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Case Report

Intellectual Disability Disorder versus Autism Spectrum Disorder: A Fragile X Syndrome Case Report

Zihinsel Gelişim Bozukluğu ve Otizm Spektrum Bozukluğu: Bir Frajil X Sendromu Olgu Sunumu

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ABSTRACT

Intellectual development disorder is a neurodevelopmental condition characterized by significant impairments in intellectual functioning and in adaptive behavior, with onset during the developmental period. It is often accompanied by neurodevelopmental and behavioral comorbidities such as autism spectrum disorder, attention deficit hyperactivity disorder, and other behavioral disturbances not specified. Fragile X syndrome is the most common inherited cause of intellectual disability disorder and frequently presents with overlapping neuropsychiatric and behavioral features, complicating diagnosis and management.

This report presents the case of a six-year-old boy previously diagnosed with autism, who was evaluated due to restlessness, irritability, and aggressiveness beginning at 12 months of age. He exhibited deficits in intellectual functioning and adaptive behavior. He was subsequently diagnosed with comorbid intellectual disability, autism spectrum disorder, attention deficit and hyperactivity disorder, and irritability. His physical phenotype was unremarkable. Genetic testing confirmed the diagnosis of Fragile X syndrome. Treatment with risperidone and methylphenidate led to behavioral improvement.

Through this article, the authors aimed to review key aspects of the clinical assessment and therapeutic approach to intellectual disability, autism and Fragile X syndrome, contextualized within the discussion of a case report.

Keywords: *Fragile X Syndrome, Intellectual Disability, Autistic Disorder, Psychomotor Agitation*

ÖZET

Zihinsel gelişim bozukluğu, entelektüel işlevlerde ve uyum sağlayıcı davranışlarda belirgin yetersizliklerle karakterize, gelişimsel dönemde başlayan bir nörogelişimsel bozukluktur. Bu durum genellikle otizm spektrum bozukluğu, dikkat eksikliği ve hiperaktivite bozukluğu gibi nörogelişimsel ve davranışsal eş tanılarla birlikte görülür; bazen ise tanımlanmamış başka davranışsal bozukluklar eşlik edebilir. Frajil X sendromu, kalıtsal zihinsel yetersizliğin en yaygın nedenidir ve sıklıkla nöropsikiyatrik ve davranışsal özelliklerin örtüşmesiyle kendini gösterir; bu da tanı ve tedavi sürecini zorlaştırır.

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Bu olgu sunumunda, 12 aylıkken başlayan huzursuzluk, sinirlilik ve saldırganlık şikayetleri nedeniyle değerlendirilen ve daha önce otizm tanısı almış altı yaşındaki bir erkek çocuk ele alınmıştır. Olguda entelektüel işlevlerde ve uyumsal davranışlarda belirgin yetersizlikler gözlenmiştir. Ardından zihinsel yetersizlik, otizm spektrum bozukluğu, dikkat eksikliği ve hiperaktivite bozukluğu ve sinirlilik eş tanıları konulmuştur. Fiziksel fenotipi belirgin bir özellik göstermemektedir. Genetik test sonucu Frajil X sendromu tanısını doğrulamıştır. Risperidon ve metilfenidat tedavisi ile davranışsal iyileşme sağlanmıştır.

Bu makale ile yazarlar; zihinsel yetersizlik, otizm ve Frajil X sendromunun klinik değerlendirmesi ve tedavi yaklaşımlarının temel yönlerini, bir olgu sunumu bağlamında ele almayı amaçlamıştır.

Keywords: *Fragile X Syndrome, Zihinsel Engellilik, Otizm Bozukluğu, Psikomotor Ajitasyon*

INTRODUCTION

Intellectual development disorder (IDD) is a neurodevelopmental disorder characterized by significant impairments in intellectual functioning and in adaptive behavior, with onset during the developmental period. The diagnosis should be confirmed by both clinical assessment and standardized neuropsychological testing. The estimated prevalence is 1%, with a higher incidence in males. IDD often presents with comorbid neurovelopmental disorders, including attention deficit and hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and various behavioral disturbances [1].

ASD is defined by persistent impairment in social interaction, alongside with restricted and repetitive behaviors and activities. While ASD may occur in individuals with average intellectual functioning, approximately 30% also meet diagnostic criteria for IDD [2]. In these cases, it is essential to determine whether the social communication deficits are disproportionate to the cognitive level. If not, the diagnosis of ASD may not be appropriate, since deficits in social communication may be subsumedunder the overall cognitive deficit. ADHD is also frequently observed in individuals with IDD and/or ASD.

Beyond formal diagnostic categories, individuals with IDD may exhibit behavioral disturbances not otherwise specified - irritability, psychomotor agitation, aggression and self-injurious behavior - that often lead to significant impairment and commonly require pharmacologic treatment. In pediatric populations with IDD, irritability is reported in nearly 60% of individuals, and aggressive behavior in 2-24.4% [3,4].

The etiology of IDD is diverse, with genetic causes accounting for more than half of the cases [5]. Among these, Fragile X syndrome (FXS) is the most common inherited cause (approximately 2% of individuals with IDD have FXS) [6]. FXS results from a full mutation in the *Fragile X Messenger Ribonucleoprotein 1 (FMR1)* gene, characterized by more than 200 CGG trinucleotide repeats and associated hypermethylation. Prevalence is estimated at 1.4 per 10000 males and 0.9 per 10000 females [6].

While physical features can be subtle in early childhood, common findings include macrocephaly, a long face, prominent ears, and joint hypermobility. Behavioral manifestations - temper tantrums, aggressiveness, hyperactivity, hyperarousal, and agitation - are often prominent, and frequently lead to initial clinical evaluation.

Management of IDD, irrespective of its cause, involves neurodevelopmental intervention targeting adaptive functioning and language, along with medications to manage co-occurring conditions or behavioral symptoms.

This case report presents the complex diagnosis and management of a child with IDD, ASD, ADHD, and behavioral issues, later identified as FXS. It emphasizes diagnostic differentiation based on DSM-5-TR criteria and highlights the challenges of co-occurring neurodevelopmental disorders. The report also addresses the limited real-world evidence on pharmacological treatment for such comorbidities, offering a balanced, practical approach for clinicians.

CASE REPORT

A six-year-old boy with a previous diagnosis of ASD was referred to a neurovelopmental and behavioral clinic due to persistent temper tantrums, irritability and aggressive behavior, reported since 12 months. Delay in motor and language milestones as well as limited interest in other children were noted.

Family history was unremarkable. He had no history of significant illness, except for prenatal identification of hydronephrosis, which resolved spontaneously. Newborn metabolic screening yielded normal results. Hearing screening was within normal limits. At the time of evaluation, the patient was

enrolled in a mainstream educational school, but was unable to benefit from neurodevelopmental intervention due to behavioral difficulties.

Physical examination revealed a long face, prominent ears, hyperflexible joints, and calluses on the hands. Anthropometricmeasurements were within normal limits. He was non-verbal, did not respond to instructions, avoided eye contact, and displayed marked irritability. He frequently left his seat and engaged in repetitive behaviors such as hand-biting.

Neurodevelopmental assessment identified poor fine and gross motor skills. He had achieved independent walking at 16 months but was unable to perform age-appropriate motor tasks. Both receptive and expressive language (the latter consisting of only two words) were significantly impaired. He was unable to complete simple cognitive tasks. He showed no interest in peers or shared activities. Symbolic and functional play were absent. His adaptive skills were also impaired.

Behavioral evaluation revealed rigid adherence to routines, stereotypic movements (hand flapping, hand biting), and repetitive manipulation of objects.

The child scored 43 on the Griffiths Mental Development Scales III, with all subscales (A - Foundation of Learning; B - Language and Communication; C - Eye and Hand Coordination; D - Personal-Social-Emotional; E - Gross Motor) scores below the expected range, the lowest being in Subscale D.

Based on clinical findings and neurodevelopmental assessment, a diagnosis of severe IDD comorbid with ASD and ADHD not otherwise specified (NOS) was established, along with associated behavioral disturbances including irritability and aggression [1]. FXS was suspected. Genetic testing, using Southern blot and polymerase chain reaction (PCR) analysis, confirmed a full mutation with hypermethylation of the FMR1 gene, consistent with FXS.

Pharmacological treatment was initiated with risperidone 0.25 mg twice daily, gradually increased to 1.5 mg/day. Clonidine was also started at 0.04 mg three times daily. After six weeks, a marked reduction in irritability, aggressiveness, and temper tantrums was observed. However, the parents reported a wearing-off effect toward the end of each clonidine dosing interval. Due to poor tolerability, clonidine was discontinued. Since guanfacine was not commercially available at the time of the patient's evaluation, long-acting methylphenidate was initiated at a dosage of 1.5 mg/kg/day. The child also began receiving neurodevelopmental therapy, with a focus on language and adaptive functioning. After six months of combined pharmacological and therapeutic intervention, there were improvements in both language and adaptive behavior, without recurrence of behavioral symptoms. No significant adverse effects were reported.

The patient was referred for ophthalmological and otorhinolaryngological evaluations, as recommended by care guidelines for children with FXS [7]. Genetic counseling was provided.

DISCUSSION

This case highlights the complexity of diagnosing neurodevelopmental disorders when multiple conditions co-occur. Initially diagnosed with ASD, the child demonstrated severe impairments in language, motor skills, cognition, and adaptive behavior that were not fully explained by ASD alone. According to DSM-5-TR criteria, a primary diagnosis of severe IDD was appropriate, with ASD and ADHD NOS diagnosed as comorbid conditions [1]. The child's social communication deficits(avoidance of eye contact, no interest in peers, lack of symbolic game) were disproportionate to his cognitive level, and he exhibited restrictive, repetitive patterns of behaviors, interests, and activities (rigid adherence to routines, hand flapping, hand biting, and repetitive manipulation of objects), supporting the diagnosis of ASD according to DSM-5-TR criteria. ADHD NOS was also diagnosed based on symptoms of inattention, hyperactivity, and impulsivity that caused significant distress, although there were uncertainties as to whether these symptoms were inconsistent with the child's developmental level.

Behavioral features such as irritability, hyperarousal, and aggression-although not core features of IDD, ASD, or ADHD-are frequently observed in individuals with FXS. In this case, they were considered associated behavioral disturbances not otherwise specified.

Following American Academy of Pediatrics (AAP) guidelines, genetic evaluation was pursued upon confirmation of IDD, leading to the diagnosis of FXS [8]. **The diagnosis of FXS must be confirmed through molecular tests like PCR (which quantifies**

the number of triplets) and Southern blot (which provides the activation ratio of the X chromosome in women and detects copy number mosaicism in men and women) [9].

Clinical suspicion of FXS was based on the presence of IDD, ASD, physical features (long face, prominent ears, hyperflexible joints, and hand calluses), and behavioral signs (hyperarousal, hand-biting, and irritability). Although dysmorphic features may be subtle in young children, the behavioral phenotype of FXS typically becomes evident in the second year of life [9]**.** Mild-to-severe IDD is present in all affected males and ASD in 60% [9]. **Hyperactivity and inattention are also observed in most boys and aggressive behavior in 20-30% [9]. Hand biting is the most common form of self-injury in FXS, affecting 26% of males [10].**

Besides transient hydronephrosis, the patient had no medical complications. Patients with FXS are at high risk of seizures (16% of males), ear infections, scoliosis, sleep disturbances (30-50%), refraction defects (17-59%), strabismus (8-40%), mitral valve prolapse after adolescence (3-12%), aortic root dilation, gastroesophageal reflux, inguinal hernia and vesicoureteral reflux [9,11,12].

Treatment for IDD is symptomatic, and involves approved medications combined with neurodevelopmental interventions, as stated above. For FXS, no targeted pharmacological treatments have been approved as well. In this case, risperidone effectively reduced aggressiveness and self-injurious behavior. Risperidone was selected due to European Medicines Agency approval for children aged five and older, with supporting evidence for efficacy in managing irritability in both FXS and ASD [9,13].Clonidine was used adjunctively for hyperarousal and aggression, although it was poorly tolerated in this case [14-16].Pharmacologic management of ADHD in FXS follows general pediatric guidelines. Methylphenidate is typically well tolerated in children over five [17]. Methylphenidate was introduced to manage ADHD symptoms, and was well tolerated without behavioral worsening.

In this patient, improvements in language and adaptive behavior were noted after the addition of methylphenidate and intensive neurodevelopmental therapy. Previous studies have reported modest improvements in attention, social skills, and academic performance in patients with FXS and comorbid ADHD treated with methylphenidate [18,19]. One study suggests an improvement in language macrostructure (cohesion and overall narrative ability), but not in microstructural elements (lexical diversity, grammatical complexity), in patients with ADHD (without other comorbid disorders) treated with methylphenidate [20].

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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