

Trisomy 4q Syndrome: A rare Syndrome Phenotypically Similar to Trisomy 18

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Citation

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Abstract

Trisomy 4q syndrome is rare and has been reported in only in a limited number of cases. We describe a case of trisomy 4q syndrome misdiagnosed as trisomy 18 syndrome due to anomalies seen on antenatal ultrasound. Postnatal chromosome analysis revealed an unbalanced translocation between the long arms of chromosome 4 and 18 leading to duplication of the majority of 4q and a small deletion of distal 18q. The infant had unique clinical features including an absent right thumb and claw like-fingers on both hands which to our knowledge have not been previously described in patients with Trisomy 4q. Several similar congenital anomalies are associated with trisomy 4q syndrome and trisomy 18. It is important that perinatologists, obstetricians and neonatologists be aware of trisomy 4q, its similarity to trisomy 18, and the possibility of misdiagnosing patients prenatally if amniocentesis and chromosomal analysis are not performed.

INTRODUCTION

Trisomy 4q syndrome is a rare condition, first described in 1971, that often presents with multiple debilitating congenital anomalies.¹ Trisomy 4q has been reported to occur due to multiple genetic mechanisms including inheritance of unbalanced translocations,^{2,3,4,5} insertions,^{6,7} or duplications^{8,9,10} and by de novo unbalanced translocations.^{11,12,13} Interestingly, the most common chromosome site involved in unbalanced translocations with 4q appears to be the distal band of chromosome 18q.^{3,4} Although, in most of cases of trisomy 4q, the majority of 4q is duplicated, the breakpoint on 4q may vary; in cases of unbalanced translocation, a small deletion of another chromosome may accompany trisomy 4q. Therefore, although most cases have similar anomalies, the variability in breakpoints and involvement of other minor chromosome anomalies may result in different phenotypes. We present an infant with distinctive phenotypic features as a result of an unbalanced translocation resulting in trisomy 4q and deletion of the distal portion of 18q.

CASE REPORT

The serum biochemical markers in a 32 year old gravida 5, para 3 Hispanic pregnant female were suggestive of fetal Trisomy 18 with a risk of >1 in 10. She was referred to the University of Kansas Medical center (KUMED) for detailed ultrasound evaluation and genetic counseling. Anomalies

identified by ultrasound at KUMED included a large atrial septal defect, a single umbilical artery, stubby and malformed fingers of one hand (Figure 1), and unilateral multicystic kidney (Figure 2). As there was a high index of suspicion of fetal aneuploidy the woman was counseled about cytogenetic confirmation; but she declined amniocentesis.

Figure 1

Figure 1: Antepartum image of the patient's stubby fingers

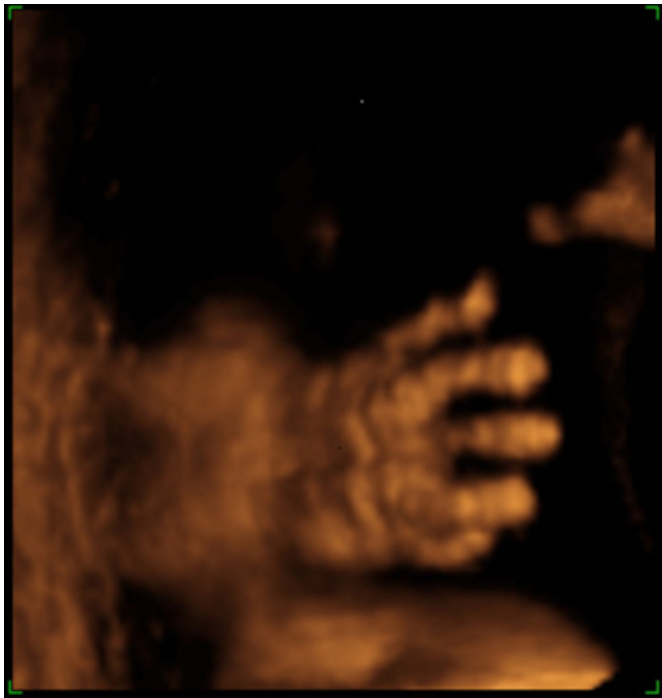
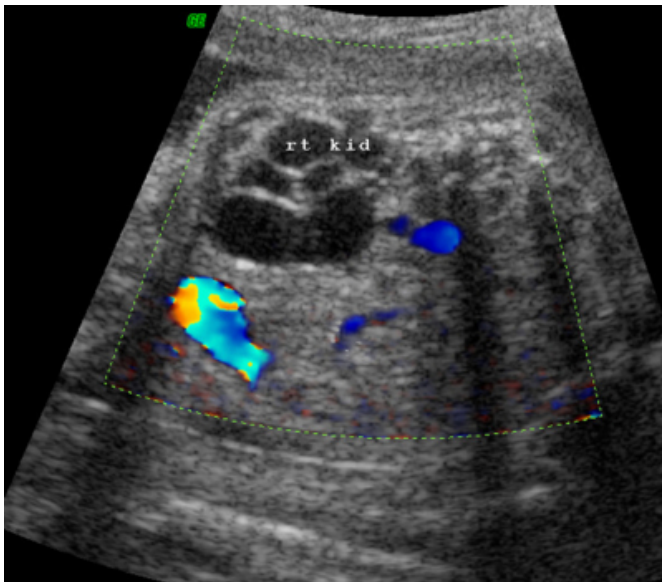


Figure 2

Figure 2: Antepartum illustration of the patient right kidney demonstrating a right renal cyst



She had three prior home deliveries in Mexico. The first child, a male infant, was born with multiple anomalies including cleft lip and palate, a possible heart defect, “contracted hands and feet”, and a genital anomaly. This child died at two months of age. Her subsequent two pregnancies resulted in healthy female infants who are alive and well.

After the initial clinic visit and fetal ultrasound, the woman underwent weekly fetal biophysical profile. She presented in labor at thirty nine weeks gestation. Upon presentation, continuous fetal monitoring was characterized by a flat, fixed heart rate of 150 BPM, with absent variability or accelerations suggestive of subacute perinatal hypoxic-ischemic insult to the fetus. Pitocin augmentation of labor was initiated which resulted in significant fetal heart rate decelerations. Pitocin was stopped, decelerations ceased, and cesarean section was considered. However, because of the strong possibility of aneuploidy (trisomy 18), there was reluctance to intervene with cesarean section. The woman was offered amniocentesis with rapid FISH (Fluorescent In Situ Hybridization) analysis for which she consented. The amniotic fluid was light brown and translucent. Six hours later the FISH test for trisomy 18, using a centromere probe for chromosome 18, was reported as negative. A cesarean section was performed for fetal intolerance to labor and a male infant weighing 2690 grams (15th centile for 39 weeks gestational age) was delivered, with Apgar scores of 3 at one minute, and 6 at five minutes. The infant required vigorous resuscitation at birth including intubation and positive pressure ventilation. Umbilical venous pH was 7.23, with a base deficit of 8.0.

Examination of the newborn infant showed multiple congenital malformations including hypertelorism, low set ears, a prominent nasal bridge, a posterior cleft palate, an inverted tragus of his left ear with an auricular tag, microcornea in the left eye, absence of right thumb, hyperflexed hands and bilateral claw-like fingers (Figure 3), a shallow sacral dimple, a small penis and bilateral cryptorchidism.

Figure 3

Figure 3: Full view of the patient immediately post intubation.



The MRI of the head revealed multiple occipital hematomas compatible with perinatal brain injury from fetal distress. The renal ultrasound showed large renal cysts bilaterally. The cardiorespiratory status was stable after three days of mechanical ventilation. Subsequently, the infant exhibited poor suck and swallow reflexes. After an upper GI study showed severe gastro-esophageal reflux, gastrostomy with fundoplication was performed. The infant later developed hydrocephalus related to the brain lesions seen at birth. A ventriculo-peritoneal shunt was placed. He had multiple shunt infections, severe failure to thrive and died at the age of 1 year.

Figure 4

Figure 4: Postpartum illustration of the patient's left hand illustrating his claw-like fingers which was seen bilaterally on his upper extremities



CHROMOSOMAL ANALYSIS

Chromosomal analysis was not performed on the first baby boy born with anomalies in Mexico. In our patient, PHA-stimulated cultures and G-banding on peripheral blood obtained after birth, revealed the following karyotype: 46,XY,der(18)t(4;18)(q25;q22). The chromosome analysis (figure 5A) indicated the presence of an unbalanced translocation resulting in three copies (trisomy) of a large portion of 4q (bands q25 through q35) and a deletion of the distal portion of 18q (q22 through q23). The karyotype of the father and one of two sisters of the patient showed that both were carriers of the t(4;18)(q25;q22) balanced translocation (Figure 5B) with no apparent gain or loss of any chromosomal material. Both the father and sister who carried the balanced translocation had normal phenotypic features. The phenotype and the karyotype of the mother and the other sister of the patient were normal.

Figure 5

Figure 5a: Karyogram of the 46,XY,der(18)t(4;18)(q25;q22) karyotype obtained from cytogenetic analysis of the patients peripheral blood illustrating two normal chromosome 4s and the derivative chromosome 18.

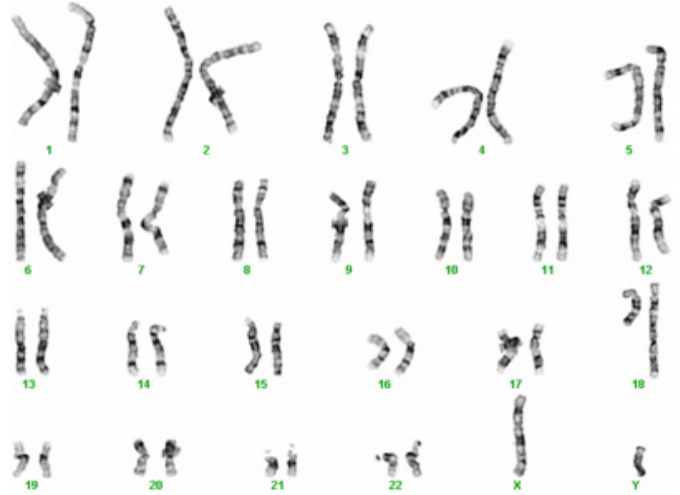
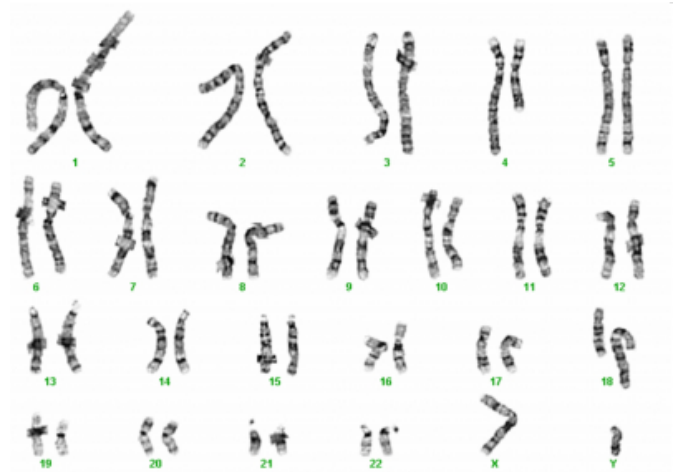


Figure 6

Figure 5b: Representative karyogram from the patient's father illustrating the balanced translocation with a 46,XY,t(4;18)(q25;q22) karyotype.



DISCUSSION

Trisomy 18 is the second most common trisomy occurring in approximately 1:6806 live births.¹⁴ In contrast, only a limited number of case reports have been published describing the rare trisomy 4q syndrome. Trisomy 4q syndrome has many antenatal anomalies similar to trisomy 18 often making it difficult to distinguish the two entities in-utero.

One of the most common chromosomal findings in trisomy 4q syndrome, similar to the abnormality in our case, is an unbalanced form of a translocation between 4q and 18q. The resulting derivative chromosome, der(18)t(4;18), produces

an extra copy of the majority of the long arm of chromosome 4 and a small deletion on the distal long arm of chromosome 18. There are eight previous case reports of trisomy 4q syndrome associated with an unbalanced translocation between chromosomes 4 and 18.^{1,2,3,4,5,15,16,17} One of these reports also describes the difficulty of early diagnosis and in differentiating the condition from common chromosomal anomalies including trisomy 18.¹⁵

Common features such as low birth weight,⁴ hypotonia,⁴ hypertelorism,^{4,15,17} sacral dimple,⁴ cleft lip and palate,^{15,17} heart defects,⁵ genital malformations,^{5,5} micrognathia,¹⁵ and ocular defects,⁴ have been reported in most patients with der(18)t(4;18). Our patient had some of these common features including hypertelorism, a posterior cleft palate, and microcornea in the left eye. In addition, he had absence of the right thumb, hyperflexed hands and bilateral claw-like fingers (Figure 3). The claw-like fingers are a feature not previously described in trisomy 4q syndrome. However, several of the anomalies that our patient had were very suggestive of trisomy 18. Low set ears, clenched hands, overlapping fingers, cryptorchidism, congenital heart defects, and cleft palate have been known to occur in more than fifty percent of trisomy 18 patients.¹⁸ In a case series of thirty-nine cases of patients with trisomy 18, Lin et al¹⁹ reported that 90% of patients with trisomy 18 have rocker bottom feet. Trisomy 4q patients have been described as having "feet abnormalities" but rocker bottom feet are rare. Our patient did not have rocker bottom feet.

The antenatal serum biochemical markers of trisomy 18 in first and second trimester are well described. However there are no published patterns of maternal serum biochemical markers for Trisomy 4q. The mother of our patient had remarkably abnormal biochemical serum markers that were consistent with trisomy 18, illustrating that similar biochemical marker can be observed in both trisomy 18 and in trisomy 4q.

In summary, we describe a case of an infant with the rare trisomy 4q syndrome in which trisomy 18 was the presumed diagnosis based on maternal serum biochemical markers and ultrasound features. A prenatal diagnostic chromosome analysis was not performed due to the mother declining amniocentesis. This report highlights the fact that serum biochemical markers and ultrasound features are screening tests and that confirming the correct chromosomal disorder requires amniocentesis and chromosomal analysis. The information from such chromosomal analysis is critical for

proper genetic counseling and for decision making regarding delivery and resuscitation of the fetus.

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