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A Rare Cause of Hypotonia: 49,XXXXX (Pentasomy X)

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Abstract

Pentasomy X syndrome is a very rare sex chromosome numerical anomaly of unknown frequency. The karyotype consists of 49,XXXXX. Musculoskeletal, craniofacial, cardiac, and kidney anomalies accompany psychomotor developmental delays. This report describes, a 16-month-old girl who presented to the pediatric neurology outpatient clinic with complaints of joint laxity and inability to hold her head upright from the age of 3-4 months. The patient exhibited dysmorphic facial features and hand-foot deformities. Genetic consultation was requested, and cytogenetic examination revealed a 49,XXXXX chromosomal anomaly. The most prominent clinical feature of 49,XXXXX patients with pentasomy is severe hypotonia. This article emphasizes the importance of cytogenetic analysis in the evaluation of hypotonicity.

Keywords: 49,XXXXX, cytogenetic analysis, development delay, hypotonia

Introduction

Pentasomy X syndrome is a rare chromosomal disorder involving three additional X chromosomes (49,XXXXX rather than 46,XX).[1] It is characterized by severe hypotonia, microcephaly, craniofacial anomalies, bone, and joint abnormalities, heart and/or kidney defects, and mental disability.[1] The incidence is not known precisely although approximately 40 cases have been reported in the literature to date.[2,3] It is important to consider chromosomal diseases when physical dysmorphism and psychomotor developmental retardation are detected in the evaluation of hypotonic infants.

Case Report

This case report describes a 16-month-old girl with no consanguinity between her parents who was referred to a pediatric neurology clinic due to joint laxity compared to her peers. Her mother was a healthy 29-year-old, and this had been her first pregnancy. The baby was born at term, weighing 2500 grams. When the infant was 3-4

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months old, the parents noticed that she was unable to hold her head erect. At the physical examination, the patient weighed 11 kg (75p), with a length of 80 cm (75-90p), and a head circumference of 46 cm (25-50p). The patient exhibited various developmental abnormalities, including micrognathia, a short neck with a low hairline, posterior positional plagiocephaly with epicanthus, and hypertelorism (**Figure 1**). Additionally, she demonstrated hypotonia, motor delays, pes equinovarus, and decreased deep tendon reflexes (**Figure 2**). She could not touch the soles of her feet at axillary suspension, and the traction test was incompatible with her age. Comprehensive clinical evaluations, including laboratory tests [complete blood count, biochemistry values, and metabolic tests (ammonia, lactate, pyruvate, plasma amino acid, urinary amino acid, urine organic acid, and tandem mass spectrometry)], imaging, and genetic analysis, were performed to identify the underlying cause. Magnetic resonance imaging of the brain revealed an "expansion in central and peripheral cerebrospinal fluid distances, and bilateral mastoid effusion, other areas being within normal limits". There were no obvious abnormalities or pathologies detected in hearing tests, abdominal ultrasonography, and babygram. Cardiac echocardiography was normal. SMN gene analysis for spinal muscular atrophy was also normal. Chromosome analysis using the peripheral blood culture method was consistent with '49,XXXXX' (**Figure 3**). The investigations revealed a diagnosis of pentasomy X syndrome, a rare chromosomal disorder. This case report highlights the importance of considering chromosomal abnormalities in the differential diagnosis of developmental delays and joint laxity in pediatric patients.

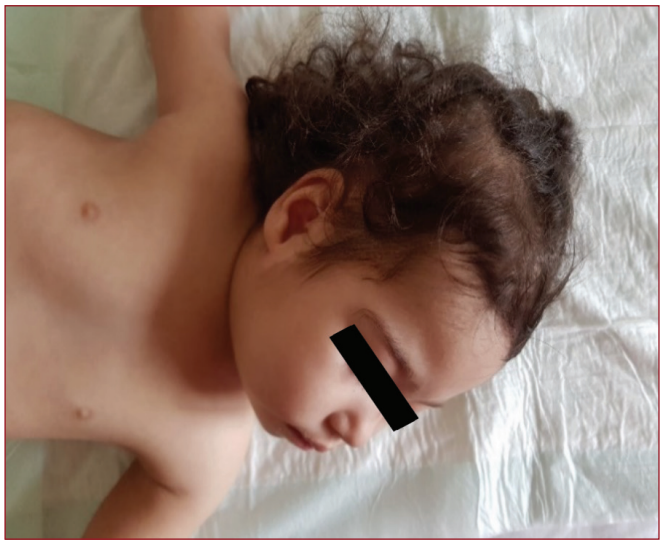

Figure 1. Facial appearance of the patient.

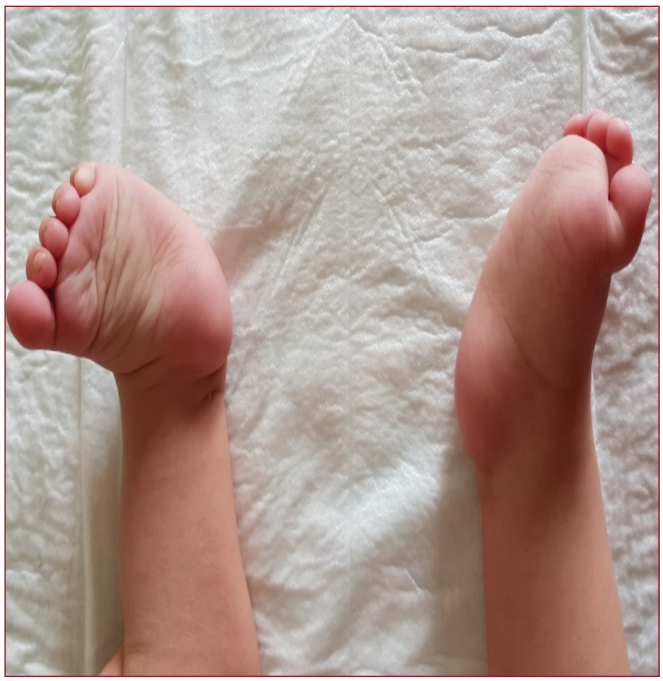

Figure 2. Pes equinovarus of the patient's lower extremity.

Discussion

Central nervous system disorders, cerebral malformations, Zellweger syndrome, lipid storage diseases, hypoxia, hemorrhage, infection, trauma, muscle diseases, muscle neuron junction diseases, motor neuron damage, spinal cord trauma, mitochondrial diseases, glycogen storage diseases, congenital disorders of glycosylation, and peripheral nerve diseases are some of the principal causes of hypotonia.[4-6] Some of these were investigated in the present case, and the chromosomal disorder pentasomy X was identified as the etiology. Pentasomy X is a very rare cause of hypotonia.

The first case of pentasomy X in the literature was reported by Kesaree and Wooley in 1963.[7] While sex chromosome numerical anomalies such as 45,X, 47,XXX, 47,XXY, 47,XYY, and 48,XXXX are seen in approximately one in 400 births, pentasomy X is a rare sex chromosome numerical anomaly of unknown frequency.[2] Approximately 40 cases with 49,XXXXX, and only five with an intrauterine diagnosis, have been reported worldwide. The condition has also been reported to occur in 1 in 85,000-250,000 females.[8-10]

Females affected by pentasomy X exhibit dysmorphic craniofacial anomalies such as microcephaly, a round face, a flattened nasal root, ear anomalies, pre-auricular skin tag, low hairline, ptosis, micrognathia, a high palate, cleft palate, thick lips, and irregular teeth. Ocular abnormalities may also be present, such as iris colobomas, hypertelorism, epicanthal folds, and upslanting palpebral fissures.[1,9] Musculoskeletal defects such as radioulnar synostosis, camptodactyly, clinodactyly, small hands and feet, thenar atrophy,

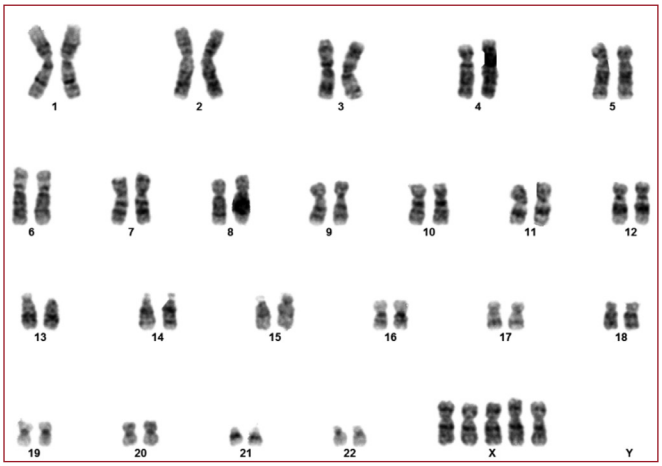

Figure 3. Pentasomy X appearance in the patient's chromosome analysis.

joint subluxation, hyporeflexia, hyperlaxity of joints, and hip dysplasia are also common in pentasomy X syndrome.[1] Our patient exhibited joint laxity, the elbow being particularly affected. Radioulnar synostosis, hydrocephalus, Dandy-Walker malformation, polyhydramnios, pleural effusion, and subcutaneous edema may be detected at prenatal ultrasonography.[8,9,11]

In some cases, pentasomy X syndrome may be accompanied by cardiac and genitourinary abnormalities such as ventricular septal defect and/or patent ductus arteriosus, horseshoe kidney, renal dysplasia, and a small uterus.[10] Although no external genital anomalies are usually detected, gonadal dysfunction and clinical infertility have been reported. Consistent with the literature, the genital examination in this study was also unremarkable. It is recommended that patients undergo pelvic/renal ultrasonography and echocardiographic examination.[1,8,9]

Some cases in the literature have been followed up with a diagnosis of Down syndrome due to clinical similarities between the two entities.[2] Cytogenetic analysis is therefore of great importance in the differential diagnosis.[3] In pentasomy, one X chromosome comes from the father and four from the mother because of non-splitting in the metaphase of meiosis.[1] According to previous studies, pentasomy is caused by a pathological X gene of maternal origin.[2] No stimulant-specific risk factor has been determined in the literature that might prompt intrauterine genetic counseling or a fetal karyotype study. Previous studies have also shown that maternal age is not a risk factor for pentasomy X.[8]

The absence of an identifiable risk factor for pentasomy X makes diagnosis difficult. The only known definite risk factor for pentasomy X is the female gender.[5] The literature reports consistent mental and growth delay in patients with pentasomy.[2,9] We applied the Denver Developmental Screening test to our patient and determined that she lagged behind her peers. Although a manifestation of immunodeficiency secondary to immunoglobulin disorder may be expected, our patient did not exhibit a history of frequent infections at clinical follow-up, and in contrast to the literature, no immunodeficiency was detected.[8,12]

Individual cases of pentasomy X may exhibit all the symptoms discussed above, and the condition can affect numerous systems. Treatment should be directed toward the specific symptoms in affected individuals. External ear anomalies can cause hearing impairment, and regular hearing screening is therefore recommended.[13] Loose joints and decreased muscle tone affect the posture of girls with pentasomy X; in a standing position, the feet are inclined inward, and ankle support is therefore needed before walking. If the patient has congenital heart disease, medical treatment or, surgical intervention may be required.[1,13] Patients should be given adequate developmental therapy, speech therapy, special education, and genetic counseling.

Conclusion

In conclusion, severe hypotonia is the most prominent clinical feature of patients with 49,XXXXX. There are thought to be more patients with pentasomy X, but that diagnosis is missed in many cases. More detailed studies and data are needed in order to identify these patients at an earlier stage. This case is therefore presented to emphasize the need for cytogenetic analysis, especially in female patients investigated for hypotonia.

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