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ORIGINAL PAPER

Cutaneous Sympathetic Dysfunction in Patients with Machado–Joseph Disease

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Abstract Although the clinical symptoms of Machado–Joseph disease (MJD) vary widely, those involving the autonomic nervous system, such as cutaneous sympathetic dysfunction, have rarely been investigated. In addition, there are no reports on cutaneous vasomotor function in patients with MJD. To determine the effects of MJD on cutaneous sympathetic function, we evaluated cutaneous vasomotor and sudomotor responses in the palms of 15 patients (mean age, 49±15 years; seven men and eight women) who were genetically diagnosed with MJD as well as in the palms of 15 age-matched, healthy controls (mean age, 48±16 years; nine men and six women). Sweat response was absent in 10 (67 %) patients with MJD, and the mean amplitude of sweat response was significantly lower ($p<0.0001$) in patients with MJD than in healthy controls following mental stress (mental arithmetic) and physiological stimuli. Although vasoconstrictive response was absent in three patients with MJD (20 %), there were no significant differences in the mean amplitude of vasoconstrictive response between patients with MJD and healthy controls. These results indicate that patients with MJD have reduced cutaneous sympathetic response, including severely impaired sudomotor functions and mildly affected vasomotor functions.

Keywords Machado–Joseph disease · Cutaneous sympathetic function · Sympathetic sweat response · Cutaneous vasomotor reflex

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Introduction

Machado–Joseph disease (MJD), also known as hereditary spinocerebellar ataxia 3, is an autosomal dominant neurodegenerative disorder caused by the expansion of CAG repeat sequences in the ATXN3 gene on chromosome 14q32.1 [1]. The clinical symptoms of MJD vary widely and include cerebellar ataxia, extrapyramidal and pyramidal signs, peripheral neuropathy, and ophthalmoplegia. Autonomic involvement, including urinary problems [2–4], sweat abnormalities [4], postural symptoms [2, 3], and constipation [3, 4], is also common in patients with MJD. Laboratory assessment of sudomotor functions in patients with MJD revealed common abnormalities in the sympathetic skin response, a classic measure used to assess sudomotor functions [3, 4]. Cutaneous vasomotor function may also be affected in MJD because vascular regulation in the skin is mediated by cutaneous sympathetic activity. However, there are no published reports on cutaneous vasomotor dysfunction in patients with MJD.

Mental stress and physiological stimuli can also evoke transient increases in sweat secretion and transient decreases in blood flow to the skin of the palms and soles. These responses are known as sympathetic sweat response (SSwR) and skin vasomotor reflex (SkVR), respectively. SSwR indicates sudomotor activity, as well as sympathetic skin response. However, sympathetic skin response does not indicate the actual amount of sweating [5], whereas SSwR is a quantitative index of sweating [6, 7]. SSwR and SkVR are both useful for assessing cutaneous sympathetic dysfunction in patients with central and peripheral disorders [6–8]. Therefore, we investigated SSwR and SkVR to determine the extent of cutaneous sympathetic involvement in patients with MJD.

Materials and Methods

Fifteen patients (mean age, 48.9±15.1 years; seven males and eight females) who were genetically diagnosed with MJD were examined. The mean duration of illness was 11.5±7.7 years, and the mean score on the International Cooperative Ataxia Rating Scale [9] was 43.6±17.8 points (range, 8–68 points). The mean length of the CAG repeats in these patients was 68.6±5.3. None of the patients with MJD presented with cutaneous vasomotor symptoms. Fifteen (mean age, 47.8±16.1 years; nine males and six females) age-matched, healthy controls were also examined. Informed consent was obtained from all patients before participation in this study, and ethical approval was granted by the Chiba University School of Medicine, Chiba, Japan. This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964.

Autonomic symptoms (postural symptoms, urinary symptoms, constipation, and sweat abnormalities) were evaluated using a nonvalidated questionnaire. Postural symptoms included dizziness, visual disturbance, and syncope, and urinary symptoms included storage symptoms (increased urination urgency, increased daytime urination frequency [>8 times/day], nocturia [more than once/night], and incontinence) as well as voiding symptoms (hesitation to urinate and feeling of incomplete emptying).

Tests for cutaneous sympathetic function were performed in a quiet room with a constant ambient temperature of 24–26 °C. Subjects were instructed to relax but stay awake. Sweat output from the tip of the thumb and cutaneous blood flow to the tip of the forefinger were measured in the supine position using a sudorometer (SKD-1000; Skinos, Nagoya, Japan) and a Doppler flowmeter (ALF21D; Advance, Tokyo, Japan), respectively. The signal was digitized online (12-bit, A/D board) at a rate of 100 Hz and stored on a hard disk. Data were analyzed using BIMUTAS II software (Kissei Comtec Co., Japan). Baseline levels were established, and sympathetic activation was assessed by having each participant perform an inspiratory gasp, mental arithmetic (serial sevens test for 15 s), and isotonic exercises (raising both lower limbs for 10 s). The sympathetic responses included increased sweat output (i.e., SSwR) and reduced blood flow to the skin (i.e., SkVR). The SSwR amplitude was measured from the baseline to the peak, and the SkVR reduction rate (i.e., SkVR amplitude) was calculated using the following formula: (reduced flow/basal flow)×100 %. SSwR and SkVR were considered absent when there was no response to any of the sympathetic activation tests.

Data were analyzed using STATISTICA for Windows release 9 (StatSoft Inc., Tulsa, OK, USA). The Mann–Whitney *U* test was used to analyze differences between the MJD and control groups. Spearman's rank correlation coefficient was used to determine any correlation between SSwR, SkVR, and the two groups. Differences were considered statistically significant when the p value was <0.05.

Results

With regard to postural symptoms, dizziness was present in four patients (31 %), but no patients had visual disturbance or syncope. Six patients (40 %) complained of urinary symptoms: storage symptoms in four (31 %) and voiding symptoms in three (20 %). Six patients (40 %) had constipation and five (33 %) had hypohidrosis.

SSwR was absent in 10 patients with MJD (67 %), whereas it was present in all healthy controls. The mean SSwR amplitude for inspiratory gasp (0.05±0.14 vs. 0.43±0.27 ml/cm^2/min, p=0.000003), mental arithmetic (0.07±0.17 vs. 0.43±0.26 ml/cm^2/min, p=0.000005), and isotonic exercise (0.05±0.13 vs. 0.41±0.32 ml/cm^2/min, p=0.000007) was significantly lower in the MJD group than in the control group (Fig. 1a). SkVR was absent in three patients with MJD (20 %), whereas it was present in all healthy controls. There was no significant difference in terms of the mean SkVR reduction rate between the two groups (Fig. 1b). Neither the SSwR amplitude nor the SkVR reduction rate correlated with age, duration of illness, or length of CAG repeat.

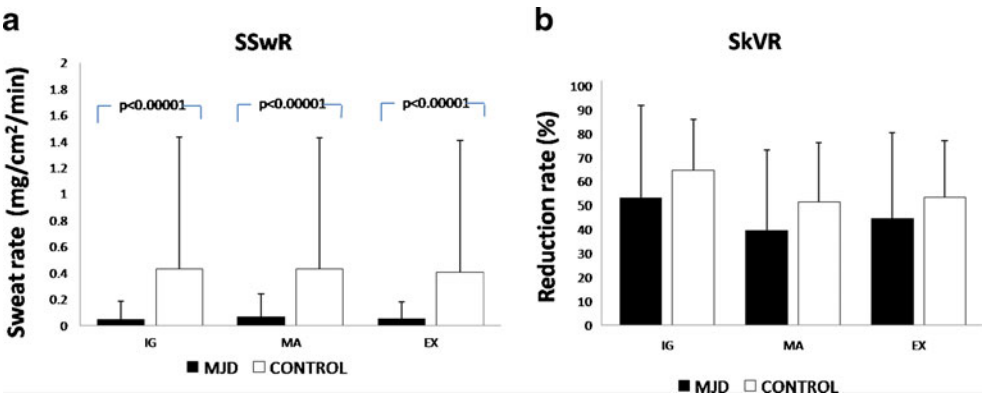

Fig. 1 **a** Sympathetic sweat response in patients with MJD and healthy controls. **b** Cutaneous vasomotor response in patients with MJD and healthy controls. *SSwR* sympathetic sweat response, *SkVR* skin vasomotor response, *IG* inspiratory gasp, *MA* mental arithmetic, *EX* isotonic exercise

Discussion

SSwR was absent in 10 (67 %) patients with MJD, and it was significantly lower in the MJD group than in the control group. Sudomotor dysfunction is common in patients with MJD. A few studies on sudomotor dysfunction in patients with MJD reported that 27–36 % patients failed to evoke a sympathetic skin response [3, 4], which reflects electrical activities of the sweat gland. The absence of a sympathetic skin response seems to be higher in these previous studies than in the present study. SSwR, which indicates the actual amount of sweating, may be more sensitive to sudomotor dysfunction compared with sympathetic skin response, which is an indirect measure of sweat gland activity.

Cutaneous vasomotor symptoms, such as changes in skin color, low skin temperature, and peripheral edema, are not rare in patients with neurodegenerative disorders such as Parkinson's disease [10]. However, patients with MJD in this study did not present with cutaneous vasomotor signs or symptoms, and their SkVR amplitudes did not differ from those in the controls. To the best of our knowledge, there are no published reports on cutaneous vasomotor symptoms in patients with MJD. However, in this study, three patients with MJD (20 %) did not present SkVRs. Some patients with MJD may have subclinical cutaneous vasomotor abnormalities. SkVR amplitudes in our patients appeared to be reduced compared with those in the healthy controls, although there was no significant difference. A future study on SkVR incorporating a larger number of patients with MJD may reveal a significant difference.

Cutaneous sympathetic dysfunction, as seen in our patients with MJD, indicates the presence of lesions in the sympathetic ganglia, which are known to be involved in MJD [11]. In this study, SSwR was recorded in the palms. Sweating in the palms and soles, known as emotional sweating, is mediated by the reticular formation, frontal cortex, basal ganglia, and limbic system, including the amygdala and anterior cingulate gyrus [6, 7, 12, 13]. In patients with MJD, lesions appear throughout the central and peripheral nervous systems, including parts of the brain that regulate SSwR, such as the substantia nigra and associated nuclei of the reticular formation [11]. In addition, voxel-based morphometry has shown atrophy of the cingulate and frontal cortices, both of which are important for SSwR generation, in patients with MJD [14]. These lesions could be responsible for the reduced SSwR in our study patients. On the other hand, SkVR is mainly mediated by the reticular formation [12, 13, 15], and supratentorial structures may not affect SkVR generation, unlike SSwR [12, 13]. Differences in the central pathways may result in the discrepancies in the SSwR and SkVR findings in patients with MJD.

We can evaluate cutaneous sympathetic function by recording SSwR and SkVR. These responses correlated with cardiovascular functions in patients with autonomic peripheral neuropathy, as assessed by conventional autonomic function tests such as the head-up tilt test and heart rate variability [8]. However, SSwR may not always correlate with cardiovascular autonomic functions in patients with central nervous system disorders [6, 7, 12, 13, 15] because several structures in the brain participate in SSwR generation. For example, patients with progressive supranuclear palsy may show a diminished SSwR, which can indicate involvement of the cingulate gyrus and frontal cortex despite normal cardiovascular autonomic functions [7]. In patients with MJD accompanied by central and peripheral nervous system involvement, cutaneous sympathetic function may not simply correlate with cardiovascular function.

Conclusion

Patients with MJD showed a diminished SSwR in the palms, indicating the possible presence of lesions in the limbic system, substantia nigra, striatum, reticular formation, or sympathetic ganglia.

Conflict of Interest The authors have no conflicts of interest to declare.

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