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Improvement of Peripheral Neuropathy by Testosterone in a Patient with 48,XXYY syndrome

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The 48,XXYY syndrome is a form of hypergonadotropic hypogonadism, characterized by tall statures, aggressive behavior, mental retardation, and stasis changes reflecting vascular insufficiency. We report a 25-year-old male with this syndrome showing a peripheral neuropathy and stasis dermatitis which were both reversed by administration of testosterone. Electrophysiologic studies, plethysmography, and thermography indicated that this treatment improved nerve conductivity and peripheral circulation. We postulate that in 48,XXYY syndrome a decrease in testosterone may result in peripheral neuropathy via nerve ischemia.

Key words : 48,XXYY syndrome, Peripheral neuropathy, Electrodiagnosis, Ischemia, Testosterone

INTRODUCTION

Originally reported by Muldal and Ockey [8] in 1960, 48,XXYY syndrome is a variant of Klinefelter syndrome (47,XXY syndrome). The reported incidence of the 48,XXYY karyotype in unselected newborn populations is about 1 in 25000 [5].

The 48,XXYY syndrome is manifest endocrinologically as hypergonadotropic hypogonadism, characterized by tall stature, aggressive behavior, mental retardation, and vascular disorders [8]. Peripheral nerve involvement has received little mention in the literature. One previous report documented a decrease in motor conduction velocities in 48,XXYY males without neurologic signs or symptoms [12].

We report clinical and electrodiagnostic observations in a patient with peripheral neuropathy as a feature of 48,XXYY syndrome. The patient also had findings consistent with a microvascular disorder. Both vascular dysfunction and neuropathy responded to testosterone therapy.

CASE REPORT

Clinical History

A 25-year-old Japanese male with traumatic brain injury was admitted to our hospital for rehabilitation 2 months after an accident.

The patient was born at term weighing 3100 grams after a breech presentation. The paternal age was 37 years, and the maternal age was 34. When he was 4 years old, he had an epileptic seizure, followed by maintenance anticonvulsant therapy. Bilateral inguinal herniorraphy was performed during childhood. His intelligence quotient was 91 in the first grade of elementary school. After he graduated from junior high school, he admitted to an institution for people with social adjustment difficulties. He could run and throw a ball before the head injury. He had not undergone karyotype evaluation or endocrinologic treatment. An elder brother showed no abnormality.

The patient fell from a height of 3 m, and was admitted to an acute care hospital. He lost consciousness 30 min after the accident, recovering alertness 2 weeks later. Based on neurologic features and findings on comput-

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ed tomography, he was diagnosed with diffuse axonal injury. Two months later, he was transferred to our hospital for rehabilitation.

Physical examination

The patient was 186 cm tall and had gynecomastia, small undescended testes, atrophy of the intrinsic muscles of the hand, 30° flexion contractures of the knees, erythema in the region of the greater trochanters and lateral malleoli, and skin ulcers in the regions of the occiput and the sacrum. No axillary or pubic hair was seen. Neurologic examination disclosed reduced muscle tone as well as muscle weakness. His dermatoglyphic patterns were unusual. The total finger ridge count was 73, nearly 2 standard deviations (SD) below the mean for Japanese males [6], and both thumbs showed radial loop patterns (overall frequency, 0.4% on the left and 0.6% on the right among Japanese males [6]). He was alert and cooperative despite mental retardation. No aphasia, apraxia, or agnosia were identified. Cranial nerve function was intact. Muscle strength was assessed as grade 3 to 4 (fair to good), except for dorsiflexion of the right ankle which was grade 1 (trace). Active extension of all proximal interphalangeal (PIP) joints of the fingers was limited by 15° to 20° with passive extension being full (deformity reflecting weakness of the intrinsic hand muscles). Light touch and pinprick sensation were diminished in the ulnar side of the right hand and the dorsal aspect of the right foot. He showed adiadokokinesis and postural tremor of both hands. Deep tendon reflexes were diminished except for the right knee jerk and ankle jerk. A Babinski reflex was present on the right. He could maintain a sitting position without a backrest, but could not stand up or walk.

Laboratory studies

Laboratory testing revealed a 48,XXYY karyotype without mosaicism in 40 lymphocytes from peripheral blood (Fig. 1). The serum testosterone concentration was low (158 ng/dL; normal range, 320 to 1030 ng/dL). Routine chemistry test results and total blood counts were normal. Vitamin B_{12}, thyroid hormones (T3 and T4), thyroid stimulating hormone (TSH), estrone, estradiol, and estriol concentrations were all within the normal range.

Imaging studies

Magnetic resonance imaging (MRI) of the brain revealed bilateral subcortical lesions with high signal intensity in T2-weighted images and low signal intensity in T1-weighted images, as well as dilation of the lateral ventricles. Another abnormality found at the left cerebral peduncle with high signal intensity in T2-weighted images and

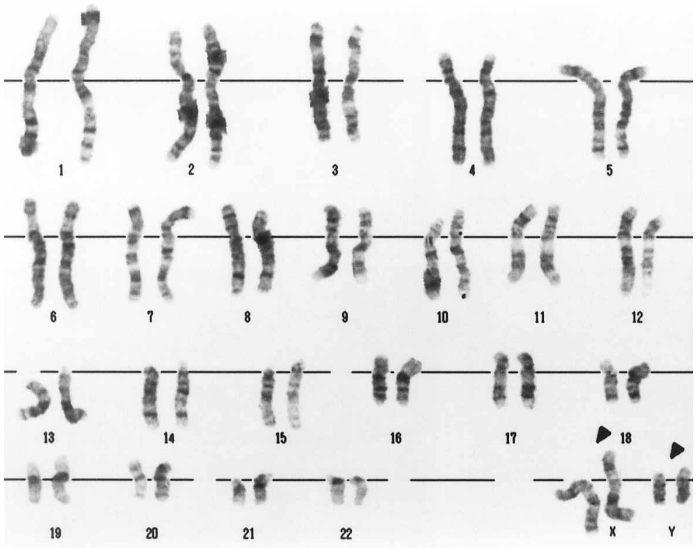

Fig. 1 The patient had a 48,XXYY karyotype.

intermediate signal intensity in T1-weighted images corresponded to Wallerian degeneration of the pyramidal tract. MRI of the cervical spine identified no cervical cord lesion. Radiographs of the cervical spine and extremities showed growth line in both radii, femora, and tibiae, but no fractures or areas of ectopic ossification. Measured ultrasonographically, testicular size was 19 × 14 × 10 mm on the right and 21 × 17 × 17 mm on the left.

Electrocardiography

Electrocardiography (ECG) showed horizontal ST depression in the leads of Ⅱ, Ⅲ, and aVF, indicating inferior wall myocardial ischemia.

Electrodiagnosis

Electrophysiologic studies were performed 3 weeks after admission using commercially available electromyographic apparatus (Viking Electrodiagnostic System; Nicolet, Madison, Wisconsin). Nerve conduction studies were performed using standard methods and latencies and velocities were compared with normative data from our laboratory (Table) [1]. The distal motor latencies of the both ulnar nerves were prolonged. The distal motor latency of the right median nerve was borderline. Decreases in motor conduction velocities were observed in the right median and ulnar nerves. The distal sensory latency of the right ulnar nerve was prolonged. Because no evoked potentials

Table Electrophysiologic evaluation of a patient with 48,XXYY syndrome including peripheral neuropathy

Nerve	Before treatment	During treatment	Normal range*
Median (right)			
Distal motor latency** (msec)	4.2	3.2	< 4.39
Motor conduction velocity (m/sec)			
Above elbow to wrist	45.7	56.5	> 49.4
Ulnar (right)			
Distal motor latency*** (msec)	5.2	3.2	< 3.44
Motor conduction velocity (m/sec)			
Below elbow to wrist	40.2	50.0	> 51.0
Above elbow to wrist	44.5	51.6	> 51.0
Distal sensory latency**** (msec)	3.9	2.6	< 3.0
Ulnar (left)			
Distal motor latency (msec)	3.7	3.8	< 3.44
Motor conduction velocity (m/sec)			
Below elbow to wrist	59.1	57.9	> 51.0
Above elbow to wrist	54.1	57.9	> 51.0
Peroneal (right)			
Distal motor latency***** (msec)	10.3		
Peroneal (left)			
Distal motor latency (msec)	8.1		

* Upper and lower limits were the mean ± 2 SD for the normative data from our laboratory.
** The distance between the recording electrode over the abductor pollicis brevis and the stimulating cathode was 7.0 cm.
*** The distance between the recording electrode over the abductor digiti minimi and the stimulating cathode was 7.0 cm.
**** The distance between the recording electrode over the little finger and the stimulating cathode was 14.0 cm.
***** The distance between the recording needle electrode in the tibialis anterior and the stimulating cathode at the fibular head was 8.0 cm.

were obtained from the surface electrodes overlying the right extensor digitorum brevis muscle upon stimulating the peroneal nerves, responses from the tibialis anterior muscles were recorded using concentric needle electrodes. The latency for the right peroneal nerve was longer than that for the left.

Electromyography (EMG) using a concentric needle electrode showed fibrillation potentials and positive sharp waves in the right tibialis anterior and peroneus brevis muscles. The interference pattern was decreased in the right tibialis anterior muscle, and no motor units were identified in the right peroneus brevis. A remarkable increase of polyphasic units was observed in all muscles examined except for the right peroneus brevis. These muscles included both first dorsal interossei, the right triceps brachii, the right gastrocnemius, and both tibialis anterior muscles. These findings were consistent with peripheral neuropathy.

Circulation studies

Plethysmography (Polygraph System, Nihon Kohden, Tokyo, Japan) and thermography (Infra-Eye, Nihon Kohden, Tokyo, Japan) were performed to evaluate peripheral vascular status 6 weeks after admission. While the patient was seated, pulse waves were recorded at the fingertips of each hand. The skin temperature of the volar aspect of the wrists, fingertips, anterodorsal aspect of the ankles, and toes were measured bilaterally. The findings are described together with those of posttreatment circulation studies in Figures 2 and 3. The resting pulse rate of the patient was uniform at 65/min, and the room temperature was maintained at 26 ℃ for each test.

Testosterone therapy

Testosterone enanthate (125 mg) was injected intramuscularly once weekly beginning at 7 weeks after admission, every 2 weeks beginning at 11 weeks, and every 3 weeks beginning at 15 weeks.

Clinical and laboratory course

Eight weeks after testosterone initiation, the patient showed the presence of pubic hair and improvement of muscle weakness, hypesthesia, joint contractures, and skin lesions. Limitation of active extension of the PIP joints was less than 5°, and muscle strength of dorsiflexion of the right ankle was grade 3 (fair). Strength of other muscles was graded as 4 (good). Light touch and pinprick sensation became normal on the ulnar side of the right hand, but still were diminished over the dorsal aspect of the right foot. Passive extension of the knees was limited, falling 15° short of the normal range. Erythema disappeared, and skin ulcers were nearly healed. The patient could walk using a cane and a short leg brace. At this time, serum concentrations of testosterone were 615 ng/dL; follicle stimulating hormone (FSH), 33.8 mU/mL (normal range, 1.8 to 13.6 mU/mL); and lutenizing hormone (LH), 19.5 mU/mL (normal range, 1.1 to 8.8 mU/mL). Electrocardiography showed disappearance of the previously noted ST depression.

The electrophysiologic evaluation was repeated following 9 weeks of treatment. On nerve conduction testing, distal motor latencies of the right median and ulnar nerves had decreased, motor conduction velocities of the right median and ulnar nerves had increased, and the distal sensory latency of the right ulnar nerve had decreased. Needle EMG studies showed a decrease in polyphasicity of motor unit action potentials recorded from both upper and lower extremities, and an increase in interference patterns of the right tibialis anterior muscle in comparison to the previous EMG. These findings indicated improvement of neuropathy.

Plethysmography and thermography repeated following 7 weeks of treatment revealed improvement of peripheral circulation. The average amplitude of five consecutive pulse waves in each fingertip was significantly higher during testosterone therapy than before (unpaired t test, $P < .05$; Fig. 2). The average skin temperatures of the five fingers or five toes were higher during testosterone therapy than before for each hand or foot (paired t test, $P < .05$). The skin temperatures of the left wrist and both ankles were higher during treatment than before, while skin temperatures before and during treatment were comparable in the right wrist. The average increase in skin temperature was 0.4 ℃ in the right fingers, 1.0 ℃ in the left fingers, 5.4 ℃ in the right toes, and 2.2 ℃ in the left toes (Fig. 3).

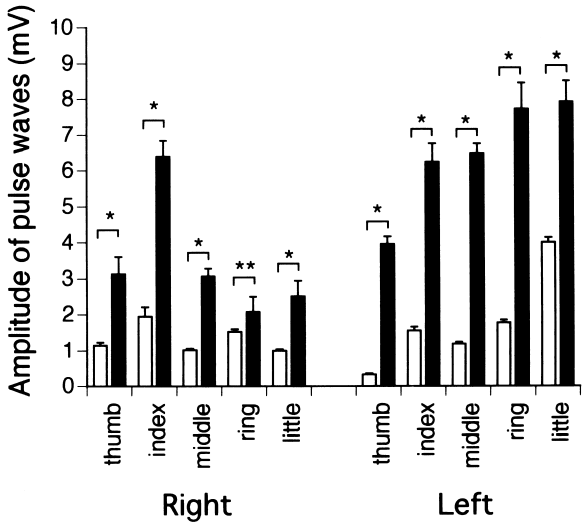

Fig. 2 Amplitudes of plethysmographic pulse waves recorded at individual fingertips. Each column with a vertical line indicates mean amplitude and SD either before (open) or during the testosterone therapy (black). *, $P < .001$; **, $P < .05$ (unpaired t test).

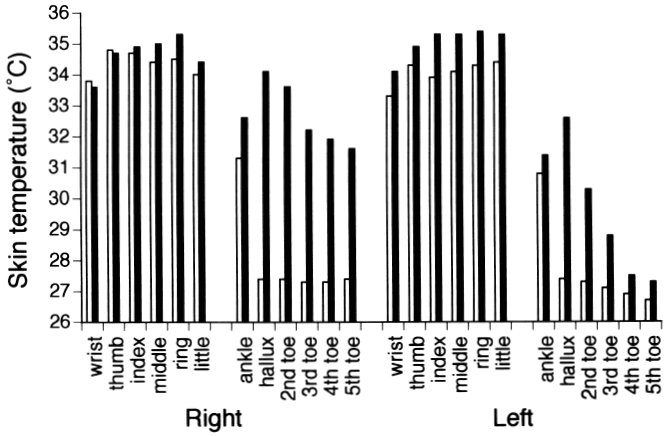

Fig. 3 Skin temperature at individual fingertips, wrists, toes, and ankles. Each column indicates mean temperature either before (open) or during the testosterone therapy (black).

DISCUSSION

Sixty-eight articles concerning 48,XXYY syndrome were found by searching through the Medline database from 1966 to March, 2000). More than 120 cases with this karyotype have been reported [3]. This is the first report of symptomatic peripheral neuropathy associated with 48,XXYY syndrome except for one study [10], in which one patient with X-linked Charcot-Marie-Tooth disease had this karyotype.

Clinically our patient had mononeuropathy multiplex involving the right ulnar nerve and the right peroneal nerve. However, nerve conduction studies and needle EMG revealed abnormalities in all extremities, and at least two nerves appeared to be involved in each limb on the right side. These electrophysiologic findings suggested subclinical polyneuropathy.

A histopathologic study of patients with

the 48,XXYY karyotype reported that arterioles and venules within the dermis exhibited moderate mural thickening consistent with the chronic stasis changes of vascular insufficiency [9]. Similarly, lack of male hormone in eunuchoid individuals reportedly resulted in a smaller vascular bed, and these changes were reversed by administration of male hormone [4].

Our patient showed multiple dermal lesions of stasis, including erythema and ulcers, and ECG findings of coronary ischemia. We presume that these changes preceded the patient's coma from head injury, although compression or other stresses related to unconsciousness may have exacerbated them.

After 2 months of testosterone therapy, we observed an increase in skin temperatures and amplitude of pulse waves in all extremities, and noted disappearance of ECG findings of coronary ischemia, indicating improvement of circulation.

Improvement of peripheral neuropathy also was demonstrated clinically and electrophysiologically. The improvement of nerve conductivity of the upper extremity was greater than one might expect from a one-degree rise of skin temperature [7]. Thus, we believe that a decrease in testosterone may produce peripheral neuropathy via a vascular disorder, and that both vascular changes and neuropathy were reversed in this patient by administration of testosterone.

The patient had not experienced a foot-drop before the accident, and we suspect that compression during coma-related immobility may have been responsible for the right peroneal nerve palsy. Nerves affected by a systemic illness, for example diabetes, are known to show increased susceptibility to chronic compression damage [2, 11]. Thus, vascular insufficiency and subclinical peripheral neuropathy could represent predisposing factors for compression damage, resulting in right peroneal palsy.

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