Klinefelter's Syndrome with Tremors, Ataxia and Parkinsonism

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ABSTRACT

Klinefelter's syndrome (KS) is the most common cause of hypogonadism in men. Essential tremor (ET) and parkinsonism have been reported in KS, but ataxia, which has been commonly reported with other causes of hypogonadism, is very rare in KS. Orthostatic tremor has not been reported. We present a case with multiple movement disorders, including gait ataxia, essential-type tremor, rest tremor, orthostatic tremor and parkinsonism.

KEYWORDS: Klinefelter's syndrome, ataxia, orthostatic tremor

INTRODUCTION

Klinefelter's syndrome (KS) is the most common cause of primary hypogonadism in males, but is also associated with several neurological disorders, including behavior problems, intellectual disability, seizures, and movement disorders. It is due to supernumerary X chromosomes, of which 47 XXY is the most common. Movement disorders are rare but have been well documented, most commonly essential tremor (ET).[1] Parkinsonism and ataxia have been reported rarely.[2] Ataxia has been reported more frequently with causes of hypogonadism other than KS,[3] but never in association with parkinsonism. No case of orthostatic tremor has been reported in association with KS and other movement disorders. Here we report a KS patient with all of these disorders.

CASE REPORT

A 49-year-old man was initially evaluated in the movement disorders clinic in 2016. He had been diagnosed as a child with XXY Klinefelter's syndrome, with hypogonadism. Subsequently, intellectual disability was recognized, followed by schizoaffective disorder, depressive type, and generalized anxiety disorder. He also developed type 2 diabetes mellitus. According to his family, the patient had action tremors of the hands for many years, affecting his ability to write and eat without spilling. About two years prior to the first movement disorders evaluation, his hand tremors had increased and leg tremors developed, which occurred only with standing. Family history included a paternal uncle with Parkinson's disease (PD) but no one else with tremors, PD or other neurological problems.

Click to view video

[1:29] https://vimeo.com/786310675

Neurological examination of the patient showing postural hand tremors, orthostatic tremors, wide-based ataxic gait, bradykinesia on finger tapping and heel tapping, facial hypomimia.

On initial evaluation in 2016, the patient was taking risperidone 2 mg daily, aripiprazole 30 mg daily, quetiapine 300 mg daily, escitalopram 10 mg daily, and clonazepam 0.5 mg daily. He had 3 types of tremors: mild resting tremors of the hands which were thought to be secondary to antipsychotics, postural and action hand tremors, and orthostatic tremor. He also had mild parkinsonism which also was thought to be secondary to the antipsychotic medications. He was tapered off the previous antipsychotics including quetiapine, and treated with clozapine, which does not cause parkinsonism, but parkinsonism persisted. Carbidopa-Levodopa 25–100 1 tab TID was tried with no benefit and discontinued. His parkinsonism symptoms continued to get worse and he also developed gait ataxia.

On examination in 2021, while taking clozapine 150 mg daily, trihexyphenidyl 4mg daily, escitalopram 10mg daily, propranolol 60 mg daily, insulin, atorvastatin, linagliptin, desmopressin, allopurinol, iron, budesonide/formoterol inhaler, his stride length was reduced. There was a flat foot strike, wide base, slow and unsteady gait, and posture was stooped.

Brain MRI showed mild ventriculomegaly, unchanged from 2009. The Dopamine Transporter Scan (DaT), which is a nuclear imaging measure of midbrain dopamine secreting cells thereby assessing pre-synaptic dopaminergic function, was normal.

In 9/2022, gait and tremors were worse (**see Video**). He had normal heel-to-shin testing, but mild ataxia on heel tapping. He needed to use his arms to push off the armrests of his chair to stand. There was tremor of legs on standing, which disappeared with walking. He had a wide base, with a very short stride. He was very unsteady and could barely move each leg, despite being supported (**see Video**). His behavior and cognition had not changed in many years despite withdrawal of all antipsychotic medications.

DISCUSSION

KS is the most common sex chromosome disorders in humans. It is thought that the majority of the affected men are not identified, presumably being phenotypically normal. Cognitive and behavioral problems are common and neurological problems are not rare among those identified, particularly epilepsy and essential type tremor. Parkinsonism has been reported with normal and abnormal DaT scan[2] in KS patients, implicating pre-synaptic dopamine deficiency in some KS patients, but unexplained parkinsonism in others. Ataxia is very uncommon in KS, although it is the most common neurological problem in other forms of hypogonadism.[3] Our patient has rest tremor, postural tremor and orthostatic tremor (which has not been reported previously) as well as ataxia. There is no report of this combination of neurological findings. Although this patient had been treated with neuroleptic medications, they had been discontinued 60 months prior to the attached video. Parkinsonism had worsened during this time, indicating that this was no longer a neuroleptic side effect.

There are only a few reports on the neuropathology of KS patients, none of which describe patients with parkinsonism, tremors, ataxia or schizophrenic-type psychiatric problems.[4] In one of the reports, focal cerebral and cerebellar megalencephaly with broad gyri, cytoarchitecturally abnormal cortex and thickened cerebral vessels were described. Most of the other studies reported non-specific changes such as neuronal loss, demyelination, gliosis, or pituitary abnormalities. There are also reports of bilateral megalencephaly with polymicrogyria and cortical dysplasia.[4] The brain MRI of our patient showed none of these abnormalities. These pathology reports may explain cognitive impairment and seizures but not the movement abnormalities of our patient. We have no explanation for the abnormalities in our patient, the localization of the pathology, or why these progressive changes should have begun when they did. It is possible that this patient may have another neurological condition co-existing with KS.

References

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