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Electrophysiological and MRI evaluation of neurological involvement in Behçet's disease

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SUMMARY Eight patients with stable Behçet's disease were studied by means of multimodality evoked potentials and magnetic resonance imaging to evaluate the possibility of an earlier and objective demonstration of clinical and subclinical Central Nervous System (CNS) involvement. It was shown that both diagnostic techniques are useful for quantitative evaluation of neurological involvement in Behçet's disease; of particular interest was the demonstration of subclinical CNS changes.

Behçet's disease (BD), originally described as a clinical triad of oral and genital aphthosis and relapsing iritis,[1] is now known to be a systemic disease involving many other organs.[2] Well documented is the occurence of arthritis,[3] venous thrombosis,[4] cutaneous lesions,[5] rectocolitis,[6] and lesions of the CNS.[7]

Neurologic involvement, considered uncommon in the past,[8] seems to be frequent, and it has been found in 28% of patients, according to O'Duffy *et al.*[9] It has been therefore suggested by these authors that it be added to the new diagnostic criteria for BD.[10] Any part of the neuraxis may be involved, and there is not a characteristic clinical pattern of the disease;[7] laboratory investigations, neuroradiological and electroencephalographic features are nonspecific, and establishing the diagnosis is often difficult.

When neurologic complications are present, the morbidity and mortality rates rise, and before the advent of cytotoxic immunosuppressive therapies death frequently occurred within one year from the onset of neurologic signs.[11]

Early diagnosis and aggressive treatment is essential in reducing or preventing progression of CNS disease.[9]

We studied eight patients with stable BD by means of magnetic resonance imaging (MRI) and multimodality evoked potentials (EPs) to evaluate the possibility of an earlier and objective demonstration of clinical and subclinical CNS involvement in BD.

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Patients and methods

All patients affected by BD seen at the San Raffaele Hospital between January, 1986 and June, 1987 entered the study. All patients fulfilled three or more of the diagnostic criteria of O'Duffy *et al*[9] except patient 8 who fulfilled two (table 1). Neurologic and ocular features are summarised in tables 2 and 3.

EP recordings

For the Somatosensory Evoked Potentials (SEPs) the median nerve was stimulated at the wrist and the tibial nerve at the ankle, with a square wave current pulse of 0·2 ms duration at 2–5 Hz. Recordings were made from different surface electrodes (Ag/AgCl) attached to the skin with collodion and filled with conducting jelly. For median SEPs (mSEPs) the following recordings were used: Erb–Fpz, Cv7–Fpz, Cv7–Controlateral Shoulder (S), C3–Fpz, C3–S, Fpz–S. For tibial SEPs (tSEPs) the recordings were: D12-iliac crest and Czl–Fpz. One thousand responses for mSEPs and 1000–4000 for tSEPs were averaged. The analysis time was 50 ms for mSEPs and 100 ms for tSEPs; the sampling time was 0·1–0·2 ms. The limits of the normal values were assigned to 2·5 SD from the control group means. Flash Visual Evoked Potentials (fVEPs) were elicited using a lamp (intensity = 3 joules) located 25 cm from the tested eye. Flashes were delivered at the rate of 1/s. For Pattern Reversal Visual Evoked Potentials (PrVEPs), a black-white checkerboard pattern on a TV screen reversing every 0·7 ms was employed. The whole stimulating field was 11; both 30′ and 15′ check size with contrast at 50% were used. Responses were recorded from Oz referred to Cz. Analysis time was 250 ms and the bandpass was 1–100 Hz. Brainstem Auditory Evoked Potentials (BAEPs) were recorded by monoaural click stimuli at 100 Db SPL, rate of 21 Hz. Two thousand sweeps were averaged for each ear. For all EPs, at least two trials were done, for the reproducibility of the traces. BAEPs and VEPs

Table 1 *Analysis of cases*

Case No	Sex	Essential criteria			Skin	Joints	Thrombophlebitis	CNS*
		Oral	Genit.	Ocul.				
1	M	+	−	+	+?	−	−	+
2	M	+	+	+	+?	−	+	+
3	M	+	+	+	+	−	+	+
4	M	+	+	+	+	−	−	−
5	F	+	−	+	−	−	−	+
6	M	+	−	+	+	+	+	−
7	F	+	+	+	−	+	+	−
8	M	+	−	+	−	−	−	−

*Previous history of CNS involvement and/or abnormal neurologic examination.

were performed with an Amplaid MK7 equipment; SEPs were performed with a Nicolet Pathfinder II.

MR Imaging

MRI was performed using a superconducting 1·5 Tesla unit manufactured by Siemens (Magnetom 2T). All brain scans were done in the orbitomeatal plane (axial plane) with sections 8–10 mm thick, and in the coronal or sagittal plane with sections 4–8 mm thick; in all cases a multiple spin-echo protocol was used with a Repetition Time (TR) of 2000 ms, and two different Echo Times (TE) of 28–35 and 100–120 ms, respectively. The T1–T2 balanced images (TR = 2000 ms; TE = 28–35 ms) provided good quality morphological information; the T2 weighted images (TR = 2000 ms; TE = 100–120 ms) were useful for characterising the lesions.

Case reports

Case 1

RG, a 36 year old male, was admitted to the S Raffaele Hospital in February 1986. He was well until 1983, when he was admitted to another hospital for headache, aphasia and lethargy. A diagnosis of cerebral oedema was made, and the patient was treated with corticosteroids. A mild ataxia persisted. In February, 1984 he had sudden loss of vision in the left eye. A retinal thrombosis was diagnosed and treated, with partial recovery. In February, 1985 he was seen for transitory quadriparesis, paraesthesias, loss of vision in the left eye, slurred speech, and vomiting. Meningoencephalitis, bilateral uveitis and birdshot-like retinopathy were diagnosed. He remembered frequent oral aphthosis in the past. A diagnosis of BD was made and he started treatment with chlorambucil and prednisone with benefit.

He was admitted to our department for re-evaluation one year later. On examination he was in good general condition. Acne was noted on his back. Neurological examination showed bilateral horizontal and vertical nystagmus, brisk tendon reflexes with bilateral Babinski sign, ataxic-spastic gait and mild signs of cerebellar involvement. Ocular examination showed corrected visual acuity of 3/10 on the right and of 9/10 on the left, bilateral macular dystrophy and peripheral retinal exudates.

Case 2

BR, a 30 year old male, was admitted in February, 1986 for reappraisal. He had a long history of oral and scrotal aphthosis and recurrent thrombophlebitis of the legs, with sequelae of post-phlebitic oedema and leg ulcers. In May, 1982 he developed a sensory-motor deficit on the right side, dysarthria and dysphagia, which improved after 3 months. A visual deficit was also noted. In March 1984 an ophthalmologist found active anterior and posterior uveitis, with signs of vitreal inflammation. A diagnosis of BD was made, and he was started on corticosteroids and chlorambucil. In 1985 he developed bilateral glaucoma and posterior cataracts. Physical examination revealed cutaneous acneic lesions and leg ulcers, with signs of chronic venous stasis. Neurological examination showed brisk tendon reflexes with bilateral Babinski responses, incoordination on the finger-nose and the heel-knee tests, mild ataxic-spastic gait. Ocular examination disclosed visual acuity of 1/10 on the right and

Table 2 *Neurological findings*

Case No	History	Neurological examination
1	Benign intracranial hypertension Meningoencephalitis	Brainstem, cerebellum and corticospinal tract involvement.
2	Right hemiparesis	Cerebellum and corticospinal tract involvement.
3	Mild dementia	Mild dementia, corticospinal tract involvement.
4	Negative	Negative
5	Benign intracranial hypertension Drop attacks	Negative
6	Negative	Negative
7	Negative	Negative
8	Negative	Negative

Table 3 *Ocular features*

Case
1 Posterior uveitis, retinal thrombosis, macular dystrophy
2 Panuveitis, cataract, vitreous inflammation
3 Anterior uveitis, lens opacities, vitreous-retinal involvement
4 Anterior uveitis, vitreous inflammation, cystoid macular oedema diffuse retinal vasculitis
5 Relapsing iridocyclitis, retinal vasculitis
6 Panuveitis, vitreal involvement, posterior pole oedema
7 Relapsing conjunctivitis, retinal vasculitis
8 Uveitis, retinal vasculitis

light perception on the left, signs of inflammation of the anterior segment of the right eye, bilateral posterior cataract which prevented funduscopic evaluation.

Case 3

PS, a 30 year old male, was admitted in February, 1986. From 1974 he had suffered from recurrent oral and genital ulcers, cutaneous eczematous lesions, bilateral reduction of visual acuity and oedema of the legs. In 1979 a diagnosis of BD and chronic alcoholic liver disease was made, and he started treatment with corticosteroids, but dropped out of therapy after some months. In February, 1984 he was admitted to our hospital for progressive deterioration of cognitive function, worsening of post-phlebitic syndrome of the legs, oral aphthous stomatitis, diffuse cutaneous folliculitis and subcutaneous nodules. A WAIS test showed IQ = 74, MD = 47%. Ocular examination disclosed active bilateral anterior uveitis, left posterior cataract, signs of vitreal and retinal involvement. Steroid therapy was advised, but inconsistently accepted. Cytotoxic immunosuppressants were not prescribed for fear of poor compliance. In September, 1984 he was admitted again for diffuse abdominal pain. High-dose prednisone was begun. From December, 1985 levamisole was added, with improvement of both genital ulcers and mental state. He was readmitted to our hospital in February, 1986 for re-evaluation. Physical examination showed folliculitis, signs of venous stasis of the legs and absence of peripheral legs pulses. Neurological examination showed a moderate memory impairment, particularly for recent events, and mild signs of corticospinal tract involvement. Visual acuity was 8/10 on both eyes, with signs of active bilateral anterior uveitis, and bilateral lens opacities.

Case 4

SN, a 33 year old male, was admitted in October, 1986 for a reappraisal. In 1983 he developed recurrent left uveitis and oral aphtosis. In 1984 he noted diffuse pyodermal lesions. He was admitted to another hospital, where the diagnosis of BD was made, and he was treated with corticosteroids. Since 1985 he had noted decrease of right visual acuity. An ophthalmologist found bilateral uveitis. On examination he appeared in good general state, and neurological examination was normal. Ocular examination disclosed a corrected visual acuity of 3/10 on the right and 1·5/10 on the left. Signs of active anterior uveitis, vitreous inflammation, cystoid macular oedema and diffuse retinal vasculitis were present.

Case 5

DGL, a 30 year old woman, was admitted in January, 1987 for re-evaluation. She had been well until May, 1986 when she experienced diffuse, severe headache for a week, associated with projectile vomiting and transitory left facial paralysis of central type. A diagnosis of possible benign intracranial hypertension was made. In June, 1986 right iridocyclitis was noted, and she started steroid treatment. In October, 1986 left iridocyclitis was discovered; she complained of oral aphthae. In December, 1986 left chorioretinitis, with macular oedema and retinal phlebothrombosis, was found. A diagnosis of BD was made. On physical examination nothing remarkable was noted. Visual acuity was 10/10 on the right and 8/10 on the left. Signs of vitreal inflammation and bilateral retinal vasculitis with cuffing of the arterioles and haemorrhages, were noted. In May, 1987 the patient presented two typical episode of drop attacks. Neurological examination was again normal.

Case 6

MM, a 12 year old boy presented in April, 1987 for re-evaluation. In 1983 he noted red, painful cutaneous nodules on the left leg, which disappeared without therapy. In August, 1984 he developed diffuse arthalgias and oedema of the left leg, with Doppler evidence of deep femoral vein occlusion. In January, 1986 a diagnosis of bilateral anterior and posterior uveitis was made; and the patient was treated with corticosteroids. When treatment was discontinued, he noted the appearance of cutaneous lesions (similar to those previously described) and oral aphthae, and uveitis worsened. In July, 1986 he was admitted to another hospital, where a diagnosis of BD was made, and he was treated with prednisone and chlorambucil at first, with cyclophosphamide from November. He was transferred to our hospital because of relapsing uveitis. On examination he was in good general health. Oral aphthae, slight oedema and collateral venous circulation over his left leg were present. Neurological examination was normal. Bilateral visual acuity was 5/10. Signs of inflammation of the anterior and posterior segment of the eyes, with vitreal involvement and posterior pole oedema were noted.

Case 7

FF, a 51 year old woman was admitted in May, 1987 for re-evaluation. She had suffered for many years from arthralgia of the large joints and recurrent polyarthritis. In 1977 she had thrombophlebitis of the right leg. In 1982 bilateral anterior uveitis was discovered, and in 1983 right posterior uveitis was diagnosed. In December, 1983 retinal haemorrhages and oedema were noted, and she started systemic steroid treatment. In November, 1986 she noted oral and genital aphthosis; a vaginal biopsy disclosed leucocytoclastic vasculitis, and a diagnosis of BD was made. In February, 1987 she had another episode of leg thrombophlebitis. On examination the patient appeared in good general health. Neurologic examination was normal. Ocular examination disclosed bilateral corrected visual acuity of 9/10, mild conjunctivitis, signs of vitreous activity in the left eye and peripheral retinal vasculitis.

Case 8

CC, a 31 year old male, was admitted in June, 1987. He had been well until November, 1986 when he noted relapsing aphthous stomatitis. Since December he had four episodes of orchiepididymitis, and subsequently a diagnosis of chronic prostatitis was made. In January, 1987 he observed reduction of vision in the right eye; in March right uveitis was found. An HLA typing was positive for HLA B51. He started steroid treatment. In June right peripheral retinal vasculitis was noted; a diagnosis of BD was made, and he was admitted to our hospital for evaluation and treatment. On examination oral aphthae were noted. Neurological examination was normal. Ocular examination disclosed bilateral corrected visual acuity of 10/10, signs of right peripheral retinal vasculitis, with altered vascular permeability, perivascular cuffing and haemorrhages on fluorangiographic study.

EPS STUDIES

BAEPs were abnormal unilaterally in two cases (n. 2–7); one patient had an increase of I–V interpeak latency (4·59 ms—normal values < 4·51) and another had a prolongation of the I-III interpeak latency (2·58 ms—normal values < 2·50).

Median SEPs were normal in all patients. Three patients had abnormalities of tibial SEPs: P40 cortical response was prolonged in two cases (47·6 ms and 48·3 ms respectively; normal values < 43) and absent in one; the N24 spinal response was normal in all these cases. The concomitant abnormal central conduction time by tSEP and normal central conduction time by mSEP suggest an alteration of dorsal columns of the spinal cord. The latency of the wave IV of flash VEP was normal in all cases; however its amplitude was reduced bilaterally in case 2 and monolaterally in case 4. With 15′ check size stimulation the major component of PrVEP was absent in two patients (bilaterally in case no. 2 and monolaterally in case n. 4); abnormal P_{100} latency was observed in five cases (three cases bilaterally). With 30′ check size stimulation the PrVEP was bilaterally absent in case n. 2; P_{100} latency was within normal limits in all other cases (table 4).

MR IMAGING

Six of the eight patients had a normal MRI brain pattern; two patients had abnormalities. In the first case (case 1) there was a small lesion in the periventricular white matter (body of the right lateral ventricle); in the second case (case 2) there were two small lesions in the left periventricular white matter (centrum semiovale and frontal horn). In both cases the lesions gave a high MRI signal intensity, either at the first or at the second echo (See figs 1 and 2).

Discussion

In 1965 Wolf *et al* reviewed 64 previously reported cases of BD with neurological manifestations, and found that estimates of the frequency of neurological complications ranged from 10 to 25%.[7]

Subsequently Chajek and Fainaru reported 41 cases of BD, and found neurological complications in 12 of them,[2] and O'Duffy and Goldstein described seven patients with CNS involvement out of 25 patients with BD.[9] It seems clear therefore that neurologic disease in BD is frequent. The mortality rate in the first report was very high (41%); others have not confirmed this poor prognosis.

Table 4

	PRVEP				*FLASH VEP*	
	P100 latency (ms)					
	Check Size 30′		*Check Size 15′*		*WAVE IV latency (ms)*	
Case No.	*RY*	*LY*	*RY*	*LY*	*RY*	*LY*
1	118	116	125	125	120	119
2	ABS	ABS	ABS	ABS	112	108
3	114	118	127	143	113	105
4	119	118	134	ABS	95	97
5	115	114	122	123	97	122
6	121	119	123	139	100	92
7	112	113	125	127	109	106
8	113	108	115	112	101	94
Normal values (mean and SD)	108·8, 4·9		112·3, 5·0		113·4, 9·3	

RY: right eye; LY: left eye

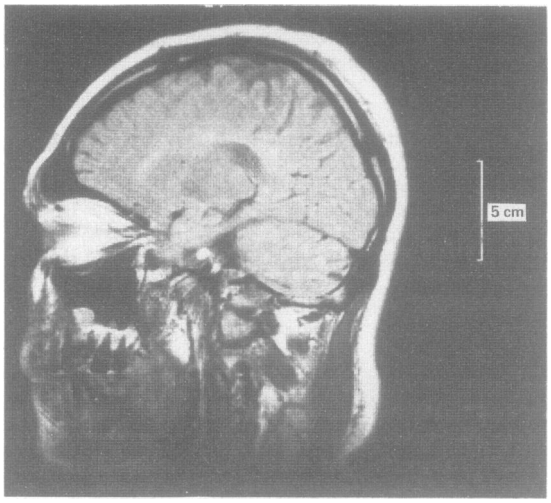

Fig 1 *Case 1 (RG). MRI study (spin-echo sequence, sagittal section, 5 mm thick). A hyperintense lesion is detectable in supraventricular white matter of the right hemisphere.*

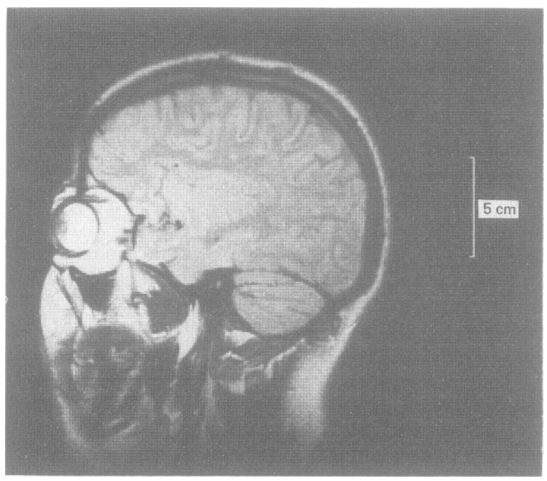

Fig 2 *Case 2 (BR). MRI study (spin-echo sequence, sagittal section, 5 mm thick). A small hyperintense lesion is detectable in the centrum semiovale of the left hemisphere.*

The clinical picture is characterised by a relapsing course and is nonspecific; meningoencephalitis, cranial nerve palsies, organic mental syndrome, seizures, coma, aphasia, paresis, extrapyramidal and cerebellar signs, spinal cord involvement and pseudobulbar palsies have all been reported.[7] Rarely, neurological findings antedate the more typical signs of BD (10 out of 200 patients, according to Kozin *et al*[12]).

Necropsy studies have demonstrated perivascular and meningeal infiltration with lymphocytes, plasma cells and macrophages, small foci of softening in the gray and white matter, often near blood vessels, gliosis and cerebral infarction in some cases.[13 14]

Diagnosis of nervous involvement in BD is often difficult. Laboratory and standard radiologic and EEG studies are usually normal, or show nonspecific changes. CSF pleocytosis or increased protein concentration is common.[7] Carotid arteriography has been normal, or has showed occlusion or displacement of intracranial vessels.[9] Brain scintiscanning can be normal, or show a focal abnormality.[12]

A few reports of computed tomography (CT) findings in neuro-BD have appeared in the literature. Focal lesions of decreased density with negative contrast enhancement,[12] or a low-attenuation mass with central enhancement,[15] or areas of contrast enhancement[16-17] have been described. Some of these lesions proved to be reversible.[15-17] Willeit *et al* reported the first thorough description of MRI findings in a case of BD with an upper brainstem mass of 12 mm in diameter showed also by a CT scan performed 4 weeks after the onset of neurological symptoms.[17] Other occasional cases have been described thereafter. Recently, a MR Brain Scanning study of 24 patients with vasculitis has been published.[18] The authors have scanned nine patients with BD, and found MRI to be a sensitive method for detecting vasculitic brain lesions. Interestingly two patients with BD and without clinical signs or symptoms of CNS lesions had visible abnormalities (multiple, mild, irregular periventricular changes) on MR scanning. Even if the CNS changes were not specific for vascular disease, additional changes which suggested the correct diagnosis were commonly seen. It was also noteworthy that a comparison with CT scanning showed MRI to be more sensitive; the authors concluded that MRI is the method of choice in patients with suspected cerebral vasculitis.

Establishing the diagnosis of CNS involvement in BD is particularly relevant in relation to therapy. In fact, though evaluation of the effects of treatment in a disease with a relapsing course is difficult, a recent study[19] found that chlorambucil was effective in 14 patients with meningoencephalitis, and superior to steroid treatment, whose efficacy has been questioned[2] or refused,[20] though others[9] found it effective in neuro-BD. This confirmed many uncontrolled observations on efficacy of immunosuppresive treatment.[21-23]

Cyclosporin therapy has also recently been shown to be effective in the treatment of severe ocular involvement in BD,[24] but severe side effects may prevent its more widespread use.[25] Because the neurological complications are considered an indicator of a bad prognosis, it seems very important to demonstrate such an involvement at an early stage. The frequency of CNS involvement in our small sample of patients with BD is high. Four patients had a positive history, two of them having both abnormal EPs and MRI pattern, and three other patients had subclinical neurophysiological findings indicating CNS alterations.

Our results should be interpreted with caution. The observed EP alterations are not specific, and are not necessarily related to CNS involvement in BD. Particularly VEP alterations could be related to ocular abnormalities, although a concomitant optic pathway involvement can not be excluded. In fact the detection of only a mild increase of P100 latency at 15′ check size stimulation may be explained by visual acuity reduction due to opacities of the media or other ocular troubles.

Two patients with clinical signs of CNS involvement had normal EPs: this finding is explained by the variable modalities of nervous involvement in BD. One of these patients had dementia, and the other had benign intracranial hypertension and drop attacks: both these conditions do not usually cause modifications of short latency EPs because sensory pathways are not involved.

The characteristics of the observed lesions on MRI could be typical of an ischaemic pattern,[20] possibly due to vasculitis, but demyelinating injury cannot be excluded on the basis of signal intensity and anatomic localisation in the white matter.[27] The age of the patients (less than 50 years) and the absence of hypertension make the presence of "unidentified bright objects" (UBOs) unlikely.[28]

The results of our preliminary study show that EPs and MRI are useful for the quantitative evaluation of neurologic involvement in BD.

The demonstration of subclinical CNS alterations in some patients is intriguing. At the moment, it is not possible to say if subclinical CNS abnormalities in BD have the same prognostic value of overt neurologic involvement; further studies are needed.

We suggest therefore that these diagnostic techniques be applied to all patients with BD, with or without CNS disease; such a study is currently going on at our hospital.

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