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Case Report

Tardive dyskinesia in a patient with Fragile X-associated Tremor/Ataxia Syndrome

Case Report and Review of Literatures

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We describe an unusual case of Fragile X- associated tremor/ataxia syndrome (FXTAS) developing orofacial-buccal "tardive dyskinesia-like" symptoms, eight years after the patient was diagnosed with FXTAS at the age of 62. His initial manifestation was intention tremor. Our patient has neither history of neuroleptics nor metocloperamide use; however he did have temporary exposures to topiramate, propranolol, solifenacin, trazodone, bupropion and riluzole. Although extrapyramidal symptoms associated with FXTAS have been previously reported in English medical literatures, we present our case as the first, to the best of our knowledge, regarding tardive dyskinesia as one of the extrapyramidal symptoms associated with FXTAS.

Keywords:Fragile X-associated Tremor/Ataxia syndrome, FXTAS, Tardive Dyskinesia, Movement disorder, Extrapyramidal symptoms

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Introduction

The term extrapyramidal symptoms (EPS) refer to a range of involuntary movement manifestations including acute dyskinesias and dystonic reactions, tardive dyskinesia, parkinsonism, akinesia, akathisia, and neuroleptic malignant syndrome. They occur owing to dopamine blockade or depletion in the basal ganglia. Since EPS due to medication's reaction or neurodegenerative diseases can manifest in a very similar presentation to that of Parkinson disease, patients presenting with EPS are likely to be initially misdiagnosed as Parkinson diseasei[1]. Occasionally, EPS are also associated with certain non-antipsychotic agents, including some antidepressants, lithium, various anticonvulsants, antiemetics and, rarely, oral-contraceptive agents [2].

Here we report a case of FXTAS who developed "tardive dyskinesia-like" orofacial-buccal involuntary movements despite a negative history of treatment with dopamine antagonists. Our best theory is that neurodegenerative diseases like FXTAS might present with EPS and possibly increase the risk of developing tardive dyskinesia, in addition to the more typical manifestations of intention

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tremor, parkinsonism, and cerebellar ataxia.

Case Report

A 71-year old retired Caucasian professor started developing progressively worsening action tremor in the 3rd decade of life that was relieved symptomatically with propranolol (a beta blocker). During the 5th and 6th decade however, he started to develop gait ataxia and oculomotor dysfunction, he was eventually diagnosed with FXTAS via DNA testing. He has been treated with topiramate (an anticonvulsant used to treat essential tremor) for the past eight years. Six years ago, he was also put on one year trial of solifenacin (an anticholinergic used for bladder incontinence), a two weeks trial of riluzole (a glutamate blocker), a six month-trial of trazadone (an antidepressant) as well as few weeks-long trial of bupropion (an antidepressant), and varenicline (an antidepressant and a nicotinic agonist used for smoking cessation). The patient eventually became wheelchair dependent due to recurrent falls and postural hypotension, urinary and bowel incontinent. Recently at age 70, the patient started developing tardive dyskinesia-like symptoms. The patient has no family history of FXTAS. He is a social drinker, has never smoked and has no illicit drug use to the best of our knowledge. On physical examination, the patient manifests horizontal and vertical nystagmus, diplopia, orofacial-buccal chewing movements, resting tremor, truncal and limb ataxia, rigidity, quadriplegic areflexia, dysmetria and dysdiadochokinesia bilaterally. A head CT scan without contrast performed reveals mild to moderate generalized atrophy, microvascular changes, and dilation of ventricular system and subarachnoid space. A brain MRI without contrast was also preformed that revealed moderate cerebral volume cortical loss and cerebellar volume loss mostly involving the vermis.

Discussion

Tardive dyskinesia (TD) is a delayed onset drug-induced side effect, described as involuntary dyskinetic movements involving the tongue, lips, face, trunk, and extremities. The medications responsible for this phenomenon are dopamine receptors antagonists like typical antipsychotics (also known as neuroleptics) and metoclopramide and to a lesser degree, atypical antipsychotics. TDs, however, apparently existed before the development of these agents [1]. One of the most interesting facts about TD is that most patients who are taking neuroleptics for years do not develop TD, and patients who develop TD caused by the same medication regimen might have a very broad range of TD severity, these observations might be explained by individual, possibly genetic susceptibility for TD [2][3]. Besides, there are conditions that increase susceptibility for TD, for instance, patients with history of fetal alcohol syndrome are vulnerable to the development of TDs, even after receiving only one dose of the causative agent [1].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines tardive dyskinesia as a medication induced involuntary athetoid or choriform movements lasting at least few weeks and persists despite discontinuation or change of the medications. As per DSM-5, to confirm a diagnosis of tardive dyskinesia, symptoms must persist for a month after discontinuation of the medication.

The pathophysiology of tardive dyskinesia remains inconsistently understood, nevertheless it is believed to be

the result of chronic blockade of Dopamine D2 and D3 receptors [4]. There are several theories about its development. The most prominent theory suggests that chronic exposure to the neuroleptics results in D2 receptor upregulation with postsynaptic dopamine receptor supersensitivity, however this theory neither explains cases of TD caused by drugs other than antipsychotics and metoclopramide nor the persistence of TD for years or even decades after discontinuation of the offending drug[5].

Another theory that is supported by animal studies proposes that damaged or dysfunctional striatal γ-aminobutyric acid (GABA)-containing neurons lead to GABAergic hypofunction and degeneration of the striatal fast-spiking GABAergic interneurons that regulate balance between direct and indirect basal ganglia pathways[6][7][30].

On the other hand, the neurodegenerative theory is supported by the irreversibility of the symptoms after discontinuation of the offending drug. Proponents of this hypothesis suggest that neuroleptics could increase lipid peroxidation and free radical formation, leading to the neuronal damage and therefore degeneration of the different neurotransmitter systems. Structural changes in the brain, including neuronal loss and gliosis in the basal ganglia after prolonged exposure to neuroleptics, were identified in animal studies and postmortem neuropathological examinations of the brains of TD patients[8][9].

Although there are reported cases of bupropion-[10] and trazodone-[11][31] associated tardive dyskinesia, our patient was only treated for a short period and discontinued eight years ago before the development of orofacial-buccal involuntary movements.

There is also one report regarding an association of acute dystonia with the use of trazodone [12].Currently, there are no reported cases associated with topiramate, riluzole, solifenacin or propranolol. Although there is an article about EPS associated with anticonvulsants [13], it is unlikely relevant to our case as the study focused on valproate and there was no association with newer anticonvulsants like topiramate that our patient is taking.

One of the theories that comes to our thinking is that these orofacial-buccal involuntary movements could be part of the natural history of FXTAS. Another theory is that, patients with neurodegenerative diseases like FXTAS may have increased risk to develop TD even with a brief exposure to offending agents and this might be supported by the neurodegenerative theory of tardive dyskinesia's pathophysiology, possible association between FXTAS [14] and multiple system atrophy [15] [16] in which both present with parkinsonism and EPS, along with the lack of the classical causes of TD causative medications intake in this patient. Besides, the patient was treated with a trial of varencline and reports have shown that varenicline may improve some symptoms of FXTAS [17].

The current definition of FXTAS is a neurological disorder caused by a premutation expansion of trinucleotides CGG (55 to 200 CGG repeats) in the fragile X mental retardation 1 (FMR1) gene, which for unknown reasons lead to overproduction of abnormal FMR1 mRNA. Fragile X syndrome, on the other hand, which is characterized by intellectual disability, seizures, and autism with onset in childhood, is caused by full expansions of more than 200 CGG repeats in FMR1 results in methylation and transcriptional silencing of the gene [18].

The onset of FXTAS is typically in the early seventh decade with men more affected than women. The major signs in affected patients are cerebellar gait ataxia, intention tremor, frontal executive dysfunction, and global brain atrophy. Other frequent findings are Parkinsonism, peripheral neuropathy, psychiatric symptoms (depression,

anxiety, agitation), and autonomic dysfunction [19]. The clinical presentation differs among affected patients with most of them manifesting with varied dominating signs, such as tremor, dementia or neuropathy [19].

MR imaging often reveals atrophy and patchy white matter lesions in the cerebral hemispheres and middle cerebellar peduncles [20]. Although the latter has been designated the 'MCP sign', occurs in about 60% of affected men, and is relatively specific for FXTAS, there has been a study that has demonstrated inconsistent results [21]. Affected females generally have less severe disease, less cognitive decline, and some symptoms different from that of men, e.g., muscle pain [22] as they are relatively protected by the presence of a normal X chromosome [26].

While the symptoms of FXTAS vary among individuals, almost all affected persons develop progressive cerebellar gait ataxia. Unexplained falls are frequent, and the tandem gait is significantly abnormal in about 50% of male carriers over age 50[23]. Although cerebellar dysfunction is a nearly constant feature that affects the gait, other impairments such as parkinsonism, sensory neuropathy [24], dysautonomia[24], and weakness[25] could contribute to postural instability. dysmetria and dysdiadochokinesia are frequently present in the upper extremities[26]. There are reported cases of oculomotor abnormalities associated with FXTAS like strabismus, diplopia and nystagmus [27].

Action tremor is a common finding in affected patients, but the severity varies among individuals [25] [23]. While some have obvious, severe tremor that impairs daily functioning, most affected patients, possibly due to poor insight related to executive dysfunction, deny symptoms of tremor despite their spouse noting that a mild, intermittent tremor has been present for months or years [26]. The tremor of FXTAS has not been quantitatively studied, but appears to be identical to the classic essential tremor [28]. Furthermore, affected persons usually have definite tremor reduction with use of medications commonly prescribed for essential tremor [26].

Parkinsonism, on the other hand, is also a frequent motor sign[23],In the early stages it is generally mild and mainly manifested by masked faces, generalized rigidity, overall bradykinesia and slow gait [26][23]. Parkinsonian posture is occasionally seen in affected patients. Resting tremor is uncommon and when present, may be due to reoccurrence of the postural tremor in the rest position [23]. Premutation carriers with Parkinsonism generally have minor and only transient improvement with dopaminergic drugs, which suggests that the underlying mechanism causing Parkinsonism is not the same as in primary Parkinson disease [26].

Gait ataxia, intention tremor, and parkinsonism worsen with increasing age and the severity of tremor and ataxia correlate strongly with increasing CGG repeat size through the premutation range [22].

FXTAS is a progressive disease, but there are no prospective studies on its natural history. A retrospective study[29] on the progression of tremor and ataxia in 55 men with FXTAS found that after the initial motor sign, usually tremor, median delay of onset of ataxia was two years, onset of falls six years, dependence on a walking aid 15 years, inability to do most daily activities 16 years, and death 21 years. Death was due to congestive heart failure, pneumonia, cardiac arrest, or progression of neurologic disease. End stage affected patients are often bedridden, dysphagic, dysarthric, parkinsonian and bowel or bladder incontinent [26].

Conclusion

After we discussed theories of TD's pathophysiology, we must agree on the following points

TD can be caused by medications other than dopamine antagonists.

TD caused by the exact same medication regimen, differs in severity among patients

There is possible genetic susceptibility in some patients.

Irreversibility of TD after discontinuation of the offending medication, which support the neurodegenerative theory of TD' pathophysiology.

TD can occur in patients with no known predisposition or medication exposure.

According to DSM V, TD symptoms must persist more than one month after discontinuation of the offending medication. But there is no clarification of the time frame gap the discontinuation of medication to the appearance of TD's symptoms, which could be days, months or possibly years.

Although TD associated with bupropion and trazadone have been reported, our patient was only treated with 6 weeks trial of bupropion and 6 months trial of trazodone. He developed TD six years after discontinuation of both drugs which might be late onset TD as there is no clear period before the onset of symptoms, and this will be the first reported case with such late onset of years.

Or perhaps TD is not be related to medications, currently or previously prescribed in our patient, and better explained by increased susceptibility of patients with neurodegenerative diseases, like FXTAS, to develop TD.

There were no previous reported cases of TD associated with propranolol, riluzole or topiramate.

Solifenacin (an anticholiergic used for bladder incontinence) on the other hand was used in a one year trial six years ago in our patient, although there are reports about TD associated with anticholinergic drugs, it tends to be reversible after discontinuation of the medications [31].

Competing interests

The authors declare that they have no competing interests.

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None

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