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Clinical Report:

A Male With Down Syndrome, Fragile X Syndrome, and Autism

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Abstract

A case of a 14-year-old boy with both fragile X syndrome and Down syndrome is described. This is the third reported case of a patient with fragile X syndrome plus Down syndrome and the first reported case in a male. Facial features are generally consistent with Down syndrome; however, a prominent forehead and jaw and macroorchidism were consistent with fragile X syndrome. Joint laxity is also present, which is consistent with both disorders. Cognitive impairment is more significant than in his siblings with fragile X syndrome, and he meets criteria for autistic disorder. Ongoing behavioral dysregulation has been significant, leading to disruption of home and school environments despite many attempted psychopharmacologic and behavioral strategies and a supportive family. Identification and treatment of underlying medical problems (esophagitis) led to improvements in sleep and behavior. We emphasize discussion of challenges in his behavioral management and present a collaborative approach to behavioral management.

Index terms

Down syndrome; fragile X syndrome; autism; intellectual disability

Fragile X syndrome (FXS) and Down Syndrome (DS) are the 2 leading genetic causes of intellectual disability worldwide. FXS occurs in ~1 of 3600 males, and is caused by a CGG trinucleotide repeat of 200 repeats or greater (normal range is <55 repeats and 55–200 results in the premutation), in the *FMR-1* gene on the X chromosome, leading to low or absent levels of the fragile X mental retardation protein.¹ FXS is associated with physical features including a long face, prominent ears, macrocephaly, and macroorchidism,^{2,3} and a behavioral phenotype including intellectual disability, autism spectrum disorders in up to 60%,⁴ hand flapping, poor eye contact, anxiety, attention-deficit hyperactivity disorder symptoms, and hyperarousal.⁵

DS is estimated to occur in 1 of 714 live births⁶ and results from trisomy of chromosome 21 in 95% of cases and translocation or mosaicism in the other 5%. Features of DS include intellectual disability, characteristic facial features, increased risk for heart and gastrointestinal malformations, hearing loss, hypothyroidism, and other medical problems.⁷ Rates of autism spectrum disorders in DS have ranged across studies from 1% to 11% depending on the sample size and the criteria used to identify cases of autism spectrum disorders.^{8,9}

Two previous cases of females with both FXS and DS have been described in the literature.^{10,11} We describe the first case of a male with FXS+DS, including clinical and behavioral characteristics. We emphasize discussion of challenges in his behavioral management and present a collaborative approach to behavioral management.

CLINICAL REPORT

Birth History and Diagnosis

The patient is a 14-year-old-white male patient with both Down syndrome and fragile X syndrome. He was born weighing 8 pounds 14 ounces to a 33-year-old G4 P3 mother via an uncomplicated vaginal delivery. In the nursery, he was noted to have feeding difficulties, hyperbilirubinemia, hypotonia, and facial features of Down syndrome leading to a chromosome analysis revealing trisomy 21. Echocardiogram at birth showed a small Atrial septic defect and mild aortic valve insufficiency that did not require intervention. He was diagnosed with fragile X syndrome at 5 months of age after diagnosis of fragile X syndrome in his older brother. The patient's fragile X DNA test showed a full mutation with bands at 1264, 711, 372, and 256 with full methylation. His fragile X mental retardation protein level was 0.5% of normal.

Developmental/Behavioral History

Review of early milestones showed global developmental delays with sitting at 18 months, walking independently at 3 years, and delayed speech with current language consisting of only intermittent use of single words. He had severe hypotonia from birth onward, which was a combined effect of both the fragile X syndrome and Down syndrome as hypotonia is a feature in both disorders. At 5 years of age, he was diagnosed with autistic disorder based on DSM-IV criteria. He received educational services primarily through his local public school, integrated in the regular education classroom for most of each school day with a full time, one-on-one paraprofessional.

Review of developmental and cognitive assessments from early childhood highlighted a longstanding difficulty in evaluating his progress. Adaptive functioning assessments obtained by parent or teacher interview varied slightly from preschool to elementary school; however, standard scores generally fell in the 30 to 50 range.

Behavioral issues have been the principal concern for this child throughout life, and we have selected relevant incidents to reflect the magnitude of his behavioral difficulties. Tantrums and physical aggression started at age 3, and during preschool aggression consisted primarily of grabbing and pinching. During the next few years, behavior problems escalated in both school and home settings. In early primary grades, he tolerated the presence of peers and allowed close proximity on an inconsistent basis, however, several aggressive outbursts resulted in physical harm to classmates. The seriousness of his behaviors led to removal from the classroom, and a requirement that he be medicated appropriately before returning to school. In third grade, the authorities were called when he hit a classmate over the head with a heavy object. His behavior at home was equally difficult and destructive, with physical aggression leading to injury in his parents and siblings, and destruction of home

furnishings. The management of his behavior has been an issue in his entire life, as his size and strength increased so did the seriousness of the situation. This impacted the entire family, leading to limitations in their social lives due to fears that he may injure a guest or that they will not be able to physically control him.

It is important to note that the patient has periods of happiness in which he engages lovingly with his family, however, currently has significant mood instability and tantrums without clear triggers. During the past year, his behavioral difficulties have necessitated placement in a group home for individuals with developmental disabilities and severe behavioral issues. This was initially effective in decreasing agitation, anxiety, and aggressive behaviors, however, he has had significant behavioral incidents when out in the community, and the other children are fearful of his behavioral outbursts and reportedly avoid contact with him.

Medical History

He had 2 sets of pressure equalization tubes in early childhood due to recurrent otitis media, and he was evaluated by orthopedics for flat feet with significant ankle pronation. At age 9, he had 2 electroencephalograms (EEGs) showing background slowing but no epileptiform discharges. During the next years, he had multiple inpatient psychiatric hospitalizations, the longest of which was 7 months duration at 11 years of age. During this hospitalization, he suffered a femur fracture while being restrained. Behavioral exacerbations related to mealtimes and sleep problems led to evaluation with an upper endoscopy that showed severe erosive esophagitis. Treatment with a proton pump inhibitor and feeding modifications led to improvements in sleep and decreased the frequency of behavioral outbursts at night. The patient's inability to describe his physical complaints likely contributed to the severity of his behavioral problems before this discovery. Language production also improved after intervention, however, daytime behavioral problems continued. A sleep study at 12 years of age was not consistent with sleep apnea.

Previous Interventions

During the years, he has been treated with a variety of psychopharmacologic medications including selective serotonin reuptake inhibitors, atypical antipsychotics, anticonvulsants, mood stabilizers including lithium, and stimulant medications with limited success. The management of his medication was and continues to be a complicated issue. He has had the benefit of international experts; however, the daily oversight of his complicated regimen has been a challenge for his primary care pediatrician, who also managed issues associated with his Down syndrome. His current combination of low-dose risperidone (0.5 mg twice daily) and bupropion (100 mg daily) has been the most effective in decreasing behavioral outbursts, however, behavioral regulation remains a challenge. In the school setting, specific curricular modifications were difficult to ascertain. A workbasket approach or modified Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH)¹² approach to intervention was used during his elementary years, however, the application appeared inconsistent and lacked fidelity to the model. A variety of behavioral interventions have been explored yielding a pattern of temporary effectiveness for approaches ranging from modified behavioral intervention to holistic approaches.

Family History

The patient is the youngest in a family of 4 children. His older sister has a full mutation, and his mother and maternal grandfather have the premutation. His older sister functions well and is currently attending community college. His older brother, who is mosaic and partially unmethylated, is high functioning and is mainstreamed in a public high school with only 1 special education class. He is treated for attention-deficit hyperactivity disorder and anxiety symptoms, and he does not have symptoms of autism spectrum disorders. His mother is

currently 48 years of age and has been treated for conditions associated with the premutation in women including hypothyroidism, anxiety, and depression. Notably, treatment of anxiety and depression were discontinued when the patient was moved to a group home. His maternal grandfather has been diagnosed with the fragile X-associated tremor/ataxia syndrome with symptoms of tremor, ataxia, and early dementia.

Physical Examination

His weight was at the 50th percentile, height at the 75th percentile, and head circumference at the 50th percentile for his age. He has upslanting palpebral fissures with epicanthal folds, a low nasal bridge, macroglossia with a high-arched, narrow palate, and a prominent chin. His ears are small and mildly prominent. He has a callus on his forehead from persistent head banging. He also has diffuse hypotonia with hyperextensible joints and decreased reflexes. He has genu valgum with flat feet and pronation at the ankles. On genitourinary examination, he is Tanner stage III, with macroorchidism (testicular volume 30 mL) and a normal phallus.

Current Developmental Assessment

Results of the Vineland Adaptive Behavior Scales—Second Edition (Vineland II) showed a current adaptive composite of 38 (± 7), which is consistent with previous assessments. His overall functioning was at ~2-year age equivalent with a relative strength in daily living skills and a relative weakness in the communication. These results are likely a slightly low estimation of his cognitive abilities due to the depressing effect of his behavior on his overall level of functioning. On the Vineland II, maladaptive behaviors fell within the clinically significant range. Standardized IQ measures were not attempted as the likelihood of completion appeared minimal, and the stress to both the child and his family did not appear warranted at this time.

He continues to meet DSM-IV criteria for autistic disorder due to significant language impairment, deficits in social interaction, and perseverative and repetitive behaviors. As previously documented, his expressive and receptive language skills fall below the 2-year level. His play skills continue to be lower than expected for a child with his cognitive skills, and he pays little attention to others around him. He demonstrates restricted interests and perseverates on certain objects and continues to grab and break items in his visual path.

DISCUSSION

This is the third reported case of a patient with both fragile X syndrome (FXS) and Down syndrome (DS) and the first reported case of a male with FXS+DS. Arinami et al first described a 5-month-old female infant born to a 40-year-old Japanese mother, who had significant hypotonia, developmental delays, and facial features consistent with DS. However, FXS features such as a prominent forehead, large ears, and a prominent jaw were noted. All growth parameters were below the first percentile, and there was no congenital heart disease.¹⁰ The second case was reported by Collacott et al and describes a 21-year-old woman born to a 41-year-old mother, with a history of significant cognitive and behavioral problems similar to our patient. She also had significant cognitive disability, limited expressive language, and severe behavioral dysregulation including hyperactivity, self-injurious behaviors, and aggressive outbursts. Her adaptive functioning measured by the Vineland showed similar results, with age equivalents ranging from 15 to 23 months, and a relative strength daily living skills. Her adaptive scores were lowest in the socialization domain, and the authors described that she was “limited in her affective responses.”¹¹ However, they further point out that “there is no gaze avoidance or other autistic traits.”¹¹ Thus, they did not feel she had autism, however, current criteria and assessment methods

were not applied. Physically, her short stature and facial features were consistent with DS, however, a prominent forehead and jaw are noted. She did not have a congenital heart malformation. In both cases, trisomy 21 and fragile X were diagnosed using cytogenetic methods, and there was a supporting pedigree with many cases of intellectual disability following an X-linked pattern. For the adult female with FXS+DS, her cognitive and behavioral deficits were more significant than her brothers with FXS alone.

Theoretically, we would expect that a male with FXS+DS would be more affected than a female due to the expression of fragile X mental retardation protein from the second X chromosome in the female leading to less severe neurobiological abnormalities of FXS. In this case, however, it sounds like the adult female and our male patient were equally affected. Considering that FXS and DS each lead to distinct neurobiological and synaptic abnormalities, it seems consistent that an individual with FXS+DS would be more significantly affected than expected for each syndrome individually. Our patient and the adult female with FXS+DS both have siblings with FXS (without DS) who are notably higher functioning without significant behavioral impairments or autism spectrum disorders (ASD).

Fragile X in combination with additional medical problems has been shown to increase the frequency of ASD in affected patients,^{4,5} and the combination of 2 genetic disorders that significantly affect neurodevelopment and cognitive functioning likely contributed to the development of ASD in this patient. Research in both FXS and DS has shown that patients with FXS+ASD or DS+ASD have lower cognitive scores than those with FXS or DS without ASD,^{13,14} and our patients' low cognitive functioning is consistent with this finding. This case raises questions about whether the subset of patients with DS who have ASD should also be tested for FXS.

In all 3 cases of FXS+DS now described, facial features are most consistent with those characteristically seen in DS, however, FXS features such as a prominent forehead and jaw are noted. Macroorchidism was also consistent with FXS, and important to note because this is the first male with FXS+DS described. Stature of the other 2 patients was below the first percentile consistent with DS, however, our patient is at the 75th percentile, which is more consistent with the slightly increased stature in childhood in FXS.¹⁵

The 2 female patients with FXS+DS were born to mothers of advanced maternal age. One study from 1988 suggested that women with the fragile X premutation had a slight but statistically significant increased risk for nondisjunction leading to an increased risk of having children with trisomy 21,¹⁶ however, this has not been replicated.

Behavior management has been the most difficult aspect of care for this patient. He has been largely unresponsive to many pharmacologic interventions. As mentioned earlier, the combination of a low-dose atypical antipsychotic with a heterocyclic antidepressant has shown the most benefit, although limited. Although atypical antipsychotics, antidepressants, mood stabilizers, and stimulants remain the mainstay of therapy for many with FXS and autism, these are not always effective in controlling the behaviors due to patients' intellectual deficits and inability to communicate. The identification and treatment of erosive esophagitis from significant gastroesophageal reflux led to treatments improving sleep and nighttime behavioral problems, an excellent example of how common medical problems must be thoroughly evaluated in nonverbal patients before addressing behavioral symptoms with psychopharmacologic strategies.

New targeted treatment options are being developed for patients with FXS to downregulate the proteins that are upregulated in FXS due to the absence of fragile X mental retardation protein. The most promising treatment is that of metabotropic glutamate receptor 5

(mGluR5) antagonists, which have been shown to rescue the FXS phenotype in mice by down regulating the mGluR5 pathway and thereby improving synaptic plasticity.¹⁷ When these agents become available for human trial, this patient may show improvement in his autistic behaviors by treating his underlying FXS instead of attempting to control the behaviors with psychopharmacology. Lithium has also shown to provide some behavioral benefit in patients with FXS.¹⁸ A previous lithium trial in this patient was not successful, however, another trial now that he is older is being considered.

Psychological and behavioral interventions for behavioral problems are equally or more important than pharmacologic treatments in many cases of FXS and DS, and this case has been especially challenging due to behavioral problems in this patient that are far more severe than what is typically seen in FXS or DS alone. Behavior modification can be used to enhance behavior controls of individuals with special needs and is well documented within the literature.¹⁹ The key to the traditional approach is to find antecedent events that trigger inappropriate behaviors and look for effective consequences to modify the behaviors. The ABC model provides a framework to identify antecedent, behavior, and consequence.²⁰ The first step in this process is typically prioritizing and defining the behavior.²¹ This was unfortunately where the process appeared to breakdown for our patient. Missing from the intervention and behavior plans were documented functional behavioral analyses, which suggests that the behavior plans were not data driven. Although identifying a single antecedent may have been difficult, documentation reveals a reactive approach to his behavior. The antecedent for many of the patient's behaviors appeared to stem from biological causes such as esophagitis or the hyperarousal associated with FXS,³ sensory processing differences,²² or developmental issues including the inability to communicate effectively. Any behavior plan that does not address these antecedents will not result in a true change in behavior. With a complicated case such as this, an intentional and holistic approach to behavior modification is warranted. A recommended approach is outlined by Hills et al.²³ This 11-step approach focuses heavily on addressing the antecedents of the behavior rather than developing consequences and requires collaboration and coordination across settings and among professionals and family members. Complex and unique cases such as this take a significant economic and emotional toll on the family and illustrate the need for case management and a collaborative approach to behavioral management.

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