

48, XXYY syndrome associated tremor

Hazel Lote,¹ Geraint N Fuller,² Peter G Bain¹

¹Department of Neurosciences, Imperial College London, Charing Cross Hospital Campus, London, UK

²Department of Neurology, Gloucester Royal Infirmary, Gloucester, UK

Correspondence to

Dr Peter G Bain, Department of Neurosciences, Imperial College London, Charing Cross Hospital Campus, London W6 8RF, UK; p.bain@imperial.ac.uk

Received 27 September 2012

Revised 4 January 2013

Accepted 28 January 2013

ABSTRACT

48, XXYY syndrome is a form of sex chromosome aneuploidy that affects between 1 in 18 000 to 1 in 40 000 males. It is not inherited and is diagnosed by karyotyping. It has similarities to 47, XXY Klinefelter's syndrome, with tall stature, micro-orchidism, hypergonadotropic hypogonadism and infertility in males. However, patients with 48, XXYY syndrome also commonly have dental problems, tremor, attention deficit disorder, learning difficulties, allergies and asthma. The tremor is typically reported as an intention tremor (in 71% of patients XXYY aged >20 years with 48), which becomes more common with age and worsens over time.

INTRODUCTION

48, XXYY syndrome is a sex chromosome aneuploidy affecting around 1 in 18 000 to 1 in 40 000 males.¹ Since its first description in 1964, there have been around 200 patients reported in the literature. The phenotype includes tall stature, hypergonadotropic hypogonadism and micro-orchidism.² This report aims to bring the syndrome to the attention of neurologists and to prompt genetic testing in male patients presenting with tremor at a young age, particularly when it is associated with tall stature, learning or behavioural disorders and dental problems. We also further characterise the action tremor seen in 48, XXYY patients.

CASE REPORT

A 22-year-old man first noticed a tremor when aged 17 years. He was referred to a neurologist when aged 19 years, for management of his tremor, which affected both hands and had worsened with age (although it did not spread). It occurred on action and improved with rest. The tremor progressed, causing his handwriting to become shaky (figure 1A) and he required two hands to drink from a cup. He had no difficulty walking or running. Neither alcohol, nor treatment with

propranolol, primidone, topiramate or gabapentin had reduced the tremor.

He had experienced learning difficulties at school, needing support to help with reading and writing. He subsequently attained a vocational qualification in Agriculture and Land Based Operations. He had an episode of depression needing psychological support aged 20 years.

He had marked hypermetropia. His sexual function was normal but he needed to shave his facial hair only about twice per month.

He had three brothers, including one with epilepsy and learning disability. His maternal grandfather developed tremor late in life.

On examination, he was anxious, 6 ft 2 ins (188 cm) tall with a slightly long face, epicanthal folds and poor dentition. There were a few beats of nystagmus on extreme rightwards gaze and also moderately broken-up smooth pursuit eye movements. He had a proximal and distal postural tremor (grade 2/10)³ and intention tremor (grade 3/10) in both arms but no rest tremor. On spiral drawing he demonstrated a grade 3/10 tremor (figure 1B). His gait and heel-toe walking were normal, with natural arm swing. There was pes planus. Testicular volume was 6 ml but the genitalia were otherwise normal.

The differential diagnosis for an upper limb action tremor in a young man includes: hyperthyroidism, drugs or drug/alcohol withdrawal states, essential tremor, dystonic tremor, spinocerebellar ataxia (SCA-12 and SCA-14), neuropathic tremor, Kennedy's syndrome (X linked bulbospinal muscular atrophy), hereditary spastic paraplegia (SPG-11), Wilson's disease, psychogenic tremor and sex chromosome aneuploidy.

Serum copper, serum caeruloplasmin, thyroid function, plasma glucose, glycosylated haemoglobin, serum calcium and phosphate were normal.

To cite: Lote H, Fuller GN, Bain PG. *Practical Neurology* Published Online First: [please include Day Month Year] doi:10.1136/practneurol-2012-000438

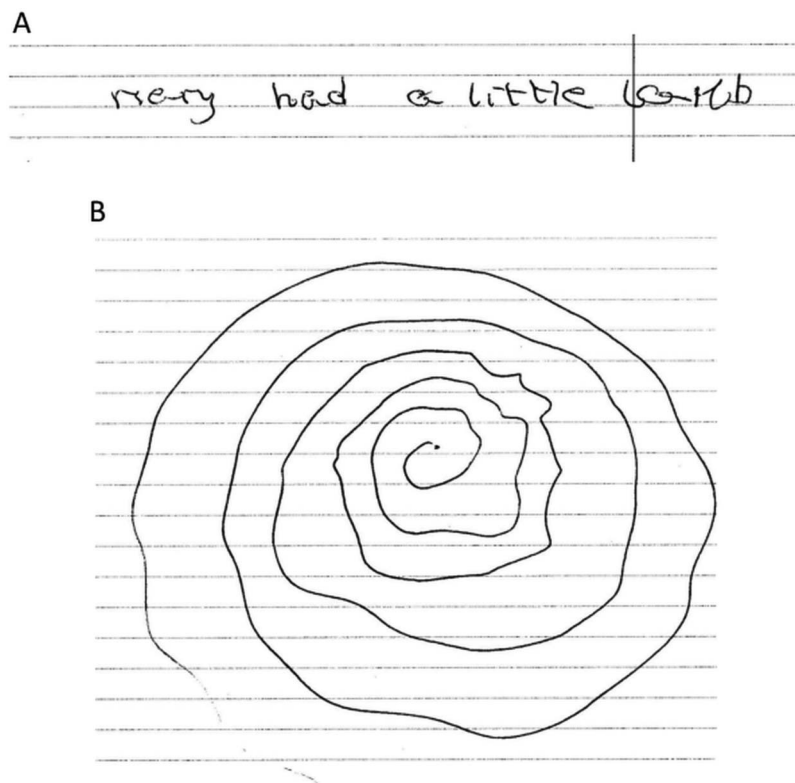


Figure 1 (A) Normal sized handwriting with slight tremor in the letters. (B) A spiral drawing showing an action tremor, which changes axis and has a wavy rather than a sawtooth appearance (maximum severity: grade 3/10).³

A blood sample sent for genetic analysis, initially to exclude fragile-X tremor/ataxia syndrome, showed 48, XXYY by karyotyping.

Further investigations showed a normal 9:00 plasma testosterone (18.1 nmol/l (9.0–35.0)). However, plasma luteinising hormone was raised at 17.8 IU/l (1.0–10.0) and plasma follicle-stimulating hormone was also elevated at 23.8 U/l (1.0–7.0). Sex-hormone binding globulin and oestradiol levels were normal.

Serum cholecalciferol (vitamin D3) was low at 35.3 nmol/l (60–105) and a bone densitometry scan showed lumbar spine and right hip bone mineral density within the osteopenic range. ECG and echocardiogram were normal.

Surface electromyography from the wrist flexors and extensors showed segregated 5–7 Hz bursts on posture and intention but not at rest. The signal activity was not consistently coherent across contralateral or ipsilateral muscle groups (figure 2).

A ¹²³I-FP-CIT single-photon emission CT scan (DaTSCAN) was normal (figure 3). A MR brain scan showed normal basal ganglia and cerebellum (figure 4) but mild periventricular hyperintensity and non-specific small periventricular white matter lesions around the right ventricle. There was an incidental Rathke's cleft cyst.

Formal neuropsychological evaluation showed an increased anxiety (hospital anxiety and depression scale), average memory but borderline performance

on all Wechsler Adult Intelligence Scale-IV indices. His executive function was intact apart from difficulty with higher level attentional cognitive flexibility tasks.

He was started on mirtazapine 15 mg daily, helping his anxiety but not the tremor.

He received counselling regarding infertility and was advised that in vitro fertilisation would be needed for him to have children.

DISCUSSION

48, XXYY syndrome is a rare sex chromosome aneuploidy typically caused by a double non-disjunction during meiosis in spermatogenesis, and as a result the extra chromosomes are usually paternal. However, occasionally this can also result from non-disjunction of the sex chromosomes in a 46, XY embryo very shortly after fertilisation.⁴

This syndrome was initially considered part of 47, XXY Klinefelter's syndrome, as both shared a common phenotype of tall stature, hypergonadotropic hypogonadism and micro-orchidism. However, it became apparent that 48, XXYY syndrome is more severe, with additional clinical, neurodevelopmental and behavioural features.

Tartaglia *et al*¹ characterised the phenotypic spectrum of 48, XXYY by examining 95 males with the syndrome, aged 1–55 years. They documented the other manifestations of the condition including: dental health problems (87.5%), learning difficulties

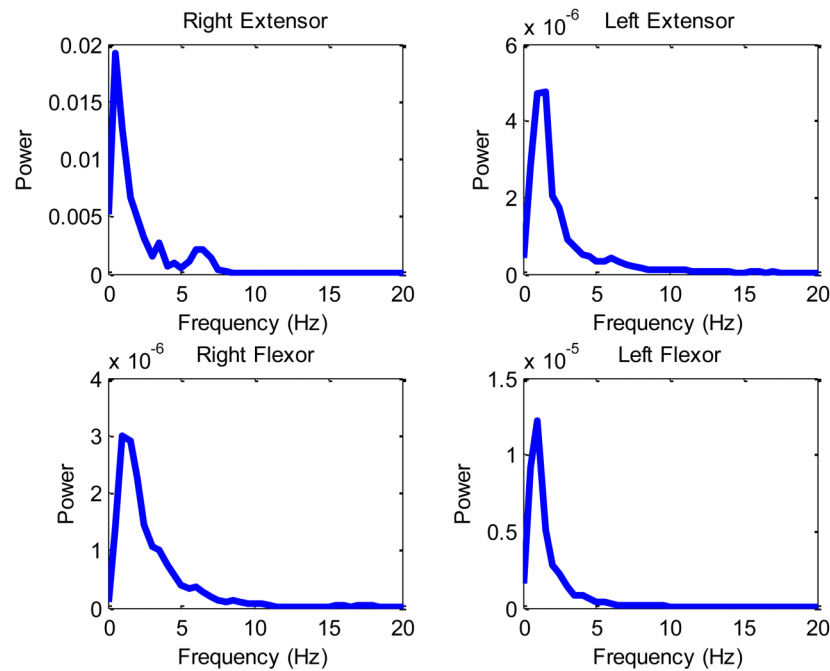
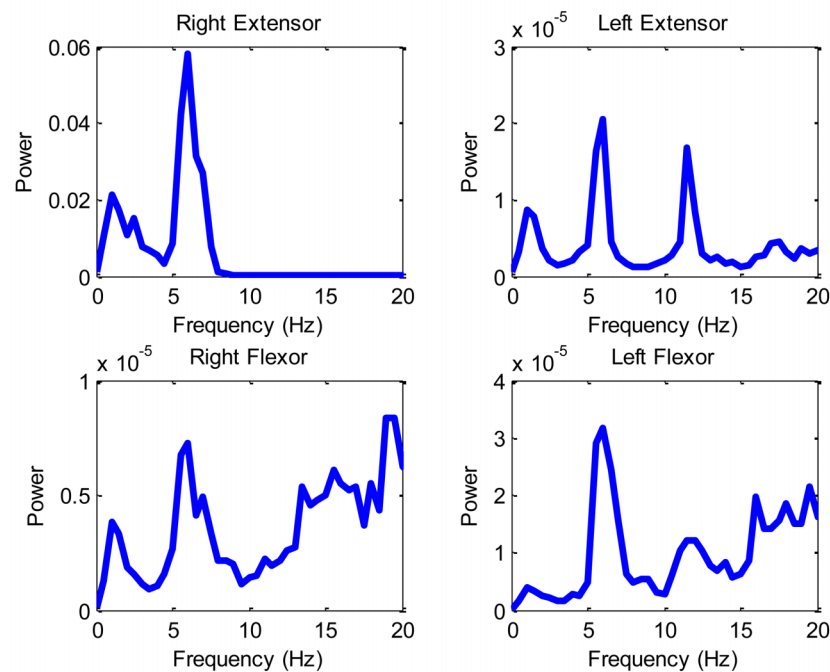
At rest**Arms held out straight**

Figure 2 Surface electromyogram, recorded bilaterally from the wrist flexors and extensors, while the patient was at rest and then with both arms held out straight, showing a 5–7 Hz postural tremor, not present at rest.

(71%), attention-deficit disorder (72%), asthma (60%), other allergies (56%), mental retardation (29%), autism (28%), scoliosis (25%), cardiac abnormalities (septal and other congenital defects, mitral valve prolapse) (19%), radioulnar synostosis (17%) and seizures (15%).¹ MRI showed white matter hyperintensities in 46%, and enlarged ventricles in 22%. Rarer findings included cortical dysplasia or

corpus callosum lipoma in 9% and agenesis of the corpus callosum in 6%.¹

Intention tremor is seen in 8% of children <10 years of age with 48, XXYY, increasing to 62% by 11–19 years and 71% of those over 20.¹ Among 10 tremulous patients with the syndrome aged 13–26 years, the tremor was upper limb postural and kinetic in all cases; only one had an intention tremor.²

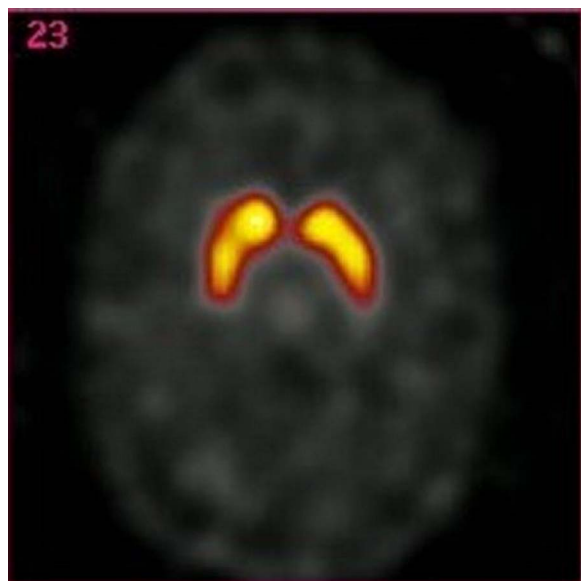


Figure 3 A ^{123}I -FP-CIT single photon emission CT dopamine transporter scan (DaTSCAN), showing good uptake in the caudate nuclei and putamina bilaterally, with a slight 'waist' between the right caudate and putamen.

Intriguingly, half of these patients had a family history of tremor. The upper limb action tremor frequency measured in one patient was 6.5 ± 1.3 Hz. One patient also had a postural tongue tremor. Two had nystagmus, four had dysarthria, three had a widened stance and three had gait ataxia, perhaps suggesting cerebellar dysfunction as a cause for this tremor.²

About 50% of patients with 47, XXY (Klinefelter's) and 47, XYY syndromes have intention tremor, illustrating that tremor is a common manifestation of sex chromosome aneuploidy. This suggests that the tremor reflects overexpression of genes homologous

to the X and Y chromosomes (ie, their pseudoautosomal regions), although an additional X may be less tremorigenic.^{2,5}

Our patient presented with a mild action (postural and intention) tremor of the upper limbs and had the clinical characteristics of 48, XXYY syndrome, namely epicanthal folds, poor dentition, a tall stature, pes planus, an action tremor and micro-orchidism, mild learning and behavioural difficulties. The diagnosis was established by karyotyping when genetic studies looking for fragile X were requested, rather than clinically. His tremor did not respond to commonly used first and second line antitremor medications (as with previous reports). We confirmed a previous finding that the postural tremor frequency is in the 5–7 Hz range.² A DaTSCAN and MRI showed no basal ganglia abnormality. The nature of the tremor, nystagmus and broken upward pursuit eye movements support the previous suggestion that the tremor has a cerebellar aetiology.^{1,2}

The importance of establishing the diagnosis of 48, XXYY syndrome is to identify other potential complications. Patients with the diagnosis need an ECG, echocardiogram, plasma testosterone, oestradiol, follicle-stimulating hormone, luteinising hormone and sex hormone binding globulin, plasma glucose, HbA1c, bone densitometry scan and MR scan of brain.

Patients should receive counselling about infertility and the nature of the condition. A valuable source of information and support for families is the XXYY syndrome project: <http://xxyyysyndrome.org>. Prenatal diagnosis is possible, although parents of a child with 48, XXYY syndrome do not have an increased risk of having a second affected child.¹

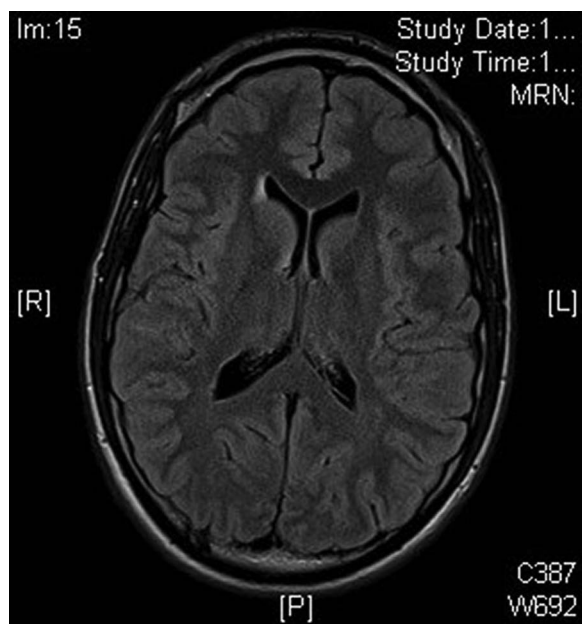


Figure 4 A cerebral MR FLAIR image demonstrating normal basal ganglia but mild periventricular hyperintensity.

Practice points

- ▶ Upper limb action tremor starting at a young age (usually second decade) in males should prompt consideration of the diagnosis of 48, XXYY syndrome.
- ▶ The action tremor associated with 48, XXYY syndrome has a frequency of 5–7 Hz.
- ▶ The tremor does not respond to the first or second line treatments used for essential tremor.
- ▶ The main clues to the diagnosis are:
 - An upper limb action tremor
 - Tall stature
 - Poor dentition
 - Learning difficulties
 - Attention deficit disorder
 - Allergies or asthma
- ▶ Having diagnosed 48, XXYY syndrome, further investigations are needed to exclude associated complications.
- ▶ Most cases of 48, XXYY probably remain undiagnosed.
- ▶ The XXYY syndrome project provides valuable information and support for families: <http://xxyyysyndrome.org>

Acknowledgements We thank Dr Nada Yousif for performing the surface EMG and Dr Stephen Gunning for the neuropsychological assessment. This paper was reviewed by Kathryn Peall, Cardiff, UK.

Contributors HL wrote the initial draft of the manuscript. GNF reviewed and edited the manuscript. PGB planned, revised and supervised the work and is responsible for the overall content. HL, GNF and PGB were involved in the management of the patient.

Competing interests GNF is co-editor of *Practical Neurology*.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Tartaglia N, Davis S, Hench A, *et al.* A new look at XYY syndrome: medical and psychological features. *Am J Med Genet Part A* 2008;146A(12):1509–22.
- 2 Tartaglia N, Borodyanskaya M, Hall DA. Tremor in 48, XYY syndrome. *Mov Disord* 2009;24:2001–7.
- 3 Bain PG, Findley LJ. *Assessing Tremor Severity*. London: Smith-Gordon, 1993. <http://ghr.nlm.nih.gov/conditions/48XYY-syndrome>
- 4 Boisen E, Rasmussen L. Tremor in XYY and XXY men. *Acta Neurol Scand* 1978;58:66–73.
- 5 Donati F, Gasser S, Mullis R, *et al.* 48, XYY syndrome in a boy with essential tremor. Comparison with 120 cases from the literature. *Monatsschr Kinderheilkd* 1992;140:216–19.