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Jacobs Journal of Neurology and Neuroscience

Research Article

Impairment of Memory Function as a Marker of Progression from Behçet's Disease to Neuro- Behçet's Disease

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Received: 01-11-2016

Accepted: 02-29-2016

Published: 03-07-2016

Abstract

Background: Behçet's disease (BD) is a rare, immune-mediated small-vessel vasculitis involving multiple body systems. It is a chronic relapsing disease that can progress to neurological complications (neuro-Behçet's disease; NBD) leading to cognitive impairment, but the extent of memory impairment in the early phase is poorly defined.

Aim: To conduct a retrospective analysis of the relationship between duration of BD and impairment of memory function.

Methods: Disease duration of BD was determined from medical records of 11 NBD patients. Following admission to our department, each patient completed two tests, the Revised Hasegawa Dementia Scale (HDS-R) and the Mini-mental state examination (MMSE), for evaluation of memory function.

Results: Age at onset of BD was 39±15 years and age at neurological onset (NBD) was 42 ± 15 years, with a mean interval of 33 ± 36 months between the two. Two patients showed simultaneous onset of BD and NBD. After adjustment of HDS-R and MMSE scores for chronological age, we found that mean disease duration of BD (months) was negatively correlated with HDS-R score ($p=0.03$, $r=-0.67$), but not with MMSE score. Among the 11 NBD patients, there was no significant difference in mean HDS-R score between the 6 patients receiving methotrexate (MTX) therapy and the 5 patients not receiving MTX (all 11 patients were receiving prednisolone). In contrast, the mean MMSE score was lower in the group receiving MTX than in the group not receiving MTX ($p<0.05$).

Conclusion: HDS-R scores were negatively correlated with disease duration of BD, and were not influenced by MTX therapy. Low scores in HDS-R, which includes items of short-term memory and verbal fluency (reflecting frontal lobe function), might be an early marker of progression of BD to NBD.

Keywords: neuro-Behçet's disease; Behçet's disease; Revised Hasegawa Dementia Scale (HDS-R); Mini-mental state examination (MMSE); memory function; disease duration; methotrexate

Abbreviations

Clinical characteristics of our NBD patients

NBD: Neuro- Behçet's Disease;
BD: Behçet's Disease;
M: Months;

HDS-R: Revised Hasegawa Dementia Scale;
MMSE: Mini-Mental State Examination;
CNS: Central Nervous System;
PSL: Prednisolone;
MTX: Methotrexate

Introduction

Behçet's disease (BD) is a multisystem relapsing inflammatory disorder characterized by recurrent oral and genital ulceration, skin lesions, arthritis and uveitis. The appearance of central nervous system (CNS) involvement in BD, usually called neuro- Behçet's disease (NBD), is the majority of patients present acute meningoencephalitis with focal lesions on MRI, followed by slowly progressive dementia with progressive brain stem atrophy [1, 2]. Cognitive impairment is evident in 46% of BD patients, with memory being the most severely affected cognitive domain [3]. However, the extent of memory impairment in the early phase is poorly defined. In this study, we examined the relationship between duration of BD and impairment of memory function in BD patients who progressed to NBD.

Subjects and Methods

This study is a cross-sectional retrospective analysis aimed at evaluating whether disease duration of BD is correlated with patients' scores in memory function tests. Memory function was examined only once in each patient, and for the purpose of this study, the duration of BD was taken to be the period from the time of BD onset until the date of the memory tests in our department.

Subjects were 11 BD patients, who presented to our Department of Neurology with initial or chronic complaints of memory impairment, headache and so on. All of them met the criteria of the International Study Group (ISD) for Behçet's disease at first admittance [4], and all were under treatment with immunosuppressive agents, prednisolone (PSL) or PSL plus methotrexate (MTX). They were diagnosed as NBD on the basis of MRI-confirmed parenchymal central nervous involvement with pyramidal signs, hemiparesis, behavioral changes and headache [5, 6]. We excluded patients with non-parenchymal secondary vascular involvement from this study, because of the difficulty of differential diagnosis versus other stroke without Behçet's disease. In this study, onset time of NBD was taken as the time when initial CNS manifestation(s) appeared. All patients received two memory function tests, the Revised Hasegawa Dementia Scale (HDS-R) and Mini-mental state examination (MMSE), for neurological assessment. HDS-R is widely used in Japan, and is consists of six sub-items: orientation (age, day, location), short-term verbal memory of three different words in different categories (cherry, cat, train, etc.), calculation (100-7 and 93-7), recall of three and four digit numbers, visual memory for five usual items and 'vegetable' term retrieval. Maximum score in HDS-R is thirty points, as in MMSE, but HDS-R has a higher relative weight of memory measures, assessing frontal lobe functions in terms of verbal fluency. An HDS-R score of less than twenty points indicates the possibility of dementia. HDS-R is much less influenced by age, gender and education than MMSE, but the scores are is significantly correlated with MMSE scores [7, 8]. It should be noted that in this retrospective study, there was a time difference of about 3 years between the age of onset of NBD (42±15 years) and the age at which the memory function tests were conducted (45±14 years).

T2 and FLAIR MRI images of all patients were obtained, and patients with non-parenchymal vascular involvement or with both parenchymal and vascular involvement were excluded from this study. All patients were taking PSL. Six were also taking MTX and five were not.

We used Pearson's correlation coefficient analysis to examine the relationship of duration of BD to HDS-R and MMSE scores in these NBD patients. The Mann Whitney U test was used to evaluate the difference of memory scores between the MTX and non-MTX groups. A value of $p < 0.05$ was accepted as statistically significant.

Results

The clinical backgrounds of the 11 NBD patients are presented in the Table. Age at onset of BD was 39±15 years and age at neurological onset (NBD) was 42 ± 15 years, with a mean interval of 33 ± 36 months. We found that the mean disease duration of BD was negatively correlated with HDS-R score after adjustment for chronological age ($p=0.03$, $r=-0.67$) (Figure). However, no such correlation was found for MMSE score. The six NBD patients receiving MTX therapy showed a significantly lower score in MMSE (22.6±2.9) than the five patients without MTX (27.8±1.5) ($p<0.05$).

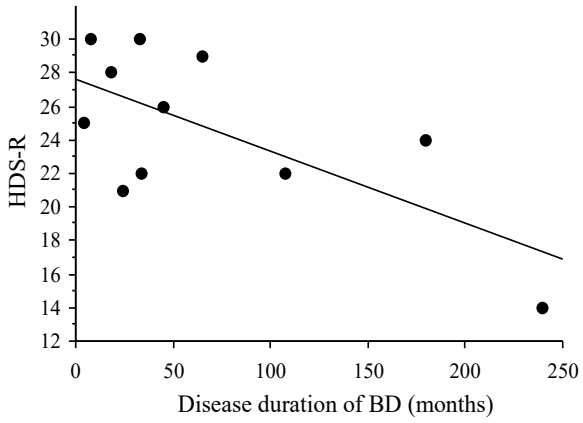

Figure 1. Correlation between the duration of BD (months) and score on the Revised Hasegawa Dementia Scale (HDS-R) for our 11 NBD patients.

Case	Gender	Age of onset of BD	Age of onset of NBD	Age at memory test	Disease duration of BD (M)	Duration between BD and NBD (M)	HDS-R	MMSE	Lesion of MRI	HLA B51	Initial CNS manifestations	Dose of PSL(mg/day) /MTX(mg/week)
1	M	24	24	27	33	0	30	30	brainstem	negative	headache	20 mg / none
2	M	49	49	58	108	0	22	24	white matter	negative	ocular pain	4 mg / 4 mg
3	F	32	33	34	24	12	21	22	white matter	positive	aseptic meningitis	10 mg / 4 mg
4	M	24	30	44	240	72	14	19	white matter	negative	memory loss	20 mg / 4 mg
5	M	52	55	55	34	26	22	20	brainstem	positive	dysarthria, ataxia	20 mg / 4 mg
6	F	62	67	67	65	65	29	28	white matter	negative	painful limb	4 mg / none
7	F	22	23	24	23	15	28	28	white matter	negative	headache, amnesia	5 mg / none
8	F	49	50	50	8	4	30	27	white matter	negative	dysexecutive function	15 mg / 4 mg
9	M	55	59	59	45	45	26	27	white matter	positive	memory loss, disturbed gait	20 mg / none
10	M	35	36	36	4	10	25	24	white matter	positive	memory loss	10 mg / 4 mg
11	F	22	31	37	180	111	24	26	basal ganglia	negative	double vision, convulsion	10 mg / none
	M6/F5	39 ± 15	42 ± 15	45 ± 14	69 ± 77	33 ± 36	25 ± 5	25 ± 4		+:4/-:7		

Table 1. Clinical backgrounds of the 11 NBD patients.

There was no difference in mean duration of BD between the MTX group (69 months) and the non-MTX group (68 months). In contrast, there was no significant difference in HDS-R score between the MTX and non-MTX groups.

HLA typing showed that 4 patients were positive for HLA-B51 allele (36.3%). MRI showed high-intensity CNS lesions in FLAIR images or T2-weighted images in all NBD patients. The main lesions were two brainstem lesions, eight cerebral white matter lesions, and one basal ganglia lesion. All patients with cerebral white matter lesions had multiple lesions in both hemispheres.

Discussion

In this study, the onset of BD coincided with the first neurological symptom in two patients, but the mean duration between onset of BD and onset of NBD in the remaining 9 patients was 34 months (range: 3 to 6 years), which is slightly shorter than in previous reports [5, 12, 13]. The large variation in duration of disease before diagnosis of NBD might be due to differences in the patients' clinical backgrounds. Therefore, in patients with a long duration of disease before diagnosis of NBD, it is plausible that memory function could already be impaired. Indeed, we found that mean disease duration of BD (months) was negatively correlated with HDS-R score ($p=0.03$, $r=-0.67$), although it was not correlated with MMSE score. The reason for the lack of correlation between duration of BD and MMSE score, in contrast to the case of HDS-R, might be the characteristic difference between the two memory function tests. HDS-R has a higher relative weight of memory measures, assessing frontal lobe functions [7, 8]. Eight of our 11 NBD patients (73%) showed white matter lesions. Other reports indicated that 70% of NBD patients had brainstem lesions [9, 10], so the site of CNS lesions could be a significant factor. Cavaco et al. reported that NBD was associated with parenchymal involvement, whereas BD was associated with white matter lesions in the frontal lobes. NBD patients tended to show impairment in a neuropsychological battery test (i.e. digit span-forward). However, Cavaco et al. concluded that disease duration did not influence cognitive functions [11].

Another issue is that low-dose weekly MTX therapy for NBD could delay the progression of CNS inflammation [14, 15]. However, when we examined the correlation between MTX therapy and memory impairment we found that there was no significant difference in mean HDS-R score between the 6 patients receiving methotrexate (MTX) therapy and the 5 patients not receiving MTX. On the other hand, MTX did affect MMSE score. This difference might be attributable to the differences in the characteristics of the two tests, as discussed above.

This study has several limitations, including retrospective analysis, cross-sectional design, and very small sample size.

Not all NBD patients were examined for pleocytosis/elevated CSF protein and interleukin 6 [9]. Further, there was a difference of about 3 years between onset of NBD and the time when memory function was tested. Longitudinal studies taking account of clinical factors, MRI lesions, disease duration and neuropsychological assessments are needed to understand the relationship between vasculitis in the CNS and cognitive dysfunction. However, prospective study is difficult because NBD is so rare, and in these circumstances, we think the present finding that disease duration of BD was negatively correlated with HDS-R score is of interest as a possible marker to aid diagnosis of NBD.

Conclusion

In patients with BD, a low score in HDS-R, which includes items of short memory and verbal fluency reflecting frontal cortex function, might be useful as an early marker of progression from BD to NBD.

Conflict of Interest

The authors have no conflict of interest.

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