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Trysomy 18: an update on prenatal diagnosis and management. A case report

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Abstract

Trisomy 18, also known as Edward's syndrome, represents the second most common chromosomal abnormality after trisomy 21 or Down's Syndrome, with an incidence of 1:6000 live births. However, the prevalence of the condition in the general population is significantly higher (i.e. 1:2000 pregnancies), and this is due mainly to the prenatal natural history of the condition which associates high rates of intrauterine fetal demise and pregnancy termination due to poor outcome. Although the prevalence of the condition has increased over the past 20 years mostly due to advanced maternal age at conception, the number of life births has decreased. Most obstetricians would agree that trisomy 18 is a lethal abnormality and would therefore counsel for termination of pregnancy leaving little, is any cases as evidence on the prenatal natural history of the condition. Interestingly, over the last couple of years, case report regarding infancy survival of children with trisomy 18 and their internet spread success-stories have begun to shift parental perception on the lethality of the condition. This case report of trisomy 18 is important because it presents the late third trimester diagnosis based on ultrasound features that are highly specific. It also reviews the few options of management available in a country were late termination is illegal.
Keywords: *trisomy18, prenatal diagnosis, natural history, screening aneuploidy*

Introduction

Trisomy 18 represents the second most frequent chromosomal abnormalities following Down syndrome and, similar to the latter the incidence of the condition is directly dependent on maternal age[(1)]. The Edwards phenotype can arise from different chromosomal abnormalities: full trisomy 18, mosaic trisomy 18, and partial trisomy 18. In the mosaic form (less than 10% of all cases) the phenotype can be highly variable from a frank Edwards with multiple structural defects and mental retardation to almost a normal individual with average intellect. To complicate matters even further, it appears that the phenotype is independent on the degree of abnormal cells[(1)].

Regarding the natural history of the condition the rates of fetal loss after diagnosis, either through miscarriage or stillbirth, is higher than those for trisomy 21[(2-4)]. According to a retrospective study from Wales than included 538 cases of trisomy 18[(5)], the rate of fetal loss decreases with advanced gestational age but after 24 weeks there is no clustering of events at a particular age these being uniformly distributed across gestation thereafter. There was a gender prevalence with male gender being twice more likely to adverse outcome than girls. The mean gestational age at demise was 32 weeks which is significantly higher than that of foetuses with Down's syndrome where the mean age of demise is 28 weeks[(6)]. These data are extremely important in counselling patients who decide for expectant management when diagnosed with trisomy 18. It is also important to note that there is a risk of recurrence of the condition of about 1% which is higher than the a priori maternal age related risk. The postnatal survival of infants with trisomy 18 is about 1.5 days. A recent report from Ireland shows than in a cohort of 18 live births of trisomy 18, the survival ranged from 1 hour to 16 weeks[(7)].

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Case Report

A 42 year-old women, 35 weeks pregnant, self-referred to labour ward because of reduced fetal movements in the last 24 hours. Routine ultrasound was performed which revealed a small symmetric fetus with severe polyhydramnios but with reassuring fetal Doppler. The patient was admitted to hospital for further investigations of polyhydramnios.

The following day a very detailed anomaly scan was performed in our Fetal Medicine Department and the informed consent was taken. There were several structural abnormalities noted which included: strawberry shaped head (Figure 1, A and B), clenched hands (Figure 2, A and B), abnormal feet (Figure 3, A and B), bilateral duplex kidneys (Figure 4, A and B), AVSD and atrioventricular septal defect (AVSD) (Figure 5, A and B).

There was also polyhydramnios (i.e. single deepest pocket of 15 cm), severe symmetrical intrauterine growth restriction, low set small ears and reduced fetal movements. All of these findings were explained and the presumptive diagnosis of trisomy 18 was made. We counselled the parents about the perinatal risks of the condition emphasizing the risk of stillbirth and neonatal death within the first couple of days. The options of obstetric care focus on maternal wellbeing versus fetal wellbeing were discussed and the parents opted for maternal focused care. We explained that in the context

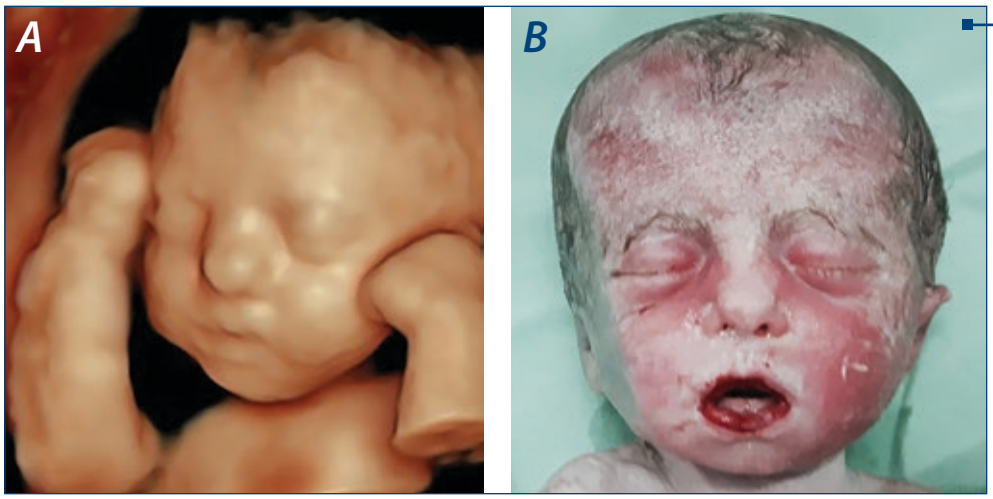

Figure 1 (A and B). Typical aspect of fetal head with brachycephaly. The BPD>OFD by flattened occipital bones. Strawberry shaped head. Also note the micrognathia

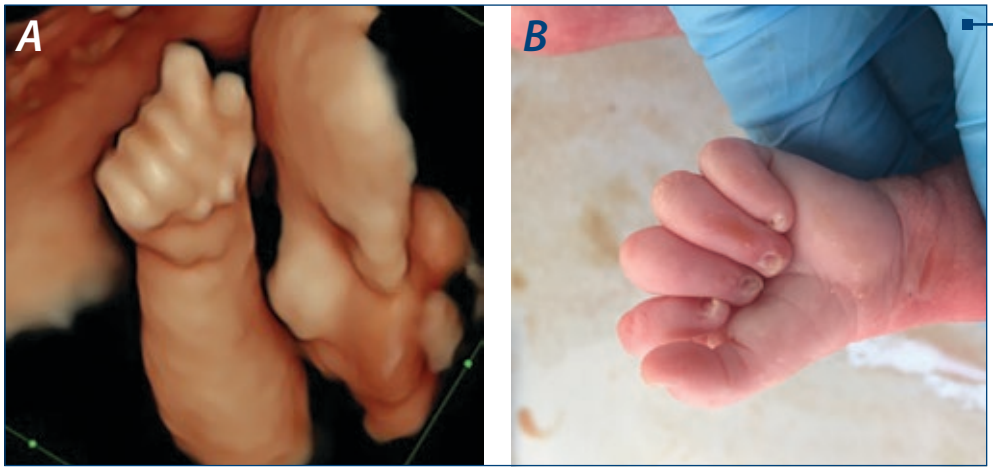

Figure 2 (A and B). Typical aspect of clenched hands with the second and fifth finger overlapping the third and fourth

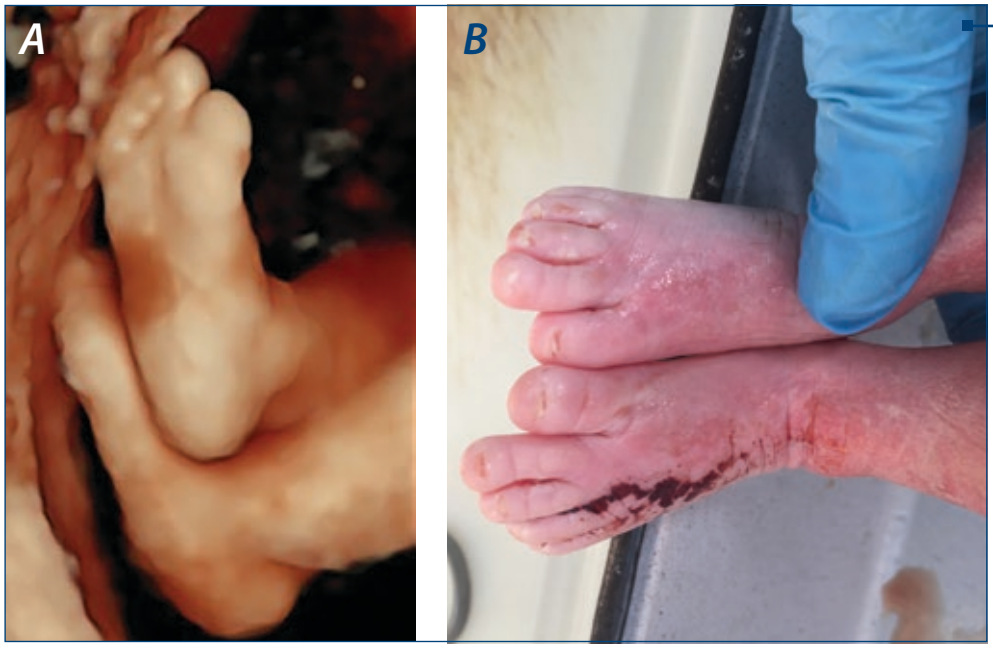

Figure 3 (A and B). Atypical aspect of fetal feet with the first finger significantly shorter than the rest

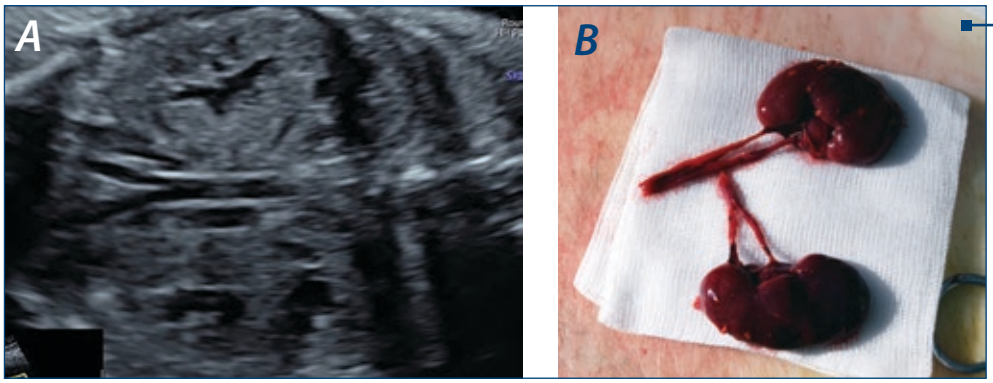

Figure 4 (A and B). *Duplex kidneys; note the ultrasound aspect with dilated ureter*

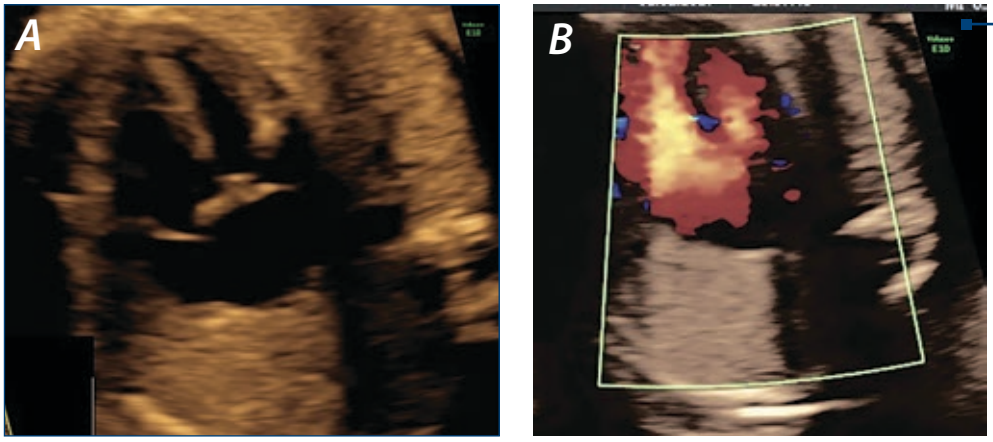

Figure 5 (A and B). *Heart defect which shows an atrioventricular septal defect, with size discrepancy between left and right. On the Color Doppler flow there is almost absent flow on the mitral valve and the filling of the left ventricle is through the ventricular septal defect*

of polyhydramnios vaginal delivery is less likely because of instable fetal lie and the risk of emergency caesarean section at the time of ruptured membranes is high. The option of amnio-drainage was discussed and the parents opted for that. An uncomplicated procedure was performed. Three liters of amniotic fluid were extracted and a sample was sent for karyotype. The results were positive for trisomy 18.

The patient was discharged from the hospital in the same day. She returned 2 weeks after with reduced fetal movements. Fetal demise was confirmed by ultrasound. Induction of labour was started the same day and she delivered a baby girl, about 2000 g weight, without any signs of viability.

Discussion

Prenatal screening for aneuploidies was initially implemented in the 60's and meant mainly screening for trisomy 21. At that time screening was based on maternal age and the cut-off was 35 years of age when the background risk is 1:150(8). These women were offered amniocentesis in early second trimester as a method of screening. A new era begun in the late of 80's when maternal serum screening using a combination of alpha fetoprotein, estriol and beta human chorionic gonadotropin (hCG) showed a specificity for Trisomy 21 of 70% for a false positive rate of 5%. This became known as the triple test or Barts test. Later the addition on inhibin A raised the specificity to 80%. The biggest change came, however, in the 90's when Nicolaides described the nuchal translucency and ultrasound examination of the fetus became part of screening for Down's. The test became known as the combined screening test and implied an adjustment of maternal age related risk based on fetal ultrasound parameters (crown rump length, fetal nucal translucency (NT), fetal heart rate (FHR) and serum biomarkers like pregnancy-associated plasma protein-A (PAPP-A) and beta-hCG)[9]. Starting with 2008 it was implemented as a national policy for screening in the UK and has been used since its making, worldwide, being the gold standard of screening in the first trimester[8-10].

It became apparent that, incidentally, when screening for trisomy 21 using the combined screening test also detects the vast majority of cases of trisomy 18 and 13 in the second and third trimester[8]. Algorithms specific for the last two conditions were created based on the same principal of a priori age related risk that is subsequently multiplied with likelihood ratios derived from standardization of NT, FHR, beta-hCG, and PAPP-A. These anomalies (i.e. trisomy 21, 13, and 18) are similar in their association with increased maternal age, increased NT and low PAPP-A, but are different in terms of levels of beta-hCG and FHR. Beta-HCG for trisomy 18 is reduced when compared to the median for gestational age. The detection rate for trisomy 18 using the combined screening test is 91% for a FPR of 2.2% at a risk of cut-off of 1:100. However, in Romania the risk of cut off is generally set at 1:250 where the combined screening test has a specificity of 95% with a false positive rate of

4%. In trisomy 18 the first trimester scan shows specific markers like early onset fetal growth restriction, a tendency for bradycardia and exomphalos in 30% of cases, absent nasal bone in 55% and single umbilical artery in 75%[11-12].

In 2011 a new era of prenatal screening commenced. It was the era of cell free fetal deoxyribonucleic acid testing. The test implies collection of maternal venous blood starting as early as 11 weeks, isolating cell free deoxyribonucleic acid and later testing for aneuploidies by either massive parallel sequencing or digital polymerase chain reaction. The test is now implemented in more than 63 countries worldwide and in the USA it has a wider addressability than first trimester combined screening test[13]. Attention should be raised firstly to the fact that the test is not a diagnostic test but rather a more accurate screening test. The practitioner should appropriately inform the patients about the limitations and the intended benefit of such a test. Recent data shows that non-invasive prenatal test (NIPT) testing in a routine low-risk population has a sensitivity of 97.4% and a specificity of 99.9% in screening for trisomy 18 with a meta-analysis including all the published work on NIPT showing a detection rate of 96.3% for FPR[14].

Starting with early second trimester and through the third trimester, Edwards syndrome displays an array of ultrasound markers, both major and minor that are highly specific for the condition. Various groups report various incidence of major structural abnormalities which can be grouped on specific organs and systems based on their incidence: growth restriction, heart abnormalities, brain abnormalities, gastrointestinal, and genitourinary. Minor markers include abnormal position of the fetal hands (more than 40%) and feet, abnormal shaped ears, single umbilical artery, and choroid plexus cysts (CPC). The usual picture of trisomy 18 in the second trimester is that of an early onset growth restricted baby, usually with increased amniotic fluid, strawberry shaped head, overlapping fingers (i.e. the second and the fifth finger lie on top of the other two), heart abnormality, exomphalos and single umbilical artery. The above findings can be all present or just a combination of them. However, the ultrasound specificity of trisomy 18 is reported to be more than 90%[15-18]. Regarding isolated CPC noted in a routine setting there has been wide debate whether it constitutes an indication for invasive testing. Although most reviews show that there is no association of isolated CPC with trisomy 18[15-17], Cho et al. showed that in his series of Edwards foetuses, CPC was the only marker evident at the 20-week scan[18].

In the third trimester of pregnancy the key ultrasound findings are fetal growth restriction (87%) and polyhydramnios (67%)[15]. The mother also reports reduced fetal movements which in half of cases leads to iatrogenic preterm birth in the context of altered fetal wellbeing[19]. The median gestational age at delivery of live Edwards was reported at 36.5 weeks[7].

Conclusions

Trisomy 18 has a very high detection rate on ultrasound by a combination of specific markers that become evident early in the second trimester. Different study groups report the specificity of detailed ultrasound examination for trisomy 18 as high as 100%. This case report is important because it presents not only major ultrasound markers for trisomy 18 but also shows the natural history of the condition that becomes less and less encountered in the era where, prenatal diagnosis gives the option of termination of pregnancy. The case is also valuable for those practitioners who are met with the situation in which parents diagnosed with trisomy 18 chose to continue the pregnancy. Care should be directed to the risk of polyhydramnios needing drainage in the third trimester and also to the timing of delivery knowing that the risk of stillbirth is high.

There is much debate between neonatologists, palliative care groups, support groups and geneticises on whether Edwards should be considered a lethal condition. Towards this process of thought come the cases of babies with Edwards that live to their first birthday and the many testimonials of parents who care for these children and want to provide the best care for them.

The present case report brings proof about the natural history of the condition and helps to develop the management of future pregnancies which are similar in their diagnosis. ■

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