Hulusi Behçet was born on February 20, 1889, in Istanbul. In 1910 he graduated from Gulhane Military Medical School, and completed his residency at the Department of Dermatology and Syphilology. During World War I, he worked at various military hospitals, after which he worked in the field of dermatology in Berlin and Budapest for a year. When he returned to Turkey he became a staff member of a state hospital which in 1933 was integrated into Istanbul University. At this time he was appointed to be Professor and Director of the Department of Dermatology. He saw the first case of 'his disease' with oral aphthous ulcers, genital ulceration, erythema nodosa and visual loss in 1924. This patient had been previously diagnosed as having tuberculosis or syphilis, but his diagnosis was a viral infection. He followed this case for many years. Another two patients with a similar picture came to his attention in 1930 and 1936. He first published these observations in 1937. In 1936 he was appointed to the editorial board of journals such as *Dermatologische Wochenschrift*, and *Medizinische Welt*. He was a member of the French, German, Austrian, Hungarian and Greek Societies of Dermatology. He died of a heart attack on March 8, 1948.

From Dilsen N (1997). History of Bechet's Disease. *Aktuel Medical Journal* (Turkish), 2, 62–5.

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Neuro-Behçet's disease: a practical approach to diagnosis and treatment

BACKGROUND

Behçet's disease is a recurrent systemic inflammatory disorder of unknown aetiology. It was first described in 1937 as the triad of recurrent oral aphthous ulcers, genital ulceration and uveitis (Behçet 1937). Males are more commonly affected than females and the onset is usually in the third decade. Criteria established in 1990 by the International Study Group for Behçet's Disease are now used for making the diagnosis (International Study Group for Behçet's Disease 1990) (Table 1). But, as well as those cited in these criteria, many other organs and systems may be involved in Behçet's disease, such as the vascular system, mainly the veins and pulmonary arteries, gastrointestinal system, joints and nervous system (Inaba 1989).

NEUROLOGICAL INVOLVEMENT

Male predominance is more pronounced among patients with neurological involvement (about 3 or 4 males for every female), and this usually starts about 5 years after the onset of the more usual symptoms of Behçet's disease (Akman-Demir *et al.* 1999). Neurological complications, which are seen in about 5% of cases (Serdaroglu *et al.* 1989), are almost entirely confined to the central nervous system (CNS), with occasional reports of peripheral neuropathy or myopathy. Therefore, this review will focus on the CNS.

There are two main categories of CNS involvement: parenchymal and non-parenchymal (Serdaroglu 1998). Because of their clinical and prognostic differences these two categories should be considered separately (Table 2).

Parenchymal CNS involvement

Parenchymal CNS involvement usually presents with a brainstem syndrome evolving over a few days or weeks. Common features are ataxia, dysarthria, hemiparesis and bilateral pyramidal signs. Usually, sphincter disturbance and cognitive-behavioural changes accompany or precede other symptoms (the 'brainstem +' type). Interestingly, cranial nerve palsies are not seen as often as would be expected, and sensory symptoms are rare (Akman-Demir *et al.* 1999).

Table 1 Diagnostic criteria for Behçet disease (International Study Group for Behçet's Disease 1990)

recurrent oral aphthae: <i>plus any two of</i>	at least three times in a year:
genital ulceration:	active lesion or scar
skin lesions:	erythema nodosum, folliculitis, other ulcerations
eye involvement:	anterior or posterior uveitis, or retinal vasculitis
positive pathergy test:	skin hyperreactivity to pin-prick (sterile pustule formed in 24–48 h, see Fig. 4)

Table 2 Features of parenchymal and nonparenchymal CNS involvement in Behçet’s disease

PARENCHYMAL INVOLVEMENT	NON-PARENCHYMAL INVOLVEMENT
Behçet’s disease +	Behçet’s disease +
Neurological symptom(s) (other than just headache)	Headache
Neurological sign(s) (± neuropsychological signs)	No other neurological symptom(s)
Parenchymal MRI findings	No neurological sign(s)* (or neuropsychological signs)
CSF pleocytosis ± raised protein	MRI: dural sinus thrombosis, normal parenchyma
	CSF: normal other than high pressure

*Other than papilloedema and sixth nerve palsy

(a)

(b)

Figure 1 (a) T2-weighted brain MRI sections of a patient at his first neurological attack. There is bilateral involvement of the brainstem (top left panel), spreading up to affect the basal ganglia on the left (bottom panels; see arrows). (b) Gadolinium T1-weighted cranial MRI sections of the same patient. There is some enhancement of the lesion on the left side of the brainstem and in the right basal ganglia (arrows).

Figure 2 T2-weighted brain MRI sections of the same patient as in figure 1 2 months after his first neurological attack when he was in remission. The earlier lesions are now almost resolved.

The best method of investigation is brain MRI. The usual and characteristic MR finding is a large T2 hyperintense lesion in the brainstem or basal ganglia region extending to the diencephalon, with a small area of central enhancement (Fig. 1). This lesion may be bilateral and have a slight mass effect. After the patient is treated, the lesion usually becomes smaller, and is then seen as scattered hyperintense spots (Fig. 2).

The clinical course is usually with attacks and remissions; the greater the number of attacks, the worse the prognosis (Akman-Demir *et al.* 1999; Siva *et al.* 2001).

Less commonly, the patient may have an isolated hemiparesis or a restricted brainstem syndrome such as a cranial nerve lesion with crossed hemiparesis. In these cases there is no cognitive impairment or sphincter disturbance. The MR lesion is usually more limited.

Occasionally the spinal cord is predominantly involved, either alone or more commonly with additional CNS findings (the 'spinal +' type), and most of these cases have a progressive course from the onset (Yesilot *et al.* 2002). An enhancing hyperintense lesion, or only an atrophic cord, may be seen on spinal MRI.

A minority of the cases (about 10% in our series) present with a multiple sclerosis-like pic-

ture (Kiyat *et al.* 2002). To complicate matters further, these cases have an MR scan resembling multiple sclerosis, with predominantly white matter lesions (Coban *et al.* 1999).

Cerebrospinal fluid (CSF) examination is a useful diagnostic tool in parenchymal neuro-Behçet's disease. It may occasionally be normal, but usually reveals a mild to moderate pleocytosis consisting of lymphocytes and polymorphs, with a slightly raised protein level. Oligoclonal bands are usually negative while the IgG index may be elevated. In addition to verifying inflammatory neurological involvement, an abnormal CSF indicates a worse prognosis, therefore justifying more aggressive treatment (Table 3) (Akman-Demir *et al.* 1999).

Table 3 Poor prognostic signs in cases with parenchymal neurological involvement (Akman-Demir *et al.* 1999)

Abnormal CSF (other than high pressure alone)
Extensive involvement (i.e. 'brainstem +')
Spinal involvement
Progressive course
> 2 attacks

Table 4 When to suspect neuro-Behçet's disease

Suspect neuro-Behçet's Disease even if the clinical picture does not fulfil the diagnostic criteria if:
<ul style="list-style-type: none">• the patient is a young male;• the neurological picture is predominantly motor and accompanied by neuropsychological findings;• MRI T2 hyperintensity extends from brainstem and/or basal ganglia to diencephalic structures;• CSF has raised protein with pleocytosis comprised of lymphocytes and polymorphs (provided there is no infection in a patient taking immunosuppressive treatment).

Non-parenchymal CNS involvement

Non-parenchymal CNS involvement mainly presents with intracranial hypertension due to dural sinus thrombosis. These patients often have a predilection to other types of vascular involvement elsewhere in the body; usually deep venous thromboses and occasionally pulmonary aneurysms (Al Fahad & Al-Araji 1999).

Clinical presentation of dural sinus thrombosis due to Behçet's disease is very similar to dural sinus thrombosis due to other reasons (Lueck & McIlwaine 2002). Subacute evolution of a severe headache worsening when flat, accompanied by nausea and vomiting, is common. Infrequently unilateral or bilateral sixth nerve palsies may be seen. Other than this and papilloedema, neurological and cognitive evaluation is usually normal. Epileptic seizures and cortical venous infarction are rare (Akman-Demir *et al.* 1996).

Brain MRI may reveal the occluded dural sinus but is otherwise normal (Akman-Demir *et al.* 1998). Conventional catheter angiography or MR-venography may be of further help.

The CSF is almost always normal, except for the high pressure. Interestingly, these cases very rarely develop parenchymal neurological involvement (Akman-Demir *et al.* 1999; Siva *et al.* 2001).

Cases with non-parenchymal CNS involvement have a significantly better prognosis than those with parenchymal involvement (Akman-Demir *et al.* 1999; Siva *et al.* 2001).

Rarely, arterial involvement of the CNS may be seen (less than 5% in our series), resulting in either a stroke-like syndrome or complications of an intracranial aneurysm.

DIFFERENTIAL DIAGNOSIS

Two important scenarios are discussed in full below. In the first case there is the patient who has no previous diagnosis of Behçet's disease, but who is seeking medical attention for a neurological problem. In the second, the patient is already known to have Behçet's disease and is presenting with neurological symptoms. Of course, patients with Behçet's disease may also have neurological symptoms due to other causes; therefore, every neurological finding should not necessarily be attributed to neuro-Behçet's disease. The occasions when you should suspect Behçet's disease are summarised in Table 4, and the diagnostic approach is summarised in Fig. 3.

Figure 3 Diagnostic algorithm for neuro-Behçet's disease.

CNS infections

In the first scenario, a slowly deteriorating neurological picture together with a cellular CSF – especially when it is polymorph-dominant – may suggest a CNS infection. But the brain MRI usually brings out a suspicion of neuro-Behçet's, and the patient should be questioned and examined for other features of Behçet's disease and with a pathergy test (see Fig. 4). In the second scenario, the patient with known Behçet's disease may be receiving immunosuppressive treatment; therefore, a neurological picture with a cellular CSF might well represent a CNS infection. Here again a typical lesion on brain MRI helps.

Multiple sclerosis

In the first scenario, especially in regions where multiple sclerosis (MS) is much more prevalent than Behçet's disease, a patient with neuro-Behçet's can be misdiagnosed as having MS. But again, a typical MRI is very helpful. However, when the MRI shows white matter lesions, negative oligoclonal bands in the CSF, predominance of motor-cognitive signs rather than sensory signs if the patient is male, this should prompt appropriate questioning and pathergy testing. However, it is not easy to resolve the diagnosis if

the two disorders are present together, or if they represent different points on a single spectrum.

Stroke

In any case of young stroke, appropriate questioning and pathergy testing is required. But we have also seen cases with diagnosed Behçet's disease and stroke due to valvular heart disease.

CNS tumours

In the first scenario, the extensive lesion in the brainstem and basal ganglia region may occasionally have a mass effect in the acute stage, and be misdiagnosed as a CNS tumour. However, the contrast enhancement pattern and the typical localisation should bring to mind Behçet's disease. In the second scenario, there may be patients with Behçet's disease who also have a metastatic or primary CNS tumour.

Headache

Not infrequently a parenchymal CNS attack may present with severe headache. However, there are always additional neurological findings. Raised intracranial pressure due to dural sinus thrombosis in a young male should always raise the possibility of Behçet's. In practice the great majority of the patients referred to our

Figure 4 A positive pathergy test: three different intensity levels of pathergy test positivity on the forearm in a patient with Behçet's disease (by courtesy of Dr Ahmet Gul, Istanbul University-Istanbul Faculty of Medicine).

A skin pathergy test tests a peculiar hyper-reactivity to a non-specific physical insult. The sensitivity for Behçet's disease seems to vary among patients from different ethnic and geographical backgrounds. In various studies from the Middle East, it is positive in 44–90% of cases (Tuzun *et al.* 1979; Friedman-Birnbaum *et al.* 1990; Ozarmagan *et al.* 1991; Krause *et al.* 2000), whereas, in American or British patients the rate is very low (Yazici *et al.* 1984; Davies *et al.* 1984). In all these places, however, the specificity is high; healthy controls and patients with other diseases are rarely positive (0–3%), chronic myeloid leukaemia patients treated with interferon being the only exception (Budak-Alpdogan *et al.* 1998). Interestingly, a prick with a blunted needle increases the positivity rate (Dilsen *et al.* 1993), whereas over-zealous skin cleaning (instead of with a conventional alcohol swab), decreases the positivity rate (Fresko *et al.* 1993).

A positive pathergy test consists of:

- application of a 20–22 gauge sterile needle to obliquely penetrate avascular skin to a depth of 5 mm;
 - an erythematous papule > 2 mm diameter at the prick site read by a physician at 48 h.
- From O'Duffy & Kokmen (1991).

neuro-Behçet's clinic have common headache syndromes such as tension headache or migraine.

Other symptoms

Any neurological or psychiatric disorder from vestibular neuroneitis to schizophrenia, may occur in patients with Behçet's disease by chance. Neurological examination, MRI, CSF, evoked potentials could help in excluding neuro-Behçet's disease.

TREATMENT

There is no class I evidence for the treatment of neuro-Behçet's disease (Siva & Fresko 2000). Therefore, the recommendations depend on anecdotal reports and personal experience. However, there have been blind and placebo-controlled studies in patients with other types of Behçet's disease (Yazici *et al.* 1999a; Yazici *et al.* 1999b). Most of these studies focus on the mucocutaneous symptoms, and drugs such as thalidomide and colchicine are superior to placebo. However, mucocutaneous involvement is usually a feature of milder cases. Therefore, studies in patients with ocular involvement may provide better insight for the treatment of the neurological complications. In an early study, azathioprine was effective in Behçet's uveitis, and a later follow-up confirmed long-term efficacy (Yazici *et al.* 1999a). In another study where cyclosporin A was compared to pulsed cyclophosphamide, the two treatments were nearly equally as effective for uveitis at 1 year (Ozyazgan *et al.* 1992). However, the potential neuro-toxicity of cyclosporin A is a concern in treating patients with CNS involvement (Kato *et al.* 2001). There are also studies suggesting benefit for interferon alpha in ocular disease, but further evidence is required (Yazici *et al.* 1999a).

An approach to patients with neurological involvement is summarised below, mainly based on our personal experience and other reviews of this issue (Akman-Demir *et al.* 1999; Al Fahad & Al-Araji 1999; Siva & Fresko 2000).

Parenchymal CNS involvement

For an acute attack our usual approach is to administer intravenous (IV) methylprednisolone 1000 mg/day for 5 days, followed by weekly repeats of 1000 mg IV for 4 weeks. We also add an oral dose of 32 mg/day on the days in-between the weekly doses. We keep the patient on 32 mg daily for a further couple of months and then

very slowly taper the dose down to 4–8 mg/day, and keep the patient at this basal dose. Other centres suggest 5–7 days of pulsed methylprednisolone with a higher dose, but again slow oral tapering (Siva & Fresko 2000).

The important point is not to stop steroids abruptly, because relapses are very common after quick tapering of the steroid dose.

If the patient has poor prognostic signs (Table 3), or if this is the second neurological attack, then an immunosuppressive agent should be added. Based on the evidence in ocular involvement (Yazici *et al.* 1999a), we prefer azathioprine (2.5 mg/kg/day) as the first line agent. However, if the attack was experienced when the patient was already on azathioprine, or if there is toxicity, then we administer monthly or three-weekly pulses of IV cyclophosphamide, 1000 mg/day.

The important point is not
to stop steroids abruptly,
because relapses are very
common after quick tapering
of the steroid dose

Non-parenchymal CNS involvement

In dural sinus thrombosis, the role of anticoagulants is still debated, and this same debate exists for the treatment of deep venous thrombosis in Behçet's disease (Yazici *et al.* 1999a). We usually prefer oral high-dose methylprednisolone, together with an antiplatelet agent such as aspirin. However, a short course of heparin is suggested by others (Siva & Fresko 2000). In this situation, the presence of any pulmonary aneurysm should be ruled out with chest CT before initiating anticoagulants because bleeding can be fatal (Hamuryudan *et al.* 1994). Long-term anticoagulation or CSF shunting are usually not indicated. Long-term immunosuppressive treatment is also not necessary unless the occlusion is recurrent or not responding to steroids alone.

In rare cases of arterial involvement of the CNS, high-dose IV-methylprednisolone and pulsed cyclophosphamide, as described above, can be given.

When to stop treatment

We usually keep the patients on a low dose of prednisolone (4–8 mg per day) for several years, even if they are asymptomatic. This may help suppress other non-neurological features of Behçet's disease. Other centres tail off treatment in a few months.

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