Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Phenomenology of Tremor In 48,XXYY Syndrome: A Case Report

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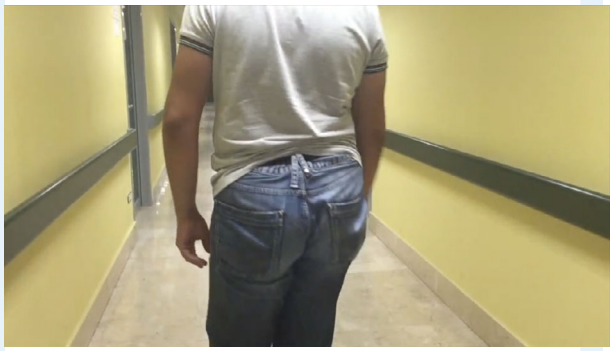
Action tremor may occur in the context of sex chromosome aneuploidies, such as Klinefelter syndrome.[1] Here, we provide an accurate clinical videotaped description of the phenomenology of tremor in a man with 48,XXYY syndrome,[2] a rare sex chromosome aneuploidy.[3]

Case Report

A 36-year-old with 48,XXYY syndrome was referred to our attention because of an action tremor in the upper limbs, which started at around age 30.

He was the product of a normal pregnancy and delivery and had delayed motor and cognitive milestones. Since childhood, he had behavioral disturbances characterized by social inhibition, introversion, apathy, as well as epileptic seizures treated with phenobarbital. He had intellectual disability and completed primary school with a support teacher. The diagnosis of 48,XXYY syndrome had been made in childhood by karyotype analysis, and he had been treated with testosterone since then. The tremor appeared in the left hand a few years before our consultation and subsequently mildly involved the right hand. The tremor impacted particularly on pouring water, holding a cup, and using cutlery. There was no alcohol responsiveness.

At physical examination, he had several facial dysmorphic features, including hypertelorism, low frontalis hairline, flattened occiput, and strabismus. His height was 185 cm. On neurological examination (Video 1), he had preserved arms swing and mild steppage of the left foot when walking. In the outstretched arms position, he could not completely extend the left arm, and he had involuntary abduction of the fingers of the left hand. He had postural and intention tremor of the upper limbs, mild on the right and moderate on the left upper limb. When writing, he had posturing of the right hand characterized by ulnar extension of the wrist. He could not write with the left hand because of the tremor and inability to hold the pen. There was no rigidity or bradykinesia. Deep tendon reflexes were globally brisk. He did not have any abnormality of sensation and strength was preserved in all body districts.



Video 1. The video shows normal stride length, velocity, and preserved arm swing when walking, with some steppage of the left foot more evident when turning. In the outstretched arm position, an asymmetrical postural tremor is evident, more prominent in the left upper limb. Incomplete extension of the left arm and involuntary abduction of the fingers of the left hand is also demonstrated. Posturing of the right hand when writing characterized by ulnar extension of the wrist is shown. While holding the pen with the left hand, abnormal posturing is evident, preventing the drawing of a spiral
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13639

Brain magnetic resonance imaging showed multiple white matter abnormalities in the periventricular zone, semi oval center, and left internal capsule. Propranolol was contraindicated because of bradycardia. Clonazepam at a dose of 0.5 mg daily determined some subjective improvement of tremor.

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TABLE 1 *Treatment of 48,XXYY associated tremor: review of published cases*

Reference	Phenomenology	Additional neurological signs	Treatment	Outcome of treatment on tremor
Tartaglia et al[3]	NA	NA	Propanolol	NA
Tartaglia et al[3]	NA	NA	Propanolol	NA
Tartaglia et al[3]	NA	NA	Amantadine	NA
Tartaglia et al[3]	NA	NA	Primidone	NA
Tartaglia et al[2]	Postural and kinetic tremor	One step deviation on tandem gait, gaze-evoked nystagmus, mild dysarthria	Atenolol, 10 mg daily; primidone, propranolol, 40 mg daily	Atenolol and primidone stopped because of side effects; some improvement by propanolol
Tartaglia et al[2]	Postural and kinetic tremor of the UL; postural tongue tremor	Saccadic ocular pursuits	None	–
Tartaglia et al[2]	Postural and kinetic tremor	Widened stance	None	–
Lote et al[5]	Postural and intention tremor	Nystagmus and broken-up pursuits	Propranolol, primidone, topiramate, mirtazapine	No improvement
Katulanda et al[8]	Intention tremor	–	No medication	–
Our case	Postural and intention tremor	Subtle dystonic signs	Clonazepam, 0.5 mg daily	Mild subjective Improvement

Abbreviations: NA, not available; UL, upper limbs.

Discussion

This is a man with 48,XXYY syndrome and action tremor associated to subtle ("soft")[4] dystonic features, other neurological signs (intellectual disability, behavioral disturbances, and epilepsy), and systemic signs (facial dysmorphism, hypergonadotropic hypogonadism, and tall stature). We believe the tremor is part of the clinical spectrum of 48,XXYY. This syndrome is a rare aneuploidy, occurring in 1:18.000–1:40.000 males,[1,3,5,6] caused by a double meiotic non-disjunction of sexual chromosomes during spermatogenesis.[5]

The manifestations of 48,XXYY syndrome involves neurodevelopmental delay, facial dysmorphisms, hypergonadotropic hypogonadism, infertility, tall stature, asthma, dental abnormalities, cognitive impairment, cardiac abnormalities, radioulnar synostosis, psychiatric disturbances, and neurological symptoms. White matter hyperintensities are described in up to 46% of patients.[1]

Tremor may occur in the context of sex chromosome aneuploidies, often manifesting as postural or intention tremor, which usually involves the upper limbs and rarely the voice and jaw.[1] This tremor has been often described in the literature as an essential tremor. Yet, these subjects have other neurological signs or systemic features or asymmetry of tremor, which are inconsistent with such diagnostic category.[1] The sex chromosome aneuploidy that more often displays tremor is Klinefelter Syndrome, in which dystonic posturing on the same body district of tremor or dystonic movements in other body districts have been reported.[7]

Action tremor has been also described in 48,XXYY syndrome.[2,3,5,8] Interestingly, in two subjects the clinical feature that triggered genetic testing for 48,XXYY was tremor, respectively, in childhood[3] and early adulthood.[5] In the largest cohort of patients with 48,XXYY (n = 95), tremor onset usually occurred in adolescence (in 8% under age 10, in 62% in the age range 11–19 and in 71% of those ages over 20 years).[3] In the same study, the most frequently described phenomenology was isolated intention tremor.[3]

Our case suggests that, on detailed neurological examination, subtle dystonia might be associated to action tremor and other neurological signs[5] in 48,XXYY. Indeed, on reviewing the videos of the 3 published cases[2] available in the MDS video library, case 3 shows dystonic posturing of the fingers of both hands, which is not described in the text (https://www.movementdisorders.org/MDS/Resources/Videos/Video-Library.htm). In the same study, all subjects had tremor combined with other neurological signs, such as saccadic pursuits, widened stance, or difficulties on tandem gait.

We acknowledge a few limitations when interpreting the origin of tremor in this subject with 48,XXYY. Electrophysiological testing has not been performed to rule out the presence of peripheral nerve involvement. However, because his deep tendon reflexes were brisk and he had normal sensation, it is unlikely that he had

neuropathic tremor. Additionally, it is unlikely for phenobarbital to be a cause for tremor, because no associations have been reported so far.[9] Moreover, testosterone administration has been reported to improve tremor in Klinefelter's syndrome.[10]

There is also little evidence on treatment of tremor in 48,XXYY (Table 1). Propranolol has been used[2,3,5] with improvement in one case.[2] In one single subject, primidone, topiramate, atenolol, and mirtazapine have not shown any results.[2] In two cases from the largest cohort of 48,XXYY, amantadine and primidone have been used for tremor, but the outcome was not described.[3]

The mechanism of tremor in 48,XXYY might relate to gene dosage effect of X chromosomes. Indeed, there are a few genes related to tremor expressed on X chromosome, such as FMR1 gene, responsible for FXTAS.[2]

In conclusion, this case report adds knowledge to the phenomenology of tremor in 48,XXYY syndrome and supports the view that tremor might be a manifestation of sex chromosome aneuploidies. Finally, our case points out, once again, the importance of an accurate clinical assessment in people with tremor, including careful assessment of systemic features, to reach a correct etiological diagnosis.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution. (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique. (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

S.M.C.: 1C, 3A, 3B

F.M.: 1A, 1B, 1C, 3B

Disclosures

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