CASE REPORT

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Tardive and Acute Dystonic Reactions Probably Related to Extended Release Methylphenidate in an Early Adolescent with ADHD

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ABSTRACT Stimulants have been the mainstay of pharmacological management of attention deficit hyperactivity disorder (ADHD) symptoms and are known to be effective and safe with the most commonly used being methylphenidate (MPH). In addition to many known side effects of stimulants such as loss of appetite, insomnia and headache; recently, cases of dystonia among children receiving MPH treatment have been reported. Dystonia in those cases may be either acute or chronic and the majority of the patients were also using other agents (e.g., antipsychotics alfa-2 adrenergic blockers etc.) in addition to stimulants. Most of those involved acute cases which emerged after treatment initiation/increase in dose or with MPH discontinuation while continuing to use antipsychotics. Here we report an early adolescent with ADHD who developed both tardive and acute dystonic reactions probably related to extended release MPH.

Keywords: Methyphenidate; dystonia; attention deficit disorder with hyperactivity

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood which is managed pharmacotherapy combined with psychoeducational and psychosocial interventions.[1] Stimulants have been the mainstay of pharmacological management of ADHD symptoms for many decades and are known to be effective and safe with the most commonly used being methylphenidate (MPH).[1] Most common adverse effects of stimulants include suppression of appetite, insomnia, dry mouth and nausea which are mostly transient and depend on timing and dosage.[1]

Tardive syndromes may encompass hyperkinetic, hypokinetic and sensory problems resulting from long term exposure to dopamine blocking agents and are termed "tardive dystonia" when dystonia is prominent. Dystonia is described as sustained, involuntary, twisting, slow movement due to spasms of antagonistic muscle groups.[2] Tardive dystonia may emerge after long-term use of antipsychotics, anti-emetics, anti-convulsants and antidepressants.[2-4] Recently, cases of dystonia among children receiving MPH treatment have been reported.[3-5] Dystonia in those cases may be either acute or chronic and the majority of the patients were also using other agents (e.g., antipsychotics alfa-2 adrenergic blockers etc.) in addition to stimulants.[3-5] Here, tardive dystonic reaction in an early adolescent patient with ADHD probably related with MPH and its management was reported.

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The patient was a twelve years old, male adolescent in seventh grade who was consulted due to "muscle spasms and aphonia" from the pediatric intensive care unit in which he was hospitalized. The complaints started three days prior and involved three episodes of 30-45 minutes each, comprising paresis and extension of the tongue, trismus, torticollis with left sided deviation, aphonia and dyspnea which led to his hospitalization. From the psychiatric history, it was learned that he was diagnosed with ADHD at 6 years old and had been receiving extended release MPH [Medikinet™ (Medikinet R, Assos Pharmaceuticals, Germany)] since then. The treatment was initially started at 10 mg/day and gradually titrated upwards with development and he had been receiving 40 mg/day for the past year. Due to emergence of motor tics when he was 7 and vocal tics at 8 years old, he was started on aripiprazole (APZ) 2 mg/day at the second year of treatment with MPH and continued to use it until 2 months ago with full remission of tics. Vocal tics such as coughing and throat clearing reemerged when he stopped APZ 2 months ago. Family history was notable for generalized anxiety disorder in his mother and vocal tics (i.e., coughing) in his father. The mother had been receiving selective serotonin reuptake inhibitors treatment for the past three years while the father had no history of treatment for tics. Past medical history including motor- mental milestones were normal. At the bedside evaluation with Udvalg for Kliniske Undersøgelser-Side Effects Rating (UKU-SERS), Abnormal Involuntary Movement (AIMS) and Extrapyramidal Symptom Rating Scales (ESRS), he scored 16, 25 and 38; respectively.[6-8] Therefore, the patient was judged to develop focal tardive dystonia affecting oromandibular movements due to MPH. Biperiden 2.5 mg was administered intramuscular (IM) and MPH was stopped. Symptoms remitted fully within an hour scores on UKU-SERS, AIMS and ESRS were 2, 2 and 3; respectively. No dystonic reactions or tics were observed at the first month of follow-up after discharge without treatment. The adolescent, parents and his teachers requested another trial of MPH due to impairing symptoms of ADHD which led to initiation of osmotic-controlled release oral delivery system (OROS) (Concerta, Janssen, USA) MPH 27 mg/day at the second month. There were no adverse effects at the first 2 months of treatment with this agent. After his prescription ran out and he could not attend the visit due to his examinations, the patient used a capsule of extended-release (ER) MPH 40 mg that he found at home. Dystonia emerged within 2 hours requiring application of biperiden 2.5 mg IM at the emergency department. The patient and his family were educated about the nature of the adverse effect and he was restarted on OROS MPH 27 mg/day. No adverse reactions emerged within three months and the patient is still being followed-up at our department. Evaluation with the Naranjo Algorithm yielded a score of 11 ("definite/certain").[9] Written and verbal informed consent was obtained from the patient.

DISCUSSION

Here we report an early adolescent with ADHD who developed both tardive and acute dystonic reactions probably related to extended release MPH. Rare dystonic reactions with MPH were previously reported.[3-5] Most of those involved acute cases which emerged after treatment initiation/ increase in dose or with MPH discontinuation while continuing to use antipsychotics.[4,5] There is only one other case of tardive dystonia that we are aware with MPH.[3] In that case, Pagliaro and et al. reported emergence of an episode of tardive dystonia in 9 years old male patient with ADHD who had been treated with ER MPH 27 mg/day and guanfacine 1 mg/day, who was treated with benztropine 1.5 mg IM and diphenhydramine 25 mg PO.[3] Their Naranjo score was 4 ("possible"). According to their review, there are 17 cases of MPH induced dystonia and in ten of those MPH was the sole agent. Most of the cases were male and dystonia involved perioral regions and neck leading to speech problems. Hypotheses on the etiology of tardive/acute dystonia with MPH included chronic MPH use leading to upregulation of dopamine transporters and relative depletion of dopamine, hypersensitivity of receptors at basal

ganglia or subtle basal ganglia damage.[3-5] As reported, most of the cases involved acute dystonic reactions emerging at the initiation of treatment or an increase in dose. A recent study also suggests that treatment naïve children with ADHD may have unrecognized vulnerabilities to dyskinesias, including dystonia.[10]

Our report includes the second case of tardive dystonia in an adolescent using MPH and is original in that he developed both acute and chronic formsof adverse effect with the same formulation. The observation that an alternative formulation of MPH may not lead to dystonia is also unique and needs to be replicated. It is generally recommended to discontinue the dopaminergic agent or switch to a non-stimulating agent in tardive dystonia but impairing and urgent symptoms of ADHD necessitated a trial with an alternative MPH formulation. Past history of motor/vocal tics in our patient requiring APZ treatment and paternal history of vocal tics suggest that either subtle damage to the basal ganglia or hypersensitivity of their receptors may have contributed to emergence of dystonia. Like the majority of other cases our patient was also male which may have also increased risk. Patients with ADHD treated with stimulants may be vulnerable to development of dyskinesias, including dystonia in both late and acute forms and the risk may be specific for different formulations. Our results should be replicated with further studies.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Merve Taşkan;* ***Design:*** *Yusuf Öztürk;* ***Control/Supervision:*** *Ali Evren Tufan;* ***Data Collection and/or Processing:*** *Merve Taşkan;* ***Analysis and/or Interpretation:*** *Ali Evren Tufan;* ***Literature Review:*** *Merve Taşkan;* ***Writing the Article:*** *Merve Taşkan;* ***Critical Review:*** *Yusuf Öztürk.*

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