CASE REPORT

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Treatment of Comorbid Schizophrenia in an Adolescent with Osteogenesis Imperfecta: A Case Report

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ABSTRACT

Osteogenesis imperfecta (OI) is a rare connective tissue disorder characterized by bone fragility, growth retardation, hearing loss, and short stature. Literature on the comorbidity of OI and psychotic disorders is limited. Antipsychotic side effects such as hyperprolactinemia, sedation, and orthostatic hypotension may increase fracture risk, presenting challenges in comorbid cases. Here, we describe a 14-year-old male with OI and schizophrenia. The patient presented with a three-month history of irritability, self-harm, auditory hallucinations, and referential delusions. His history included multiple fractures, leading to OI diagnosis at age 8. He was admitted with acute psychotic disorder and treated with aripiprazole 20 mg/day, resulting in significant symptom improvement. No new bone fractures were observed during one year of follow-up. This case highlights the management of comorbid OI and schizophrenia. Fracture risk is a critical concern in OI patients. Clinicians should carefully select antipsychotics in the presence of psychosis and closely monitor patients to minimize adverse effects.

Keywords: Adolescent, antipsychotics, osteogenesis imperfecta, schizophrenia, side effects

INTRODUCTION

Osteogenesis imperfecta (OI) is an inherited connective tissue disease characterized by bone fragility and deformity, growth retardation, blue sclera, hearing loss, short stature and hyperlaxity (Sillince et al. 1979, Sillence 1988). The prevalence of OI is estimated to be approximately 1 in 10,000 births (Rauch and Glorieux 2004). The most common genetic causes of OI are pathogenic variants in the *COL1A1* and *COL1A2* genes, which encode the alpha1 and alpha2 chains of type I collagen (Chetty et al. 2021).

Schizophrenia is a serious psychiatric disorder that affects approximately 1% of the population worldwide. The disorder, which presents with symptoms such as psychosis, apathy, withdrawal, and cognitive impairment, negatively affects the individual's social and occupational functioning, and self-care (Mueser and McGurk 2004). While antipsychotic medications play a fundamental role in the management of schizophrenia, their serious side effects should also be taken into consideration (Muench and Hamer 2010).

Common side effects of antipsychotics include sedation, dry mouth, constipation, akathisia, weight gain, hyperprolactinemia, and sexual dysfunction. More serious side effects include acute dystonia, tardive dyskinesia, neuroleptic malignant syndrome, myocarditis, and agranulocytosis (Stroup and Gray 2018). Furthermore, it has been reported that antipsychotics may increase the risk of bone fractures due to side effects such as hyperprolactinemia, sedation, and orthostatic hypotension (Stahl et al. 2010).

The association between antipsychotics and fracture risk has been investigated in several studies. In a large-scale case–control study, the likelihood of hip or femoral fractures was reported to be significantly higher among individuals using antipsychotics, with this increase being more pronounced during long-term use (Hugenholtz et al. 2005). A meta-analysis including nineteen observational studies demonstrated that

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fracture risk was approximately 1.5 times higher, and this effect was more evident with first-generation antipsychotics (Lee et al. 2017). In a similar meta-analysis, antipsychotic use was found to be associated with an increased risk of both hip fractures and overall fractures (Papola et al. 2018). In a meta-analysis conducted by Guo et al. (2024), more than 3.4 million patients from 28 studies were examined; it was reported that both typical and atypical antipsychotics among psychotropic drugs increase the risk of falls and fractures. Therefore, caution should be exercised in the selection and monitoring of antipsychotics in the treatment of OI patients.

There are a limited number of studies in the literature on the relationship between OI and psychiatric disorders. Studies conducted on children and adults diagnosed with OI have reported findings such as feelings of being different, social isolation, difficulties in interpersonal relationships, fear of fracture, and depressive symptoms (Tsimicalis et al. 2016). Studies investigating the coexistence of OI with psychosis and mood disorders include a few case reports. These include: a case of acute postpartum psychosis developing in a 27-year-old woman diagnosed with OI (Koch and Bauer 2012), a 33-year-old patient showing psychotic symptoms together with OI (Özkorumak et al. 2017), and two cases of schizophrenia observed alongside OI diagnosis in the same family (Chodirker and Varsamis 1972). The patients in the first two cases were treated with risperidone. To the best of our knowledge, no case reporting the coexistence of OI and early-onset schizophrenia has been found. In this case report, a 14-year-old male patient diagnosed with schizophrenia and OI who was hospitalized with psychotic symptoms and then followed up for one year is presented, and treatment options are discussed in light of the existing literature.

CASE PRESENTATION

A 14-year-old male patient applied to a city hospital's child and adolescent psychiatry outpatient clinic with irritability, agitation, self-injurious behaviors, auditory hallucinations, and referential delusions for the past three months. The patient had worsening self-care and social withdrawal for the previous five months. According to his mother, the patient had become more aggressive than usual and had started keeping the curtains in his room constantly closed, believing he was being watched by others. The patient stated that he heard voices insulting and belittling him. He also said he thought people in the park across from his house were looking at him and mocking him.

The patient was an eighth-grade student, an only child, and lived with both parents. During the mental status examination, his clothing was appropriate for his socioeconomic status. His short stature and reduced self-care were noticeable in his appearance. His affect was irritable and anxious. Speech output was reduced. Memory and orientation were normal. Clinically, his intellectual capacity gave the impression of mild intellectual disability. Thought content was poor. Auditory and visual hallucinations and delusions of reference were detected. Reality testing and judgment were impaired. Insight into his symptoms was limited.

Although his developmental milestones were normal during the preschool period, he only acquired reading and writing skills in the second grade of elementary school. His academic performance during elementary and middle school was below that of his peers. At the age of eight, he was diagnosed with OI after a pathogenic variant was detected in the *COL1A1* gene during examinations conducted due to multiple bone fractures. In order to avoid bone fractures during childhood, he spent most of his time at home. As a result, his peer relationships were always limited. Five relatives, including his mother and aunt, had a diagnosis of OI. Although there was no history of mental illness in his family, it was reported that his father had shown untreated paranoid symptoms in his twenties.

The patient who was assessed at our hospital's child and adolescent psychiatry outpatient clinic was considered to have a preliminary diagnosis of acute psychotic disorder and was admitted to the inpatient unit for arrangement of treatment. To investigate possible organic causes underlying the first psychotic episode, consultations were requested from the departments of pediatric neurology and pediatric metabolism. Biochemical tests were performed, and brain magnetic resonance imaging (MRI) and electroencephalography (EEG) examinations were performed. Brain MRI revealed deepening of hemispheric cortical sulci and enlargement of the third and lateral ventricles, consistent with cerebral atrophy. The fourth ventricle appeared normal in shape and position, basal cisterns were intact, and both the pons and mesencephalon demonstrated normal signal characteristics (Fig. 1). Since no previous brain MRI was available, a comparison could not be made. The patient's metabolic tests, EEG, abdominal ultrasonography**,** and fundus examination were normal. The evaluations did not reveal any organic pathology that could explain the psychotic condition. According to the results of the Wechsler Intelligence Scale for Children – Revised (WISC-R) and clinical evaluation, the patient was found to have mild intellectual disability. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime Version, DSM-5 was administered to the patient, and the findings were considered consistent with a diagnosis of early-onset schizophrenia. The patient's antipsychotic treatment was planned and a consultation was requested from the pediatric endocrinology department regarding the initiation of aripiprazole. It was determined that the patient had undergone dual-energy X-ray absorptiometry (DEXA)

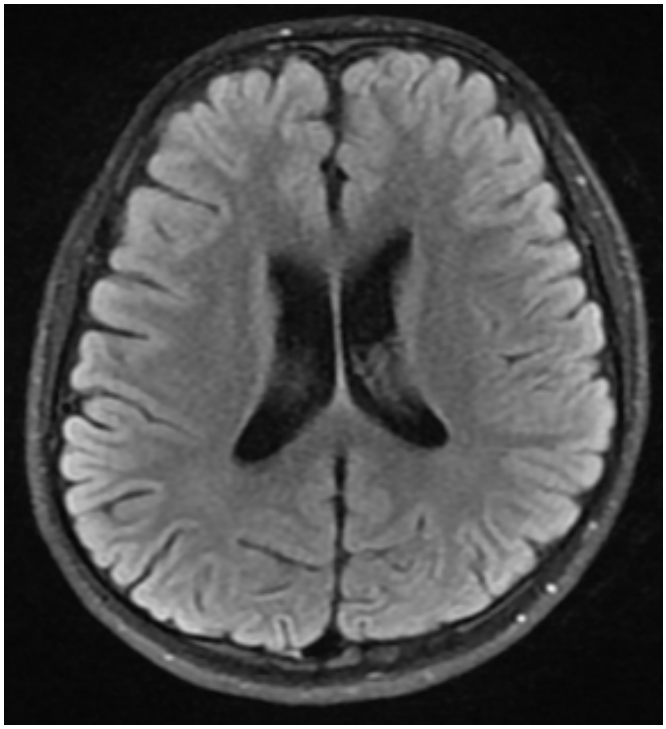

Figure 1. Brain MRI shows cerebral atrophy consistent with deepening of the hemispheric cortical sulci and enlargement of the third and lateral ventricles.

evaluation two months prior to hospitalization. The most recent DEXA results were as follows: L1–L4 BMD: 0.748; Z-score: –2.0; height-adjusted BMD SDS: 1.69. Pediatric endocrinology consultation revealed no contraindication to initiating aripiprazole. The treatment was arranged as aripiprazole 20 mg/day during his 30-day hospital stay. Starting from the patient's admission, routine biochemistry, complete blood count, and prolactin levels were examined weekly. The patient's prolactin level was within the reference range, and no pathological findings were detected in other laboratory tests. Improvement was observed in both positive and negative symptoms with the treatment administered. The Scale for the Assessment of Negative Symptoms score used to evaluate negative symptoms decreased from 64 to 44. The Scale for the Assessment of Positive Symptoms score, which evaluates positive symptoms, decreased from 35 to 18. After a 30-day inpatient treatment period, the patient was discharged with the current treatment, as his psychotic symptoms had subsided and a significant increase in his functioning had been observed. The patient was followed up at the outpatient clinic for one year after discharge, and it was observed that he remained stable in terms of psychotic symptoms and did not experience any bone fractures with aripiprazole 20 mg/day treatment. At the end of the one-year follow-up period, the patient's assessment revealed a Scale for the Assessment of Negative Symptoms score of 30 and a Scale for the Assessment of Positive Symptoms score of 13.

DISCUSSION

This case presentation describes a 14-year-old male patient diagnosed with early-onset schizophrenia comorbid with OI, a rare hereditary connective tissue disorder. While the current literature includes several case reports describing the coexistence of OI and psychotic disorders in adults, to the best of our knowledge, this case report is among the first reported in the adolescent age group. Furthermore, the fact that aripiprazole treatment resulted in improvement in psychotic symptoms and did not cause new bone fractures during one year of follow-up provides noteworthy findings regarding the management of this rare comorbidity.

As mentioned above, due to the patient's first psychotic episode and the findings of cerebral atrophy, underlying organic pathologies were investigated, but no organic pathology associated with the psychotic episode was detected. Case reports of cerebral atrophy accompanying OI have been reported in the literature (Brooks et al. 1989, Khandanpour et al. 2012). Furthermore, cerebral atrophy is a neuroanatomical finding that can be observed in both intellectual disability and schizophrenia (Spencer et al. 2005, Yang et al. 2025). The clinical relevance of this finding in our case could not be clarified due to the absence of previous brain MRI.

The comorbidity of OI and schizophrenia is rare, and recent studies have shown that in patients with schizophrenia, the *COL1A1* gene and several other collagen genes function differently, and this may be associated with structural and inflammatory processes in brain tissue (Bhuiyan et al. 2024). The *COL1A1* gene mutation is one of the primary causes of OI. Therefore, the coexistence of both OI and schizophrenia in our case suggests that the same gene may play a role in the development of both diseases; however, this relationship requires further investigation in the future.

The risk of bone fractures during antipsychotic treatment is of critical importance for these patients. Antipsychotic drugs remain the most commonly used agents in the treatment of schizophrenia today. However, various studies conducted in recent years have revealed that the use of these drugs may be associated with an increased risk of bone fractures (Hugenholtz et al. 2005, Lee et al. 2017, Papola et al. 2018, Guo et al. 2024). Hyperprolactinemia caused by antipsychotic drugs leads to low bone mineral density (Maixner et al. 1999). This condition has been associated with bone fractures. Long-term use of some antipsychotics that cause hyperprolactinemia can impair bone mineralization and increase the risk of hip and femoral fractures secondary to falls (Meaney et al. 2004, Milovanovic et al. 2016). Studies have demonstrated that amisulpride and risperidone are associated with a higher risk of hyperprolactinemia compared with clozapine, olanzapine, and quetiapine (Markianos et al. 2001, Bressan et al. 2004). On the other hand, aripiprazole carries a lower risk of

hyperprolactinemia because it acts as a partial agonist on the dopamine D2 receptor (Lieberman 2004). Furthermore, numerous studies have reported an increase in the rates of osteopenia and osteoporosis in patients with schizophrenia (Renn 2009, Wu 2013). This is not solely due to antipsychotic use, but may also be related to unhealthy lifestyle habits of schizophrenia patients. A sedentary lifestyle, poor nutrition, smoking, and spending time indoors, which are more common among patients with schizophrenia, may predispose these patients to a higher risk of fractures (Kishimoto et al. 2012).

Other side effects of antipsychotic drugs that increase the risk of bone fractures include orthostatic hypotension and an increased risk of falls due to sedation (Gugger 2011). Most studies have reported a low incidence of orthostatic hypotension at therapeutic doses of aripiprazole (Marder et al. 2003, Potkin et al. 2003). Furthermore, atypical antipsychotics such as clozapine, olanzapine, and quetiapine are thought to have more pronounced sedative effects, whereas aripiprazole has fewer sedative effects (Drici and Priori 2007). For these reasons, aripiprazole 20 mg/day was chosen as the treatment option in the presented case, as it has a low side effect profile in terms of hyperprolactinemia, orthostatic hypotension, and sedation at an appropriate dose, and the patient's treatment was successfully carried out.

In conclusion, this study presents a case of an adolescent with comorbidity of OI and schizophrenia. The management of OI patients with rare comorbidities, such as schizophrenia, requires careful monitoring due to the increased risk of bone fractures. In clinical practice, antipsychotic drug selection should be made with great care, and patients should be closely monitored for potential side effects. This case presentation aims to contribute to the limited information in the literature by describing the diagnosis, treatment, and follow-up processes of a patient with OI and early-onset schizophrenia.

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