A Child with Kabuki Syndrome and Autism Spectrum Disorder

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ABSTRACT

Kabuki syndrome (KS) is characterized by skeletal abnormalities, short stature, characteristic facial features, postnatal growth delay, and mental retardation. There are only a few case reports that present the co-existence of KS with autism spectrum disorder (ASD) in the literature. Herein we present the case of a boy with KS and ASD and discuss the possible shared etiologies. A 4-year-old boy was brought by his parents with complaints of no speech, hyperactivity, enuresis complex, temper tantrum, self-injury, and harming people or objects. We determined the lack of speech and eye contact, stereotypical behavior, and impaired social interaction and diagnosed him with autism and severe mental retardation via a psychiatric assessment. He had been followed up by pediatricians until he was 2 years old. Pediatricians noted his long eyelids with eversion of the lateral third of the lower eyelid, de-

pressed nasal tip, short stature, long palpebral fissures, brachydactyly, and fetal finger pads in their physical examination. The boy who has an operated ventral septal defect and seizures was diagnosed with KS when he was 5 years old. We recommended his parents to apply to a special education agency and kindergarten for him. Our case is a new example of the coexistence of KS and ASD in addition to the very few cases in the literature. Genetic analyses conducted in the existence of specific genetic syndromes, such as KS, may provide opportunities for understanding the genetic etiology of ASD and new scope in terms of novel treatment approaches.

Keywords: Autism spectrum disorder, Kabuki syndrome, etiology

INTRODUCTION

Kabuki syndrome (KS) (OMIM 147920) is a disorder of multiple congenital disorders with mental retardation and has an unknown origin. In KS, eversion of the lateral eyelid, arched eyebrows with sparseness of the lateral third, a depressed nasal tip, and prominent ears are the striking facial features in almost all patients. Skeletal anomalies, short stature, postnatal developmental retardation, mental retardation, and dermatoglyphic findings are among other common features (1).

Autism and autism-like behaviors, such as difficulties in communication and social interaction, have been found in some patients with KS (2). There are no diagnostic and confirmatory imaging or laboratory (genetic) examinations. The syndrome is diagnosed clinically (2). There are findings indicating that the molecular pathology in KS is caused by mutations in genes involved in histone modification and responsible for the production of histone methyltransferase and histone demethylase (MLL2 and KDM6A, respectively). The MLL2 mutation is present in 55–65% of patients having KMS (3). Mutations have been usually reported to arise de novo (3).

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by a developmental delay and a deviation in reciprocal social interaction, language and communication, and repetitive patterns of behavior or interests (4). ASD is an umbrella term covering hundreds of neurological syndromes associated with autism that are generally similar to each other but have different causes, outcomes, and treatment responses.

Epidemiological studies have reached the conclusion that there is no single etiologic factor, but rather a complex and multifactorial etiology in autism (5). Today, it has been reported that only 15–20% of individuals with autism have an identifiable etiologic factor (6).

At our clinic, we evaluated a patient diagnosed with KS upon difficulty in understanding and delay in speech, and we found some mental findings that could not be solely explained by cognitive impairment. As a result of his psychiatric evaluation, the patient was diagnosed as having “autistic disorder” falling within the spectrum of “ASD.” To date, KS has been diagnosed only in 350 patients worldwide. The prevalence of ASD has been reported to be 1 in 88 individuals. In the literature, there are a few studies reporting patients having KS with ASD (2,7). The random comorbidity of these two disorders in our patient was thought to be interesting in terms of possible common etiologic features and gene association.

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CASE

A 4-year-old male was admitted to our clinic with complaints of being unable to speak, restlessness, delayed toilet training, self-injury, tantrums, and meaningless utterances. The patient was the second child of a 25-year-old mother. Our patient was born at a gestational age of 39 weeks and 2 days by cesarean section. Cesarean section was chosen due to oligohydramnios developing before delivery and a congenital heart disease in the fetus. The patient had no family history of a similar disorder.

It was learned that the patient had been admitted to the hospital many times for diagnostic purposes and treatment. He was diagnosed with epilepsy for having cyanosis and not crying at birth, and an antiepileptic therapy was introduced. At the age of 6 months, he was operated for VSD, which decreased the frequency of his seizures. During his follow-ups, a genetic consultation was requested for atypical phenotypic features, epilepsy, and a ventricular septal defect. Considering multiple system abnormalities and his clinical status, he was diagnosed with KS at the genetic department. The patient underwent a diffusion MRI and abdominal ultrasonography, yielding no abnormalities at the age of 5.

His hearing test established a mild hearing loss in his right ear. The physical examination findings of the 7-year-old patient appearing younger than his age were atypical facial features: long palpebral fissures, long eyelashes, arched eyebrows with sparseness of the lateral third, broad nasal root, and anteverted ears. Moreover, he had brachydactyly and fetal finger pads. Evaluation of his motor development revealed he was able to hold his head when he was 10-months old, sit without support when he was 14-months old, and walk with support when he was 2-years old. His had his first words at the age of two and two-word sentences at the age of four. He knew a limited number of words and could construct limited sentences. He had no toilet training.

He was first brought to our clinic at the age of four for delayed speech, not being able to construct any sentences, and difficulty in understanding. Detailed examination of the patient followed up for 1.5 years with a diagnosis of moderate mental retardation also revealed signs and symptoms of autism. His psychiatric examination showed delayed speech, no consistent response to his name, responding to and following only simple commands, and not being able to start a conversation himself. His social communication and interaction were limited and he was not able to interact with his peers.

Our patient had no imaginative play and was displaying stereotypical behavior, such as rocking, hand flapping, and whirling. He was attracted to rotating objects, such as the washing machine and toy wheels, and was interested in inanimate objects, such as the tape player, mobile phone, and waste bin cover. He was playing routine games and biting his arm, and exhibiting frequent crying and temper tantrums.

The Ankara Development Screening Inventory was administered to the patient having a limited vocabulary and difficulty in sentence formation. The said inventory revealed that he had a severe developmental delay (8). The Autism Evaluation Form checking symptoms of "autistic disorder" was administered according to the DSM-IV diagnostic criteria (9). Moreover, the Autism Behavior Checklist having a cut-off score of 39 (10) was administered, and the patient scored 113. Then, the Aberrant Behavior Checklist (11) was administered, and the patient scored a total of 72 points. The patient, who was being followed-up with KS, was diagnosed as having "autistic disorder" and "severe mental retardation." A special education report was issued to ensure special education support. His parents were advised on the importance of a special education sup-

port for the patient to be able to communicate with his peers and have some self-care skills. Subsequently, follow-ups were planned at regular intervals.

In his psychiatric evaluation performed after one year, it was seen that his vocabulary improved and that he was able to form two-word echolalic sentences, look at a pointed object, and, although inconsistent, occasionally point out things.

As the literature contains studies reporting gene mutation in patients having KS with mental retardation, a gene analysis was conducted, and the heterozygous missense mutation c.15634G<C (MLL2 gene in exon 48) was found to be compatible with KS.

DISCUSSION

We report the case of a patient having communication and interaction difficulties, stereotypical behavior, and atypical facial features and seizures. In the literature, there are only a few cases of KS with ASD. The investigation of coexistence ASD and certain conditions as well as KS may help us shed light on the etiology of ASD.

It is known that multiple genetic factors play a role in autism. As long as genes associated with autism and the effects on the development of the brain are not explored, it would not be easy to find an effective treatment method (12). As autism is a disorder associated with multiple genes, establishing the responsible gene may prevent inheritance or help administering suitable treatment (13).

Chromosomal anomalies have been found in patients with KS having autism. Abnormalities in the 8th, 15th, and X chromosomes have been established to be common in autism and KS (12,14). Similar to Angelman and Prader-Willi syndromes, KS may be associated with autism through common genes (2,15). Pre-implantation genetic screening of a case with KS from a pregnancy established by in vitro fertilization revealed no abnormalities. Similarly, Ho and Eaves (16) reported that their patients had a normal karyotype, and the comorbidity of KS and autism was interpreted to be associated with perinatal complications (7). No prenatal or perinatal reasons have been proven to cause autism yet. Karyotype analyses are insufficient in diagnosing some genetic diseases; thus, further genetic evaluation is required.

MLL2 and KDM6A mutations that are thought to be responsible for KS generally create an early stop codon and truncate the protein before it is functional. Non-functional proteins have potentially harmful effects too. In case of any pathology caused by an early stop codon, the strategy is to ensure readthrough at the stop codon and the production of a functional protein. Aminoglycosides and non-aminoglycosides, thought to be effective in this process, have been used and are potential treatment options in genetic diseases such as hemophilia, beta thalassemia, spinal muscular atrophy, Duchenne muscular dystrophy, and cystic fibrosis. In this regard, in a study conducted on patients having KS, it was reported that response to gentamicin significantly differed and that the c.12844C>T mutation exhibited the highest gentamicin-induced readthrough efficiency (3).

Genetic analysis to be performed in such patients may help provide clues on the etiology of ASD. Besides, genetic treatments are thought to improve autistic symptoms in children having comorbid genetic diseases. Today, treatment goals have been defined in some specific genetic syndromes, and their effects on ASD symptoms are currently being studied (17). In this regard, it is important to identify specific genetic etiologies in children having ASD.

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