Neurological complications in Behçet’s syndrome

D. Kidd, A Steuer, A. M. Denman and P. Rudge

1The National Hospital for Neurology and Neurosurgery, London and the Departments of 2Immunology and 3Rheumatology, Northwick Park Hospital, Harrow, UK

Summary

The neurological complications of Behçet’s syndrome have not been characterized with clarity. We present the clinical features, imaging characteristics and CSF findings of a series of 50 patients seen at the National Hospital for Neurology and Neurosurgery over the past 10 years. In this series, vascular complications had a low prevalence, whereas involvement of the brainstem was common; spinal cord lesions, hemisphere lesions and meningoencephalitis also occurred. Optic neuropathy, vestibulocochlear and peripheral nerve involvement occurred, but were rare. The prognosis for recovery was in general good, and the majority of those followed-up over a median of 3 years (range 1–19 years) had only single attacks. One-third of patients underwent further attacks, and four underwent progressive deterioration leading to disability. Factors suggesting a poor prognosis are repeated attacks, incomplete recovery, progressive disease course and a high level of CSF leucocytosis during acute attack. These data should be of help in the further definition of the clinical characteristics of this rare neurological disorder and in the planning of treatment trials.

Keywords: neurological diseases; Behçet’s syndrome; MRI; CSF

Introduction

Behçet’s syndrome is an episodic disorder of unknown aetiology or pathogenesis, characterized by recurrent oral and genital ulceration and panuveitis. Constitutional disturbance is common, and there is malaise, fatigue and loss of weight. Skin involvement, characterized by erythema nodosum, pustular eruptions or pseudofolliculitis, is also common, and there is an oligoarthropathy of large joints such as the knees, ankles and shoulders. Involvement of the lungs, gastrointestinal tract and kidneys has also been noted, but is rare (O’Duffy, 1994).

Epidemiology

Behçet’s syndrome is most common in the countries around the eastern shores of the Mediterranean, the Middle East and Eastern Asia, particularly Japan, where the prevalence was 7/10⁵ in 1974 (Yamamoto et al., 1974). In Turkey the prevalence was found to be higher in rural than in urban areas (37/10⁵ versus 8/10⁵) (Yurdakul et al., 1988). There has been only one published survey of the disease in the UK (Chamberlain, 1977), in which the prevalence was found to be 0.4/10⁵. There has been no epidemiological study of cases of Behçet’s syndrome with neurological complications, other than those that have reported the prevalence of such complications in hospital populations attending specialist Behçet’s syndrome clinics. Authors whose patient populations were sufficiently high have suggested a prevalence of 5.3% in Istanbul (Serdaroglu et al., 1989), 16% in Casablanca (Benamour et al., 1990), 25% in Alexandria (Assaad-Khalil et al., 1993) and 3.3% in a nationwide survey in Iran (Davitchi et al., 1997). In an autopsy series, 20% of 170 cases of patients with Behçet’s syndrome showed pathological evidence for neurological involvement (Lakhanpal et al., 1985).

Diagnosis

The diagnostic criteria are summarized in Table 1 (International Study Group for Behçet’s Disease, 1990). These are based on a cohort of 914 patients from several centres around the world. Clinical features were compared with those of 308 patients with connective tissue diseases who had also had recurrent oral ulceration. Use of the new criteria offered an increase in diagnostic sensitivity and specificity compared with previously published diagnostic criteria. Although it was specified that recurrent oral ulceration was a prerequisite, it was acknowledged that cases existed in which there was pathologically proven Behçet’s syndrome without oral ulceration; it was stated that the criteria would exclude only 3% of patients in whom recurrent oral ulceration was not a feature.
The aetiology is unknown; an infective agent has long been postulated but has never been identified. Neutrophil hyperfunction and an increase in the CD8 cell ratio all) cases, and the CSF is in general inactive. Arterial thrombosis is rarer, and aneurysm formation has been reported (Wechsler et al., 1989).

Involvement of muscle (Arkin et al., 1980; Lang et al., 1990), causing a polymyositis, appears to be rare. Peripheral neuropathy has been reported (O'Duffy and Carney, 1971; Rougemont et al., 1982), with nerve biopsy and electrophysiological characteristics of a non-vasculitic axonal neuropathy. A predominately motor polyradiculopathy has also been reported (Bakouche and Guillard, 1984).

Neuropathology

The first paper to describe the neuropathology of such cases was in 1944 (Berlin, 1944); in this report the basal meninges were seen to be thickened and multiple foci of cellular infiltration within the meninges and parenchymal lesions were observed. Silfverskiold described findings in a patient who had died within 5 days of the onset of a severe brainstem syndrome and saw that there was considerable swelling of the brainstem with multiple foci of cellular infiltration and perivascular inflammatory cell cuffs (Silfverskiold, 1951). McMenemey and Lawrence described these cases and others; in these, as in the others published previously, the brainstem was predominately involved, and areas of softening with cellular infiltration and perivascular cuffing were seen (McMenemey and Lawrence, 1957). Lesions also involved the cortex and other grey matter structures, in which loss of neurons was seen. Rubinstein and Urich reported a further case in which the patient died after a 6 year disease course characterized initially by relapses and then progressive deterioration (Rubinstein and Urich, 1961). Their findings were typical of those previously described: there was a chronic meningoencephalitis with inflammatory cell infiltration and circumscribed areas of necrosis with loss of all tissue elements, accumulation of lipid-laden macrophages and gliosis. Although the white matter was more often involved, there was clear evidence for lesion formation within the grey structures, including the cortex, basal ganglia and brainstem nuclei. A large series from Japan (Kawakita et al., 1967)
summarized the findings in nine cases from that country and compared them with the 13 published from Europe and North America. No difference was noted. Miyakawa and colleagues and Yamamori and colleagues described cases in which marked cerebral atrophy was seen; in these cases involvement of the cortex with marked loss of neurons was observed in addition to the white matter findings noted in previous reports (Miyakawa et al., 1976; Yamamori et al., 1994). Lueck and co-authors, from this institution, published the post-mortem findings of their case, who had presented with a relapsing then progressive meningoencephalitis without systemic features in which the neuropathology showed features characteristic of Behçet’s disease (Lueck et al., 1993). Hadfield and colleagues have shown that there is a marked infiltration by neutrophils and eosinophils as well as by lymphocytes, and there is at times marked axonal degeneration within lesions (Hadfield et al., 1996). No evidence for vasculitis has been found in this or other pathological studies.

Current study
The purpose of this study was to define further the various clinical syndromes associated with this disorder, to characterize the various immunological and imaging abnormalities seen and to attempt to identify clinical and immunological prognostic factors for subsequent disease activity. We also investigated possible differences in these characteristics between patients of European stock and those born in regions with higher disease prevalence.

Patients and methods
The medical notes of all patients admitted to the National Hospital for neurological investigation and treatment with a diagnosis of Behçet’s syndrome over the past 15 years were reviewed. Most had been under the care of one of the authors (P.R.). Many had been referred by another (A.M.D.), and in order to follow-up their cases the medical notes of such patients were scrutinized at Northwick Park Hospital. The diagnosis of Behçet’s syndrome was accepted if the clinical course and features fulfilled the International Study Group criteria (International Study Group for Behçet’s Disease, 1990). Statistical comparison of groups used the Mann–Whitney test.

Results
Fifty patients were studied; their mean age was 31 years (SD 6 years). Thirty-one (62%) were male. Thirty-nine were of European stock, three were born in Iran, three in Turkey, two in the Indian subcontinent and three in North Africa. All but one had had mouth ulcers, 41 had had orogenital ulceration and 29 had developed uveitis. Systemic symptoms, such as oligoarthritis (20 cases) and skin lesions (22 cases), were relatively common, although in 30 cases the neurological syndrome arose in conjunction only with orogenital ulceration and/or uveitis. The median latency from onset of systemic symptoms to neurological presentation was three (0–28) years. Twelve patients presented first with neurological symptoms. In one case, published previously (Lueck et al., 1993), the diagnosis was made only at autopsy, following a neurological illness without any evidence of a systemic disturbance at all.

Neurological presentation (Table 2)
Twenty-five patients presented with a meningoencephalitis involving the brainstem, seven with spinal cord syndromes and five with hemisphere signs. Four presented with symptoms and signs of meningitis and encephalopathy alone. One patient had signs of an optic neuropathy for which no other cause has been found. One presented with bilateral facial weakness, two with acute vestibular disturbance due to an isolated vestibular lesion, and one with isolated bilateral sensorineural deafness. Vascular complications were rare in our series; two presented with cortical venous thrombosis. Four patients presented with intracranial hypertension alone.

In the patients with isolated brainstem disturbance, the disorder had a tendency to arise subacutely over days. Twenty patients presented with ataxia and ocular motor dysfunction, one having signs indicating a pontine disturbance and two having bulbar symptoms, with dysarthria and dysphagia. The severity of the accompanying long tract signs was variable. In two cases the patient presented acutely with a severe brainstem encephalitis requiring intensive and ventilatory care. Isolated cranial nerve lesions also occurred; in these cases lesion of nerve VII was the most prevalent (three cases, of which two also had trigeminal involvement).

Seven patients presented with spinal cord disease; two of these patients presented with a severe transverse myelitis with paraplegia, two with a Brown–Séquard syndrome and the others with sensory disturbance with increased reflexes and sphincter disturbance but without weakness.

Of the patients with hemisphere disturbance, four presented with hemiparesis and one with hemisensory disturbance alone. Three had seizures, including one patient who presented de novo with hippocampal complex partial seizures.

Symptoms of meningitis that preceded or were an important

<table>
<thead>
<tr>
<th>Table 2 Clinical presentation in the 50 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningoencephalitis with brainstem involvement</td>
</tr>
<tr>
<td>Spinal cord involvement</td>
</tr>
<tr>
<td>Hemisphere involvement</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Isolated intracranial hypertension</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis*</td>
</tr>
<tr>
<td>Cranial neuropathy*</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>V + VII</td>
</tr>
<tr>
<td>VII</td>
</tr>
<tr>
<td>VIII</td>
</tr>
</tbody>
</table>

*Some patients shared different clinical subgroups.
part of the clinical syndrome in those with parenchymal involvement were common, arising in 16 out of the 39 cases.

Two patients presented with an isolated vestibulopathy; one of these patients showed evidence for canal paresis and a preponderance of directional rotation on electronystagmography.

Cortical vein thrombosis was seen in two cases, one of whom showed evidence of concurrent meningitis. One presented with a hemisphere lesion with seizures due to cortical vein thrombosis (Fig. 1) and the other with intracranial hypertension. Isolated intracranial hypertension was seen in three other cases, in whom no evidence for meningitis was found.

**Ethnic differences**

Eleven (22%) patients were not born of Northern European stock. There was no difference in the age of onset of the disease [23 years (range 10–52 years) versus 27 years (range 10–44 years), \( P = 0.34 \)], age at onset of neurological complications [31 years (range 14–52 years) versus 28 years (range 18–44 years), \( P = 0.54 \)] (non-European and European subjects, respectively), characteristics of the systemic disease and the characteristics of the neurological disorder. Similar conclusions have been drawn in a series from France (Wechsler et al., 1988). Six patients had had a brainstem syndrome, two a cord lesion, two a hemisphere disturbance and one isolated intracranial hypertension. The prevalence of CSF and imaging abnormalities was also non-significantly different.

**Imaging results**

Imaging showed MRI abnormalities in the clinically affected area in all but one case of those presenting with a brainstem syndrome (Table 3). The other was a normal CT scan. In three cases in addition to the brainstem lesion, multiple predominantly periventricular white-matter lesions were seen in the hemispheres bilaterally. Lesions correlated well with the clinical syndrome; 20 showed lesions within the midbrain or superior cerebellar peduncle (Fig. 2), sometimes extending to the diencephalon, one showed a single lesion within the pons, and two showed medullary lesions. Severe atrophy was noted in cases with progressive disease (Fig. 2). In two cases, in whom the clinical syndrome was of a severe acute brainstem disturbance, the entire brainstem was seen to be involved (Fig. 3) and considerable brainstem swelling was observed in the acute phase (Fig. 4).

All those with hemisphere syndromes showed multiple white matter lesions in both hemispheres, which tended not to be localized to the periventricular regions. Among patients with cord syndromes, spinal cord imaging was undertaken in three cases; the image was abnormal in two cases, one showing a high signal intensity lesion with and one without adjacent cord swelling (Fig. 5). In two other cases the brain alone was scanned, and this was normal in both cases.

In the single patient with an isolated optic neuropathy, imaging showed no abnormality, including the optic nerves. In the two patients with isolated vestibulopathy and the single case with bilateral deafness, imaging of the brain was normal.

In patients presenting with meningitis alone or isolated intracranial hypertension, imaging of the brain was normal in each case.

**CSF results**

CSF examination was carried out in 18 of 25 patients with brainstem disturbance; CSF was active in 17 cases, in which leucocytosis was seen. In 11 of the latter cases there was an increase in protein concentration (Table 3). Those with meningitis and encephalopathy had abnormal CSF in all four cases, whilst half of the samples examined were abnormal in patients with hemisphere and spinal cord disturbance. Among those presenting with isolated intracranial hypertension the CSF was abnormal in one case, and in the single cases of those with dural vein thrombosis, optic neuropathy and isolated vestibulopathy, CSF was normal. Intrathecal synthesis of immunoglobulin was not observed in the cases studied; matched serum/CSF bands were seen in seven cases (18%). In one case a monoclonal band was seen which had disappeared 6 months later when the CSF examination had been repeated during a reappraisal of the diagnosis.

The difference between median CSF protein concentration in the brainstem group and the meningoencephalitis group
Table 3 MRI and CSF results in patient subgroups, divided into the clinical syndromes with which they presented

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Number</th>
<th>MRI</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No data</td>
<td>Normal</td>
<td>Local</td>
</tr>
<tr>
<td>Brainstem</td>
<td>25</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cord</td>
<td>7</td>
<td>2</td>
<td>3*</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Meningitis</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>ICH</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

OB x/x = oligoclonal immunoglobulin bands in CSF/serum; WCC = CSF white cell count; ICH = intracranial hypertension. *Two normal brain MRI, one normal cord MRI.

Fig. 2 T₂-weighted MRI (1.5 T; TR 3000 ms, TE 91 ms) of a patient with multiple brainstem attacks and a progressive disease course, showing a lesion within the midbrain, and brainstem and cerebellar atrophy.
Fig. 3 T₂-weighted MRI (0.5 T; TR 3800 ms, TE 92 ms) of a patient who presented with an acute brainstem syndrome with apnoea requiring prolonged ventilatory support, showing very pronounced high signal intensity abnormalities throughout the brainstem.

was significant ($P = 0.042$); in all other cases CSF protein and white cell count were not significantly different between groups ($P > 0.05$).

**Evoked potentials**
The visual evoked potential was measured in 10 cases; it was abnormal in one case. Sensory evoked potentials were measured in eight cases and were normal in each case. Brainstem auditory evoked potentials were measured in 12 cases and abnormalities were detected in two cases, in which there was a delay in conduction at the level of the pons in patients with brainstem dysfunction.

**Clinical follow-up**
Thirty-five (70%) patients have been followed-up for a median of 3 years (range 1–19 years). All four cases of intracranial hypertension underwent shunting procedures and have remained well. Recovery from attacks with parenchymal lesions was in general good; the majority of patients recovered well without residual disability. Three patients (one with transverse myelitis and two with a brainstem disturbance), however, made no improvement and are left with severe neurological impairments. Further attacks occurred in 12 patients, in whom a median of one relapse (range 1–6) has arisen to date. Relapse occurred frequently in patients with brainstem involvement at onset (Table 4), and eight patients had further brainstem attacks. One patient with cord involvement initially had a further cord syndrome, and one each with cord involvement and hemisphere involvement had a brainstem attack at a later point. Four patients have subsequently undergone progressive deterioration leading to severe impairment and disability; all of these patients had brainstem disturbance initially and all have had further attacks. There were two deaths, both owing to aspiration pneumonia with severe brainstem impairment.

In an attempt to identify significant prognostic factors during the first neurological attack, CSF protein and white cell count were measured. There was no significant difference in CSF protein or white cell count between patients followed up who had had a single attack and those whose attacks were
Fig. 4 T_1-weighted MRI (0.5 T; TR 420 ms, TE 15 ms) following injection of gadolinium–DTPA of the same patient as in Fig.3, showing swelling of the brainstem and enhancement of the lesion within the pons.

Discussion

In this large clinical series of patients with neurological involvement in Behçet’s syndrome the incidence of brainstem involvement was high (52%) and that of vascular complications low (4%). Involvement of the hemisphere, spinal cord and optic nerves was also seen. No difference was noted between the small number of non-Northern European-born patients and the others. Patients with active disease showed a mixed lymphocyte and neutrophil pleocytosis and there was no evidence for intrathecal synthesis of immunoglobulin. Imaging revealed lesions localized to the clinically affected areas in most cases examined, with evidence for lesion dissemination in a further three cases. The prognosis for recovery following acute relapse was in general good, the majority of patients becoming symptom-free. However, of those who were followed-up 28% underwent further attacks and 14% became significantly disabled as a consequence of either the absence of recovery or the development of a progressive disease course. It should be noted, however, that in this series the median follow-up was 3 years (range 1–19 years); a longer follow-up may reveal a more frequently relapsing disease than these data suggest. This may also account for the lower incidence of progressive disease than that noted in other studies, although we did take care to follow up patients who returned to the rheumatology clinics in order to minimize this potential bias.

One patient presented with signs of optic neuropathy, for which no alternative cause has been found; imaging was normal and CSF immunoglobulin oligoclonal bands were absent. Optic neuropathy is rare in Behçet’s syndrome, only a handful of cases having been published (Colvard et al., 1977; Kansu et al., 1989). Pathological examination of one case has shown gliosis and demyelination within the nerve (Colvard et al., 1977).

Of particular interest are the three patients who presented with or developed vertigo or hearing loss. There has been only one report of auditory findings, in a small series of patients with Behçet’s syndrome (Brama and Fainaru, 1980). In two of our patients, initial asymmetrical hearing loss progressed to involve both ears, but there were fluctuations, often over a period of weeks, in the magnitude of the hearing deficit. Extensive tests of auditory function showed that the hearing decline was due to hair cell loss; both patients showed recruitment on assessment of loudness discomfort level and the stapedius reflex measurement; they had normal brainstem auditory evoked potentials and absent echoes. The intolerance of loud sounds reported by one patient is also consistent with hair cell loss. Both had recurrent attacks of severe vertigo that resolved over 1–4 weeks. Only one of the patients had abnormal caloric responses, indicating loss
Fig. 5 $T_2$-weighted MRI (1.5 T; TR 5000 ms, TE 130 ms) of a patient who presented with an acute disturbance of sensation in the upper and lower limbs, with urgency of micturition, showing a cord lesion adjacent to C2.

of horizontal canal function on one side. Ultimately this patient developed complete vestibular failure. Both patients had normal vestibulo-ocular reflex suppression on rotational and caloric testing, indicating a peripheral origin of the dysfunction. Thus the three patients with auditory vestibular abnormalities or symptoms all had a progressive peripheral rather than a central nervous system disorder, which to some extent mimicked Menière’s syndrome.

Previous clinical series have been small with a variable follow-up. In one of the larger series (Serdaroglu et al., 1989; Akman-Demir et al., 1996b), which followed-up 15 patients who had had abnormal neurological signs out of a series of 45 who had had neurological symptoms, seven were stable and three had died (one during a relapse); of the remaining five, one had had two further relapses and four had undergone progressive deterioration without superimposed relapse. In this group of patients the incidence of CSF abnormalities was higher than in those who were stable, and the authors submitted that this may offer prognostic information. In our series, disabled patients at follow-up had a higher median CSF white cell count during the acute attack than those who had improved and remained stable. More recent reports (Akman-Demir et al., 1996c; Bohlega, 1996; Siva et al., 1998), in which larger patient groups have been studied, have shown a frequency of relapse similar to that in our own series, but a greater frequency of progressive disease course (30–40%). They suggest that adverse prognostic factors include young age of onset, brainstem involvement, high frequency of relapse and the presence of CSF abnormalities. In addition, one group has suggested that a primarily progressive (progressive from symptom onset) disease course may exist (Akman-Demir et al., 1996c). Our series and those of others suggest that in general the prognosis for isolated intracranial hypertension and dural venous sinus thrombosis is good following satisfactory treatment. For those with parenchymal involvement it appears that prognosis is related to the
frequency and number of further attacks and the development of a progressive disease course. The pathophysiology of this is not clear but is likely to be linked to progressive axonal degeneration leading to atrophy, as has been intimated in multiple sclerosis (Kidd et al., 1996, 1998; Trapp et al., 1998). Further prospective studies are required in order to define further the pathophysiology of the disease course and the prognostic features.

In our series no patient showed intrathecal synthesis of immunoglobulin. Other papers (Sharief et al., 1991; McLean et al., 1995; Serdaroglu, 1998) have reported series in which the majority showed evidence of blood–brain barrier dysfunction but few papers have shown intrathecal synthesis of IgG, and Gille and colleagues reported that oligoclonal immunoglobulin bands disappeared from CSF following an acute attack (Gille et al., 1990). This is in stark contrast to multiple sclerosis, in which persistent oligoclonal bands are present in the CSF of 97% of patients (McLean et al., 1990; Zeman et al., 1996). Sharief and colleagues found a greater incidence of IgA and IgM bands (Sharief et al., 1991), which may suggest an alternative antigenic stimulus, and Jongen and colleagues in a single case found that IgM and IgA bands disappeared following recovery from episodes of meningococcal meningitis (Jongen et al., 1992). In neurosarcoidosis, oligoclonal bands are also infrequent (McLean et al., 1995); indeed, there is recent evidence to suggest that they may also be absent, as in Behçet’s syndrome (V. Chamoun and L. J. Thompson, personal communication). The mixed pleocytosis and high frequency of neutrophils was noted in early publications and was subsequently confirmed (Nakamura et al., 1980). These authors also noted that the CSF cell count diminished in response to steroid administration, prompting speculation that there is an anti-inflammatory role for steroids rather than simply an anti-oedema mode of action.

Our series confirms the findings of previous MRI studies that have shown that involvement of the clinically affected region alone is most common. Most prevalent is the lesion of the midbrain extending to the basal ganglia or internal capsules (Kermode et al., 1989; Morrissey et al., 1993; Wechsler et al., 1993; Coban et al., 1996; Tali et al., 1997). In acute lesions there may be oedema, and enhancement is present in the majority of cases (Kazui et al., 1991; Tali et al., 1997). T2-weighted hypointensity is seen in chronic lesions. There is a close clinical–radiological correlation (Morrissey et al., 1993; Wechsler et al., 1993; Akman-Demir et al., 1998). A striking feature noted by many (Kermode et al., 1989; Al-Kawi et al., 1991; Hussell et al., 1991; Gerber et al., 1996; Akman-Demir et al., 1998) is that T2-weighted white matter lesions reduce in size markedly in conjunction with clinical recovery and often become invisible, at least on low-strength magnets (Kermode et al., 1989; Tali et al., 1997). Brainstem atrophy may be striking, as evident in several of our cases (Fig. 2) and noted by others (Morrissey et al., 1993; Wechsler et al., 1993; Coban et al., 1996).

The largest published study involved 15 patients with parenchymal involvement; atrophy was seen in three cases, involvement of the brainstem and basal ganglia alone in eight cases, and in three further cases periventricular lesions were seen in addition to brainstem lesions. MRIs were normal in two cases, scanned at least 11 months after resolution of the clinical attack (Wechsler et al., 1993). In a further 10 patients with cerebral vein thrombosis, MRI of the brain was normal and the imaging abnormality was restricted to the venous system. In a further five cases with headache alone without intracranial hypertension, three of whom had CSF pleocytosis, MRI was normal. More recently (Akman-Demir et al., 1998), a study of a series of 59 patients with brainstem involvement and 14 with intracranial hypertension has shown similar findings.

Magnetic resonance spectroscopy investigations have been published for only three cases (Nussel et al., 1991), in which a reduced NAA/Cr (N-acetyl aspartate/creatinine + phosphocreatine) ratio was seen in the acute phase, which subsequently normalized following clinical recovery; in all three cases substantial radiological recovery had occurred. No long-term or systematic studies have been published.

Few electrophysiological studies have been published (Nakamura et al., 1980; Besana et al., 1989; Rizzo et al., 1989; Stigsby et al., 1994); abnormalities of brainstem auditory evoked potentials are most frequent, and are more prevalent in patients in acute attacks than in patients studied in remission. Visual evoked potential abnormalities are also common in other series, although not in ours; this is interesting in view of the fact that the optic nerve is involved clinically in a small minority of cases (Colvard et al., 1977; Kansu et al., 1989). Characteristically, recordings show reduced amplitude with little or no prolongation in latency. This is in contrast to that of demyelination, in which it is characteristic to see prolonged latency with temporal dispersion but normal amplitude (Halliday et al., 1972). Visual evoked potential abnormalities occurred in patients without uveitis with frequency equal to that in patients who had had ocular involvement (Stigsby et al., 1994). A study of central motor conduction times in 20 patients, 13 of whom had neurological symptoms and signs, has shown that abnormalities comprising

Table 4 Frequency of relapse and site of further attacks according to clinical subgroup at presentation

<table>
<thead>
<tr>
<th>Clinical subgroup</th>
<th>No. of cases with relapse</th>
<th>Site of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>25</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Cord</td>
<td>7</td>
<td>Cord</td>
</tr>
<tr>
<td>Hemisphere</td>
<td>5</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Meningitis</td>
<td>4</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Intracranial</td>
<td>4</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td></td>
<td>Progressive vestibular failure</td>
</tr>
</tbody>
</table>

Neurological complications in Behçet’s syndrome

2191
mild conduction slowing and reduction in amplitude were present in half of those with abnormal neurological signs, and also arose in those without signs (Parisi et al., 1996). In our series the prevalence of evoked potential abnormalities was low (two out of 12 patients in whom data were available).

There has been no prospective placebo-controlled trial of any form of treatment in Behcêt’s syndrome with neurological complications. Anecdotal evidence has pressed forward the opinion that use of corticosteroids is mandatory in acute attacks and possibly thereafter. Intravenous methylprednisolone is often given in acute attacks. Other forms of immunosuppressive treatment, such as azathioprine, cyclophosphamide, chlorambucil and cyclosporin A, have been advocated as maintenance therapy (Serdaroglu, 1998). Colchicine is thought to act by inhibiting neutrophil chemotaxis (Matsumara and Mizushima, 1975). For adequate treatment trials one must turn to the ophthalmologists, who have shown clearly that the use of cyclosporin A in uveitis results in an alteration of the visual prognosis in this complication of the disease (Graham et al., 1985; Masuda et al., 1989). More recently, reports of beneficial effects on systemic features of the disease with tacrolimus (Ishioka et al., 1994; Sakane et al., 1995) and interferon α-2a (Alpsoy et al., 1994; Azizlerli et al., 1996) have been published. Treatment for dural venous sinus thrombosis involves anticoagulation; Wechsler and colleagues advocate the concurrent use of corticosteroids (Wechsler et al., 1992), although again this has not been established by means of a prospective clinical trial.

In summary, this clinical series of patients with Behcêt’s syndrome with neurological complications has shown and confirmed that, in general, patients develop subacute episodes of neurological dysfunction predominantly situated within the brainstem, but also the hemisphere and the spinal cord. Involvement of the optic nerve was seen, but is exceedingly rare; involvement of the spinal roots, peripheral nerves and muscle is also rare and was not seen in this series. MRI reveals lesions that enhance and show close clinical–radiological correlation. Evidence for lesion dissemination is uncommon, in contrast to multiple sclerosis. The spinal fluid shows a mixed pleocytosis with predominance of lymphocytes but also neutrophils, and intrathecal synthesis of immunoglobulin is not or very rarely seen. The majority of patients do not undergo relapses, but those who do have a poor prognosis for the development of fixed impairments and disability, and a proportion develop a progressive course with accumulating disability. No formal trial of treatment in this disorder has been published, and there is now an urgent need to do so through multicentre clinical trials.

References


Neurological complications in Behcet’s syndrome


Received February 8, 1999. Revised June 6, 1999. Accepted June 14, 1999