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Case Report

TRISOMY 9 MOSAICISM SYNDROME IN A FEMALE CHILD

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Abstract: Trisomy 9 is a rare genetic condition with multiple anomalies. Our case is the first we are aware of in the Texas Panhandle. We present this case to draw awareness of this rare syndrome to providers and facilitate proper management.

Key Words: Small for gestational age, mosaic, microphthalmia, Trisomy 9, micrognathia

INTRODUCTION Trisomy 9 mosaic syndrome (T9MS) is a rare genetic syndrome with the initial cases described in 1973 [1,2]. Trisomy 9 is believed to be viable only in the mosaic form [3,4]. Fluorescence in-situ hybridization analysis of autopsies from patients previously described as non-mosaics revealed the presence of both euploid and trisomy 9 cells when both blood and fibroblast cells were analyzed, indicating that these patients were born in the mosaic form [3]. Clinical symptoms vary greatly in range and severity, depending on the percentage of cells with the extra chromosome 9 [5]. The main features of T9MS are craniofacial features with a bulbous nose, microphthalmia, dislocated limbs, and other anomalies of skeletal, cardiac, genitourinary, and central nervous systems. The most prevalent physical findings include prenatal onset of growth deficiency [6]; narrow bifrontal facial diameter; short, up slanting palpebral fissures; deeply set eyes; prominent nasal bridge; micrognathia; and low set/misshapen ears [7,8]. Due to the rarity of this syndrome, it can be misdiagnosed or underdiagnosed.

Our case is the only known case in Amarillo, Texas, to date. We report our journey of diagnosing a female preterm newborn with subtle dysmorphic features who was small for gestational age (SGA), and later confirmed as a case of T9MS.

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CASE PRESENTATION A female infant was born to a current G1P1 28-year-old, at 36 weeks and 1 day, via cesarean section due to fetal distress following induction of labor for severe maternal preeclampsia. The infant was the first child of non-consanguineous Caucasian parents. The infant was an SGA neonate (<10th percentile) at 1957 gm, length 45 cm (25th percentile) and with head circumference of 29 cm (<3rd percentile). At birth, microcephaly, low set posteriorly rotated ears, a prominent nasal bridge, patent nares, very tiny nasal openings, left microphthalmia, arched eyebrows, and bilaterally positive red reflexes were noted. Normal heart sounds with a grade 3/6 systolic heart murmur were heard at birth. The murmur resolved by the time of hospital discharge at 6 weeks of age, and no echocardiogram was done. The infant had mild hypotonia and a single palmar crease. No major anomalies were detected in the remaining systems.

Hospital Course The patient initially had poor nipple feeding due to her dysmorphic features and SGA status. A head ultrasound was done on the day of life 1 that showed a left sub-ependymal cyst. A subsequent head MRI was negative for malformation or periventricular leuko-malacia. A repeat MRI as well as a CT scan at 6 months of age were normal. Complete oral feeding was achieved at 6 weeks of age (42 weeks post-conceptional age). Renal ultrasound showed mild bilateral pelviectasis along with a normal renal doppler study. A genetic specialist was consulted at 6 weeks of life who agreed that the infant had subtle dysmorphic features, and that while the patient did not match any specific syndrome at that time, her differential diagnosis included De Lange and Goltz

syndromes. However, the geneticist did not run any labs or tests prior to NICU discharge. Per the genetic specialist, follow-up at one year of age was recommended for testing, if developmental delays were observed.

Post-neonatal Period The patient was followed on an outpatient basis by Texas Tech high risk clinic as well as her primary care physician. The patient experienced a gross developmental delay. By 19 months, she was not walking, crawling, or talking. However, she achieved a regular solid food diet at this time. She began to walk at 2 years of age, however, her gait remained unsteady. She continued to have a persistent language delay up until age 5. Despite adequate diet, from 2 to 4 years old, all 3 growth parameters remained at less than the 3rd percentile. These growth trends and developmental delays were noted by both her primary care physician as well as the neonatologist in Texas Tech high risk clinic. The primary geneticist who evaluated the patient in the NICU had retired. Given these concerns, the patient was referred at two years-of-age to a genetic specialist in Fort Worth, Texas, affiliated with Cook Children's Hospital. With the subtle dysmorphic features and noted delays, the genetic subspecialist suspected T9MS. His diagnostic work-up included chromosome analysis/karyotype and microarray. The chromosomal study confirmed trisomy 9 mosaicism, with about 43% mosaic (47 XX+9, and 46 XX). Due to her moderate mental and psychomotor impairments, the child was enrolled in special education school, with occupational, speech, and physical therapy. She was being followed by Turn Center for the above therapies past five years of age. The patient is currently 8 years old and has benefited greatly from early childhood intervention which includes speech, occupational, and physical therapy. She uses sign language and enjoys playing with her friends.

DISCUSSION T9MS is a rare chromosomal disorder in live-born infants. Complete trisomy 9 accounts for 2.4% of spontaneous abortions [4]. The term mosaic indicates that some cell lines of the body have an extra chromosome 9, trisomy (resulting in 47 chromosomes), while others have the normal chromosome pairs. The trisomy is responsible for the symptoms and physical anomalies that characterize T9MS. A recent case study supported the role of non-invasive prenatal testing by maternal plasma DNA sequencing as a potential mode of screening for T9MS [9].

Patients typically show growth deficiencies which begin prenatally and continue as failure to thrive during infancy and on into childhood. Mental and psychomotor retardation have been described [4]. In our case, the child displayed mild hypotonia, in addition to moderate mental and psychomotor impairment. Patients tend to have distinctive abnormalities of the skull and facial region. These include microcephaly, sloping forehead with narrow temples, broad nose with bulbous tip, slit-like nostrils, micrognathia, abnormally wide fontanels and cranial sutures, prominent upper lip and receding lower lip, high arched palate, cleft lip, cleft palate, short palpebral fissures, deep-set eyes, microphthalmia and low-set malformed ears [10]. Our case had some very subtle craniofacial abnormalities as a preterm neonate that became more apparent in childhood. Other features of T9MS include hydrocephalus, Dandy-Walker malformation and congenital heart defects (present in two-thirds of cases such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus). Complications secondary to heart defects such as heart failure and pulmonary hypertension may be found, depending on the severity of the mosaicism. In males, cryptorchidism, micropenis, and hypospadias have been described. Renal abnormalities such as renal cysts and hydronephrosis have been reported. Musculoskeletal abnormalities include scoliosis, congenital hip dislocation, club feet, rocker-bottom feet, narrow chest, rib defect, hypoplasia of nails or phalanges, and simian crease. Additional physical features include corneal opacities, epibulbar dermoids, pulmonary hypoplasia, diaphragmatic hernia, and gastroesophageal reflux [10,11].

Prognosis of T9MS depends on the severity of the mosaicism and the extent of the trisomy cells involving the major organs, such as the central nervous system and heart. Management of T9MS depends on symptoms and care is largely supportive involving a multidisciplinary team. T9MS has a high neonatal morbidity rate, although, in cases of mosaic trisomy 9 with a low proportion of trisomy cells, there have been reports of survival until late childhood [4].

CONCLUSION This case study increases awareness of T9MS to aid in prompt diagnosis and management amongst providers. This study encapsulates our understanding of the genetic inheritance and prognosis of this rare syndrome. Knowledge of T9MS will assist providers in the appropriate management and timely genetic counseling of families of an affected child. To our knowledge, no standardized manual or materials on

providing care to a child with T9MS exists. With increased awareness and dissemination of knowledge on T9MS, we hope to fuel the creation of a resource tailored specifically towards the specialized care these children require.

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