Rare Association of Sensorimotor Polyneuropathy and Klinefelter Syndrome (47,XXY): Case Report

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Introduction

Klinefelter syndrome refers to a group of chromosomal disorders in which there is at least an extra X-chromosome added to a normal karyotype 46,XY. However, the classic form of this syndrome is the one in which there is only an extra copy of the X-chromosome, resulting in the karyotype XXY. Other forms include 48,XXYY, 48,XXXY and 49,XXXXY [1]. The diagnosis is usually made during adolescence or early adulthood in males presenting with small testes with gynecomastia and hypergonadotropic hypogonadism. Characteristics of these syndromes are: infertility, small testes, decreased facial hair, gynecomastia, decreased pubic hair, a small penis and a tall body habitus. In parallel with this, in adulthood they present with loss of libido, decreased muscle bulk and tone, and an increased risk of mortality from diabetic complications [1, 2].

Neurological characteristics include: language-based learning disorders (80%), difficulties with planning and inhibitory control, deficits in short-term auditory memory and auditory processing, as well as motor delay with truncal hypotonia and motor planning deficits [3].

Here, we present the case of a patient diagnosed with Klinefelter syndrome (47,XXY) that was associated with polyneuropathy.

Case Report

A 50-year-old man referred to the Neurology Clinic, Athens University, complained of pain, numbness and tingles in both sides distally in the feet, which had commenced 10 years prior to admission. A progressive expansion of the inferior surface of the...
Klinefelter Syndrome

Sensorimotor Polyneuropathy and Complete Laboratory Investigations – were excluded by several appropriate clinical and serological examination were normal. There were no cranial abnormalities. All other aspects of the neurological examination were normal.

Other causes of peripheral neuropathy – such as diabetes, sarcoidosis, leprosy, malignancy, connective tissue disease, toxic exposure, nutritional deficiency and family history of neuromuscular disorders – were excluded by several appropriate clinical and laboratory investigations.

Routine hematological tests and chest X-ray were normal. Complete serological tests – including erythrocyte sedimentation rate, C-reactive protein, complement 3, complement 4, anti-nuclear antibodies, anti-DNA antibodies, rheumatic factor, cryoglobulin and immunoelectrophoresis – were obtained and found to be normal. Serum and urine specimens were tested for monoclonal protein. Serum immunofixation electrophoresis was normal. Serum antibodies to myelin-associated glycoprotein, GMI and GQ1b were not present. Glucose, glycosylated hemoglobin, 2-hour oral glucose tolerance test and laboratory investigations of CSF were normal. The CSF Venereal Disease Research Laboratory testing and Western blot for Lyme disease were negative. Only thyroid-stimulating hormone (TSH) values were altered in the first measurement, but this was not confirmed in consecutive measurements. The thyroid gland was not palpable, and the patient was clinically euthyroid. Additionally, the ultrasound of the thyroid gland was normal.

Electromyography was performed. Nerve conduction studies showed mildly decreased motor and sensory conduction velocities, with significantly reduced amplitude of the motor and sensory compound action potentials, without block or dispersion. There was electromyographic evidence of chronic denervation and signs of active denervation. On the basis of these results, a diagnosis of sensorimotor axonal polyneuropathy was made.

Biopsy of the sural nerve was performed. Histology revealed fiber loss. Axonal degeneration was the predominant feature. The immunohistochemical study was negative to antihuman polyclonal antibodies (IgA, IgG, IgM), C3 and fibrinogen. Morphometric study revealed significant loss of myelinated fibers (2,433 ± 1,245). The mean axonal diameter was decreased (2.87 ± 0.93 μm). The g ratio was markedly decreased (0.42 ± 0.11) and supported the histopathological findings of mainly axonal involvement. The histograms of fiber diameter distributions showed damage to all diameter fibers.

Discussion

We report the clinical case of a patient with diagnosed Klinefelter syndrome who was also affected by symmetrical sensorimotor polyneuropathy. Klinefelter syndrome is the most common sex chromosome disorder, and is usually associated with autoimmune diseases, osteoporosis, primary hypothyroidism, diabetes mellitus, breast and prostate cancer, and leukemia. Polyneuropathy may represent a potentially hypogonadal complication of Klinefelter syndrome or alternatively could be a coexisting morbidity. A previous study [4] has shown that hypogonadal men with diabetes mellitus and diabetic foot neuropathy clinically improved following administration of testosterone. However, testosterone deficiency may have adverse effects on nerves other than the cavernosal nerve, as Traish et al. [5] showed that castration reduced NOS-containing nerve fibers, innervating corpus cavernosum tissue, and lead to reduced thickness of the nerve sheath of the cavernosal nerve in castrated animals. Unfortunately, our patient was initially on testosterone therapy, but decided to stop because it made him aggressive.

Moreover, three diseases in which hypogonadism is present have been linked in case reports with polyneuropathy: (1) Rud syndrome linked with hypogonadism, mental retardation, retinitis pigmentosa and hypertrophic polyneuropathy [6]; (2) Möbius sequence connected with axonal peripheral neuropathy and hypogonadotropic hypogonadism, in which administration of pulsatile gonadotropin-releasing hormone led to alleviation of the symptoms [7], and (3) familial cerebellar ataxia associated with hypogonadism and sensorimotor axonal neuropathy [8].

Nevertheless, the neuropathy presented could potentially be linked to another cause known to cause such a clinical entity. Among the causes we have found in the literature, both diabetes mellitus and thyroid dysfunction are related to Klinefelter syndrome. In fact, approximately 40% of people with Klinefelter syndrome have had a diabetic glucose tolerance test [1]. However, all diabetes-related tests were normal in our patient, ruling out the possibility of diabetes-induced neuropathy. We have dis-
cussed and investigated all the possible causes of poly-
neuropathy, and seen that diabetes is a more frequent fac-
tor which may be a complication of Klinefelter syndrome.

The relationship of our study to the others cited here
was explained at the beginning of this section. Parallel to
this, it has recently been observed that men with Kline-
felter syndrome have lower values of free T4 and lower
free T4:free T3 ratios, even in the absence of differences
in TSH, free T3, TSH:T4 ratios, thyroid volumes, or the
prevalence of thyroid antibodies [8]. However, despite the
lack of assessment of thyroid antibodies and free levels of
hormones in our client, thyroid disease could be more or
less excluded [9].

Matsubara et al. [10] described benign neurogenic
amyotrophy in a patient with Klinefelter syndrome as an
independent type of motor neuron disease, and suggested
that the X-chromosome plays an important part in the
biology of motor neurons.

Klinefelter syndrome tends to be associated with auto-
immune diseases and especially with connective tissue
disorders [11]. Nevertheless, our extensive clinical exami-
nation and complete serological tests, as well as the find-
ings from the nerve biopsy, were negative for systemic
autoimmune connective tissue disease.

Another cause could be vasculitis, which has been
linked with Klinefelter syndrome in a single case report
[12]. However, were this the case, the biopsy would have
been expected to present evidence of vasculitis or nerve
ischemia.

Conclusion

This report showed a patient with diagnosed Klinefel-
ter syndrome, in whom symmetrical sensorimotor poly-
neuropathy developed in late adulthood.

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