

[CASE REPORT]

A Rare Case of Klinefelter Syndrome Accompanied by Spastic Paraplegia and Peripheral Neuropathy

Ryo Sasaki, Yasuyuki Ohta, Yoshiaki Takahashi, Keiichiro Tsunoda, Koh Tadokoro, Kota Sato, Jingwei Shang, Mami Takemoto, Nozomi Hishikawa, Toru Yamashita and Koji Abe

Abstract:

Klinefelter syndrome is a chromosomal disorder with a typical karyotype of 47, XXY, accompanied by various neurological symptoms. We herein report the first case of Klinefelter syndrome with a rare mosaic form of 47, XXY and 48, XXXY, combined with both spastic paraplegia and peripheral motor neuropathy. This case showed spasticity and hyperreflexia with pathological reflexes and ankle clonus as well as muscle weakness in all extremities. A motor nerve conduction study and the magnetic motor evoked potential suggested motor axonal neuropathy and corticospinal tract disorders. The present case suggests that Klinefelter syndrome can present with both upper and lower motor neuron degeneration.

Key words: Klinefelter syndrome, mosaic form, peripheral neuropathy, spastic paraplegia

(Intern Med 58: 437-440, 2019)

(DOI: 10.2169/internalmedicine.1048-18)

Introduction

Klinefelter syndrome is a chromosomal disorder with an X-chromosome added to a normal karyotype 46, XY. The typical karyotype of Klinefelter syndrome is 47, XXY, but other karyotypes have also been reported, such as 48, XXXY; 48, XXYY; 49, XXXXY and the mosaic form variants (46, XY/47, XXY and 48, XXXY/49, XXXXY) (1). Patients with Klinefelter syndrome usually present with small testes, gynecomastia, hypergonadotropic hypogonadism and neurological symptoms, such as mental retardation and intellectual disability. However, spastic paraplegia and peripheral neuropathy have so far only rarely been reported.

We herein report a rare case of Klinefelter syndrome (47, XXY/48, XXXY mosaic form) accompanied by both spastic paraplegia and peripheral neuropathy.

Case Report

A 10-year-old boy was diagnosed with mental retardation without a family history of neurological disease. He lived in

a handicapped facility for 45 years but showed no motor disabilities. However, he developed mild muscle weakness at 55 years of age in his right upper and lower extremities (U/E and L/E, respectively) and showed difficulties writing and walking. After a year, his muscle weakness had progressed, and he could no longer raise his right arm or stand alone. He visited a local hospital and showed spasticity and muscle weakness in all extremities (A/E, R>L) and bilateral gynecomastia. Four months later, he was admitted to our hospital for a further examination.

He was 156 cm tall and weighed 52 kg. He showed a childish face (Figure A), feminine voice, bilateral gynecomastia (Figure B), arrowheads), micropenis (Figure C), 5 cm from the pubis), no palpable left testis (Figure C), black arrowhead) and sexual perversion. A neurological examination showed muscle weakness (R>L, distal>proximal), spasticity and hyperreflexia in A/E with bilateral pathological reflexes (snout, Hoffmann, Trömner, Wartenberg, Babinski and Chaddock) and bilateral ankle clonus. His full-scale intelligence quotient (FSIQ) had decreased to 61 (average: 90-110). A serum analysis showed an elevated erythrocyte sedimentation rate (56/89 mm for 1/2 h). A pituitary hormone analysis showed a low testosterone level (0.5 ng/mL, normal

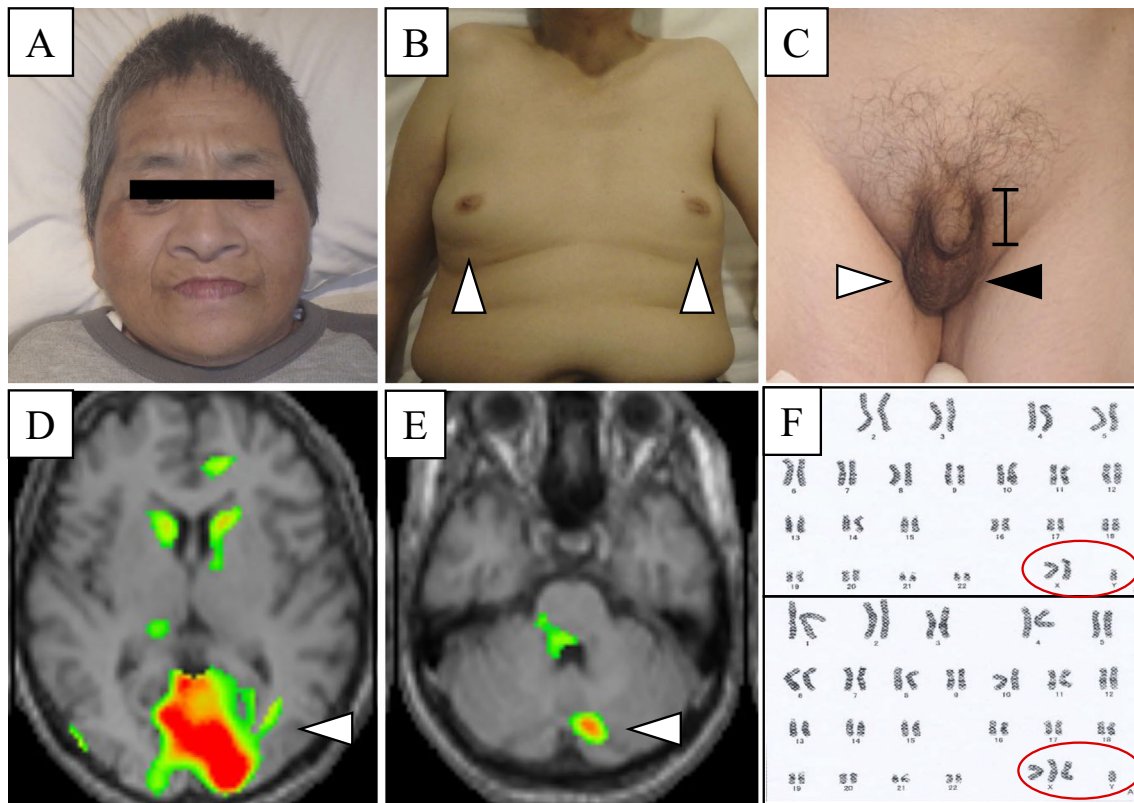


Figure. (A) The childish face of the present case. (B) Bilateral gynecomastia (arrowheads) in the present case. (C) Micropenis (bar), right normal testis (white arrowhead) and empty left scrotum (black arrowhead) in the present case. (D, E) ^{99m}Tc -ECD-SPECT showing hypoperfusion in the bilateral occipital lobe (D, arrowhead) and cerebellum (E, arrowhead). (F) A chromosome analysis showing mosaic form of 47, XXY/48, XXXY. ^{99m}Tc -ECD-SPECT: ^{99m}Tc -ethylcysteinate dimer single-photon emission computed tomography

range 2.0-7.5 ng/mL) and high levels of FSH (63.7 mIU/mL, normal range 2.0-8.3 mIU/mL) and LH (32.9 mIU/mL, normal range 0.8-5.7 mIU/mL). The findings of a cerebrospinal fluid test were normal. Chest and abdominal computed tomography (CT) showed muscle atrophy of A/E and left cryptorchidism (data not shown), but head magnetic resonance imaging (MRI) showed a normal pituitary with no remarkable changes. ^{99m}Tc -ethylcysteinate dimer single-photon emission computed tomography (^{99m}Tc -ECD-SPECT) showed hypoperfusion in the bilateral occipital lobe (Figure D), arrowhead) and cerebellum (Figure E), arrowhead). A motor nerve conduction study showed a low amplitude (1.4 mV, normal >5.5 mV) and normal nerve conduction velocity in the right ulnar nerve. Sensory nerve conduction of the right ulnar nerve were normal, but an F wave was not derived. The magnetic motor evoked potential (MEP) showed no derivation on right scalp stimulation. A chromosome analysis showed a mosaic form of 47, XXY (2/30 cells) (Figure F), upper panel) and 48, XXXY (20/30 cells) (Figure F), lower panel), which suggested Klinefelter syndrome.

The patient was ultimately diagnosed with Klinefelter syndrome accompanied by spastic paraplegia and motor axonal neuropathy. He was scheduled to have his undescended

left testis removed from his abdominal cavity in order to prevent testicular cancer and was moved to a local hospital for the surgical operation and follow-up.

Discussion

The present case showed pyramidal signs, including spasticity and hyperreflexia with pathological reflexes and ankle clonus, as well as muscle weakness in A/E (R>L), mental retardation, a childish face (Figure A), feminine voice, bilateral gynecomastia (Figure B), arrowheads) and micropenis (Figure C). His testosterone level was low (0.5 ng/mL) and his FSH and LH levels were high (FSH 63.7 mIU/mL and LH 32.9 mIU/mL). A motor nerve conduction study of the right ulnar nerve suggested motor axonal neuropathy, and an MEP analysis suggested corticospinal tract disorders. Based on the chromosome analysis finding of a mosaic form of 47, XXY (2/30 cell) and 48, XXXY (20/30 cell), he was diagnosed with Klinefelter syndrome (Figure F) accompanied by both spastic paraplegia and motor axonal neuropathy.

Klinefelter syndrome is a genetic condition characterized by extra copies of the X chromosome. These extra copies of the X chromosome result in small testicles and a low production of testosterone, which cause various symptoms, in-

Table. Previous Reports of Klinefelter Syndrome Accompanied with Neuropathy or Spasticity.

Reference	Age	Symptom	Other
9	29y.o.	Spasticity, hyperreflexia, muscle atrophy and weakness in L/E	47XXY Muscle biopsy showed neurogenic changes
6	25y.o.	Peripheral neuropathy	48XXYY
10	5y.o.	Spastic paraplegia	47XXY Family history (+)
7	50y.o.	Sensorimotor polyneuropathy	47XXY Symptom was symmetric
Present case	56y.o.	Spastic paraplegia Peripheral neuropathy	47XXY/48XXXY mosaic form

cluding a tall stature, gynecomastia, small testes, decreased verbal intelligence and increased risks of various complications, such as diabetes mellitus, hypothyroidism, osteoporosis and cryptorchidism (2). The typical karyotype of Klinefelter syndrome is 47, XXY. Newborn screening studies have shown the incidence rate of 47, XXY to be 1:650 in male infants (3). Other karyotype forms of Klinefelter syndrome, such as 48, XXYY, 48, XXXY and 49, XXXXY, are rare, occurring at a rate of 1: 50000 in male infants, and rare mosaic forms of different karyotype combinations, as in the present case (47, XXY and 48, XXXY) (Figure F), have also been reported (4).

In the present study, we counted the chromosomes using the Giemsa-banding method (G-band method) with a commercial test kit (SRL, Tokyo, Japan). However, in the G-band method, it is difficult to detect small chromosomes shorter than 5 Mb (5). Thus, there is a possibility that the technician might miscount small chromosomes. Furthermore, the G-band method sometimes shows variation in measurements due to technicians' skills, as they must count chromosomes under visual observation, allowing for human error. Other chromosome count methods, such as single-cell sequencing or multiplex multicolor banding, can analyze small (≤ 500 kb in size) chromosomes mechanically. To determine how to achieve the most accurate chromosome count, a further examination will be needed.

Previous reports have described only two cases of Klinefelter syndrome accompanied by neuropathy (Table) (6, 7), probably due to testosterone deficiency. A previous report showed that the extra copies of the X chromosome disturb testosterone synthesis, reducing the number of NOS-containing nerve fibers and hampering the nerve functions (8). Testosterone deficiency also induces diabetes mellitus and hypothyroidism, accompanied by peripheral neuropathy. However, the present case did not have diabetes mellitus or hypothyroidism. Furthermore, there have only been two cases of Klinefelter syndrome accompanied by both spastic paraplegia and motor neuropathy (9, 10). These cases suggest a relationship between upper and lower motor neuron degeneration and the extra X chromosome in Klinefelter syndrome.

We considered the possibility of several major hereditary spastic paraplegias (SPGs), such as SPG3A, SPG4 and SPG

31, but they usually show a pure form of SPG, presenting only with spasticity. The present case may have involved the complicated form of SPG, presenting with several other symptoms in addition to spasticity. However, to our knowledge, no types of hereditary SPG clearly matched the present case, which was accompanied by peripheral neuropathy and mental retardation without cerebellar ataxia or brain MRI abnormalities. Therefore, based on our review of previous reports of Klinefelter syndrome, we suspected the present case to be one of Klinefelter syndrome accompanied by SPG and peripheral neuropathy. However, we did not perform an exome analysis in the present case, which was the main limitation of this case report. Further examinations will be needed to rule out potential comorbid gene mutations.

We herein report the first case of Klinefelter syndrome with a rare mosaic form of 47, XXY and 48, XXXY, combined with spastic paraplegia and motor axonal neuropathy. The present case suggests that Klinefelter syndrome can present with both upper and lower motor neuron degeneration.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This work was partly supported by a Grant-in-Aid for Scientific Research (B) 17H0419619, (C) 15K0931607, 17H0419619 and 17K1082709 and by Grants-in-Aid from the Research Committees (Kaji R, Toba K, and Tsuji S) from the Japan Agency for Medical Research and Development (AMED).

Acknowledgement

We appreciate the cooperation of the patient.

References

- Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* **364**: 273-283, 2004.
- Frühmesser A, Kotzot D. Chromosomal variants in Klinefelter syndrome. *Sex Dev* **5**: 109-123, 2011.
- Tartaglia N, Ayari N, Howell S, D'Epagnier C, Zeitler P. 48, XXYY, 48, XXXY and 49, XXXXY syndromes: not just variants of Klinefelter syndrome. *Acta Paediatr* **100**: 851-860, 2011.
- Jesus ED, Maribel A, Eliakym A, et al. 47,XXY/48,XXXY/49, XXXXY mosaic with hydrocephaly. *J Med Case Rep* **1**: 94, 2007.
- Bakker B, van den, Bos H, Lansdorp PM, Foijer F. How to count chromosomes in a cell: an overview of current and novel technolo-

- gies. *Bioessays* **37**: 570-577, 2015.
6. Izumi S, Tsubahara A. Improvement of peripheral neuropathy by testosterone in a patient with 48,XXYY syndrome. *Tokai J Exp Clin Med* **25**: 39-44, 2000.
 7. Kararizou E, Mentis AF, Gkiatas K, Davaki P. Rare association of sensorimotor polyneuropathy and Klinefelter syndrome (47,XXY). *Med Princ Pract* **20**: 480-482, 2011.
 8. Traish AM, Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. *J Sex Med* **3**: 382-407, 2006.
 9. Matsubara S, Yoshino M, Takamori M. Benign neurogenic amyotrophy in Klinefelter's syndrome. *J Neurol Neurosurg Psychiatry* **57**: 640-642, 1994.
 10. Uzicanin S, Catibusic F, Terzic S, Zubcevic S. Familiar spastic paraplegia presenting in a boy with Klinefelter syndrome. *Med Arh* **61**: 52-53, 2007.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

© 2019 The Japanese Society of Internal Medicine
Intern Med 58: 437-440, 2019