Atomoxetine Treatment in a Patient with the Comorbidity of Attention Deficit Hyperactivity Disorder and Fragile X Syndrome

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ABSTRACT
Fragile X Syndrome is a genetic disease defined by cognitive and behavioral characteristics that accompany apparent physical features. Male individuals are affected by this syndrome more severely, and it is the most common cause of mental retardation in men. The most common accompanying psychiatric conditions are mental retardation, autism, Attention Deficit Hyperactivity Disorder (ADHD), anxiety disorder, depression, sleep disorders and aggression. Anxiety, depression, shyness and social withdrawal are more common in female individuals. The diagnosis and treatment of the ADHD and selective mutism in a female adolescent patient who was Fragile X full mutant will be discussed in this case report.

Keywords: ADHD, atomoxetine, fragile X syndrome

INTRODUCTION
Fragile X Syndrome was first described by Martin and Bell in 1943 as a mental retardation form. For this reason, it is also called as Martin Bell Syndrome, and is the most common cause of the inherited mental retardation and mental retardation in males. The prevalence of it is 1/5000-7000 in males, and 1/4000-6000 in females (1). In Fragile X Syndrome, there is an increase in the number of the CGG trinucleotide repetitions in the promotor area of the FMR1 gene in Xq27.3. This repetition number is normal between 5-44; the gray zone is between 45-54; and the premutation carrier is between 55-200; and the full mutant is over 200 (2). Pre-mutation carriers are more common, and it is estimated that its prevalence is 1/300-450 in males, and 1/150-200 in females (3). Premutation carriers has been associated with premature ovarian insufficiency in females, and with Fragile X-related tremor/ataxia in males (2). In this case report, selective mutism and ADHD in an adolescent female patient with full mutant Fragile X is discussed.

CASE PRESENTATION
A 13-year-old female patient was admitted to our outpatient polyclinic with complaints of shyness, being introvert and not being able to talk to anyone except her mother, father and several close relatives. She did not establish verbal communication with her teacher and friends at school. She had her complaints since pre-school period. We learned that she was followed-up in Child and Adolescent Psychiatry when she was 6-8 years old, and used risperidone; however, discontinued the drug because of weight gain, and she did not continue her
follow-ups. It was observed in the psychiatric examination that she was 1-2 years older than she looked and had central obesity, she established limited eye contact, understood and carried out the commands, but did not respond to questions verbally, just nodded to mean “yes-no”, and smiled from time to time. We also learned that the patient did not talk to her teachers and friends at school, and that she had learned the letters but could not combine them to read. Psychometric evaluation could not be carried out for the patient due to selective mutism and it was considered that she had mild mental retardation clinically. In her background medical history, it was determined that she was born 1100 grams 35-week section due to intrauterine growth retardation. She was breastfed for nearly a month, and started to sit at the age of 1, walked at 1.5, and spoke at the age of 2.

She was followed-up in the Pediatric Endocrinology outpatient polyclinic for hypothyroidism and obesity, and received thyroid hormone replacement therapy. In her background, it was determined that her father walked with a limp on the right foot due to a cerebral palsy sequel. According to the information received from her father, we learned that her mother could not go out alone and had weak self-expression ability (social phobia?). Her 12-year-old sister had serious mental retardation, and could not walk, talk, and take care of herself. It was considered that the patient had selective mutism, and fluoxetine (40 mg/day), sertraline (150 mg/day) and citalopram (30 mg/day) were used, respectively; and the dose of each drug was increased gradually; however, no improvements were seen in the mutistic symptoms of the patient with the SSRI treatment. Atomoxetine treatment was started for ADHD attention deficit dominant type, and the treatment was increased gradually to 80 mg/day. No adverse effects were observed with atomoxetine. After six months of atomoxetine use, the attention deficit symptoms of the patient regressed, she learned reading and writing and read the text messages on her phone. She did not start talking in the clinic, only she read a short text in one of the interviews. It was learned from her teacher that she had good attention to the lessons, fullfilled her tasks, rarely talked to her friends and sometimes answered the questions with one word. Genetic examination was carried out to the patient due to mental retardation, and the karyotype was determined to be 46 XX, 13 ps+, 15 ps' Fragile X full mutant. In the genetic examination of the family, no pathology was determined in the father and siblings; and the genetic examination of the mother was determined as 46 XX, Fragile X premutant.

**DISCUSSION**

Fragile X Syndrome is a complex syndrome, and has neuropsychiatric features (1). The cognitive and emotional phenotype of the syndrome depends on the FMRP amount produced. The clinical characteristics are large ears, long face, mandibular prognathism, strabismus, hypotonia in babies, epilepsy, hyperextensibility in joints, flat foot, pectus excavatum, macro orchitis, mitral valve prolapsus, and obesity (2). The psychiatric conditions that accompany Fragile X Syndrome are weak eye contact, ADHD, anxiety disorder, repetative motor behaviors, autism, depression, sleep disorders, mental retardation and aggression (4). Attention deficit and impulsivity are more frequent than hyperactivity in girls (5). Anxiety and attention problems increase with furthering age (6). Intellectual disability is more common in boys with Fragile X syndrome than girls. %70 of females have an IQ in the borderline to normal range; however, learning and emotional difficulties are common (4). In a study that was conducted on female children and adolescents who had Fragile X Syndrome, more deficit was reported in the social skills of girls who had Fragile X Syndrome, and they were determined to be more depressive compared to the control group (7). Anxiety, shyness and social avoidance are considered as more serious problems than depression. Selective mutism must be considered when the verbal interaction of the child is limited in specific places and with specific individuals. In the literature, it was reported that selective mutism improved in puberty period in a patient that was diagnosed with Fragile X syndrome (5).

The treatment involves behavioral and medicine therapies. It was shown that folic acid has positive effects on motor coordination, language and speech; however, its
use is contraindicated in patients with epilepsy (2). Stimulants (methylphenidate and amphetamine) are used to treat ADHD symptoms. Clonidine can be used in ADHD and sleep problems (8). Selective serotonin reuptake inhibitors can be used for aggressive behaviors, anxiety and depression (1). The positive effects of sertraline has been shown in the development of language in 2-6-year-old children (9). Minocycline strengthens the synaptic bonds and its positive effects on anxiety have been shown (10). Lithium, valproic acid and antipsychotics are used in various mood and behavior problems (8).

In this case report, the diagnosis and treatment process of selective mutism and ADHD-attention deficit dominant type in a Fragile X full mutant 13-year-old girl whose mother was Fragile X premutant has been discussed. It is considered that fluoxetine may be beneficial in cases with SM accompanied with Fragile X (11). However, our case did not benefit from the pharmacological treatments that were used in selective mutism. It is considered that this might be due to the late admission for treatment, negative sociocultural and socioeconomic factors, and the patient’s mental status being not suitable for cognitive behavioral treatment. Case reports have been reported that methylphenidate decreased the attention deficit, hyperactivity and impulsivity symptoms in patients who had Fragile X syndrome that met the ADHD criteria (12). Atomoxetine has been shown to be effective in the treatment of individuals with ADHD and comorbid anxiety disorder (13). Both methylphenidate and atomoxetine reduced the symptoms of ADHD and anxiety; but atomoxetine was more effective in anxiety symptom reduction (14). In our case, atomoxetine treatment was employed for attention deficit symptoms, and it was observed that there was a decrease in the attention deficit symptoms, and the patient learned reading and writing with atomoxetine treatment. In the light of these data, it is considered that using atomoxetine is beneficial in the treatment of ADHD in patients who have Fragile X syndrome.

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**REFERENCES**