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Rubral Tremor Associated with Klinefelter Syndrome: A Case Report and Literature Review

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Abstract

Introduction: Previous case series suggested an association between Klinefelter syndrome (KS) and tremor, but most reported cases had ET-like tremor. Also, previous studies did not suggest any suitable treatments for the tremor.
Case Presentation: The current report presented a case of KS that his rubral tremor led to the KS diagnosis at the age of 43. Regular anti-tremor medication was immediately started along with testosterone therapy; none of which were effective on the tremor. Next, a table of KS patients was provided with a tremor to elucidate the type of tremor and medical treatments in the patients. The result of the literature review of the most effective therapy for tremor in such patients showed that primidone, propranolol, gabapentin, and levetiracetam were not always effective, while deep brain stimulation of the ventral intermediate nucleus showed promising results.
Conclusion: Since tremor in KS has an unknown origin, it may not be responsive to regular anti-tremor medication; therefore, deep brain stimulation (DBS) of the ventral intermediate (VIM) may be the best therapy for such patients

Keywords: Klinefelter Syndrome,, Rubral Tremor, xxy, Deep Brain Stimulation, Drug Therapy

1. Introduction

Klinefelter syndrome (KS) with the incidence of approximately 1 in 1000 live male births is the most common congenital aneuploidy in males. It is usually defined by the existence of extra X chromosome (s) in the affected males (1). 47, XXY is the most common genotype of KS patients, although other genotypes such as 48, XXXY and 46, XY/46, XXY mosaicism are also reported. Hypogonadism, infertility, and cognitive impairment are among the most reported manifestations of this syndrome (2).

Rubral tremor is a coarse resting tremor, which usually exacerbates while active (3). It is usually associated with the diseases that cause lesions in superior cerebellar peduncle, midbrain tegmentum, and posterior thalamus. Although previous case reports and studies showed a link between essential tremor and KS (4, 5), none of them reported rubral tremor, as far as the authors know. Here is the report of a man whose rubral tremor led to the KS diagnosis for him for the first time (6). The current study aimed at further elucidation of KS diagnosis and complications through considering new aspects of rubral tremor.

The current report presented a patient with KS and rubral tremor and a review of literature. PubMed, Scopus, and Web of Science were searched until December 2016 with the terms "Klinefelter* (Title/Abstract) OR XXY Syndrome(Title/Abstract) OR 48, XXYY Syndrome(Title/Abstract) OR Xxyy Syndrome(Title/Abstract) OR XXY Trisomy(Title/Abstract) OR XXXY Male(Title/Abstract)) AND Tremor*". Also, Google Scholar was searched with the exact words "Klinefelter AND tremor AND case report" anywhere in the article; also "(Klinefelter OR XXY) AND Tremor" with all the words in the title of the article were searched. Overall, 20 pages of Google Scholar were analyzed. Search results were included if the paper had a new case of KS with any tremors. To avoid duplication, review articles were not included.

2. Case Presentation

A 43-year-old male was referred to the neurology clinic with a chief complaint of generalized tremor in the extremities and head, which started from childhood with a progressive pattern. He was diagnosed with essential

tremor and had been taking propranolol, gabapentin, topiramate, primidone, levetiracetam for a year. Since he poorly responded to the treatment, he was referred to the current for re-evaluation. The subject looked young, medium height male with reduced facial and body hair. His balance was Impaired while walking and he complained of disruption in the delicate works. He reported increased tremor with stress and anger. He also had voice tremor. Mitral valve stenosis was recorded in his previous medical history. On physical examination, gynecomastia and delays in the development of primary and secondary sexual traits was observed. Neurological examination showed intact mental status with mild cognitive impairment (MMSE = 27). Cranial nerve examination and motor function were both normal. His deep tendon reflex was +2 and his Babinski reflex was normal. He had bilateral action and intention tremor with higher frequency on the left side during finger to nose test. The heel to shin test was mildly abnormal, but no nystagmus was observed. His tandem gait was abnormal; also, he had ataxic gait. Overall, the differential diagnosis was structural lesions, thyroid, and metabolic disease, the Wilson disease, SCA-3, ataxia-telangiectasia, and fragile X syndrome. To limit the possibilities, head magnetic resonance imaging (MRI), electromyography and nerve conduction velocity (EMG-NCS) and lab tests were ordered. Head MRI was clear, and EMG-NCS showed moderate to severe carpal tunnel syndrome (CTS) with no neuropathy. Lab results showed osteopenia other than slight anemia (hemoglobin: 13 g/dL). Low testosterone (0.79 nm/L) and high follicle-stimulating hormone (FSH; 33.1 IU/L) levels caused suspicion to chromosomal abnormalities; therefore, karyotype determination was ordered next. Reports of cytogenic investigation revealed karyotype of 48, xxxy (7), 47, xxy (8) mosaicism compatible with the Klinefelter syndrome.

3. Discussion

The current report presents a case of KS to support the previous idea that KS may manifest as tremor, and this tremor may be the main reason of their diagnosis, especially in older ages. The current study showed that the tremor in KS patients was not necessarily ET- like and according to the table, it can manifest in a different range of type and severity.

Koegl-Walner et al., reviewed 39 cases of patients with KS and stated that most of them had postural and kinetic tremor resembling ET. They also reported that all of their patients had their tremor started in childhood (4). In contrast, in another study., said that only 8% of their review population had their tremor started under the age of 10 (9). The current study, in line with that of Walner et al., showed that most of the patients started their tremor in the adolescence.

Although previous studies suggested that propranolol and primidone were effective in 30% to 70% of ET cases (10), the study by Walner et al., and the current study showed mild or no benefit to them. The current case took levetiracetam, primidone, propranolol, and gabapentin, but showed no improvement. This can also support the theory that tremor in these patients is not always ET- like; therefore, regular medication for ET was not the excellent choice for their treatment. The current study cannot suggest any assuring medication, but 3 of the 60 patients underwent VIM-DBS and it was 100% successful; therefore, VIM-DBS, may be an alternative treatment in cases with no response to anti-tremor medication.

In another study, in a review of 35 brain MRIs of patients with XXYY showed a 46% incidence of T2, white matter hyperintensities and a 23% incidence of enlarged ventricles. In that study, males with XXYY with white matter hyperintensities did not increase rates of tremor when compared with those without white matter finding (9). In contrast, some other studies showed higher grey-matter volume in the parietooccipital and sensorimotor cortices, and reduced volume in insular and temporal regions such as subcortical structures similar to the amygdala and hippocampus (1); however, only 2 cases in the current study had documented abnormal MRIs. This can propose that tremor was not a result of a cortical abnormality in such patients and more of a genetic origin.

Lateralization effects were inconclusive in previous studies. Regarding the fact that KS patients also have language disabilities, some studies said the hyperintensity in gray matter was more in the right side, but other studies showed no difference; here most of the cases had an equal tremor in both sides (1).

In the current study, patients with early onset of tremor had an early diagnosis of KS. Therefore, it can be hypothesized that tremor was not a consequence of hormonal imbalance, but a phenomenon due to genetic factors. Lack of response to testosterone therapy in most of the current study cases can also approve that hypothesis. Also, several X-linked tremor disorders have characteristics similar to those of KS that can demonstrate why many of the current study cases were diagnosed during a test to approve fragile X syndrome. Other than that, most of the patients with resting tremor besides kinetic and postural tremor had xxyy or xxxy genotype.

Lack of specific documented data was the major limitation in the current work. It is possible that some of the patients with KS had early testosterone therapy that prevented the tremor in the first place; it is also possible that many of the undiagnosed patients had tremors and their

tremor responded well to regular anti-tremor drugs.

Even with the above limitations, the current study was worthy because it suggested that tremor, not especially ET- like, was a symptom in patients with KS and clinicians should consider KS as a possibility when encountering tremor along with other symptoms. The current study also said that regular anti-tremor medication mostly had no benefit for them; although deep brain stimulation showed promising results, since not many patients undergo these procedures, further studies are needed to find a suitable drug therapy replacement. Overall, karyotyping is recommended for male patients with tremor resistant to anti-tremor medications. It was also suggested to conduct future studies toward elucidation of the genetic aspects of tremor in KS to find the best treatment.

supplementary material

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