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【 CASE REPORT 】

Duchenne Muscular Dystrophy Successfully Treated with Aripiprazole in a Patient with Autism Spectrum Disorder Symptoms Including Irritability

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Abstract:
Duchenne muscular dystrophy (DMD) is associated with neuropsychiatric disorders, and patients often present with autism spectrum disorder (ASD). We herein report a case of DMD accompanied by ASD that was successfully treated with aripiprazole, an atypical antipsychotic that has been used for treating irritability in child and early adolescent patients with ASD. The patient was diagnosed as having DMD at 3 years of age. Although he developed severe psychotic symptoms including irritability, insomnia, hallucinations, and delusions at 17 years of age, all the symptoms were successfully treated with aripiprazole without any detectable side effects.

Key words: Duchenne muscular dystrophy, aripiprazole, autism spectrum disorder, irritability

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Introduction

Duchenne muscular dystrophy (DMD) is a genetic disorder caused by mutations in the *DMD* gene, which encodes dystrophin, on the X-chromosome (1). Although DMD is characterized by progressive losses of muscle strength and function, cognitive impairment and neuropsychiatric symptoms such as autism spectrum disorder (ASD) are also prevalent in approximately 20% of such cases (2, 3). DMD patients with mutations downstream of the *DMD* gene exon 63, which affects the brain-specific dystrophin protein 71 (Dp71), have brain abnormalities and deficits, with a high incidence of ASD and attention deficit hyperactivity disorder (ADHD) (4). Pediatric patients with ASD struggle with restricted, repetitive behaviors, interests and activities, which limit the efficacy of educational and behavioral approaches (5, 6). Although aripiprazole is mainly used in the treatment of schizophrenia and bipolar disorder, this medicine is also approved for the treatment of irritability in child and early adolescent patients with ASD (aged 6-17 years) (7-9). We herein report a case of DMD with a frameshift variant of exon 70 in the *DMD* gene that was successfully treated with aripiprazole in a patent whose ASD symptoms included irritability.

Case Report

We experienced a case of DMD associated with severe psychotic symptoms in a 19-year-old Japanese male patient. He had no family history of neuromuscular disorders. He was born through cesarean delivery. He had elevated serum creatine kinase levels in early infancy. At 3 years of age, although there was no abnormality in his multiplex ligation-dependent probe amplification analysis, he was diagnosed as having DMD by a muscle biopsy. At a later date, a genetic test with target gene sequence capture followed by a next-generation sequence revealed a frameshift variant (p. Leu 3376fs) of exon 70 in his *DMD* gene. He was also diagnosed to have a pervasive developmental disorder at 4 years of age by a psychiatrist and has since been followed up in the psychiatry department. With the revision of DSM-5 cri-

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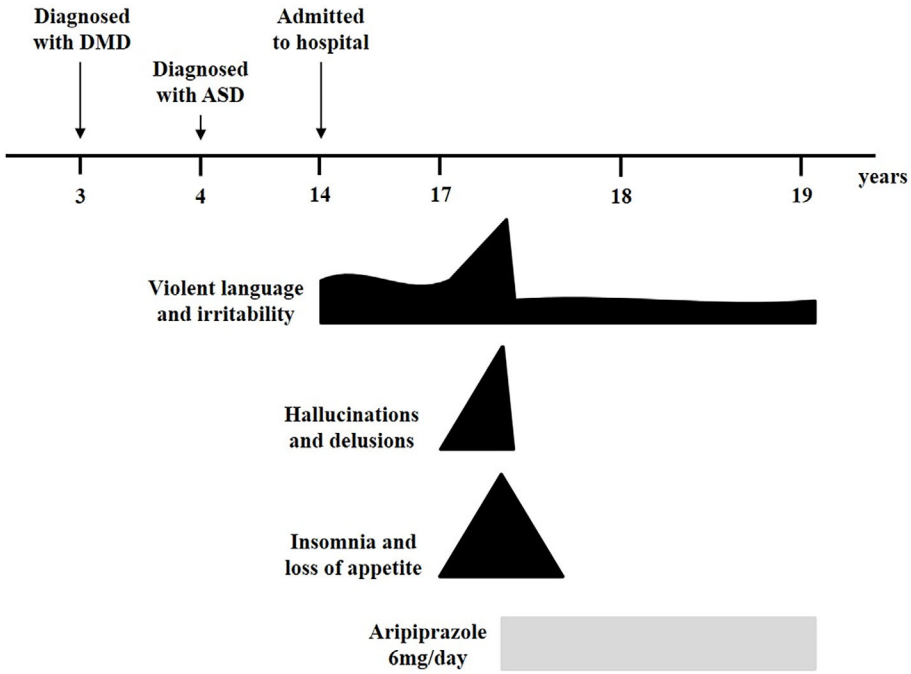

Figure. **Clinical course. His clinical course is summarized as indicated. DMD: Duchenne muscular dystrophy, ASD: autism spectrum disorder**

teria, he was diagnosed to have ASD. He refused steroid therapy for fear of side effects. He lost his ambulatory capacity at 9 years of age, and his muscle weakness gradually progressed. He was admitted to our hospital for long-term recuperation when he was 14 years old. On admission, he showed cognitive impairment. Brain magnetic resonance imaging (MRI) revealed mild cerebral atrophy compared to that in subjects of the same age. He displayed characteristics of irritability and shyness with strangers. In the Wechsler Intelligence Scale for Children (WISC-IV) test, his full-scale intelligent quotient (FSIQ) score was 49, verbal comprehension index score was 55, perceptual reasoning test score was 60, working memory index score was 57, and processing speed index score was 61 on admission. He easily got angry and often had panic symptoms when things did not go his way. At this stage, educational and behavioral approaches, such as sensory integration therapy and Pivotal Response Treatment, were effective for treating such psychiatric symptoms. He started medical treatment, including carvedilol and captopril, for heart failure at 15 years of age. Owing to respiratory failure at night, he received noninvasive positive pressure ventilation at 16 years of age.

There was no significant change in the symptoms of ASD from the age of 14 to 17 in hospital. When he was 17 years old, he fell in love with a ward nurse. He wanted to leave the hospital and live with her. As his wishes were not fulfilled, the frequency of his panic attacks increased. Simultaneously he had insomnia, lost his appetite, and broke out into violent language. Furthermore, he had symptoms of hallucinations and delusions, for example, that his drink was poisoned and the ward nurse with whom he fell in love was killed by another nurse. As educational and behavioral approaches became ineffective, we decided to start pharmacotherapy. After we consulted psychiatrists, aripiprazole therapy was started at a dose of 6 mg/day. His psychotic symptoms improved more or less after administration. From the next day after administration, his violent language and irritability subsided clearly compared to when he fell in love with the ward nurse. His hallucinations and delusions disappeared promptly and completely. Although there were some fluctuations, his insomnia improved and his appetite recovered within a few days. Neither recurrence of psychiatric symptoms nor side effects due to the treatment were found. The continuous administration of aripiprazole beyond 18 years of age was approved by the National Hospital Organization Suzuka Hospital ethically. Informed consent was obtained from the patient and his family. Therefore, by expert opinions, we decided to continue the aripiprazole dose for fear of recurrence of his psychotic symptoms even after he turned 18 years old. Neurological examination results were unchanged at approximately 2.5 years of follow-up without changing the dose of aripiprazole, at 19 years of age (Figure).

Discussion

We herein report a case of DMD accompanied by ASD that was successfully treated with aripiprazole. The prevalence of ASD ranges from 3% to 21% in DMD (2-4). Other highly prevalent psychotic symptoms include ADHD and obsessive-compulsive disorder (10). Although treatment for the core symptoms of ASD is limited to psychosocial therapies, accompanying symptoms may be treated with medication (11). Irritability is often observed in patients with ASD

and it is a common target of pharmacological treatment (12, 13). Risperidone and aripiprazole are the only medications for irritability associated with ASD (12). Aripiprazole is an atypical antipsychotic drug with a partial agonist of serotonin 5-HT1A and dopamine D2 receptors (14, 15). Aripiprazole is favorable for children and adolescents, considering its minimal side effects as compared with risperidone (16). Although there are diagnostic and therapeutic challenges for neuropsychiatric comorbidities in DMD, it has been reported that fluoxetine was effective for the treatment of an obsessive-compulsive disorder in a nine-year-old patient with ASD (17).

In this case, as we had difficulty in treating the symptoms associated with ASD despite the psychosocial therapies, we decided to start aripiprazole therapy. Aripiprazole is started at 1 mg/day in general (18). However, he had psychotic symptoms that required immediate treatment, and psychiatrists considered the possible negative effects of aripiprazole at 1 mg/day. Therefore, aripiprazole therapy was started at 6 mg/day, as an off-label administration.

Although aripiprazole has been administered to children and adolescents with ASD at ages 6-17 years old (18), evidence of its efficacy is insufficient in patients over 18 years of age. In this case, we started to administer aripiprazole when the patient was 17 years old and continued the treatment for approximately 2.5 years based on expert advice. Recently, it has been reported that aripiprazole, mirtazapine, and alprazolam are effective in treating psychotic symptoms in a middle-aged patient with Becker muscular dystrophy (19). To our knowledge, this is the first reported case of DMD in a patient whose ASD symptoms included irritability were successfully treated with aripiprazole at this age. Although the treatment was effective and no side effects have been observed to date in our patient, we should continue a cautious follow-up by paying attention to adverse events such as diabetes, impulse control disorder, and tardive dyskinesia (18). Patients with ASD are often quite sensitive to changes in their environment (20) as shown in this case. Some evidence suggests that affective symptoms in patients with ASD may mediate the emergence of psychotic symptoms (21). Patients with ASD experiencing anxiety are likely to develop psychotic symptoms such as hallucinations, odd thoughts, and bizarre behaviors (22) as demonstrated in this case. Although it did not meet the diagnostic criteria for schizophrenia (23), the psychotic symptoms found in this patient were similar to schizophrenia. It has been reported that ASD and schizophrenia share several genetic and behavioral features (24). We need to observe these clinical symptoms carefully.

A frameshift variant of exon 70 in the *DMD* gene was the cause of DMD in the present case. Few studies have been reported on variants of exon 70 in the *DMD* gene, but these variants are shown to result in a premature translation termination (25). The *DMD* gene contains 79 exons and seven promoters. There are several brain-specific dystrophin isoforms, including dystrophin protein 140 (dp140) (mutations downstream of exon 45) and dp71 (downstream of exon 63) (26). Those isoforms play an important role in the function and development of the human brain (27). Although the roles of dp140 and dp71 in the brain remain unclear, some reports indicated that the risk of cognitive impairment is associated with the location of mutations within the *DMD* gene (4, 27, 28). The risk and severity of cognitive impairment are shown to be associated with the cumulative loss of *DMD* genes such as dp71 (10). The rare mutations in the *DMD* gene downstream of exon 63 affect all dystrophin products including dp71 (26). Dp71 is a functionally versatile protein that is implicated in the neuropathophysiology of DMD, and is also associated with the most severe intellectual impairment in patients with DMD (10, 29). It is thus plausible that the frameshift variant of exon 70 in the *DMD* gene led to the severe neuropsychiatric symptoms in our patient.

In conclusion, this case report illustrates the effectiveness of aripiprazole therapy for irritability with ASD in a patient with DMD. Thus, we may consider administering aripiprazole as a treatment option for DMD.

The authors state that they have no Conflict of Interest (COI).

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