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Use of fluoxetine for treatment of Machado-Joseph disease: an open-label study

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Context – Machado-Joseph Disease (MJD/SCA3) is an autosomal dominant spinocerebellar degeneration that evolves to disability and death. Experimental data have shown that serotonin is an important cerebellar neurotransmitter and that impairment of the serotoninergic cerebellar system can induce cerebellar ataxia. *Objectives* – To evaluate the efficacy of fluoxetine, a serotonin reuptake inhibitor, in treating neurologic dysfunction in patients with MJD. *Patients and methods* – Thirteen MJD patients were treated with fluoxetine (20 mg/day) and were followed-up for 6 weeks. Outcome measures included functional capacity, standardized neurologic and cognitive ratings. The Montgomery-Asberg depression rating scale was used to control depressive symptoms. *Results* – There was no significant improvement in motor abilities after 6 weeks of treatment. *Conclusions* – These results suggest that fluoxetine has no benefit in motor function of patients with MJD/SCA3.

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Key words: Machado-Joseph disease; fluoxetine; polyglutamine diseases; serotoninergic system; spinocerebellar ataxias

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Machado-Joseph disease (MJD) is a multisystem degeneration of the central nervous system, inherited as an autosomal dominant disorder (1–3). The gene is on chromosome 14q32.1 (4), and contains a CAG repeat motif in the 3′ region of the coding sequence, which is selectively expanded in MJD patients (5). Normal alleles vary from 12 to 41 repeats, whereas expanded alleles vary between 66 and 84 repeats (5).

Disease manifestations usually start during adulthood, with a mean ± SD age at onset of 32 ± 12 years, among Brazilian patients (6), or 37 ± 14, among Portuguese and Azorean descents (7). The wide range of clinical manifestations include: gait and limb ataxia; dysarthria and dysphagia; a pyramidal syndrome, with brisk deep tendon reflexes, Babinski sign and spasticity; a supranuclear, progressive external ophthalmoplegia (PEO), mainly with limitations of upward gaze and of convergence, and less frequently, a nuclear PEO; extrapyramidal signs, including dystonia, rigidity and bradykinesia; a lower motor neuron disease, with fasciculation and amyotrophy; loss of tactile, algesic and vibration senses; eyelid retration, loss of weight and sleep disorders (7, 8). Patients will become confined to a wheelchair and will later be bedridden. The median survival time after onset is 17 years (6).

No therapy is established until now. Isolated reports, open label trials and double-blind trials have been done, using trimethoprim-sulfamethoxazole (9), L-dopa (10), buspirone (11, 12), and tetrahydrobiopterin (13). Significant improvement was demonstrated only for subjective experience, but not for any objective neurologic signs.

One approach to symptomatic treatment is to modify the neurotransmitter systems in the cerebellum (11, 14). One of these, the serotoninergic system, appears to play a role in regulating motor output that is mediated by central pattern generators, such as locomotion. Experimental data have shown that serotonin is an important neurotransmitter and that impairment of the serotoninergic cerebellar system can induce cerebellar ataxia (15).

The selective inhibitors of serotonin reuptake are currently considered first-line therapy for depression because of their ease in prescribing and superior side-effect/safety profile. Fluoxetine has been widely used as an antidepressive agent and has few side-effects. Several of our patients with

MJD also show depressive symptoms, and for this reason, antidepressive therapy was started, using fluoxetine. In many instances, there were subjective reports of gait improvement. Furthermore, it is known that neurons in several brainstem nuclei send serotoninergic nerve endings to the molecular, Purkinje's cell, and granular layers of the cerebellum, and that deep cerebellar nuclei also contain serotoninergic cell bodies (16). For these two reasons, we speculate if fluoxetine would have an objective effect on movement deficits presented by MJD patients.

Patients and methods

Thirteen molecularly confirmed MJD patients (seven men and six women; age range 18–62 years; mean 41 ± 13 years) were studied. The MJD polymorphic expanded regions were analyzed according to conditions previously described (17). Their clinical and molecular data are shown in Table 1. All patients had undergone complete physical and neurological examinations before the study. All patients also gave informed consent for the study.

They were treated with fluoxetine (20 mg/day) and were followed up for 6 weeks. Prior to and after fluoxetine treatment patients were functionally assessed using the Extended Disability Status Scale of Kurtzke (18) and the Unified Parkinson's Disease Rating Scale (19), which also assess non-cerebellar effects of MJD, e.g. dysphagia, spasticity and sleep disorders. The severity of ataxia was evaluated using cerebellar function scores from Kurtzke Functional Systems. A score of 0 indicates normal performance or absence of symptoms. Higher scores indicate worse functioning (1, abnormal signs without disability; 2, mild ataxia; 3, moderate truncal or limb ataxia; 4, severe ataxia; 5, unable to perform coordinated movements).

Cognitive aspects were controlled using: Mini Mental State (20), Digit Span (21), Word Span (22), Famous Faces Test, Visual Test, Praxis and Gnostic Tests, Memory-Text Test, Memory Color-Figure Test, Language Tests (23), Visual-Perception Test (24). The Montgomery-Asberg depression rating scale was used to control depressive symptoms (25).

For statistical analysis, Mann–Whitney Wilcoxon rank sum test was used to compare the ordinal clinical rating scores before and after the treatment. Statistical significance was defined as $P < 0.05$ with the use of a Bonferroni adjustment for multiple comparisons.

Table 1 Clinical characteristics of 13 subjects with Machado-Joseph disease (seven males, six females)

Variable	Mean	Range	SD
Age	41	18–62	13
Age of onset	31	12–55	12
Disease Duration	10	3–20	5
CAG expansion	75	71–81	3
Disability Status (EDSS*)	4	2.5–6	1

* The extended disability status scale of Kurtzke.

Results

The comparison between each neuropsychologic test, depression and motor ratings at baseline and after 6 weeks of treatment are summarized in Table 2.

Fluoxetine was well tolerated by most of the patients but one subject showed impairment of the gait. After 6 weeks of fluoxetine therapy, patients showed no significant difference in motor performance (Table 2). Only one of the 13 subjects who completed the study presented improvement in motor scales.

There was a significant reduction of depressive symptoms after 6 weeks of treatment ($P < 0.01$) (Table 2). However, this lost significance after the Bonferroni correction was applied. Fluoxetine had no effect on the other neuropsychological test performance. Beyond an improvement in the visual perception test with fluoxetine treatment that was

Table 2 Scores for cognitive performance, depression and motor ratings between baseline and 6 weeks of treatment

	Baseline		Week 6		Comparison	
Measure	Mean	SD	Mean	SD	*P*	*P′*
Montgomery-Asberg	11	6	6	4	0.007*	0.112
Mini Mental State	26	2	27	2	0.33	1
Digit span	7	3	6	1	0.2	1
Word span	6	1	8	2	0.77	1
Visual recognition	8	3	8	2	0.75	1
Famous faces	18	2	18	2	0.91	1
Praxic function	11	1	11	2	0.3	1
Gnostic function	8	1	8	0	0.13	1
Calculation	7	3	7	3	0.68	1
Abstraction	2	1	2	1	0.2	1
Visual perception	1	1	2	0	0.025*	0.4
Memory to text	5	2	5	3	0.58	1
Memory to colors and shapes	2	2	2	2	0.39	1
Language	15	1	15	2	1	1
UPDRS	46	11	44	10	0.32	1
EDSS	4	1	4	1	1	1

* Statistical significance. Wilcoxon signed rank test. $P' = P$ with the use of a Bonferroni adjustment for multiple comparisons.

EDSS, The Extended Disability Status Scale of Kurtzke. UPDRS, The Unified Parkinson's Disease Rating Scale.

significant, none of the other comparisons had *P*-values less than 0.05 before applying the Bonferroni correction (Table 2).

Discussion

To our knowledge, this is the first study about the effect of a serotonin reuptake inhibitor on MJD patients. Buspirone, a 5-HT1A serotonin agonist, has been reported to ameliorate gait and leg ataxia in an undiagnosed sample of mildly affected SCA patients in an open-label (11) and in a double-blind study (26). There has also been an isolated report on the buspirone benefit in one patient with MJD (12). However, other authors have found that buspirone has no benefit for cerebellar ataxia (27). L-5-hydroxytryptophan, a serotonin precursor, has been tested on various types of ataxia, with mixed, but generally negative findings (14, 28, 29). The rationale for the experimental use of serotonin (or its precursors) in the symptomatic treatment of cerebellar ataxia is that serotonin should act as an important neurotransmitter in cerebellar function, because of its input from serotonin secreting dorsal raphe nuclei (11, 30).

Although there is some evidence that serotonin receptor stimulation could help patients with cerebellar symptoms, our results do not support these effects on MJD patients. Fluoxetine has no beneficial effect on motor abilities measured by functional scales. However, these results should be carefully analysed, because of the limitations of the present study, such as small sample of patients, the employment of a modest dose of fluoxetine, and a short period of observation.

Fluoxetine reduced depression symptoms and improve ''visual-perception test'' after 6 weeks of treatment. However, these analyses have lost significance after a Bonferroni correction to limit the likelihood of spurious reporting of differences that may occur by chance when considering multiple indicators. We were concerned, however, that using the Bonferroni correction for multiple comparisons might have been too conservative, thus masking differences between depressive symptoms before and after fluoxetine treatment. Improvement observed in the ''visual-perception test'' would support the hypothesis that a specific cognitive deficit may occur in patients with MJD. The notion that the cerebellum may actually be involved in visuospatial organization has been suggested by the findings of impaired visuospatial manipulations in patients with cerebellar syndromes (31). Further studies on the cognitive aspects of MJD and the role of the serotoninergic system on these aspects are required.

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