Case Reports

Tremor and Klinefelter’s Syndrome

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Abstract

Background: Klinefelter’s syndrome (KS) has been associated with tremor, but reports on tremor phenomenology and treatment are limited.

Case Reports: Patient 1 is a 17-year-old male with a dystonic tremor treated with deep brain stimulation (DBS). Patient 2 is a 57-year-old male with a predominantly left hand resting tremor and dystonic features.

Discussion: Our cases suggest that the tremor in patients with KS may be dystonic in nature. Patient 1 is also the third reported case of successful treatment with DBS. These cases have implications for elucidating the underlying neurobiological mechanism of tremor and identifying treatment options.

Keywords: Tremor, dystonia, Klinefelter’s, 47, XXY, sex chromosome, deep brain stimulation (DBS).

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Introduction

Klinefelter’s syndrome (KS) is a chromosomal disorder in males classically defined as a 47, XXY karyotype. This syndrome is characterized by hypogonadism, infertility, and gynecomastia. It is also frequently associated with tall stature, disproportionately long extremities, developmental delay, mood problems, and behavioral issues.¹–⁵

Previous reports have reported essential tremor (ET) in KS patients.⁶–¹⁴ ET is predominantly an action tremor, with a resting component associated with more severe and long-standing disease in about 19% of patients.¹⁵ Many reports of tremor associated with KS were published more than 30 years ago, prior to when ET characteristics were clearly defined.⁶–⁹

Since 2000, there have been five case reports of KS patients with tremor.¹⁰,¹¹,¹³,¹⁴ Patients predominantly have postural and kinetic tremor affecting bilateral upper extremities, with few patients having head and voice tremor. Mild resting tremor was previously reported in five KS patients.¹⁶,¹⁷

Table 1 summarizes tremor phenomenology in KS patients. Harlow and colleagues demonstrated that patients with KS more frequently self-report tremor compared to a non-KS population.¹² In their study, the prevalence of self-reported tremor was 63.4% in 44 KS patients and 13.7% in 95 controls. There was no difference in family history of tremor between the two populations (p=0.376). Unfortunately, the questionnaire used was designed for detecting ET, and none of the questions specifically asked about the presence of a resting tremor.¹⁸ Moreover, the questionnaire was found by its writers to have a modest sensitivity of 73%. False negatives were usually in patients found to have milder tremors during clinical exams. Thus, information on the phenotypic expression of tremor in KS is narrow.

The literature on KS-associated tremor treatment is even more limited, with only a few case reports mentioning medication trials.⁸,¹⁰,¹¹,¹³ Deep brain stimulation (DBS) in the ventral intermediate (VIM) nucleus of the thalamus is a Food & Drug Administration-approved indication for ET. Two patients who underwent DBS implantation in the VIM showed marked improvement following surgery.¹⁰,¹⁶
Here, we present two KS patients with significant hand tremors with novel features who experienced improvement following DBS.

**Case Descriptions**

**Patient 1**

A 17-year-old right-handed male with KS (47, XXY) was evaluated for a high amplitude dystonic tremor in both hands that started at age 7. Treatment with primidone 50 mg twice daily, propranolol 120 mg long-acting once daily, and topiramate 25 mg three times a day failed to adequately control the tremor. Physical exam was notable for tall stature, long arms, and gynecomastia. His tremor was severe on the right and moderate on the left; it was also dysrhythmic being most prominent during posture and intention and subtly present at rest. Dystonic finger posturing was noted with posture and intention. Using the National Institutes of Health collaborative genetic criteria (NIHCGC) scale, his tremor was rated as Grade 4 on the right and

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**Table 1. Review of Literature: Klinefelter Syndrome (47 XXY) Patients with Tremor Phenomenology**

| Reference         | Patient No. | Age of Onset (years) | Tremor Phenomenology                                                                 |
|-------------------|-------------|----------------------|-------------------------------------------------------------------------------------|
| Finley et al.28   | 1           | 15                   | Fine irregular tremor of hands, exacerbated with stress                              |
| Zuping et al.29   | 2           | 10                   | Tremor of both arms                                                                 |
|                   | 3           | N/A                  | Coarse tremor of both hands                                                          |
|                   | 4           | N/A                  | Unilateral arm tremor                                                                |
|                   | 5           | N/A                  | Coarse tremor of both hands                                                          |
|                   | 6           | N/A                  | Tremor                                                                               |
| Baughmann et al.6 | 7           | 11                   | Action tremor upper limbs                                                            |
|                   | 8           | N/A                  | Mild postural and action tremor of arms                                              |
|                   | 9           | N/A                  | Mild postural and action tremor of arms                                              |
|                   | 10          |                      | Moderate postural and action tremor of arms, head tremor                              |
| Boltshauser et al.8| 11          | N/A                  | Mild rest and marked action tremor                                                   |
| Boisen et al.9    | 12          | N/A                  | Mild postural and/or intention tremor                                                |
|                   | 13          | N/A                  | Mild postural and/or intention tremor                                                |
|                   | 14          | N/A                  | Mild postural and/or intention tremor                                                |
|                   | 15          | N/A                  | Mild postural and/or intention tremor                                                |
|                   | 16          | N/A                  | Mild postural and/or intention tremor                                                |
|                   | 17          | N/A                  | Mild postural and/or intention tremor                                                |
| Telfeian et al.30 | 18          | 4                    | Marked intention tremor of both upper limbs, right more affected than left, marked head tremor |
| Harlow et al.31   | 19          | 63                   | Moderate head tremor, mild vocal tremor, severe symmetric bilateral upper limb action tremor (kinetic and intention more than postural tremor) |
| Kinoshita et al.13| 20          | 61                   | Postural tremor of hands, exacerbation with stress                                  |
| Coutinho et al.14 | 21          | 14                   | Postural and action tremor of both hands, rest tremor                               |
| Burdick et al.17  | 22          | 13                   | Action tremor in the both hands with, slight resting tremor on the right           |

Abbreviations: N/A, Not Applicable (information not given).
Grade 3 on the left.19,20 No tremor was present during standing or walking. The neurological examination was otherwise normal, and no ataxia was noted. Family history was reported as positive for his father, who had an action tremor. Brain magnetic resonance imaging (MRI) was normal for age.

At age 18, the patient underwent DBS surgery with the stimulating electrode implanted in the VIM of the left thalamus. Six months later, the patient had a stimulating electrode implanted in the VIM of the right thalamus. Two months following each surgery and DBS programming session, the tremor of both hands decreased to Grade 1 on the NIHCGC scale (Video 1). Residual dystonic finger posturing of both hands persisted following the decrement in tremor. The patient continues to have excellent control of his tremor in both hands 28 and 22 months after left- and right-sided surgeries, respectively.

**Patient 2**

A 57-year-old left-handed male with KS (47, XXY) developed a continuous large amplitude tremor of the left hand in 2009 that was worse with rest than action. The rest tremor was not the classical pill-rolling tremor. It involved mainly the wrist joint and not the metacarpophalangeal joints; again, different from typical Parkinson’s disease (PD) rest tremor. Over the next few weeks, he also developed tremor in his right hand and left leg. The tremor responded well to diazepam, which the patient required regularly for the first 6 months, after which his tremors occurred less frequently and with decreased amplitude. However, the left hand tremor continued to interfere with his work as an electrician. The patient was unsure whether his tremor decreased with alcohol, and family history for tremor was negative.

On examination, the patient was tall with long extremities and gynecomastia. In the left hand, there was a variable moderate amplitude, 3–5 Hz resting tremor, and a slightly lower amplitude postural and kinetic tremor (Video 2). The action tremor presented without significant (<1 s) latency of onset and appeared worse with pronation than supination. There were intermittent dystonic movements of the head but no resting or action tremor of his right hand or either leg. No rigidity, bradykinesia, micrographia, or stooped posture was noted. Serum copper and ceruloplasmin levels to assess for Wilson’s disease were normal. An MRI showed mild prominence of both lateral ventricles, a common finding in KS patients. There were no white matter abnormalities. Topiramate up to 100 mg/day did not decrease the tremor, and the patient did not want to try additional medications. He continues to be free of incoordination, stiffness, or imbalance.

**Discussion**

We have described two patients with KS and disabling tremor. One has a predominantly unilateral, resting more than action tremor along with dystonic head movements and no other features of parkinsonism. The other has severe, bilateral, medically refractory dystonic tremor that strongly responded to bilateral DBS in the VIM. To our knowledge, this is the first reported case of a KS patient with tremor presenting with a predominant resting component, the first reported cases of dystonic features in KS, and the third reported case of DBS in a KS patient with hand tremor. The excellent outcome of Patient 1 as well as the first two reported cases of DBS in KS patients10,16 suggests
that DBS in the VIM may be an effective treatment for medically refractory tremor in KS patients.

While it is possible that VPA use contributed to the tremor seen in Patient 2, VPA is more commonly associated with symmetric postural tremor. Importantly, the patient lacked other features of parkinsonism including micrographia despite having a tremor for almost 3 years, making PD and related diseases unlikely.

The tremor of Patient 2 showed dramatic asymmetry. Another reported case of significant tremor asymmetry in a KS patient was associated with diffuse white matter changes including in the right putamen and left thalamus. In contrast, our patient’s MRI did not demonstrate significant asymmetry.

While there was a wide range of age of tremor onset in case reports on KS, most patients developed tremor at a young age. In the study by Harlow and colleagues, the average age of tremor onset in KS patients was 20 years in cases and 38 years in controls. This, along with the presence of dystonic hand movements in Patient 2 and the dystonic hand posturing in Patient 1 indicates that the tremor seen in KS is not ET; rather, it is more likely a dystonic form of tremor. Recently, two large series reported that 47–55% of patients with adult-onset dystonia have action tremor, and 5–12% have upper limb resting tremor.

A high prevalence of tremor in KS patients has been noted. Interestingly, other sex chromosome aneuploidies have been associated with tremor. In one report, an intention tremor was seen on exam of 45% of 95 males with 48, XXY syndrome. In another report on the same syndrome, 50% of 28 patients self-reported a tremor, and 10 patients subsequently examined all had an action tremor. In one patient, the tremor was unilateral. Notably, the vast majority of patients in both reports developed tremor before the age of 20. Furthermore, in two older reports on males with 47, XYY syndrome, a high preponderance of action tremor in males with 47, XYY syndrome was found. The average age of tremor onset in patients in these studies was also young (less than 30 years old).

These reports on aneuploidies and tremors with similar presentation suggest common underlying mechanisms. Low testosterone levels have been theorized to be responsible for abnormal neurological development or physiology, but this seems unlikely. First, 47, XYY subjects have normal testosterone levels both pre- and postnatally. Second, two case reports on testosterone treatment in KS led to conflicting results: one patient showing improvement, the other no change.

Further, in Patient 2 described here, there was no change in tremor during significant variation in his serum testosterone levels from below to above normal range.

Another possible mechanism is that there are dose effects of genes on sex chromosomes that escape inactivation. This increased gene dose has been theorized to modify tremor expression, which is a non-sex chromosome genetic disorder. Alternatively, it is possible that dose effect of genes on the X chromosome cause a tremor independently of the genes located on somatic chromosomes responsible for ET by altering neurodevelopment or function. Given Patient 1’s dystonic hand tremor, Patient 2’s dystonic head movements and asymmetric tremor of the extremities, and the presence of asymmetry seen in some sex chromosome aneuploidy patients, we think this latter mechanism is most likely. This gene dose hypothesis suggests that since syndromes of supernumerary X and Y chromosomes both lead to tremor, there may be homologous regions on the X and Y chromosomes. Further investigations are warranted to clarify our understanding of the mechanism leading to tremor in patients with KS and other sex aneuploidy syndromes.

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