Case Reports

Tremor during orthostatism as the initial symptom of Machado–Joseph disease

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Highlights

- We treated a case of tremor during orthostatism, whose underlying disease was Machado-Joseph disease (MJD).
- The tremor improved with clonazepam, trihexyphenidyl, and a rotigotine patch.
- This is a report with a video clip of tremor during orthostatism.
Introduction.

Machado-Joseph disease (MJD; spinocerebellar ataxia type 3), the most frequent autosomal dominant cerebellar ataxia in Japan [1], is caused by CAG repeat expansions in the ataxin-3 gene (ATX3). The clinical presentation of MJD includes progressive cerebellar ataxia; oculomotor, pyramidal, and extrapyramidal disorders; and peripheral neuropathy. Parkinsonism, including tremor, is sometimes observed, but few reports have characterized this manifestation of MJD [2]. Here, we present a case of MJD with tremor during orthostatism (TO) as the main symptom.

Case report.

A 60-year-old man was admitted to our hospital. He presented with dizziness and unsteadiness 6 years prior to admission. One year after onset, he presented with tremor in his right thigh; the tremor then spread to both sides. His tremor worsened; standing and turning caused falls.

The patient’s family history is shown in Figure 1A. His maternal aunt (II-1), diagnosed with Parkinson’s disease, had upper and lower tremor in her 50s and died at the age of 67 years. His mother (II-5) was diagnosed with spinocerebellar degeneration at another hospital. His maternal uncle (II-6) had unsteadiness at the age of 28 years and gait
disability in his 50s; the maternal uncle's son (III-8) used a wheelchair in his 30s and became bed-ridden. One brother (III-6) was schizophrenic; another (III-7) was diagnosed with pure cerebellar type spinocerebellar degeneration. Neither underwent genetic analysis.

He did not have bulging eyes, nystagmus, or saccadic eye movements. He had mild wide-based gait, but no dysmetria or decomposition in the nose-finger-nose or heel-knee-shin test. He had slight cogwheel rigidity in the right upper limb. He had mild tremor in his four extremities when supine or sitting, which was markedly exacerbated when standing (Video). The patient had mild tremor in his four extremities in the supine position and marked tremor in the standing position. Both were exacerbated by mental calculations. The tremor was 4-5 Hz and regular, in both the proximal and distal lower limbs.

Hyporeflexia without pathological reflexes was observed in his four extremities. He had no weakness in his extremities but had paresthesia in his lower legs.

Brain magnetic resonance imaging (MRI) revealed mild cerebellar atrophy but no basal ganglia abnormalities. $^{123}$I-ioflupane single photon emission computed tomography ($^{123}$I-FP-CIT SPECT) revealed low uptake in the putamen (Figure 1B). Cardiac radioactivity in $^{123}$I-metaiodobenzylguanidine (MIBG) was normal (2.33 H/M
ratio in the delay phase). No epileptiform discharges were noted in the electroencephalogram. No giant somatosensory evoked potentials following stimulation of the medial and tibial nerves were observed. Surface electromyograms (Video) showed regular groping discharges of 50–100 ms, with amplitudes of 4–5 Hz, in the bilateral tibialis anterior and gastrocnemius muscles. Synchronous discharge when supine and competitive discharge when standing suggested parkinsonian tremor and myoclonus.

We diagnosed him with MJD because his ATX3 CAG repeat was extended to 65/25. His tremor improved slightly with clonazepam treatment, and moderately with the addition of trihexyphenidyl to his treatment regimen. Finally, although it still persisted, his tremor improved markedly with the rotigotine patch.

L-dopa and trihexyphenidyl treatment improves lower-limb tremor in patients with MJD [2]. Here, while clonazepam, and trihexyphenidyl led to mild improvement, he showed marked improvement with rotigotine.

Discussion.

His symptoms were similar to primary orthostatic tremor (POT.) POT is characterized by a subjective feeling of unsteadiness during stance. Its clinical findings are limited to only palpable fine amplitude muscles when standing and confirmed with an EMG recording with a typical 13-18 Hz pattern[3]. In our case, the amplitude of tremor was
large, which we could confirm by inspection. EMG recording showed a 4-5 Hz pattern, which was different from typical POT. It was rather like “TO” which was reported previously [4].

Patients with MJD sometimes experience tremor; TO is relatively rare but it does occur. TO sometimes coexists with other Parkinsonism and responds to dopaminergic treatment, while POT does not [4]. The etiology of TO was reported to be likely to involve the cerebello-thalamo-cortical loop and nigro-striatal dopaminergic pathway in addition to the basal ganglia [5].

In this patient, the nuclear imaging findings showed normal MIBG and altered $^{123}$I-FP-CIT. This is compatible to the diagnosis of MJD, not Parkinson’s Disease. According to the $^{123}$I-FP-CIT SPECT findings, rotigotine was the most effective. However, all three treatments were effective, particularly the combination of all three treatments. The effectiveness of the treatment observed in our case may provide further evidence to support the pathogenesis theory proposed by Bonnet [4]. We emphasize that MJD should be considered in the differential diagnosis of TO.

**Conclusion.**

We present a case of MJD with TO as the initial symptom. MJD should be considered in the differential diagnosis of TO.
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**Ethical standard:** This study followed the tenets of the Declaration of Helsinki.

Genetic analysis was approved by the Medical Ethics Committee of the Hokkaido University Faculty of Medicine and Graduate School of Medicine. Written informed consent was obtained from the patient.
References


Figure Legend:

**Figure 1A: Patient family tree.**

The patient’s maternal aunt (II-1), diagnosed with Parkinson’s disease, had upper and lower tremor in her 50s and died at the age of 67 years. His mother (II-5) was diagnosed with spinocerebellar degeneration at another hospital. His maternal uncle (II-6) had unsteadiness at the age of 28 years and gait disability in his 50s; his maternal uncle’s son (III-8) used a wheelchair in his 30s and became bed-ridden. One brother (III-6) was schizophrenic; another (III-7) was diagnosed with pure cerebellar type spinocerebellar degeneration. Neither underwent genetic analysis.

**Figure 1-B: $^{123}$I-ioflupane single photon emission computed tomography ($^{123}$I-FP-CIT SPECT) findings.**

$^{123}$I-FP-CIT SPECT revealed low uptake in the putamen. The specific binding ratio was 3.06.

Video Legend:

The patient had mild tremor in his four extremities in the supine position and marked tremor in the standing position. Both were exacerbated by mental calculations. Surface electromyogram revealed a synchronous tremor pattern in the supine position and a competitive pattern in the standing position. Although it partly remained, the tremor
during orthostatism improved after treatment.
A) 

B) 

specific binding ratio = 3.06 (rt. 3.10, lt. 3.02)