DDX3X Syndrome, A Rare Genetic Disorder with New Clinical Manifestations: A Case Report

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ABSTRACT

DDX3X syndrome is a rare genetic disorder affecting females and present mainly with developmental delay and intellectual disability. This syndrome can also present with autistic features. This is a 5 years old girl with typical features of DDX3X syndrome associated with hypothyroidism and cyclical vomiting disorder, two different conditions which have not been mentioned in the literature before. The aim of this case report is to increase the awareness of pediatricians toward this genetic disorder in order to diagnose any associated condition as early as possible and formulate a planned intervention with a multidisciplinary team

Keywords: DDX3X Syndrome, Intellectual disability, Neurodevelopmental disorder

INTRODUCTION

DDX3X Syndrome is a recently discovered X-linked neurodevelopmental disorder affecting females mainly[1]. This syndrome is caused by different mutations involving the DDX3X gene which is carried on the X chromosome[2]. The DDX3X gene encodes a unique helicase involved in mRNA (Messenger Ribonucleic Acid) biogenesis, RNA metabolism, and mRNA translation[2]. The first few cases were reported in 2014 and it's estimated that 600 cases exist around the world[3]. Patient's with DDX3X syndrome typically suffer from developmental delay, intellectual disability, behavioral problems, hypotonia, microcephaly, and musculoskeletal disorders like scoliosis and joint instability[4].

Other associated conditions might include seizures, congenital heart disease, ophthalmologic disorders, respiratory problems, endocrinopathy in the form of precocious puberty and possibly brain MRI abnormalities like ventriculomegaly and corpus callosum agenesis[4]. There are no characteristic dysmorphic features, but an upturned nose, long face and hypertelorism can be present[4]. Given the main clinical manifestation of intellectual disability and developmental delay, this disorder is often misdiagnosed as Rett syndrome or autism spectrum disorder.

DDX3X syndrome is diagnosed via comprehensive genomic tests like whole exome sequencing which identifies mutations within the DDX3X gene[5].

CASE PRESENTATION

This is a five years old Bahraini girl who was diagnosed with developmental delay. She was born at full term via spontaneous vaginal delivery with APGAR score of 9 and 9. Her growth parameters including weight, length and head circumference upon delivery were normal for the given gestational age. Neonatal examination was evident for hypotonia. She was born to a 31 years old healthy mother, who had uneventful pregnancy course with no recent maternal illness or infections. This is their third child, and the remaining siblings are two healthy boys. Parents are not consanguineous, and the father is healthy. There is no family history of known genetic disorder or developmental delay.

At the age of one year upon routine pediatric follow up she was noticed to have microcephaly along with delayed motor and speech milestones and some autistic features. Basic investigations for inborn error of metabolism such as lactate, ammonia, and Tandem Mass Spectrometry were normal. Thyroid, liver, and renal function tests were normal. Brain MRI was done and yielded a normal image. After that we lost follow up with the patient.

She presented again to our emergency department at the age of five years with history of severe vomiting, and she was found to have ketotic hypoglycemia which required intravenous fluid therapy. She was still having delayed speech and language milestones, meanwhile her delayed motor skills had already resolved by this age. Physical examination revealed spastic and hypertonic lower limbs compared to the previously noted hypotonia during infancy, however, her power and deep tendon reflexes were normal. Moreover, she had abnormal wide-based gait and pes planus. Her facial features became more prominent and revealed an elongated face, but no other dysmorphic features were noted. No scoliosis or other joint abnormalities were detected. Echocardiogram was normal. However, a repeat thyroid function test revealed hypothyroidism for which thyroxine was initiated. Upon further history taking, the parents elaborated that they sought abroad medical advice where she was diagnosed with intellectual and autistic disorder.

A decision was made to perform whole exome sequencing after obtaining parental approval. The result showed a heterogenous pathogenic variant in the DDX3X gene which is consistent with the genetic diagnosis of X-linked dominant mental retardation type 102.

DISCUSSION

We present a case of a very rare genetic disorder in a Bahraini child who was born to a Bahraini family. This is the first case to be reported in the middle east with this syndrome as far as our knowledge. Given

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the rarity of this syndrome and the limited available literature, there will always be room for reporting new cases with new and unique clinical manifestations concerning DDX3X syndrome.

It is estimated that the prevalence of intellectual disability is around 3% with a gender preference toward males[6]. However, mutations in DDX3X gene are a common cause of intellectual disability in females, and accounting for total 1%-3% of unexplained intellectual disability among females[7].

Developmental delay is the main clinical presentation of DDX3X syndrome, occurring in all affected females[4,5,8]. The second most common clinical manifestation is hypotonia, occurring in 80% of patients with this syndrome[5]. Autism spectrum disorder is the third most common clinical feature that young females can present with during the routine pediatric follow ups in the clinic[4]. The incidence of ophthalmologic problems in these patients ranges from 32%-39%, mainly of refractive errors and cortical visual impairment[4,5,8]. Our patient had myopia which required intervention with medical glasses. Movement disorders can occur in up to 61% of DDX3X cases, ranging from mild akinesia to devastating dystonic episodes[5,8]. This patient had wide-based gait, which is well documented in the literature as well[5,8].

Our patient exhibited the typical clinical features of DDX3X syndrome. The combination of developmental delay and intellectual disability along with autistic features in a female who had neonatal hypotonia and microcephaly, should drive the physician to search for gene mutations involving the DDX3X gene. But due to the scarceness of this syndrome, it can be very challenging initially to suspect this diagnosis, and genetic testing will eventually be required.

Moreover, our patient has also developed some other associated conditions which were not mentioned previously in the literature. Our patient was noted to have multiple episodes of severe vomiting occurring in the early morning every two to three months, and with each episode she developed ketotic hypoglycemia which required admission to the ward in multiple hospitals. An extensive workup for hypoglycemia didn't reveal a specific cause for the hypoglycemia and a clinical diagnosis of cyclical vomiting disorder was made.

Snijders Blok et al. reported the development of precious puberty in about 13% of patient with DDX3X syndrome[4]. Meanwhile, our patient didn't develop precious puberty, she did have hypothyroidism which required treatment with thyroxine, an important disorder involving the endocrine system, which was not reported in the literature, herby expanding the list of endocrine conditions associated with DDX3X syndrome.

CONCLUSION

DDX3X syndrome is relatively recent and a rare genetic disease, yet a common cause for intellectual disability among females. In our case the patient presented with the main clinical features of DDX3X syndrome, but also had other associated conditions like hypothyroidism and cyclical vomiting disorder which were not previously reported. We would like to increase the awareness of this genetic disease among physicians and mainly pediatricians who commonly face problems associated with milestones development and behavior problems like autism spectrum disorder, in order to diagnose any associated condition as early as possible and formulate a planned intervention with a multidisciplinary team.

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