Cognitive Impairments in Machado-Joseph Disease

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Background: Cognitive function of Machado-Joseph disease (MJD) patients has not been clarified.

Objectives: To determine the characteristics of cognitive dysfunction in MJD patients and to assess the relationship of dysfunction to age at onset, age at examination, disease duration, education, ataxia, depression, anxiety, and CAG repeat length.

Design: Case-control study.

Setting: Research-oriented hospitals.

Participants: Sixteen genetically confirmed MJD patients able to complete neuropsychological tests and 20 control subjects matched to patients by age and education.

Main Outcome Measures: Neuropsychological tests, including general cognition, verbal and visual memory,

working memory, visuospatial and constructional ability, language, executive function, depression, and anxiety.

Results: Machado-Joseph disease patients scored significantly lower than controls in verbal and visual memory, in visuospatial and constructional tasks, and in phonemic and semantic fluency tasks. None of these impairments correlated with CAG repeat length, age at onset, age at examination, disease duration, or education. Verbal fluency (words named in a category) correlated with the International Cooperative Ataxia Rating Scale score.

Conclusion: Machado-Joseph disease patients have verbal and visual memory deficits, visuospatial and constructional dysfunction, and verbal fluency deficits, all unrelated to CAG repeat length.

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ACHADO-JOSEPH DISEASE (MJD), first reported in North American families of Portuguese-Azorean ancestry,1 is now found throughout the world and is the most prevalent autosomal dominant cerebellar ataxia in North America, Europe, and much of Asia. Machado-Joseph disease is caused by an expansion of CAG trinucleotide repeats in a gene located at chromosome 14q32.1.2 The wide range of clinical manifestations includes cerebellar ataxia, pyramidal signs, progressive external ophthalmoplegia, exophthalmos, dystonia, and peripheral neuropathy. Machado-Joseph disease is a slowly progressive neurodegenerative disease, and patients typically will become confined to a wheelchair and later be bedridden.

Few reports have described cognitive impairment in MJD, and these were anecdotal or based on a small number of patients. For the most part, these previous studies lacked adequate control subjects. Therefore, no consensus concerning features of cognitive dysfunction in MJD has been established.

One study³ noted slow processing of visual information in demanding tasks and deficient shifting of visual attention in 6 MJD patients. Another study⁴ described executive dysfunction and depressive symptoms in 6 MJD individuals. In still another study,⁵ only verbal memory deficits were found in MJD, while dysexecutive syndrome and verbal memory deficits were found in spinocerebellar ataxia 1 and 2.

In the present study, we evaluated a wide range of cognitive functions in a large number of Japanese MJD patients. We used well-matched control subjects to determine the characteristic features of cognitive impairments in MJD.

METHODS

Sixteen genetically confirmed MJD patients and 20 control subjects were the subjects for the study. The characteristics of these subjects are shown in **Table 1**. All were native Japanese speakers. Severity of ataxia was rated on the International Cooperative Ataxia Rating Scale.⁶ Genomic DNA was extracted from patient leukocytes. MJ-N (5'-TCGTGAAACAATG-

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Table 1. Clinical Characteristics of Machado-Joseph Disease (MJD) Patients and Controls*

Characteristic	Control (n = 20)	MJD (n = 16)	
Male-female ratio	9:11	7:9	
Age at examination, y	47.5 ± 15.5 (27-74)	48.2 ± 15.4 (28-73)	
Age at onset, y		38.5 ± 13.5 (18-61)	
Disease duration, y		9.8 ± 4.5 (2-16)	
CAG repeat length		71.6 ± 3.6 (66-80)	
Education, y	13.0 ± 2.3 (9-17)	12.3 ± 2.5 (8-16)	

^{*}Data are given as mean ± SD (range) unless otherwise indicated.

TATTTTCCTTATG-3') and MJ-RN (5'-GATGTGAACTCT-GTCCTGAT-3') were used as primer pairs for polymerase chain reaction analysis. Genomic DNA (200 ng) was subjected to polymerase chain reaction. Reaction volume was 20 μL , and amplification and CAG repeat size analysis were carried out as previously described. $^{2.7}$ Paid volunteers were recruited as control subjects. They were selected from a larger control subject pool to ensure that their ages and education were comparable to those of the MJD patients. Control subjects had no history of any neurologic or psychiatric disease that affected cognition. Written informed consent was received in advance from MJD patients and control subjects. The study was approved by the ethics committee of the Department of Neurology, Nagoya University Hospital.

Each patient underwent a standard cognitive status assessment. All of a patient's neuropsychological tests were given on the same day. The Mini-Mental State Examination was used as a screen.8 Estimates of the IQ were derived from the information, digit span, and picture completion subtests of the Wechsler Adult Intelligence Scale–Revised, as described elsewhere. 9 To evaluate working memory, the digit span subtest of the Wechsler Adult Intelligence Scale-Revised was used. 10 Visual memory was examined using visual reproduction subtests 1 and 2, and visual paired associates subtests 1 and 2 of the Wechsler Memory Scale-Revised.¹¹ Verbal memory was examined using logical memory subtests 1 and 2 of the Wechsler Memory Scale-Revised. Sequential commands and object naming subtests from the Western Aphasia Battery were selected as measures of language functions. 12 To evaluate verbal fluency, subjects were asked to name as many items as possible within 1 minute from a semantic category (animals) and from a phonemic category (Japanese nouns starting with the Japanese Kana character Ka). To assess executive function, the simplified version of the Wisconsin Card Sorting Test¹³ was used. Constructional ability was tested using the block design subtest of the Wechsler Adult Intelligence Scale-Revised¹⁰; in addition to the original scoring (timed), one scoring was done without speed credits (untimed) to take into account the motor deficits of patients with MJD. In this scoring, the number of completed problems was compiled in the absence of a time limit. 14 All subjects completed a self-reporting instrument concerning anxiety and depression (Hospital Anxiety and Depression Scale).15

Statistical comparisons were made using the Mann-Whitney test. Differences were considered significant at *P*<.05.

RESULTS

NEUROPSYCHOLOGICAL TESTS

Seven patients could ambulate without assistance. Three others used a cane or an item of furniture to assist in walk-

Table 2. Results of Neuropsychological Tests in Machado-Joseph Disease (MJD) Patients and Controls*

Test	Control (n = 20)	MJD (n = 16)	<i>P</i> Value
Mini-Mental State Examination	29.0 ± 1.5	28.5 ± 2.4	.70
IQ	100.5 ± 10.5	92.1 ± 14.4	.70
Logical memory 1	24.4 ± 9.0	17.4 ± 8.5	.04
Visual reproduction 1	37.8 ± 3.5	34.4 ± 7.7	.44
Visual paired associates 1	14.1 ± 3.7	9.0 ± 5.0	.04
Logical memory 2	20.5 ± 8.4	12.6 ± 9.1	.02
Visual reproduction 2	34.3 ± 7.5	26.1 ± 11.1	.03
Visual paired associates 2	5.5 ± 1.1	3.3 ± 2.4	.04
Block design, timed	39.6 ± 9.3	26.9 ± 11.3	.001
Block design, untimed	9.6 ± 0.6	7.9 ± 2.1	.008
Sequential commands	77.6 ± 4.4	75.2 ± 7.4	.27
Object naming	60.0 ± 0.0	59.8 ± 0.8	.26
Verbal fluency, phonemic	11.9 ± 4.1	6.4 ± 2.9	<.001
Verbal fluency, category	20.2 ± 6.0	13.4 ± 6.7	.005
Digit span, forward	7.4 ± 2.0	6.9 ± 2.0	.65
Digit span, backward	6.0 ± 1.7	5.8 ± 2.1	.92
Digit span	13.3 ± 3.2	12.8 ± 3.6	.57
Categories	3.1 ± 1.8	3.1 ± 2.2	.88
Total errors	19.4 ± 7.9	24.3 ± 13.0	.30
Perseverative errors of Nelson	4.2 ± 4.0	10.0 ± 11.2	.13
Depression	3.7 ± 2.6	9.3 ± 3.1	<.001
Anxiety	4.7 ± 2.6	7.1 ± 2.7	.01

^{*}Data are given as mean ± SD unless otherwise indicated.

ing. Six patients were wheelchair bound. Machado-Joseph disease patients did not differ significantly from controls with regard to Mini-Mental State Examination score or IQ (Table 2). No significant difference in the working memory (digit span) or language functions such as sequential commands and object naming was evident between MJD patients and controls. No significant difference in any score was noted on the Wisconsin Card Sorting Test. Machado-Joseph disease patients had difficulty with logical memory subtests 1 and 2, visual reproduction subtest 2, and visual paired associates subtests 1 and 2 of the Wechsler Memory Scale-Revised. Visuospatial and constructional function, as tested using block design with and without a time limit, was impaired in MJD patients. Machado-Joseph disease subjects had significant problems in naming nouns from phonemic and semantic categories. Machado-Joseph disease patients were more depressed and anxious than controls.

CORRELATIVE STUDY

Next, we statistically analyzed the relationships between the cognitive dysfunction results and neurologic findings of age at onset, age at examination, disease duration, education, ataxia (International Cooperative Ataxia Rating Scale), depression, anxiety, and CAG repeat length using the Spearman rank correlation coefficient (**Table 3**). Scores that differed between MJD patients and controls (logical memory subtests 1 and 2, visual reproduction subtest 2, visual paired associates subtests 1

[†]Mann-Whitney test. Statistical significance was set at P<.05.

Test	CAG Repeat Length	Age at Onset	Age at Examination	Disease Duration	Education	International Cooperative Ataxia Rating Scale	Depression	Anxiety
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Logical memory 2	.74 (.09)	.79 (07)	.60 (13)	.40 (21)	.98 (.04)	.07 (47)	.62 (11)	.02 (-0.59)
Verbal fluency, phonemic	.83 (.07)	.22 (.32)	.35 (.25)	.87 (03)	.88 (.004)	.11 (40)	.30 (25)	.03 (-0.55)
Verbal fluency, category	.55 (.16)	.39 (.22)	.66 (.12)	.40 (21)	.94 (.01)	.03 (-0.56)	.75 (07)	.05 (50)
Digit span, forward	.25 (.31)	.02 (59)	.005 (70)	.009 (65)	.03 (.57)	.22 (30)	.47 (.22)	.63 (10)
Digit span, backward	.18 (.36)	.16 (34)	.18 (32)	.41 (19)	.02 (.60)	.40 (20)	.54 (13)	.07 (45)
Digit span	.11 (.42)	.03 (56)	.02 (61)	.08 (43)	.02 (.60)	.33 (24)	.89 (.06)	.18 (33)
Categories	.65 (09)	.07 (45)	.04 (51)	.11 (39)	.13 (.42)	.03 (53)	.92 (.004)	.36 (22)
Total errors	.52 (.17)	.14 (.38)	.07 (.47)	.04 (.53)	.08 (41)	.02 (.62)	.91 (01)	.37 (.25)
Perseverative errors	.95 (003)	.46 (.20)	.29 (.28)	.16 (.37)	.26 (25)	.02 (.59)	.92 (004)	.50 (.20)
of Nelson	(1000)	(.20)	()	(.0.)	()	()	(100 1)	()

^{*}Data are given as P value (ρ value). Statistical significance was set at P<.05 (Spearman rank correlation coefficient). Results of the other tests listed in Table 2 were not correlated with any of the variables assessed.

and 2, block design, phonemic fluency, and category fluency) showed no significant relation to CAG repeat length, age at onset, age at examination, disease duration, education, or depression. Among cognitive function tests, only logical memory subtest 2 and phonemic fluency were significantly related to anxiety, and only category fluency was significantly related to International Cooperative Ataxia Rating Scale scores.

Digit span and Wisconsin Card Sorting Test scores were significantly related to age at onset, age at examination, disease duration, and education. However, no significant differences in digit span and Wisconsin Card Sorting Test scores were evident between MJD patients and controls.

COMMENT

In this study, we describe verbal and visual memory deficits, impairment of verbal fluency, and visuospatial and constructional dysfunction in MJD patients. Previous studies³⁻⁵ have shown deficits of verbal memory, visual information processing, visual attention shifting, and executive function, including verbal fluency. Visual memory deficits and impairment of visuospatial and constructional function in MJD are new findings of this study. Because tasks of visual reproduction 2 and visual paired associates were impaired in MJD patients, we can assume that visual memory impairment is present in MJD patients. Furthermore, the task of visual paired associates does not need constructional abilities; therefore, the visual memory deficits observed in MJD are not the consequence of constructional dysfunction.

Left temporal lobe damage has been reported to cause verbal memory deficits, ¹⁶ with right temporal lobe damage resulting in visual memory deficits. ¹⁷ Combined verbal and visual memory deficits in MJD in this study suggest possible bilateral temporal lobe dysfunction. Impairment of verbal fluency is considered to reflect frontal lobe damage, ¹⁸ and the visuospatial and constructional dysfunction shown in the block design test is thought to result from damage to the parietal lobe. Based on these observations, we believe that widespread multiple regions of the cerebral cortex show dysfunction in

MJD patients. This view is supported by functional imaging results, in which defects of blood flow spread throughout the cerebrum in MJD.¹⁹

Widespread neuropathologic involvement in MJD patients²⁰ has been thought to spare the cerebral cortex. However, an immunohistochemical study²¹ using a specific antibody against expanded polyglutamine (polyQ) demonstrated nuclear accumulation of mutant MJD protein in neurons of the cerebral cortex, although the degree of protein accumulation and cortical disruption varied between cases. Therefore, one possible reason for the wide-ranging cognitive dysfunction in MJD patients may be a similarly wideranging involvement of cortical neurons.²²

Another possible explanation for cognitive impairment in MJD is disruption of cerebellar modulation of neural circuits. The cerebellum is reported to have connections with prefrontal,23 posterior parietal,24 and superior temporal²⁵ cortex via the pons. Indeed, cerebellar disorders generally are known to impair verbal fluency, visuospatial function, and memory.²⁶ Moreover, functional imaging studies provided evidence of activation of the cerebellum during a memory task²⁷ and verbal fluency task.²⁸ In MJD, the cerebellum and related structures, including cerebellar peduncles and dentate nucleus, are closely involved. Cognitive impairment in MJD could result from involvement of cerebellar cortical circuits, although most cognitive impairments were poorly correlated with severity of ataxia in this study. In addition to cerebellar connections, disruption of the basal gangliathalamocortical circuitry in MJD patients, including the substantia nigra and subthalamic nucleus, may take part in cognitive impairment. The basis for cognitive dysfunction in MJD may be multifactorial; further functional imaging studies, including functional magnetic resonance imaging, are needed to resolve this issue.

In MJD patients, age at onset and certain neurologic signs, such as ophthalmoplegia, pyramidal signs, dysphagia, and dystonia, have been shown to be related to CAG repeat length. ^{7,29} In the present study, although all MJD patients showed deficits of verbal memory, visual memory, verbal fluency, or visuospatial and constructional ability, scores of these neuropsychological tests were

not related to CAG repeat length, age at onset, or disease duration. These results suggest that CAG repeat expansion beyond the normal range may lead to cognitive impairments, with severity unrelated to length of expansion. On the other hand, MJD patients in this study showed varying combinations and severity of cognitive impairments; such heterogeneity among MJD patients may have obscured any relationship between cognitive deficits and CAG repeat length. Determining which stage of MJD shows onset of cognitive dysfunctions and whether these deteriorate together with motor dysfunction awaits further investigation. Longitudinal study, including neuropsychological examinations of "asymptomatic" gene carriers, may yield answers to these questions.

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