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Proton MRS in Behçet's disease with and without neurological findings

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Abstract Our aim was to investigate whether neurological impairment in Behçet's disease (BD) can be assessed by means of proton MRS and whether it can assist in prognosis. We used single-voxel MRS to measure metabolites in regions of normal-appearing pons, basal ganglia and periventricular white matter (PWM) in 32 patients with chronic BD patients with and without neurological deficits and 29 control subjects. Patients had significantly higher N-acetylaspartate (NAA)/creatine (Cr) and choline (Cho)/Cr ratios in the basal ganglia than the controls. The Cho/Cr ratio in the PWM was also significantly higher in the patients. MRS enabled clear discrimination of patients and controls and also revealed spectral differences between non-neuro-Behçet's disease and neuro-Behçet's disease in the basal ganglia. MRS can be used to assess brain involvement in BD even if structural changes are absent.

Keywords Behçet's disease · Brain · Magnetic resonance spectroscopy

Introduction

BD is a systemic inflammatory disorder of unknown aetiology. The classical triad of oral and genital ulcerations with uveitis was described by a Turkish dermatologist Hulusi Behçet in 1937 [1]. The diagnosis is based solely on clinical findings; diagnostic criteria were established in 1990 [2]. The central nervous system (CNS) is involved in up to 15% of cases [3, 4], most commonly with cerebral and spinal cord lesions, cerebral venous thrombosis and meningitis. MRI is currently the modality most sensitive to the lesions of neuro-Behçet's disease (NBD) [5, 6, 7]. Despite improved MRI techniques, clinical characterisation of the disease by structural imaging is weak.

Magnetic resonance spectroscopy (MRS) has the advantage of simultaneous detection of several metabolites from various biochemical pathways [8]. Its use in the brain has led to better understanding of normal spectral patterns and their alterations in different diseases [9].

MRS is promising for better clinical characterisation of cerebral vasculitis with common pathological features even with normal-appearing brain [10, 11].

Our aim was to investigate whether neurological impairment in BD can be assessed by means of MRS and whether it can be sued in prognosis or to characterise the severity of the disease.

Material and methods

We performed MRS on 32 patients (16 men, 16 women) with definite BD, based on criteria proposed by the International Study Group for Behçet's disease [2] and on 29 healthy subjects. Patients had routine brain MRI: axial and sagittal T1-weighted (TR/ 450 TE 10 ms), axial T2-weighted (TR 5336 TE 120 ms) coronal T2-weighted fluid-attenuated inversion-recovery (TR 6000 TE 110 TI 2000 ms), and contrast enhanced (Gd-DTPA 0.1 mmol/kg) axial T1-weighted images. Patients who had received corticosteroids during the month preceding the MRI examination were excluded. The patients were divided into a group of nine patients with no neurological symptoms or signs (non-NBD) and an NBD group of 21 patients with neurological symptoms or signs such as headache, dizziness, diplopia, facial numbness, hemiparesis or vertigo. We noted the duration of disease and medication, including colchicine.

MRS was carried out on a 1.5 tesla whole-body imager, using a combined MRI and spectroscopic imaging protocol. We used a transmit/receive quadrature birdcage head coil. Informed consent was obtained from all subjects. The protocol consisted of routine sagittal, coronal and axial T2-weighted images, plus MRS. The routine images were used to identify anatomical structures and to confirm the absence of any structural or signal abnormality. The left (dominant) hemisphere basal ganglia and periventricular white matter (PWM) were studied in right-handed control subjects and patients. The contralateral brain regions were not studied, because of time limitations.

Single voxel MRS was performed in all subjects, using a point-resolved spectroscopy sequence (PRESS), TR 2000 TE 136 ms, 128 averages. We placed 13×13×13 mm voxels in the pons, left basal ganglia and PWM. Prior to MRS, shimming was performed to optimise field homogeneity and water suppression was optimised using automated routines provided by the manufacturer. The water signal was suppressed by a chemical-shift-selective saturation pulse. A 1000 Hz spectral sweep width was used, with data size 1024 points. The magnitude spectra were processed automatically using baseline correction and curve-fitting procedures to determine the resonance areas of N-acetylaspartate (NAA), creatine (Cr) and choline (Cho). Analysis of the spectra was performed with the manufacturer's spectroscopy software package. Resonances were assigned as follows: NAA 2.0, Cr 3.02 and Cho 3.2 ppm. We calculated peak area metabolite ratios NAA/Cr, Cho/Cr and NAA/Cho. For each patient, T.B and K.S. assessed whether the spectra were diagnostic.

All statistical analyses were performed using SPSS 10.0. The results are presented as mean ± standard deviation to facilitate comprehension of the tables. The Mann-Whitney U two-tailed test was used to assess differences in the metabolite ratios of pons, basal ganglia and PWM between controls and patients and between the NBD and non-NBD groups. Bivariate correlation analysis using Pearson's coefficient was performed to assess the relationship between the spectroscopic data and other independent variables, including the clinical features, duration of the disease and the patient's age. A P value < 0.05 taken as statistically significant.

Results

The clinical data and metabolite ratios are shown in Table 1. No significant difference between the mean ages of the groups was observed. The metabolite measures obtained from each brain region showed no sex- or age-dependent differences in the control

Table 1 Demographic data and mean metabolite ratios (mean ± SD) by clinical group. *Cho* choline*Cr* creatine *NAA* N-acetylaspartate

	Control group (29)	Behçet's disease		
		No neurological involvement (9)	Neuro-Behçet's disease (21)	All (30)
Age (years)	31.0 ± 6.9	33.3 ± 13.9	34.7 ± 11.0	34.3 ± 11.7
Range	(21–55)	(18–55)	(20–54)	(18–55)
Male/female	16/13	3/6	12/9	15/15
Duration of disease (years)	–	7.3 ± 5.8	7.8 ± 4.3	7.5 ± 4.7
Pons				
Cho/Cr	1.66 ± 0.68	1.31 ± 0.27	1.73 ± 0.79	1.60 ± 0.69
NAA/Cr	2.32 ± 0.78	2,00 ± 0.63	2.22 ± 1.07	2.16 ± 0.96
NAA/Cho	1.48 ± 0.41	1.59 ± 0.44	1.32 ± 0.44	1.40 ± 0.45
Basal ganglia				
Cho/Cr	0.83 ± 0.18	0.86 ± 0.24	1.00 ± 0.22 [b]	0.96 ± 0.23 [c]
NAA/Cr	1.36 ± 0.23	1.49 ± 0.28	1.59 ± 0.33 [b]	1.56 ± 0.31 [c]
NAA/Cho	1.64 ± 0.27	1.79 ± 0.38	1.61 ± 0.36	1.66 ± 0.37
Periventricular white matter				
Cho/Cr	0.97 ± 0.23	1.18 ± 0.16 [a]	1.16 ± 0.26 [b]	1.17 ± 0.23 [c]
NAA/Cr	1.78 ± 0.47	1.98 ± 0.31	1.82 ± 0.40	1.87 ± 0.38
NAA/Cho	1.82 ± 0.33	1.78 ± 0.31	1.64 ± 0.47	1.68 ± 0.43

[a] $P < 0.05$ vs control group
[b] $P < 0.05$ vs control group
[c] $P < 0.05$ vs control group

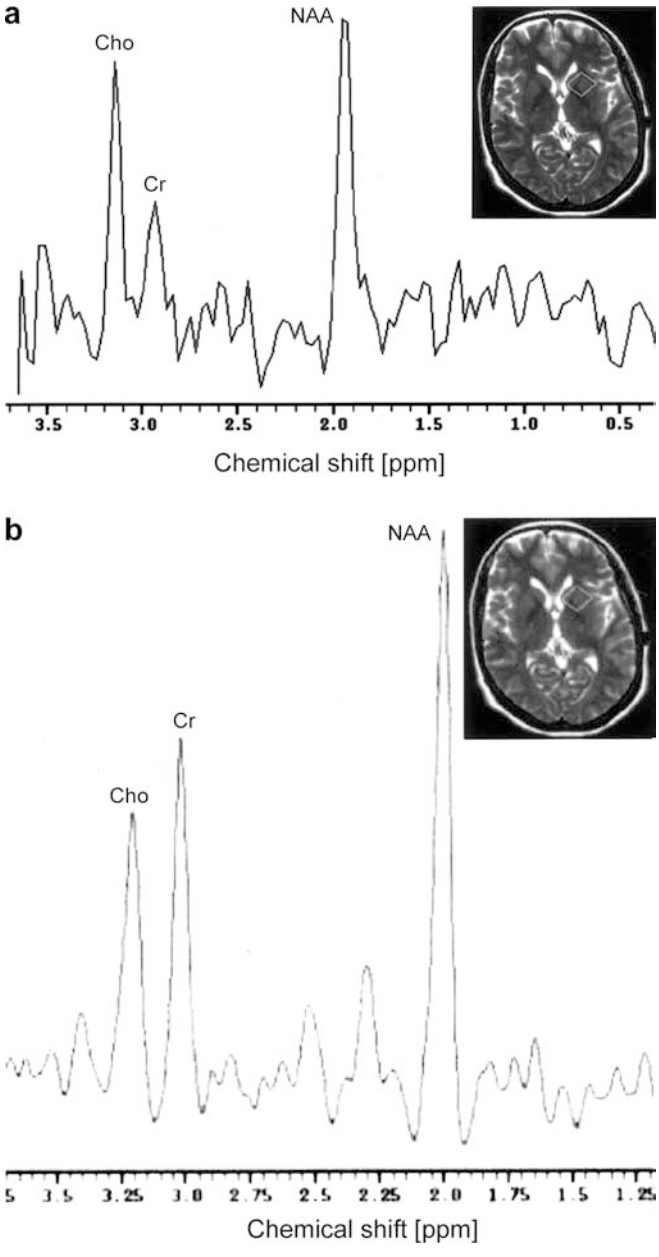

Fig. 1a, b Single voxel MRS of the basal ganglia; the position of the voxel is indicated a white rectangle. **a** The normal-appearing left basal ganglia in a patient with neuro-Behçet's disease for 2 years and vertigo reveals an increase in choline (Cho). **b** Spectrum from left basal ganglia of a healthy 27-year-old woman. *Cr* creatine *NAA* N-acetylaspartate

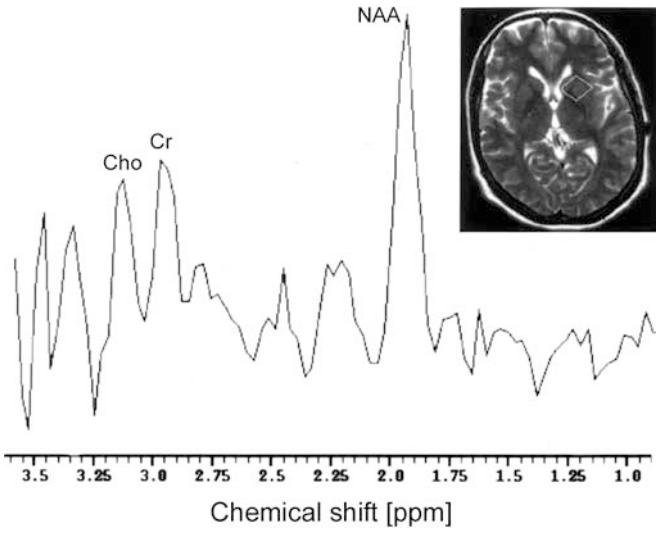

Fig. 2 Single voxel MRS of the left basal ganglia in a patient with neuro-Behçet disease for 4 years, complaining of diplopia, reveals an increase in NAA

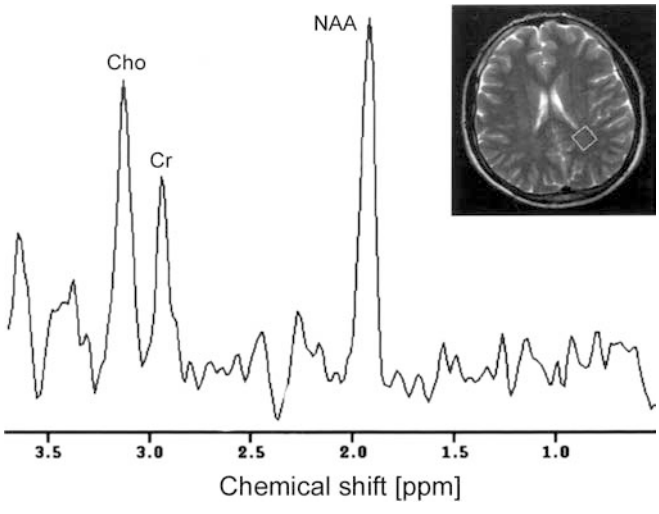

Fig. 3 Single voxel MRS from periventricular white matter in a patient diagnosed 4.5 years previously, with persistent headache and dizziness, shows an increase in Cho

subjects. MRI of the patients did not reveal any lesion, gliosis or atrophy.

In the 29 control subjects, 24 pontine, 23 basal ganglia and 27 white-matter spectra and in the 30 patients, 27 pontine, 28 basal ganglia and 25 white-matter spectra were judged as being of adequate quality for analysis. In two patients the spectra were inadequate.

Patients had higher Cho/Cr ratio in the basal ganglia than the controls ($P = 0.037$), and this ratio was significantly higher the in NBD group than in the control subjects ($P = 0.019$) (Fig. 1a, b). Patients also had a higher NAA/Cr ratio in the basal ganglia than the controls ($P = 0.006$), and between the patient groups, this ratio was higher in the NBD group ($P = 0.004$) (Fig. 2).

Cho/Cr was significantly higher in the PWM in patients ($P = 0.002$) (Fig. 3) and in the NBD group ($P = 0.014$) than in controls; non-NBD patients had also an increased ratio. The metabolite ratios obtained from the pons were not statistically different between non-NBD patients and control subjects.

Discussion

BD is a systemic vasculitis, which affects predominantly the small venules of the CNS and consists of disseminated meningoencephalitis with perivascular cell infiltration, infarcts with small necrotic areas surrounding blood vessels, haemorrhage, loss of myelinated fibres, and gliosis [12, 13, 14]. Vasculitis, like inflammation in other tissues, is caused by many different agents and pathogenetic mechanisms: however, these different causes produce only a limited number of histological expressions of injury. The major type of injury to nervous tissue in vasculitis is ischaemia. Therefore, the same clinical manifestations can result from aetiologically and pathogenetically different vasculitides [15, 16]. In NBD, lesions appear secondary to the small vessel vasculitis, and the anatomy of the intra-axial venous structures explains the dominant involvement of the upper brain stem and diencephalic structures [17].

Neurological involvement is most commonly manifest as brain-stem or corticospinal tract syndromes, increased intracranial pressure, isolated behavioural symptoms or headache [17, 18]. CNS disease has potentially serious consequences, including severe functional impairment or death [12].

Brain MRI is usually abnormal in patients who have unequivocal clinical evidence of CNS involvement and normal in those without [19]. Whereas presentations such as motor hemisyndromes, meningeal syndromes, seizures and cranial nerve palsies usually do not represent a diagnostic problem, other more subtle or equivocal syndromes related to CNS involvement, such as mild cognitive deterioration and headache, may be misinterpreted and contribute to underestimation of the actual prevalence [20].

The most common sites of lesions on MRI are in the basal ganglia, brain stem, internal capsule and white matter [12, 19]. Extensive involvement of the basal ganglia and/or brain stem was found to be highly specific for NBD [18]. In a previous study designed to differentiate NBD from multiple sclerosis and systemic lupus erythematosus, MRI indicated the correct diagnosis in all the acute but in only 40% of the chronic cases of NBD [21]. Single-photon emission computed tomography (SPECT) shows perfusion abnormalities in areas apparently normal on MRI and demonstrated hypoperfused areas in all of a group of children with NBD; it was claimed to be more sensitive and useful than MRI in this context [22]. In another study, SPECT showed abnormalities prior to their progression to morphological damage detectable by MRI, even in patients with no overt neurological involvement [23]. Overall, the association between imaging criteria and chronic stage BD remains weak.

In an MRS study of three patients with NBD during an acute illness, MRS revealed a lower NAA/Cr ratio in the lesion than on the normal side, which became normal during clinical recovery. Although the MRS findings were not reported to be pathognomonic for NBD, they confirmed brain involvement. Monitoring changes in NAA/Cr ratio with MRS may reflect the effects of therapy during acute illness in NBD [24].

In BD, lesions in the brain stem and diencephalon have been attributed to oedema, since they resolve completely or partially on follow-up MRI. The lack of correlation between the severity of clinical and MRI findings supports this suggestion [12, 17]. In our study MRI of the patients with evidence of neurological involvement was normal. As the lesions become more chronic, there is gliosis, atrophy and, in some cases, thickening and fibrosis of the meninges [25]. It is reported that the distribution and intensity changes of these residual lesions closely correspond to pathological descriptions of secondary demyelination [26, 27, 28]. In most inflammatory demyelinating lesions, the progress in destruction of myelin structures leads to an increase in Cho/Cr [29]. Hypoxia and ischaemia have been invoked to explain the microangiopathy-related metabolic shifts occurring in white matter. In the chronic stages of microangiopathy, NAA decreases and Cho increases have been reported. Oedema in the white matter, hypoperfusion preceded by rapid changes of hyper- and hypotension, and secondary demyelination may be the underlying mechanisms [11].

Our patients, both NBD and non-NBD groups, had increased Cho/Cr in the PWM, and the former also in the basal ganglia. These metabolite changes suggest microangiopathy-related secondary demyelination in PWM and basal ganglia in BD, with MRS revealing subclinical involvement of the PWM in asymptomatic patients.

NAA/Cr was increased in the basal ganglia of the patients, especially the NBD group. A probable explanation is reduction of Cho and Cr, more so in the latter. This may be explained by reduced metabolism due to glial damage, with relative sparing of the neurones in the basal ganglia.

Although our data are limited by small sample sizes, a relatively wide age range and our measuring only one hemisphere, MRS allowed clear discrimination between BD patients and control subjects, biochemical abnormalities occurring even in normal-appearing brain. It also revealed spectral differences between patients with and without clinical findings. It may serve to assess subclinical neurological involvement in BD, even when structural changes are absent. Further investigation of a large group of patients will be required to see whether it is useful in prognosis tool or for assessing the severity of the disease.

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