Dentatorubropallidoluysian Atrophy with Prominent Autonomic Dysfunction

Ayako Shioya¹, Hiroshi Takuma², Norio Ohkoshi³, Kuniyoshi Hirano⁴, Tomohiko Ishihara⁵, Kazuhiro Ishii⁶ and Akira Tamaoka⁷

Abstract:
We herein report a 45-year-old man with dentatorubropallidoluysian atrophy (DRPLA) who presented with mild dementia, ataxia, and involuntary movement and developed constipation, dysuria, and orthostatic hypotension. Thermography revealed an abnormal thermal response of the skin to cold stimulation. Skin temperature reflects the skin blood flow and is regulated by the sympathetic nervous system. Thermography is currently used to study diseases associated with vasomotor dysfunction of the skin. The thermography results suggested the possibility of autonomic dysfunction. Although little is known regarding autonomic dysfunction in DRPLA, this report demonstrates the importance of autonomic dysfunction in DRPLA.

Key words: dentatorubropallidoluysian atrophy, autonomic dysfunction, thermography

Introduction
Dentatorubropallidoluysian atrophy (DRPLA) is an autosomal dominant neurodegenerative disorder and a form of spinocerebellar degeneration (SCD). DRPLA is caused by the expansion of trinucleotide (CAG) repeats in the atrophin 1 (ATN1) gene in the short arm of chromosome 12 (1, 2). Patients with DRPLA with a younger age of onset (generally <20 years old) mainly exhibit progressive myoclonus, epilepsy, and mental retardation; conversely, those with a late onset commonly exhibit cerebellar ataxia, choreoathetosis, and dementia (3, 4). Autonomic nervous system dysfunction is uncommon in DRPLA.

Several types of autonomic nervous dysfunction occur in SCD, including multiple system atrophy (MSA). In Japan, previous studies investigating autonomic dysfunction in SCD (5) reported orthostatic hypotension (OH) in 27.3% of all patients with SCD but only in 3.6% of patients with DRPLA. In contrast, temperature disturbance, which is a less-frequent symptom than other forms of autonomic dysfunction, was observed in 2.5% of all patients with SCD but was not observed in any patients with DRPLA.

Body temperature control largely depends on the skin via subcutaneous arteriolar and vasomotor sympathetic functions (6). Thermography is currently used to study diseases associated with skin vasomotor dysfunction (7).

We herein report a 45-year-old man with genetically confirmed DRPLA and significant OH who had an abnormal thermal response to cold stimulation on thermography, despite being unaware of sweating abnormalities.

Case Report
The patient was a 45-year-old Japanese man. He had been a slow runner in his teens and had an unstable gait in his 20s. He began to fall frequently at 44 years old and was admitted to our hospital at 45 years old. He had no risk factors for cerebrovascular diseases, such as hypertension, diabetes mellitus, or hyperlipidemia. His child, mother, brother, aunt, and nephew had been diagnosed with SCD without any autonomic disfunction.
A cranial nerve examination revealed saccadic eye movements and slurred speech. He had no limb weakness, and his extremities had normal deep tendon reflexes. The finger-to-nose test showed bilateral dysmetria, whereas the heel-to-knee test showed dysmetria and decomposition. The patient had a wide-based gait and exhibited choreic movement of the limbs. Regarding the autonomic nervous system, he had constipation, dysuria, and OH, and his systolic blood pressure decreased to 40 mmHg without an elevation in the heart rate during the tilt table test. Horner's syndrome and erectile dysfunction were not apparent. Brain magnetic resonance imaging revealed atrophy and T2-weighted white matter hyperintensities in the cerebellum, cerebrum, and brainstem. Genetic testing was performed for autosomal dominant causes of ataxia, including SCA1, SCA2, SCA3, SCA6, and SCA17. Expansion of the ATN1 CAG repeat on chromosome 12q was detected in 65/21; thus, he was diagnosed with DRPLA.

Thermography was used to evaluate the autonomic nervous system. The examination was performed under the following conditions: 1) at baseline at standard room temperature and 2) during a cold stress test (CST), which was carried out at a room temperature of 26°C and air humidity of approximately 50% using a JTG-4310S (Japan Electron Optics Laboratory, Tokyo, Japan). The patient was allowed to acclimatize for 20 min before testing, and baseline thermal images were acquired. After soaking both hands for 1 min in cold water maintained at 10°C, skin temperatures in the regions of interest (ROIs) were measured. The main thermal ROIs were the skin of the dorsum manus and the finger dorsum. The recovery rate (RR) of skin temperature was calculated as follows:

\[ RR = \frac{(T_{0\text{pre-immersion}}-T_{0\text{post}})}{(T_{0\text{pre-immersion}}-T_{X\text{post}})} \times 100 \, \% , \]

where \( T_{0\text{pre-immersion}} \) = baseline skin temperature, \( T_{0\text{post}} \) = skin temperature immediately after CST, and \( T_{X\text{post}} \) = skin temperature at X min post-CST. The patient’s baseline temperature was lower than that of healthy controls measured at Tsukuba University of Technology, and the CST showed a significant decrease in the RR (Fig. 1, 2). In other autonomic function tests, the H/M value was normal in early and delayed iodoine\(^{123}\)-labeled metaiodobenzylguanidine (\(^{123}\)I-MIBG) images (early image H/M value, 2.15; delayed image H/M value, 2.35). Regarding the heart rate variability, the coefficient of variation in R-R intervals (CVR-R) was 2.36%, which was within the normal range (8).

**Discussion**

We encountered a patient with DRPLA who presented with severe OH. To our knowledge, this is the first case report of thermography in a patient with DRPLA.

Thermography is currently used to study diseases that lead to skin vasomotor dysfunction, and its combination with cold stimulation is used to quantify thermal reduction in relation to sympathetic vasoconstriction and subsequent thermal recovery (7). Few reports have discussed thermography in patients with neurodegenerative diseases (7, 9). Thermography of patients with Parkinson’s disease (PD) compared to healthy controls revealed that patients with PD displayed abnormal thermal responses when exposed to CST, suggesting cutaneous autonomic dysfunction (7). In another study, patients with PD also exhibited a significant reduction in the RR in the CST compared to healthy controls (9). In our case, the baseline temperature and RR after cooling were lower than those in healthy controls. Our patient was young and did not have arteriosclerosis, which is a potential cause of the reduced blood flow. Although cutaneous autonomic dysfunction was observed in MSA (5), PD (7), diabetes mellitus (10), and Guillain-Barré syndrome (11), the patient was not diagnosed with any of these diseases. Furthermore, the patient had no medical history of any other disease that could lead to autonomic dysfunction. Given these findings, we considered that the decrease in the RR reflected skin sympathetic nerve dysfunction, which was one of the clinical presentations in this case of DRPLA.

Autonomic dysfunction of various degrees is frequently observed in patients with neurodegenerative diseases. Autonomic dysfunction is one of the core manifestations of MSA, and loss of the intermediolateral nucleus (IML) is
Figure 2. CST results [measured temperature (A) and recovery rate (B)]. A, B: The baseline temperatures in the third fingers were 33.3°C (left) and 34.5°C (right) and in the hand dorsum were 33.4°C (left) and 33.4°C (right). The thermal recovery rates at 15 min post-CST for the third fingers were 31.0% (left) and 34.3% (right) and for the hand dorsum were 63.2% (left) and 64.1% (right). In terms of the mean baseline temperature, the patient had lower results bilaterally in the third fingers and hand dorsum than in healthy controls measured at Tsukuba University of Technology [normal values: third finger, 35.7±0.7°C and hand dorsum, 34.5±0.9°C, respectively (mean±SD)]. Similarly, the recovery rate of the patient after the CST was significantly lower than that in healthy controls [normal value thermal recovery rate: third finger, 97.4±6.5%; hand dorsum, 94.8±8.3% (average value±SD)]. CST: cold stress test, \( T_{0 \text{pre-immersion}} \): baseline skin temperature, \( T_{0 \text{post}} \): skin temperature immediately after CST, \( T_{X \text{post}} \): skin temperature at X min post-CST, SD: standard deviation
thermography, were observed. However, Horner’s syndrome and erectile dysfunction were not apparent. In the examination, the H/M value of [123I] MIBG myocardial scintigraphy and CVR-R were within the normal ranges. A decreased cardiac uptake of MIBG on [123I] MIBG cardiac scintigraphy has been reported in PD and dementia with Lewy bodies (DLB) (16). Furthermore, postmortem studies in pathologically confirmed PD and DLB have shown that the number of tyrosine hydroxylase-immunoreactive axons, a marker for sympathetic axons, of the heart was decreased, which was believed to be the mechanism underlying the reduced cardiac MIBG uptake (16). Previous studies demonstrated that neuronal degeneration with Lewy bodies occurs in broad areas of the sympathetic nervous system (i.e. hypothalamus, Edinger-Westphal nucleus, dorsal motor nucleus of the vagus, intermediolateral cord, sympathetic ganglia, enteric nervous system, and cardiac and pelvic plexuses) (17). In addition, Yoshida suggested that this complicated pathological background might be involved in the variety and severity of various autonomic dysfunctions (17). In DRPLA, the etiology of the autonomic dysfunction remains unclear, and there are intranuclear inclusions, but not Lewy bodies, on neuropathological examinations (18). The complicated background similar to PD may be involved in the autonomic dysfunction, which may be responsible for the various symptoms and examination results observed.

In conclusion, we treated a patient with DRPLA who repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). The authors state that they have no Conflict of Interest (COI).

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