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EARLY PRENATAL DIAGNOSIS OF DOUBLE TRISOMY 48, XXY+18 (KLINEFELTER-EDWARDS SYNDROME) IN THE FIRST TRIMESTER

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ABSTRACT:

Double aneuploidies are rare chromosomal anomalies. Double trisomy 48, XXY+18 or Klinefelter-Edwards syndrome is an extremely rare form of double aneuploidy, with only a few cases reported in the literature. In most cases, the clinical features of trisomy 18 seem to predominate while the features of Klinefelter syndrome are usually missing, since most of them do not become clinically evident before puberty. We present a rare case of 48, XXY+18 or Klinefelter-Edwards syndrome diagnosed in the first trimester during routine dating scan. Increased nuchal translucency, generalized edema of the skin (anasarca) and omphalocele were noted, leading to chorionic villous sampling, with the subsequent karyotype revealing a double trisomy 48, XXY + 18. This is the first reported case of Klinefelter-Edwards syndrome detected in the first trimester. The possibility of this rare anomaly should be considered in the differential diagnosis of increased nuchal translucency in the first trimester of pregnancy.

Introduction

Double aneuploidies are rare chromosomal anomalies; most cases are found in spontaneous abortions, while they are extremely rarely found in liveborn infants [1, 2]. Double aneuploidies may involve different combinations of autosomal or sex chromosome trisomies or monosomies, including a double autosomal trisomy with a normal number of sex chromosomes, a combination of autosomal trisomy with sex chromosome trisomy and a combination of autosomal trisomy with sex chromosome monosomy. Previously reported double aneuploidy syndromes include Edwards-Down (48,XX+18+21 or 48,XY+18+21), Down-Klinefelter (48,XXY+21), Down-Turner mosaicism, Down-XYY (48,XYY+21), Patau-Klinefelter (48,XXY+13), Edwards-Turner mosaicism, Edwards-XXX (48,XXX+18), Edwards-XYY (48,XYY+18), and Klinefelter-Edwards syndrome (48, XXY+18) [3]. To date, less than 20 cases of Edwards-Klinefelter syndrome in newborns have been reported in the literature [4-6]. We present herein a rare case of double trisomy 48, XXY+18 (Klinefelter-Edwards syndrome), presenting with abnormally increased nuchal translucency, generalized edema of the skin (anasarca) and omphalocele in the first trimester ultrasound scan. This is to the best of our knowledge the first reported case of Klinefelter-Edwards syndrome detected as early as the first trimester of pregnancy.

Case report

A 32 year-old white woman, G1, P0 was referred for routine first trimester ultrasound scan. Her past medical history included hypothyroidism. Her previous obstetric-gynecological, family and social history were unremarkable. The woman presented at 12 weeks and 6 days gestation, and pregnancy was redated based on the crown-rump length (CRL) to 12 weeks and 0 days. The nuchal translucency (NT) was found to be increased, measuring 8.6 mm (Figure 1), and generalized edema of the skin (anasarca) (Figures 2 and 3) and fetal omphalocele with only bowel content (Figure 4) were noted. The fetal heart rate was at the upper normal limits (174 bpm). The calculated risk for Down syndrome based on the woman's age was 1 in 523, while the risk based on woman's age and NT was 1 in 4 for Down syndrome, 1 in 5 for Edwards syndrome and 1 in 8 for Patau syndrome. Full consultation regarding increased risk of chromosomal abnormalities, malformation syndromes and congenital heart disease was provided and chorionic villous sampling (CVS) was offered. The woman decided to undergo CVS, and fetal karyotype showed a double trisomy Edwards-Klinefelter syndrome (48, XXY + 18). Following these results, the woman opted for termination of pregnancy in the first trimester.

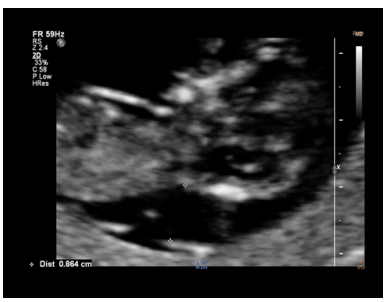

Figure 1: A case of a fetus with double trisomy 48, XXY + 18 on routine first trimester ultrasound scan. The nuchal translucency (NT) was increased, measuring 8.6 mm.

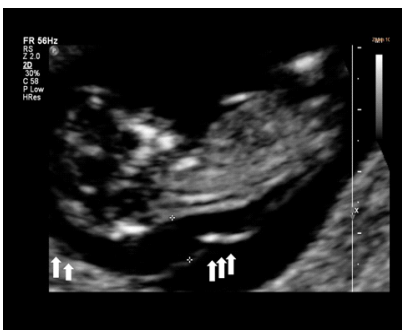

Figure 2: Sagittal view of the fetus with double trisomy 48, XXY + 18 showing generalized edema of the skin (anasarca) (arrows).

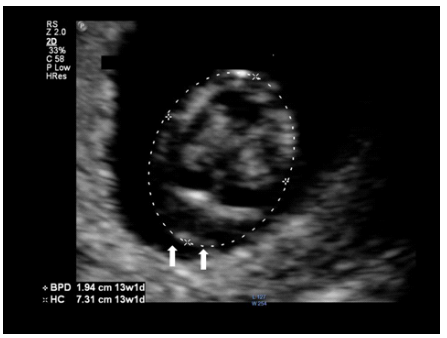

Figure 3: Transverse view of the fetal head showing generalized edema of the skin (anasarca) (arrows).

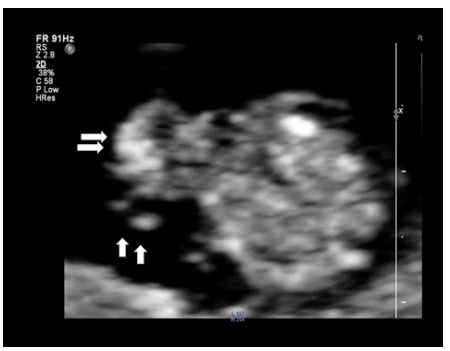

Figure 4: Transverse view of the fetal abdomen showing omphalocele with bowel content (arrows)

Discussion

Trisomy 18 or Edwards syndrome is the second most common autosomal trisomy at birth following trisomy 21. The live born prevalence is estimated to be 1/6,000-1/8,000, but the overall prevalence is higher (1/2,500-1/2,600) due to the high frequency of fetal loss and pregnancy termination after prenatal diagnosis [7]. Typical abnormalities of trisomy 18 include "strawberry head", typical facial appearance with malformed ears, prominent occiput, microphthalmia, small mouth and micrognathia; overlapping and flexion deformity of fingers (clenched hand); rocker-bottom feet; renal abnormalities; congenital heart defects; and intrauterine growth restriction [7].

Klinefelter syndrome (47, XXY) occurs in 1/500 to 1/1,000 live male births; most newborns have no significant dysmorphism and no signs and symptoms; minor congenital abnormalities, particularly clinodactyly, occur in about 25% of cases [8, 9]. Before puberty, boys with 47, XXY appear normal, though most require some help in school, particularly in reading and spelling. The majority of cases are identified in adulthood with tall, slim stature, small testes, male infertility, and an increased risk of developmental problems [9, 10].

Double aneuploidies may present with features of both chromosomal anomalies. The following phenotypic variations may be seen as well, due to gene interactions between the two anomalies: further malformations, early death, and an entirely different phenotype [1, 3]. In most, if not all, cases of double aneuploidy involving autosomal and sex chromosomes the clinical features of the sex chromosomal abnormality are usually missing, apparently because some sex chromosome abnormalities do not have characteristic clinical features (XXX; XXY), while others might not become clinically evident until puberty (XXY) [10]. In the present case the phenotype of trisomy 18 seemed to predominate, and this has been consistently found in the literature [4-6]. It particular, the nuchal translucency was increased, and generalized skin edema (anasarca) and fetal omphalocele were present. However, it is noteworthy that in the present case the fetal heart rate was at the upper normal limits; this was an unexpected finding since in a previous study [11], the fetal heart rate was increased in trisomies 21, 13 and in Turner syndrome, while it was decreased in trisomy 18 and triploidy, and remained unchanged in all other sex chromosome abnormalities.

In most cases (in more than 96%), the additional chromosome in trisomy 18 is maternal in origin, while in almost 50% of cases of Klinefelter syndrome an X and the Y chromosome are paternal in origin [10]. Possible mechanisms of Klinefelter-Edwards syndrome include nondisjunction in both gametes leading to double aneuploidy in the zygote or alternatively, a single global defect causing multiple nondisjunctions in a single gamete [10].

Thus far, no more than 20 cases of double trisomy 48, XXY+18 or Edwards-Klinefelter syndrome have been reported [4-6]. In most of these cases, diagnosis was made postnatally, while late prenatal diagnosis was possible only in the second and third trimester [6, 12, 13], precluding the option of early termination of pregnancy. To the best of our knowledge, this is the first case of Klinefelter-Edwards syndrome detected in the first trimester of pregnancy and the prominent ultrasonographic finding was increased nuchal translucency, anasarca, omphalocele and mild tachycardia of the fetus. Hence, the possibility of this rare anomaly should be considered in the differential diagnosis of increased nuchal translucency in the first trimester of pregnancy.

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