

The Presence of Periodic Limb Movement Disorder in a Patient with Diabetes Mellitus and Optic Atrophy (Wolfram Syndrome)

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Wolfram syndrome (WFS) is characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD), together known as DIDMOAD. This syndrome is a rare autosomal recessive neurodegenerative disorder and typically begins with insulin-dependent diabetes mellitus. Periodic limb movement disorder (PLMD) is characterized by periodic episodes of repetitive, highly stereotyped, limb movement during sleep, which results in disturbed sleep. Its pathophysiology is unclear. It is associated with many conditions, but we were unable to find a previous report regarding WFS accompanied by PLMD. We therefore report, for the first time, about a patient with WFS presenting with PLMD and discuss its pathomechanism with a literature review. **Sleep Med Res 2014;5(2):67-71**

Key Words Periodic limb movement disorder, Wolfram syndrome, Diabetic autonomic neuropathy.

INTRODUCTION

Wolfram syndrome (WFS) is a rare autosomal recessive neurodegenerative disorder, also known as diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.¹ It was first described in 1938, as four siblings with diabetes mellitus and optic atrophy were first reported by Wolfram.¹ Typically, patients show diabetes mellitus, followed by optic atrophy in first decade of life, diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early in the fourth decade.¹ Diagnostic criteria are the presence of insulin-dependent diabetes mellitus (IDDM) and optic atrophy unexplained by any other disease.² Genetic studies undertaken to identify mutations in the WFS1 gene and CISD2 gene can be helpful for diagnosis.³ Other neurological abnormalities include an absent gag reflex, gait ataxia, cold intolerance, horizontal nystagmus, loss of taste or smell, autonomic neuropathy, cerebellar dysarthria, and seizures.² There have been no previous reports of a WFS patient associated with periodic limb movement disorder (PLMD). Here, we describe a 26-year-old man with WFS who presented with PLMD.

CASE REPORT

A 26-year-old man visited the neurology outpatient department of our center. He complained of bilateral leg spasms and jerky movement during sleep, which started 7 years prior to the current authors' evaluation. The patient complained of poor sleep, which was described as fragmented, not restorative, and with a mean sleep latency of 1 hour/night. Daytime fatigue, somnolence, and depression were also reported. His complaint was aggravated by oily food intake, fatigability, and relieved by leg massage. He had suffered progressive visual deterioration since 13 years old, and finally became blind. IDDM was diagnosed at the age of 7, for which he was receiving insulin, although he had rather poor control of his blood sugar. He

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also complained of dyspepsia, urinary difficulty, and constipation, problems he had experienced for the past several years. He had one older brother and parents, but there was no family history of similar conditions among other family members. In his neurological examination, we found bilateral blindness, mild paresthesia, and numbness in his legs. Otherwise, there were unremarkable findings regarding his mental state, memory, language, pyramidal system, extrapyramidal system, cerebellar system, deep tendon reflex, and pathologic reflex. In his ophthalmologic inspection, we found normal fundus, retina, and intraocular pressure. He was found to have bilateral optic atrophy without diabetic retinopathy (Fig. 1).

Using polysomnography (PSG), the sleep architecture showed an increased amount of stage N1, N3, and rapid eye movement (REM) stages, and decreased amount of stage N2. Sleep latency was 2 minutes. The number of REM episodes was 5. Sleep efficiency was about 77%. Eight episodes of obstructive sleep apnea and 5 episodes of sleep hypopnea were observed. The patient's

apnea-hypopnea index was 2.8/h and respiratory disturbance index was 2.9/h, which meant the patient did not have sleep apnea syndrome. The patient did not complain of any urge to move the legs throughout the day, especially at night or rest. A suggestive immobilization test demonstrated no limb movement. We did not find cataplexy, nightmares, sleep paralysis, sleep attack, or snoring. PSG showed that the periodic limb movement (PLM) index was 109.2/h and PLM arousal index was 38.0/h (Fig. 2). REM sleep behavior disorder and obstructive sleep apnea syndrome were not observed in the PSG recording.

Spinal magnetic resonance imaging (MRI) showed normal appearances of the spinal cord, medulla oblongata, and up to the observed area of the pons. A brain MRI, taken 11 years ago, showed no abnormalities. A nerve conduction study showed no remarkable findings. Based on an autonomic function test, autonomic dysfunction and small fiber neuropathy were identified (Fig. 3). Quantitative sudomotor axon reflex test showed



Fig. 1. Fundoscope. Fundoscopic finding of the blind patient with insulin-dependent diabetes mellitus secondary to Wolfram syndrome shows optic atrophy but no diabetic retinopathy.



Fig. 2. Electromyography in polysomnography. Polysomnographic recording of a patient shows the evidence of typical periodic limb movement during sleep; that is, frequent, periodic, and repetitive electromyographic bursts over the tibialis anterior muscle.

sympathetic postganglionic sudomotor dysfunction or sweat gland abnormalities in the leg. A urodynamic study showed detrusor overactivity with impaired contractility, and a gastric emptying scan showed significantly delayed gastric emptying. The complete blood count, electrolyte and chemical panel were unremarkable.

We diagnosed this patient with WFS due to the presence of juvenile onset IDDM and optic atrophy. Dyspepsia, numbness of legs, urinary difficulty, and constipation were considered complications of the diabetic autonomic neuropathy. The patient could be diagnosed as PLMD based on the PLM detected

in PSG, the poor sleep quality, and the excessive daytime sleepiness. We prescribed clonazepam 0.5 mg and ropinirole 0.5 mg at bedtime, however, the jerky legs movements did not improve and he complained of drug side effects at the 1-month follow-up. We were unable to observe further responses and the clinical course due to cessation of follow-up.

DISCUSSION

Our patient was diagnosed with WFS by the presence of

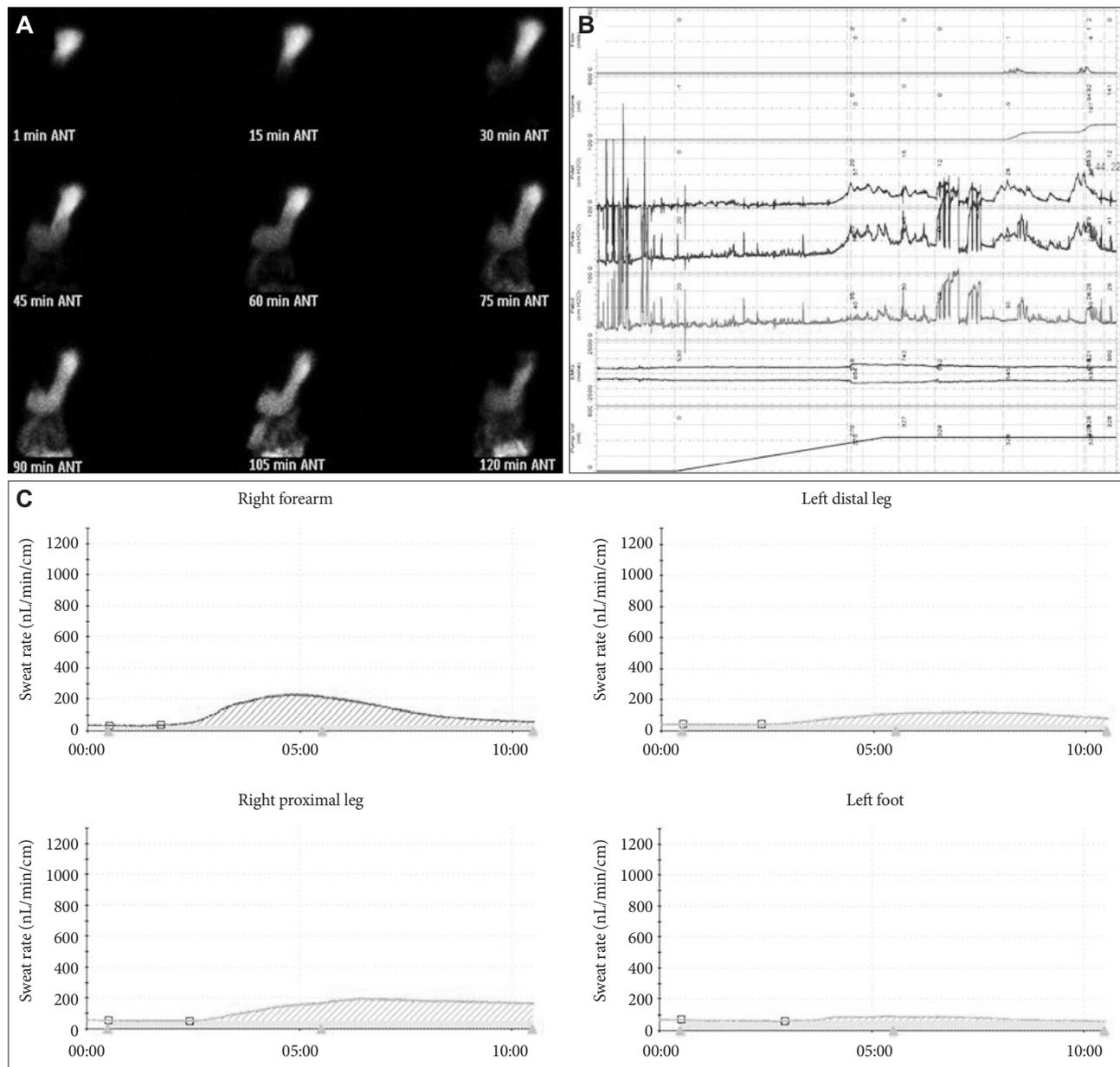


Fig. 3. Gastric emptying scan, urodynamic study, and QSART. A: Gastric emptying scan shows significantly delayed gastric emptying. B: Urodynamic study shows phasic detrusor overactivity in the filling phase and detrusor underactivity in the voiding phase. These findings suggest detrusor overactivity with impaired contractility. C: QSART shows a decreased total sweat volume and persistent sweat activity, especially in left distal leg and left foot. These findings suggest sympathetic postganglionic sudomotor dysfunction or sweat gland abnormalities. QSART: quantitative sudomotor autonomic reflex.

IDDM and optic atrophy, although we did not perform genetic analyses. Since the initial recognition of the WFS1 gene by Inoue et al.,⁴ different research has determined more than 50 distinct mutations of this gene.⁵ Accordingly, it is postulated that WFS is a heterogenic disorder and may not be confirmed by a gene test. Additionally, in a previous study of 6 Spanish families with a total of 7 WFS patients, Domènech et al.⁶ reported no mitochondrial DNA abnormalities. The basic criteria for the diagnosis of WFS are based on clinical manifestations; the co-existence of insulin-treated, juvenile-onset diabetes mellitus and optic atrophy occurring before 15 years of age.⁷ The combination of diabetes mellitus and optic atrophy has positive predictive and a negative predictive values of 83 and 1%, respectively.⁸

Any secondary causes that induce PLMD were not observed in our young patient. Physiologically, PLMD is found more frequently in elder patients than in younger patients,⁹ and isolated PLMD at a young age is uncommon.¹⁰ Nevertheless, PLMD occurred in this patient and this specific character deserves discussion. In young patients, drugs including anti-dopaminergic agent can induce PLMD.^{11,12} Parkinsonism, autism, attention deficit hyperactivity disorder, Tourette syndrome, and metabolic disease can cause PLMD, also.^{10,12,13} PLMD can be seen in many conditions, such as obstructive sleep apnea, narcolepsy, REM sleep behavior disorder, essential hypertension, congestive heart failure, end-stage renal disease, and peripheral neuropathy.¹⁴ However, any explainable secondary causes for young onset PLMD were not found in this patient.

We suggest that PLMD can develop in patients with WFS according to the pathomechanism of PLMD. Although the pathophysiology of PLMD is not clear yet,¹⁴ we will explain pathophysiology of PLMD in view of autonomic dysfunction. The sympathetic overactivity related to diabetic autonomic neuropathy might contribute to the generation of PLMD in this patient with WFS.

Sympathetic tone augmentation is initiated during the course of diabetic autonomic neuropathy development.¹⁵ Because the vagus nerve, which is the longest autonomic nerve and mediates 75% of the overall parasympathetic activity, tends to be involved early in the course of diabetic autonomic neuropathy development, sympathetic tone augmentation results.¹⁵ Sympathetic denervation related to orthostatic hypotension develops in advanced or severe autonomic neuropathy.¹⁵ In our patient, diabetic autonomic neuropathy was identified, but orthostatic hypotension which would indicate advanced autonomic neuropathy and sympathetic denervation was not found. Although these findings are not direct evidence of sympathetic tone augmentation, it may be a reasonable explanation for the relative sympathetic tone augmentation in this patient. We suggest that our patient has sympathetic tone augmentation from the course of diabetic autonomic neuropathy.

In studies with electroencephalography and heart rate vari-

ability, sympathetic activation was found to reach greater intensities in patients with isolated PLMD than in control patients, and PLMD developed frequently in association with arousals and autonomic activation.¹⁶ Sympathetic activation occurs periodically in the setting of the physiologic sleep-wake control and, if it overcomes a certain threshold, it triggers or facilitates PLMD.¹⁶ The neuroanatomical studies demonstrate that the pathogenesis of restless legs syndrome and PLMD are associated with the dopaminergic neurons of the hypothalamic A11 nucleus, which is a descending pathway linked to preganglionic sympathetic neurons, dorsal horn, interneurons, somatic motor neurons, and the striatum.¹¹ This descending pathway seems to form a sympatho-excitatory system and regulates sympathetic outflow, and dysregulation of this system results in PLMD.¹⁷ These findings suggest that an augmented sympathetic system contributes to the generation of PLMD. In addition, in a previous study with a cohort of diabetes type 2 patients, the prevalence of PLMD in the population of type II diabetes patients was greater in comparison to the general population of the same age.¹⁸ Therefore, we suggest that sympathetic overactivity related to diabetic autonomic neuropathy may contribute to the generation of PLMD in this patient with WFS, although a causal relationship between PLMD and WFS cannot be completely confirmed.

Periodic limb movement disorders are modulated in their periodicity by descending supraspinal, probably reticular, influences.¹⁴ Abnormal brain MRI findings in the patients with WFS are found in brainstem atrophy, in addition to generalized brain atrophy.^{2,8} Therefore, it is assumed that WFS may contribute to the pathomechanism of PLMD in association with brainstem atrophy. However, we could not find any brainstem atrophy in our patient.

In conclusion, we report the first case of WFS and PLMD, and we consider that diabetic autonomic neuropathy in this patient is a feasible explanation for the PLMD, although we were unable to exclude isolated PLMD as a co-morbidity. Our case supports the hypothesis that autonomic dysfunction in results in PLMD, and may give a direction to the study of the pathophysiology of PLMD. Further studies exploring the pathophysiology of PLMD are needed.

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Conflicts of Interest

The authors have no financial conflicts of interest.

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