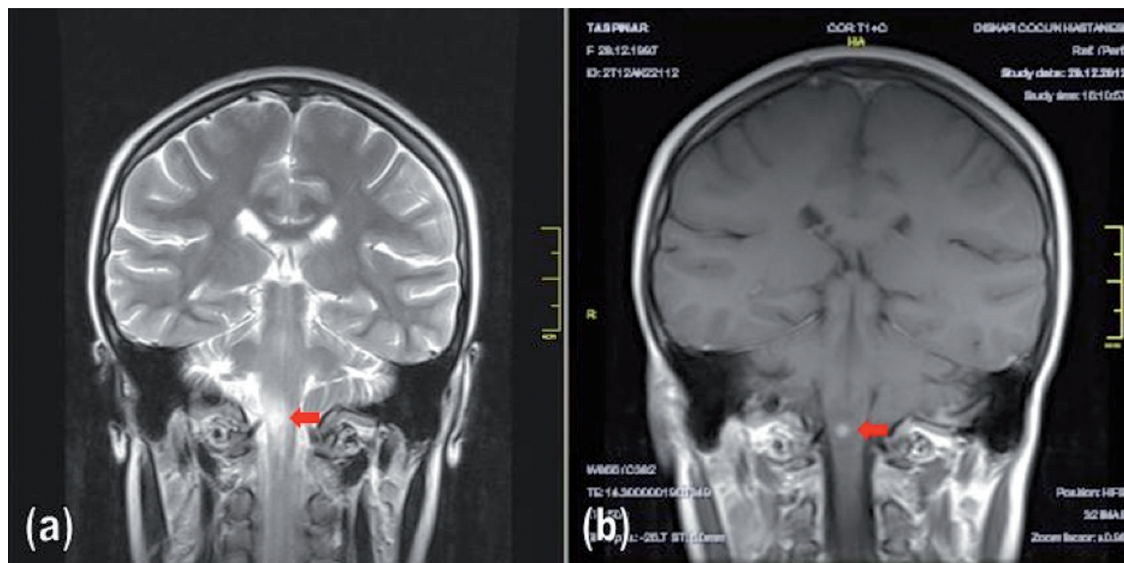


Fig. 2. Cranial axial flair MRI scan shows lesion on mesencephalon (patient no. 1)

medical history, the clinician should be aware of the possibility of NBD.

Headache is the most common neurological symptom in BD. Migraine and tension headache are the most common type (18, 19). Uluduz *et al.* reported in their study that CVST is the major neurological involvement in paediatric BD, and parenchymal disease is seen less in contrast to the adult population. In our small series, one patient had CVST and two patients had parenchymal involvement. In Turkey, CVST seems to be the predominant type of neurological involvement in BD children. On the other

hand, the parenchymal involvement type is more frequent in France, Israel and Saudi Arabia (10, 15, 26). Despite the fact that CVST is an important and frequent finding of NBD patients in Turkey, we had only one patient with CVST. This result might be due to our limited number of patients. Serdaroglu reported that intracranial hypertension with or without dural sinus thrombosis can be seen in 11–35% of all NBD patients (5). Three of our patients had intracranial hypertension. Two of them showed neither parenchymal involvement nor CVST. Only one had sinus

**Fig. 3.**

(a) Non-contrast T2 weighted axial brain image shows hyperintense bulbar lesion (arrow). (b) On contrast enhanced T1 weighted sequence, lesion shows uptake of the contrast matter (arrow) (patient no. 2).

**Fig. 4.** MRI venography shows an absent flow in the left transverse sinus, sigmoid sinus, and internal jugular vein presenting CVST (arrows) (patient no. 5).

thrombosis on her MR venography. Even though patient 3 and 4 had a normal cranial MR and MR venography results, as they gave a good response to steroid therapy and did not even developed any new neurological findings, further neuroimaging investigations were not performed to exclude cranial involvement.

There have been no prospective controlled studies on the treatment of NBD. The main aim of the treatment is to reduce the inflammation that causes vascular and parenchymal damage. In acute episodes pulse or oral high dose corticosteroids could be administered. Addition of other immunosuppressive drugs at the first attacks and in case of recurrence is controversial. In parenchymal involvement, corticosteroids, azathioprine, cyclophosphamide, meth-

otrexate and anti-tumour necrosis factor (anti-TNF) drugs can be used. For dural sinus thrombosis corticosteroid therapy is recommended. It is also controversial to use anticoagulant agents in sinus thrombosis. Some authors recommended only corticosteroid therapy as inflammation is the major factor which can lead to a vasculitic process, whereas others suggest adding an anticoagulant therapy (5, 6, 27). Our patient who developed CVST was started on anticoagulant treatment in addition to oral prednisolone. Her symptoms resolved after starting the treatment. The drugs given to our patients and their outcome are summarised in Table III.

In conclusion, our study has shown that neurological involvement could be the first manifestations of BD in children. Although neurological symptoms are

not accepted as criteria for BD, clinician should be aware of the possibility of NBD which can change the management procedures. In addition, if a patient has a diagnosis of pseudotumour cerebri, a detailed work-up should be done to identify the underlying manifestations, including BD.

Our study had some limitations. The main limitation is the small sample size which might have influenced our results. However, this study supports the finding that NBD, although rare, can be seen in childhood. Further studies are needed on the clinical features and management of NBD in a paediatric population.

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