CASE REPORT / OLGU SUNUMU

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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Acute Dystonic Reaction Following Methylphenidate Discontinuation During Combination Therapy with Risperidone: A Case Study

Risperidon Tedavisi ile Kombinasyon Kullanımda Metilfenidat Tedavisinin Kesilmesine Bağlı Gelişen Akut Distonik Reaksiyon: Bir Olgu Sunumu

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Abstract

Attention deficit hyperactivity disorder (ADHD), a prevalent neurodevelopmental disorder, is characterized by attention deficit, hyperactivity, and impulsivity. It frequently accompanies psychiatric disorders, such as oppositional-defiant disorder, anxiety, and mood disorders in children. Current studies indicate a rising use of atypical antipsychotics in conjunction with psychostimulants to treat ADHD and co-occurring disorders. However, the combination therapy may heighten the risk of adverse effects due to drug-drug interactions. One of these side effects is acute dystonic reaction (ADR), an extrapyramidal symptom characterized by involuntary muscle contractions, particularly in the head and neck region. In this case report, a 6-year-old male patient with ADHD who was initially treated with risperidone and later started on methylphenidate is presented. After discontinuing methylphenidate, the child developed ADR, involuntary contractions in his face and neck. The abrupt cessation of methylphenidate in combination therapy with risperidone resulted in the occurrence of dystonia as an extrapyramidal system side effect. Symptomatic improvement was observed with the biperiden treatment. Pharmacodynamic interactions between methylphenidate and risperidone, particularly involving dopamine pathways, were implicated in the development of ADR. This case report emphasizes the importance of recognizing and managing potential side effects, such as dystonia, when altering combinations of psychostimulant and antipsychotic medications. It also highlights the need for cautious dose adjustments and gradual tapering of medications to mitigate the risk of movement disorders. Additionally, the case underscores the significance of considering individual risk factors, medical history, and genetic predispositions in treatment decision-making.

Keywords: Acute dystonic reaction, attention-deficit hyperactivity disorder, child, methylphenidate, risperidone

Öz

Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB), yaygın bir nörogelişimsel bozukluk olup dikkat eksikliği, aşırı hareketlilik ve dürtüsellikle karakterizedir. Bu bozukluk genellikle, çocuklarda, karşıt olma karşıt gelme bozukluğu, anksiyete ve duygudurum bozukluklar gibi psikiyatrik bozukluklarla birlikte görülmektedir. Güncel çalışmalar, DEHB ve eşlik eden bozukluklar tedavi etmede atipik antipsikotiklerin psikostimulanlarla birlikte kullanımında artış olduğunu göstermektedir. Ancak, bu kombinasyon tedavisi, ilaç-ilaç etkileşimleri nedeniyle yan etki riskini artırabilmektedir. Bu yan etkilerden biri, özellikle baş ve boyun bölgesinde istemsiz kas kasılmalar ile karakterize bir ekstrapiramidal semptom olan akut distonik reaksiyondur (ADR). Bu olgu raporunda, başlangıçta risperidon ile tedavi edilen ve daha sonra metilfenidat tedavisine başlanan 6 yaşındaki dikkat eksikliği hiperaktivite bozukluğu (DEHB) tanılı bir erkek hasta sunulmaktadır. Metilfenidatın kesilmesinin ardından, çocukta, ağız ve boyun bölgesindeki istemsiz kas kasılmaları-ADR- gelişmiştir. Metilfenidatın risperidon ile kombinasyon tedavisi sırasında aniden kesilmesi, bir ekstrapiramidal yan etki olan distoniye neden olmuştur. Biperiden tedavisi ile belirtilerde iyileşme gözlemlenmiştir. Metilfenidat ve risperidon arasındaki özellikle dopamin yolaklarını içeren farmakodinamik etkileşimler, ADR gelişiminde rol oynamaktadır. Bu olgu sunumu, psikostimülan ve antipsikotik ilaç kombinasyon değişikliklerinde distoni gibi potansiyel yan etkilerin tanınması ve yönetilmesinin önemini vurgulamaktadır. Ayrıca, hareket bozuklukları riskini azaltmak için ilaçların dikkatli doz ayarlamaları yapılması ve kademeli olarak azaltılması gerekliliğine dikkat çekmektedir. Ek olarak, bu olgu ile birlikte, tedavi kararlarında bireysel risk faktörleri, tıbbi geçmiş ve genetik yatkınlıkların dikkate alınmasının önemi vurgulanmaktadır.

Anahtar Kelimeler: Akut distonik reaksiyon, dikkat eksikliği hiperaktivite bozukluğu, çocuk, metilfenidat, risperidon

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by attention decifit and/or hyperactivity and/or impulsivity, with symptoms often persisting throughout life (1). Psychiatric diagnoses such as oppositional defiant disorder (ODD), conduct disorder, anxiety disorder, and mood disorders are commonly associated with ADHD in 50-70% of children and adolescents (2). As our understanding of comorbidity in ADHD improves, the concurrent use of atypical antipsychotics with psychostimulant drugs is increasingly prevalent, in line with the current literature (3). On the other hand, drug combination therapies may increase the incidence of some side effects because of drug-drug interactions (3,4).

Acute dystonic reaction (ADR) is an extrapyramidal system side effect that occurs mostly due to antipsychotic and antiemetic drugs. It is typically characterized by involuntary, persistent, or spasmodic muscle contractions in the head and neck region (5). Although it usually affects the eye (oculogyric crisis), jaw, tongue (dysarthria) and neck muscles (torticollis), it may also affect the trunk muscles (opisthotonus, Pisa syndrome). Oculogyric crisis, a specific form of ADR, refers to deviation of the eyes, usually upwards and sometimes laterally, for a certain period of time due to contraction of the extraocular eye muscles (6).

In clinical practice, it is crucial to recognize ADR, an emergent and potentially life-threatening side effect that can arise from the use of a combination of psychostimulant and antipsychotic drugs. In this case report, we describe the clinical presentation and management of ADR that occurred after discontinuation of methylphenidate (MPH) administered concurrently with risperidone.

Case Presentation

A male child who had been followed up in Ankara University Faculty of Medicine, child and adolescent psychiatry outpatient clinic for two years, was first referred to our clinic in December 2021. The case was 4 years old at the time, and he underwent psychiatric evaluations in infant mental health unit and was diagnosed with Global Developmental Delay, Speech-Sound Disorder and ADHD with autistic traits. Subsequently, he was referred to special education by providing psychoeducation to the family, and risperidone 0.25 mg/day was started for ADHD symptoms.

During prenatal inquiries, it was revealed that the mother had experienced two miscarriages before the current pregnancy, and during this pregnancy, she underwent antibiotic treatment for a urinary tract infection. Regarding the delivery history, it was disclosed that she delivered via cesarean section at 36 weeks of gestation, with bradycardia noted on NST, but no complications arose during or after delivery. Postnatal early developmental milestones were a bit delayed. For example, speaking the first word at 1.5 years, walking at 1.5 years, and pointing at 1.5 years.

Upon inquiry into the child's current psychiatric complaints and functioning in home and school settings, it was revealed that he lacked adequate social interactions, refrained from engaging with peer groups at school, was easily distracted during lessons, and had difficulty following instructions. Comorbid medical conditions involved thinness of the pituitary gland and pectus carinatum, and the patient was followed up in the pediatrics endocrinology and pediatric pulmonology departments without any prescribed medication.

Upon reviewing the family history, it was found that his mother had bipolar disorder, and her grandmother had depression. His brother received a genetic diagnosis (Linked 20 deletion) and was followed up with intellectual disability (ID) and ADHD. Although there was no confirmed genetic diagnosis for the father, it was noteworthy that he displayed a dysmorphic facial feature during the psychiatric interview.

After the initial diagnostic interview, follow-up appointments were scheduled every 2 months. At the age of 4 years and 3 months, the IQ score on the Stanford-Binet intelligence scale was 63, indicating mild ID. Following psychiatric evaluations at our outpatient clinic, the child was diagnosed with mild ID, ADHD, Speech-Sound Disorder, and Social (Pragmatic) Communication Disorder. During the follow-up visits, in May 2022, immediate-release MPH at a dose of 10 mg/day was initiated, and in June 2022, the dose was increased to 20 mg/day. In August 2022, the risperidone 0.5 mg/day was added. Because of increased hyperactivity in September 2022, immediate-release MPH treatment was discontinued, and extended-release MPH at a dose of 10 mg/day was initiated. The patient, who partially benefited from the treatment, had the extended-release MPH dose increased to 20 mg/day in May 2023, with the addition of short-acting MPH at a dose of 10 mg/day to be used if necessary in the afternoon. Throughout the follow-up period, the patient responded positively to this treatment and did not report any side effects.

In October 2023, when he was 6 years old, a comprehensive psychiatric evaluation was conducted. The patient appeared younger than his chronological age in terms of physical development and had a dysmorphic appearance. He responded when called by name, maintained eye contact, and demonstrated joint attention skills and social reciprocity. However, his social interaction was limited and of poor quality. During the interview, his attention span was shorter than expected for his age and developmental level, and he displayed hyperactivity. The patient exhibited limited speech content, articulation difficulties, and

prosodic errors. While his receptive language skills were in line with those of his peers, the child had a flat affect with minimal use of gestures and facial expressions, and did not engage in spontaneous conversation initiation. There were no concurrent repetitive motor behaviors (stereotypy), insistence on sameness or highly restricted, fixated interests, or sensory hypo- or hyper-sensitivities. His current psychiatric diagnoses was established as "Mild ID, ADHD, Speech-Sound Disorder, and Social (Pragmatic) Communication Disorder".

In the last referral to our clinic (October 2023), psychiatric scales, including the Conners Rating scale, Atilla Turgay DSM-IV-Based Screening and Evaluation scale, and Child Behavior Check List/6-18 years for parents and teachers were completed. These rating scales also confirmed the diagnoses of ADHD accompanied by subclinical ODD. To determine autism characteristics, the Autism Spectrum Screening Questionnaire scale score filled out by the parent for the child was 22, above the clinical cut-off value (7), supporting the diagnosis of ADHD with autistic traits of the case. Due to the persistence of hyperactivity symptoms, the dose of long-acting MPH was increased to 30 mg/day in combination with risperidone (0.5 mg/day).

Approximately two weeks after this psychiatric appoinment, he presented to paediatric emergency department with the complaints of inability to close his mouth, throwing his head back, upward deviation of eye, involuntary neck spasms and unsteady walking. At around 11.00 a.m. in the morning, contractions in the neck started, he could not close his mouth, could not eat, and these symptoms did not go away and continued, and he was admitted to the emergency department. He was conscious and had no urinary/fecal incontinence at the time of emergency presentation. When the pediatric was examined, there were no contractions in the rest of the body or signs of epileptic seizure or postictal confusion. There was no fever, infection history, or rash present. In the pediatric emergency department, with a prediagnosis of acute dystonia, current medications were discontinued, and 5 mg/mL intramuscular biperiden was administered. A few hours later, the symptoms resolved and there was no recurrence.

The child applied to our outpatient clinic the next day accompanied by her mother, who reported that the contractions did not recur. Upon further inquiry into the medication history, it was discovered that on the day of the incident, the mother had skipped his morning dose of MPH after the dose had been increased, and had taken the prescribed risperidone treatment the previous evening. Additionally, the mother reported that during a follow-up visit in June 2023, approximately 2-3 weeks after the long-acting MPH dose was increased from 10 mg/day to 20 mg/day, the patient experienced similar contractions and difficulty closing his mouth. However, these episodes were briefer and less severe; therefore, they did not warrant a hospital visit. As a result of psychiatric evaluation and medical history, a prediagnosis of ADR due to MPH withdrawal during the combination use of risperdone was made. Antipsychotic medication (risperidone) was discontinued, and the patient was switched to the long-acting MPH 12-h form. During subsequent follow-ups, there were no signs of dystonia recurrence in the patient, who demonstrated improvement with the treatment. The current MPH dose remains at 27 mg/day, with no reported adverse effects.

Discussion

In this case report, it was indicated that the abrupt discontinuation of MPH during combination therapy with risperidone resulted in the rare occurrence of dystonia. Similar cases of experiencing ADR when the stimulant component is removed from a treatment regimen consisting of antipsychotic and stimulant combination have been previously reported (3,4,8,9).

ADR is an extrapyramidal symptom (EPS) marked by involuntary, transient, or enduring muscular contractions, notably affecting the head, neck, and face. ADR, as a psychiatric emergency, commonly emerges shortly after the initiation of an antipsychotic medication regimen and antiemetic pharmacotherapies. In the literature, there have been a few reports of rebound dystonia upon cessation of MPH treatment, particularly during concurrent use of antipsychotics (5,10). ADR presentations have also been reported following the administration of MPH in the absence of antipsychotic usage (11,12). Another case developed acute focal dystonia with MPH following an increase in dosage (13). In our case, a possible explanation for the development of dystonia could be the first scenario, the cessation of MPH during concurrent usage with risperidone and MPH.

The effects induced by psychostimulants, exemplified by MPHs, are intricately associated with the dopamine transporter. This association stems from the binding of these stimulants to the dopamine transporter, which consequently precipitates escalated dopamine levels within the synaptic cleft (14). Dystonic reactions may manifest as a withdrawal symptom following chronic MPH use due to dopaminergic neurotoxicity, which leads to the downregulation and sensitization of dopamine pathways at the striatal level and the destruction of axon terminals in the striatum and caudate nucleus, resulting in permanent sensitivity (15,16). Risperidone is a selective monoaminergic antagonist with high affinity for serotonin (5-HT-2) and dopamine D2 receptors. It can be argued that MPH indirectly increases synaptic dopamine levels in the striatum and, upon withdrawal, leads to a significant decrease in dopamine, thereby potentially augmenting antipsychotic activity and consequently increasing the risk of EPS. Intentional or accidental abrupt discontinuation

of MPH during combination therapy (with risperidone) may disrupt the established dopaminergic balance, precipitating movement disorders (3,17). Additionally, psychostimulants, as evidenced by their ability to reduce D2 antagonist binding, may decrease risperidone binding to D2 receptors within the striatum. In other words, stimulants may competitively inhibit risperidone, increasing risperidone binding upon stimulant withdrawal, resulting in EPS (18). In conclusion, the use of MPHs during antipsychotic treatment is a risk factor for dystonia; thus, clinicians should be aware of these potential EPS side effects and exercise caution when combining psychostimulants with any antipsychotic medications (3).

The established risk factors for ADR include young age, male gender, primary psychotic disorder, and previous episodes of dystonic reactions (19). In this case, the presence of male gender, school-age child, and previous history of dystonic reaction aligns with possible risk factors. Moreover, considering the medical and psychiatric comorbidities in the case, as well as the increased genetic risk burden within the family, it is conceivable that our patient harbors a genetic disorder predisposing him to neurodevelopmental disorders and drug interactions, resulting in susceptibility to dystonic symptoms (20,21). Therefore, advanced genomic testing, such as microarray analysis and/or exome sequencing, is warranted for further assessment.

Another explanation of the vulnerability of side effects in this case might be the presence of comorbidities such as ID and ASD, which have been emphasized to potentially lower the effectiveness of MPH (22), and increase the likelihood of side effects beyond expectations (23). In our case, there were also comorbidities accompanying ADHD, including ID, ODD, and autistic traits, which could have made the patient more susceptible to adverse effects.

It has been announced that biperiden has shown efficacy for treating dystonia due to MPH withdrawal (9). Similarly, in our case, dystonia improved following this treatment and did not recur thereafter.

This case report informs clinicians about potential side effects, such as dystonia, that may arise when altering combinations of psychostimulant and antipsychotic medications, and suggests that abrupt cessation of stimulants may lead to the development of movement disorders. Therefore, appropriate caution should be exercised when adjusting medication doses or discontinuing a medication from a psychostimulant and antipsychotic combination. Clinicians should be aware of potential side effects, including dystonia, when the stimulant component of a psychostimulant and antipsychotic medication combination regimen is altered (4). To mitigate the complex pharmacodynamic drug-drug interaction risk between MPH and risperidone, it may be necessary to implement slower dose reduction or titration for both agents before cessation or initiation, or to initiate a prolonged washout period when transitioning between agents (24).

The precise underlying mechanisms of ADR side effects of MPH and risperidone combination therapy remain uncertain. However, the findings of this case study suggest that initiating stimulant therapy at a low dose and gradually tapering doses, especially when used concomitantly with antipsychotics in children and adolescents, may be beneficial.

Ethics

Informed Consent: Informed consent was obtained from the child and his parents.

Authorship Contributions

Surgical and Medical Practices: R.D.T., Ü.B., D.T., Concept: R.D.T., Ü.B., Design: R.D.T., Ü.B., Data Collection: Ü.B., D.T., Literature Search: R.D.T., Ü.B., Writing: R.D.T., Ü.B.

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