Dopa-responsive dystonia masked by biperiden dependence: A case report

Biperiden bağımlılığı ile maskelenen dopa-duyarlı distoni: Bir olgu sunumu

Abstract

Anticholinergic drugs are widely employed for the treatment of various conditions, including extrapyramidal symptoms. However, recent research suggests a potential link between the misuse of anticholinergics and inherited movement disorders, such as dopa-responsive dystonia (DRD). This report presents a case study of a 61-year-old woman who had been experiencing involuntary movements, including dystonia and tremors, for 30 years. Initially, she was prescribed anticholinergic agents like biperiden, which provided partial relief. Nevertheless, her symptoms gradually worsened, and she developed a tolerance to anticholinergics. Subsequently, a diagnosis of DRD was confirmed, and her symptoms exhibited significant improvement following treatment with levodopa. This case underscores the importance of healthcare professionals being aware of the potential association between anticholinergic misuse and inherited movement disorders. Early identification and management of underlying conditions like DRD can aid in preventing unnecessary and potentially harmful utilization of anticholinergics, thereby enhancing patient outcomes and reducing the risks of dependence and abuse.

Keywords: Antichlonicergic syndrome; case report; dopa-responsive; dystonia

Öz

Antikolinerjik ilaçlar, ekstrapiramidal semptomlar (EPS) da dahil olmak üzere bir dizi durumu tedavi etmek için yaygın olarak kullanılmaktadır. Bununla birlikte, ortaya çıkan kanıtlar antikolinerjik kötüye kullanımı ile Dopa–Duyarlı Distoni (DDD) gibi kalıtsal hareket bozuklukları arasında olası bir bağlantı olduğunu göstermektedir. Distoni ve tremor dahil olmak üzere 30 yıllık istemsiz hareket öyküsü olan 61 yaşında bir kadın olguyu sunuyoruz. Başlangıçta kısmi rahatlama sağlayan biperiden başta olmak üzere çeşitli antikolinerjik ajanlarla tedavi edildi. Ancak semptomları zamanla kötüleşti ve antikolinerjiklere karşı tolerans geliştirdi. Kapsamlı değerlendirmelerden sonra hastaya DDD teşhisi konmuş ve levodopa semptomlarında belirgin bir iyileşme sağlamıştır. Bu makale, özellikle ailesinde hareket bozukluğu öyküsü bulunan hastalarda, antikolinerjik kullanımı ile kalıtsal hareket bozuklukları arasındaki potansiyel ilişkinin önemini vurgulamaktadır. DDD gibi altta yatan durumların erken tanınması ve yönetimi, antikolinerjiklerin gereksiz ve potansiyel olarak zararlı kullanımını önleyerek hasta sonuçlarının iyileşmesine ve bağımlılık ve kötüye kullanım riskinin azalmasını sağlayabilir.

Anahtar Sözcükler: Antikolinerjik sendrom; distoni; dopa-responsif; olgu sunumu

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INTRODUCTION

Dopa–responsive dystonia (DRD) is a multifaceted movement disorder resulting from genetic mutations that lead to deficits in the synthesis of neurotransmitters, particularly dopamine (1). These deficiencies give rise to the distinctive symptoms of DRD, manifesting in diverse forms such as dystonia-parkinsonism, myoclonus dystonia, and other dystonic disorders (2,3). DRD is a rare genetic disorder, with an estimated prevalence of 1 in 2 million individuals, and it can present at any age (2). Recent research has shown that DRD is often underdiagnosed, leading to delayed or missed diagnosis (2). One study revealed that the median duration from symptom onset to diagnosis was eight years, emphasizing the need for heightened awareness of this condition among healthcare professionals (2). Early diagnosis is essential for effectively managing DRD, typically involving lifelong treatment with L-dopa therapy (1). However, limb dystonia is usually the first sign of DRD and may be accompanied by tremors, gait abnormalities, and other motor symptoms (1,4). The severity and progression of these symptoms can vary greatly among individuals, and some patients may experience non-motor symptoms such as cognitive impairment, psychiatric disorders, and autonomic dysfunction (1).

Several studies have consistently demonstrated a significant association between DRD and psychiatric comorbidities, particularly depression, anxiety, and obsessive-compulsive disorder (OCD) (4). For example, Furukawa et al. found that a considerable proportion of DRD patients (25%) experienced depression, a rate significantly higher than that of the general population (5). López-Laso et al. (2011) also reported a higher prevalence of anxiety in patients with DRD than in healthy controls (4). In addition, some patients with DRD have reported OCD symptoms, suggesting a possible link between the disorder and dysregulation of the serotonergic system (6). This link may be explained by the involvement of serotonergic pathways in the pathogenesis of DRD, as serotonin is a crucial neurotransmitter that regulates mood and emotions (1). DRD patients have been shown to have a higher propensity for developing these comorbidities compared to the general population, and their presence can exacerbate motor symptoms and negatively impact the quality of life of affected individuals (4,7). These psychiatric comorbidities can worsen the motor symptoms of DRD and harm the quality of life of affected individuals (4,6). The co-occurrence of depression and DRD is not uncommon, and evidence suggests that depression may exacerbate DRD symptoms (4). Moreover, DRD has been associated with suicide attempts, underscoring the importance of timely and accurate diagnosis, especially in cases where patients exhibit unexplained symptoms or have a family history of movement disorders (1). Management of DRD through L-dopa therapy can be successful if initiated promptly and accurately (1,2).

Anticholinergic medications, such as biperiden and trihexyphenidyl, are commonly used to prevent and treat the dystonia side effects of neuroleptics. However, prolonged use of these medications can lead to dependence and abuse. Furthermore, anticholinergic drug abuse has been linked to DRD, highlighting the need for healthcare professionals to be aware of this association (2,8). Identifying and appropriately managing underlying conditions like DRD can prevent unnecessary and potentially harmful anticholinergic agent usage, leading to better patient outcomes and reduced risks of dependence and abuse (8).

The findings of this study suggest that there is a potential link between DRD and anticholinergic drug abuse. Healthcare professionals should be aware of this link and should evaluate patients with unexplained symptoms or a family history of movement disorders for DRD. Early diagnosis and treatment of DRD can help to prevent the development of serious health problems.

CASE

We presented the case of a 61-year-old female patient with a history of depression and suicide attempt who was referred to our psychiatric clinic to manage biperiden abuse. The patient presented with gait disturbances and lower extremity dystonia since the age of 10. The gait disturbances were characterized by slow, unsteady gait with small, tremulous steps. Initial symptom improvement was observed with scopolamine, an anticholinergic drug, which her brother and aunt had also used for similar complaints. The patient had pre-

viously been hospitalized for depression and a suicide attempt following the birth of her second child at the age of 27. After hospitalization, her depressive symptoms improved, and her level of functioning increased. However, she was readmitted to the hospital due to arm and leg stiffness. Upon evaluation, the patient was diagnosed with drug-induced dystonia and prescribed biperiden. Despite biperiden treatment, the patient's symptoms persisted, although with some functional improvement. Subsequently, the patient resumed using scopolamine, which partially relieved her symptoms and allowed her to maintain her daily routine.

During a hospitalization for depressive symptoms and suicidal ideation, the patient developed stiffness in her extremities, leading to a diagnosis of drug-induced dystonia. Biperiden was prescribed, but dystonic contractions persisted despite the medication, although the severity did not significantly affect her daily activities. Consequently, she took biperiden (10-15 mg/day) for nearly three decades. It is important to note that her depressive symptoms improved after her initial hospitalization, leading to enhanced functioning. However, the prolonged use of biperiden for dystonia management raises concerns regarding the potential development of tolerance, dependence, and adverse effects. Therefore, a comprehensive evaluation of the long-term consequences of biperiden use in the treatment of drug-induced dystonia is essential.

This patient was referred to our university hospital's psychiatric clinic for the management of biperiden abuse. The referral was prompted by the patient's repeated requests for biperiden prescriptions, and the patient had a history of suicide attempts and hospitalizations. Although the patient had a long history of biperiden use, she had stopped taking the medication until recently, when she resumed it. Despite receiving various treatments during previous hospitalizations, the patient had not been prescribed biperiden until her recent request for the drug. Given these circumstances, the patient was admitted to our clinic for diagnostic clarification and the development of an appropriate management plan. The patient's psychiatric history revealed a lack of remission during the illness. On her mental state examination, the patient demonstrated adequate self-care. She was polite and interested in communicating with the interviewer. Her mood was slightly depressed and she was anxious about the treatment process. She was fully conscious with orientation to time, place and person with adequate attention. There were no problems with immediate, recent or remote memory. The patient showed a coherent and logical thought process, with no signs of thought derailment or flight of ideas. Her speech was articulate and well structured, conveying her thoughts and feelings with clarity. She demonstrated a rich vocabulary and used appropriate grammar and syntax in her communication. In terms of thought content, the patient showed a realistic understanding of her circumstances and acknowledged her concerns about the ongoing treatment process. Her expressions of mild depression and anxiety were accompanied by coherent explanations of the associated emotional experiences. She articulated her worries and anxieties about treatment outcomes, demonstrating insight into her psychological well-being. There were no phobias, obsessions or delusions in her thought content. Additionally, there were no observable perceptual abnormalities, such as hallucinations or illusions. The patient did not report any distortions in sensory experiences or unusual perceptual phenomena during the evaluation.

Overall, the patient's mental state examination revealed a well-organized thought process, coherent speech, and a balanced understanding of her own mental state. Her ability to express herself articulately and reflectively, while providing insight into her emotional experiences, showcased her engagement and capacity for introspection.

During the patient's hospitalization, it was observed that a gradual tapering of biperiden dosage resulted in gait disturbances. A neurological examination was conducted, which revealed bilateral foot dystonia in the absence of any withdrawal symptoms. The patient was referred to the neurology department for further evaluation. The neurology team suspected that the patient's symptoms might be related to dopaminergic pathways, given the presentation of dystonia without any significant abnormalities on magnetic resonance imaging of the brain. As such, the patient was initiated on low-dose levodopa therapy. Notably, the patient demonstrated a significant improvement in symptoms following levodopa administration and completely recovered within a week. The patient reported feeling

better than ever before. Based on these findings, a diagnosis of DRD was confirmed, highlighting the importance of considering DRD as a possible diagnosis in patients presenting with dystonic symptoms, even without a family history.

DISCUSSION AND CONCLUSION

DRD is a relatively uncommon yet clinically significant neurological disorder characterized by childhood or adolescent onset of dystonia that responds to levodopa therapy. Despite its distinctive clinical features and the availability of definitive genetic tests, DRD remains underdiagnosed. Levodopa therapy plays a dual role as both a diagnostic tool and an effective treatment for childhood-onset dystonia, highlighting the importance for clinicians to be knowledgeable about the clinical spectrum of DRD and consider it as a potential differential diagnosis, even in the absence of a family history. Additionally, tetrahydrobiopterin, a co-factor involved in serotonin and norepinephrine synthesis, has been implicated in mood-related effects in DRD. While there are reports of depression in individuals with DRD, the relationship between DRD and mood disorders is not yet fully understood. In our patient's case, dystonia resulting from antidepressant use was initially misdiagnosed as biperiden sensitivity, leading to a delayed diagnosis and treatment (1,2,9).

Moreover, there have been reports of potential misuse of biperiden as an anticholinergic agent, particularly among patients with psychotic disorders who are not using neuroleptics. Biperiden has been found to improve negative psychotic symptoms and inhibit neuroleptic-induced anhedonia, potentially explaining its misuse. Interestingly, biperiden has also shown mood-elevating effects in healthy individuals, although the exact mechanism of its anticholinergic dependence remains unclear (6,8).

This case report presents a patient who had been treated with biperiden for 30 years for undiagnosed symptoms related to dopa-responsive dystonia (DRD), resulting in drug-induced dystonia. The patient did not exhibit signs of addiction, such as craving, withdrawal, seeking behavior, or functional impairment. To our knowledge, this is the first report documenting the long-term use of biperiden for DRD without a definitive diagnosis. Initially misdiagnosed with depression, the patient received various antidepressant medications, including fluoxetine and escitalopram, without significant improvement. Following the onset of dystonia, treatment with biperiden resulted in marked symptom improvement. However, the diagnosis of DRD was not established until 30 years later. This case report emphasizes the importance of a comprehensive diagnostic approach in patients presenting with dystonic symptoms, particularly those with a family history of DRD. Genetic testing and personalized medication management can significantly enhance patient outcomes.

Further research is warranted to understand the underlying mechanisms of DRD and to develop effective treatments that address the intricate relationship between mood disorders, dystonia, and pharmacological interventions. The case also raises questions regarding the efficacy and safety of biperiden in managing drug-induced dystonia, necessitating additional research in this area. Current treatments for dystonia have limited effectiveness, underscoring the need for continued investigation into the underlying pathophysiological mechanisms of this condition (6,8).

This case underscores the importance of considering DRD as a potential diagnosis in patients presenting with dystonia, even without a family history. Personalized treatments based on genetic and phenotypic characteristics may offer improved symptom relief and enhance patient outcomes. Furthermore, ongoing research is essential to advance our understanding of the complex relationship between mood disorders, dystonia, and pharmacological interventions.

In conclusion, this case report highlights a situation where the diagnosis of DRD was initially obscured by biperiden dependence. The case emphasizes the broad spectrum of phenotypes associated with DRD, ranging from asymptomatic to severe dystonia and including symptoms of depression and suicidal ideation. Therefore, clinicians must exercise caution when managing patients suspected of having DRD, as early diagnosis and treatment can significantly improve outcomes. Additionally, our findings suggest the need for caution when treating patients with biperiden dependence, as it may mask the underlying diagnosis of DRD and complicate patient management. Further studies are

necessary to elucidate the underlying mechanisms of DRD and explore novel therapeutic options that can enhance symptom control and minimize the risks associated with long-term medication use.

Conflict-of-interest and financial disclosure

The author declares that he has no conflict of interest to disclose. The author also declares that he did not receive any financial support for the study.

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