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The Process of Diagnosing Xia Gibbs Syndrome in A Male Child with Autism Spectrum Disorder and AHDC1 Gene Mutation: Case Report

Burcu KARDAŞ, Beyza TOPÇU, Ayşe BÖYÜK ŞAHİN, Şahika Gülen ŞİŞMANLAR

Kocaeli University School of Medicine, Child and Adolescent Psychiatry, Kocaeli, Türkiye

ABSTRACT

Xia Gibbs Syndrome (XGS) is a rare disorder with different phenotypic and behavioral manifestations and clinical reflections known to develop as a result of de novo mutations in the AT-Hook DNA binding motif (AHDC1).

Our patient was first evaluated in the pediatric psychiatry clinic at the age of 2 because of speech delay. The patient was followed up with a diagnosis of cognitive retardation and joint hypermobility was found as a result of pediatric neurology consultation due to his dysmorphic appearance. No pathology was found in detailed blood tests and imaging studies. During the follow-up period, it was determined that the cognitive skills gained between the ages of 4–4.5 started to regress, there was no joint attention, but there was stereotypic movements and limitation in eye contact. In the detailed genetic evaluation performed due to the deterioration in the clinical course and the addition of the diagnosis of Autism Spectrum Disorder, a mutation compatible with Xia Gibbs Syndrome was found in the whole exon sequencing test.

Repeated psychiatric and medical evaluation as part of a multidisciplinary approach in rare genetic diseases such as Xia Gibbs Syndrome is important for educational planning and treatment of comorbidities. With this case, we wanted to emphasize the importance of psychiatric follow-up and further investigations especially in cases with loss of acquired skills after diagnosis.

Keywords: AHDC1, autistic disorder, case report, genetic diseases, intellectual disability, Xia Gibbs Syndrome

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INTRODUCTION

Xia Gibbs Syndrome (XGS) is a rare disease that has been described in recent years and occurs as a result of heterozygous mutation in the AT-Hook DNA binding motif (AHDC1), which encodes proteins involved in basic tasks such as DNA repair (1,2,3,4). It is characterized by mental retardation, structural anomalies of the brain, general developmental delay, feeding and sleep problems, dysmorphic facial appearance and short stature (1). Approximately 250 patients have been reported since 2014 when it was described (1,2). Although it has been reported to be rare, it is predicted that undiagnosed cases are more common because it has a broad phenotypic appearance and advanced genetic tests are not performed (5,6,7). In this article, we aimed to discuss a male patient who was initially diagnosed with mental retardation and diagnosed with Xia Gibbs Syndrome in advanced tests ordered with the addition of autism symptoms and regression in cognitive skills to the clinical picture from a psychiatric point of view in the light of the literature.

Highlights

- **Xia Gibbs is a rare syndrome which is frequently misdiagnosed.**
- **Our case had autism spectrum disorder, dysmorphic appearance and intellectual disability.**
- **Heterozygous c. 1937_38 delTG variant was detected in the ADHC1 gene.**
- **Regular and multidisiplinary follow-up is important for the diagnosis of XGS.**

CASE

A 7 years and 4 months-old male patient attends the 2nd grade in a special lower class. He was admitted to child psychiatry for the first time at the age of 2 due to the lack of meaningful words and sentences. As a result of the psychiatric evaluation performed at the age of 2, he was evaluated as moderately retarded in cognitive development. Neurological examination, MRI and karyotype analyses performed as a result of consultations requested due to dysmorphic appearance were interpreted as normal; EEG could not be evaluated because of non-compliance. Metabolic analyses (urinary organic acids, plasma amino acids and tandem MS) were found to be within normal limits.

In the developmental history, it was learnt that regular follow-up was provided, the baby was born as a result of a planned pregnancy, the

Correspondence Address: Burcu KARDAŞ, Kocaeli University School of Medicine, Child and Adolescent Psychiatry, Kocaeli, Türkiye • **E-mail:** burcu-atar@hotmail.com
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mother received levothyroxine treatment due to hypothyroidism during pregnancy, but there was no smoking, alcohol or substance use. The baby was born post term at 41 weeks gestational week, 3750 grams, by normal spontaneous vaginal delivery. The patient had no complications during labor and received phototherapy for jaundice for 1 day after delivery. When the neurodevelopmental stages were questioned, it was learnt that supported sitting was at the age of 7 months and walking was at the age of 18 months. When the family history was evaluated, the mother was 39 years old, high school graduate and diagnosed with hypothyroidism; the father was 42 years old, high school graduate and healthy. There was no consanguinity between the parents and the patient had a 14-year-old healthy sister. In the family history, there was no known medical or psychiatric history except for the history of diabetes mellitus and hypertension in the father's parents.

The follow-up process of the patient was continued with interviews with the family, clinical observation and Denver II Screening Test applications. In the psychiatric follow-up of the patient at the ages of 2.5 years, 3 years and 3.5 years, it was determined that there was partial progress with special education, but moderate cognitive retardation continued. It was observed that he spoke one word, could fulfil simple commands, was partially interested in his peers and tried to communicate. He was described by the family as a very active, impulsive child with focusing problems. In addition to cognitive developmental delay, attention deficit hyperactivity disorder (ADHD) was also diagnosed. During this period, our patient received special education and speech therapy and was followed up with behavioral suggestions for ADHD, and did not receive any medical treatment. At the age of 4 and 4.5, it was learnt that his communication decreased, his vocabulary did not increase in the process and he still could not acquire toilet training. Psychiatric examination revealed limited eye contact, inability to communicate and stereotypic behaviors such as flapping wings. In the Denver II Developmental Screening Tests, partial progress was observed until the age of 4, but in the following tests, partial regression in personal-social and self-care skills, which were more prominent in language, fine motor and gross motor areas, was remarkable (8). The patient was referred for pediatric neurology, pediatric metabolism and genetic consultations again because of his dysmorphic appearance and change in the clinical picture (regression in cognitive skills and addition of autism symptoms to the picture).

The patient did not come to the controls for about two years due to the onset of the pandemic process, and he applied to our clinic again at the age of 6 years and 4 months to renew his health board report. It was learnt that neurological and metabolic examinations were repeated in the process and the patient was diagnosed with Xia Gibbs Syndrome with the whole exon sequencing test performed when he was 5 years old. The heterozygous c. 1937_1938 delTG (p. Val646AlafsTer) variant in the AHDC1 gene was evaluated as a possible pathogenic variant. As a result of the psychiatric examination, it was observed that he could partially provide his self-care skills with the support of his mother, his eye contact was limited, he did not have joint attention, he was not alienated when his mother left the room, he did not look when his name was called, he did not have imitation skills, he did not use gestures and mimics in addition to the absence of meaningful words, and his interest sharing with the interviewer was limited, and it was determined that Autism Spectrum Disorder (ASD) symptoms continued to increase. The result of the Childhood Autism Rating Scale (CARS) performed in the presence of a clinician was evaluated as mild-moderate autism with a score of 32 (9). In addition to these, medical treatment for ADHD was recommended due to the persistence of features such as short attention span, difficulty in focusing, and higher than expected mobility in clinical interviews.

DISCUSSION

In some children diagnosed with autism, a picture called regressive autism is described, which is characterized by sudden or gradual loss of previously acquired skills and apparently normal development between the first 2–3 years of life. Most of the researchers have emphasized that regression especially in language skills is the main feature (10). It has been suggested that there are different genetic mechanisms underlying regressive autism. There are studies showing that the rate of seizures, neuropsychiatric diseases and autoimmune diseases in the family is higher in children with regressive autism. Therefore, further neurological and genetic evaluations are recommended (11).

Xia Gibbs syndrome is a rare genetic syndrome with a broad phenotypic presentation which may be accompanied by epilepsy, global developmental retardation, variable brain anomalies, language and speech retardation and autistic behavior patterns (1,2). It is thought that the heterogeneity in the clinical presentation and the complexity of the relationship between the affected gene region led to diagnostic difficulties (1). The fact that our patient was diagnosed a long time after the first presentation supports this situation. The fact that pediatric neurology outpatient follow-up was performed in an external center and in different clinics, advanced neurological examinations were not performed at the first presentation and the clinical picture showed changes in the process may be considered among the reasons for the delayed diagnosis.

Our patient has typical features of the XGS spectrum including global developmental delay, motor coordination disorder, short stature, facial dysmorphisms, laryngomalacia, ataxia, visual disorders (strabismus and refractive errors) and ASD features (1,6,7,12). In our patient, unlike other patients with moderate cognitive retardation, it was observed that his social skills were too low to be explained by his existing cognitive retardation. With advancing age, retardation in social and communication skills, poor use of language, difficulties in understanding non-verbal social cues, and difficulties in initiating and maintaining interactions become more pronounced. It was thought that the restriction of the social environment during the pandemic led to the exacerbation of the existing ASD symptoms. In addition, the regression in the language and motor skills he had acquired was also associated with the disappearance of the educational support he received during the pandemic. In the DSM-5 diagnostic criteria for ASD, it is stated that "ASD symptoms should be present in the early developmental period, but developmental expectations in the social field may not fully emerge until they exceed their limited capacity" (13). Although developmental and communicative problems were present in our patient before 48 months of age, it was thought that autistic symptoms became more prominent over time and with the negativities caused by the pandemic process in the social and educational field.

When the literature was reviewed, it was reported that XGS was associated with neurodevelopmental and psychiatric disorders (7,12,14). Similar to ASD cases not accompanied by a syndromic diagnosis, it was observed that males were affected more frequently than females in individuals with ASD accompanied by XGS (12). As in other neurodevelopmental disorders (ADHD, language development disorders, etc.), boys are affected more severely than girls (7,12). One of the mental disorders reported to accompany XGS is ASD. It has been reported that patients with XGS accompanied by ASD share the same etiopathogenetic factors and mutations in synaptic genes (12). Therefore, it has been reported that epilepsy is seen as a comorbidity in both diseases (12). However, a comorbidity of epilepsy was not observed in our case. In addition, ADHD comorbidity has been reported in patients with XGS in a literature review (12). The coexistence of these two neurodevelopmental disorders has also been associated with a common genetic background (12). In

addition, it has been reported that the comorbidity of ADHD may worsen the impaired social functioning in individuals with ASD (12). In our case, ADHD comorbidity was thought to be one of the factors leading to a delayed diagnosis of ASD. Various behavioral patterns have also been described in patients with XGS. Studies have reported various behavioral problems including aggression, self-harming behavior, anxiety disorders, poor social interaction, sleep disorders and impulse control (7,14,15). In our patient, sleep problems, aggressive and impulsive behaviors were learned both in the family history and as a result of clinical observation.

As a result neurodevelopmental disorders may present to clinics with different presentations and additional diagnoses may be made in repeated interviews as in our case. Psychiatric evaluation in neurodevelopmental disorders is important in planning educational interventions for the patient (such as speech therapy, ASD-oriented trainings), guiding parents on appropriate behavior management, or effectively regulating the treatment of mental disorders (ADHD, aggression, anxiety, etc.) when necessary. In this case report, it is aimed to contribute to future research on the clinical presentation and management of patients with Xia-Gibbs Syndrome with functionally impaired, poor social communication and behavioral difficulties.

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