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Prenatal Diagnosis of Partial Trisomy 21 Associated With Maternal Balanced Translocation 46xx Der 21 t(21q;22q) With Pericentric Inversion of Chromosome 9

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Abstract:
This communication reports prenatal diagnosis of partial trisomy 21 resulting from balanced translocation (21q;22q) in a 36-year-old gravida 7, para 1 woman. The lady had only one living child and there was history of recurrent spontaneous first trimester abortions. Triple test was abnormal in the present conception. In addition, the woman had pericentric inversion of chromosome 9, a finding scarcely reported previously with carrier status in Indian literature. A few cytogeneticists consider this as a normal variant. However, many reports in the recent literature link pericentric inversion of chromosome 9 with infertility, recurrent abortions and a number of other abnormal conditions. A review of the relevant literature pertinent to the case is provided. (J Postgrad Med 2003;49:154-156)

Key Words: Trisomy 21, translocation (21;22), prenatal diagnosis, inversion 9

Down syndrome (DS) is the commonest autosomal aneuploidy with most cases resulting from a supernumerary chromosome 21 (classical trisomy). Small proportions of cases of DS result from partial trisomy from translocation between chromosome 21 and other autosome. The frequency of partial trisomy has been shown to vary from 2.2% to 13.7% in Indian studies.¹

Pericentric inversion of chromosome 9 (PIC9) is one of the most common balanced structural chromosomal aberrations.² Despite being categorised as a minor chromosomal rearrangement that does not correlate with an abnormal phenotype, many reports have raised conflicting views regarding the association of PIC9 with subfertility, recurrent abortions and other abnormal clinical conditions.²⁻⁸

This communication reports successful prenatal diagnosis of partial trisomy 21, 46 XX der (21) t (21q;22q) associated with balanced translocation with PIC9 in a phenotypically normal mother.

Case History
A 36-year-old gravida 7, para 1 woman with a single living issue, was referred for the prenatal diagnosis. She had one healthy male offspring of 7 years. Her first, second, third, fifth and sixth pregnancy had culminated in spontaneous first trimester abortions for which no cause could be found. Her TORCH titres and rheumatological work-up including anti-cardiolipin antibodies were normal. Neither she nor any of the abortuses had been subjected to cytogenetic analysis. Her ultrasonography done at the 12, 21 and 28 weeks of present conception did not reveal any abnormal markers. Triple screening test done in view of an advanced maternal age showed low serum α-fetoprotein levels. The beta-HCG levels in the serum and unconjugated estriol levels in urine were elevated.

Amniocentesis was performed at 17th week of gestation and culture was set up in 5% CO₂ atmosphere for 16 days. Culture indicated metaphases with 46-chromosome complement. G banding of each metaphase revealed partial trisomy 21, 46 XX der (21) t (21q;22q) complement (Figure 1). Maternal karyotype done from peripheral blood leukocyte set in RPMI for 72 hours revealed metaphases with 45-chromosome complement with translocation between chromosome 21 and 22. In addition, there was inversion in p11-q11 segment of one of the chromosome 9 (Figure 2). The foetus did not inherit this pericentric inversion of chromosome 9. Paternal karyotype was normal.

The diagnosis of partial trisomy 21 was made. Parents were counselled and they opted for medical termination of pregnancy. Foetus was not subjected to karyotype examination as per parental wish.

Discussion
Recurrent pregnancy loss occurs in approximately 1% of women in the reproductive age. Uterine anomaly, parental chromosome anomaly, polycystic ovarian cystic disease, infections and anti-phospholipid antibody syndrome are notable among aetiological factors responsible for recurrent mis-

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carriages. But, a definite cause can be established in only 50-60% of the couples.

Participation of genetically unbalanced gametes in the process of fertilisation is a well-recognised cause of spontaneous abortions. The imbalance may be familial as in our case or may arise de novo and can be detected by cytogenetic studies of the abortus. Unbalanced gametes may also arise during meiosis when a balanced chromosome rearrangement is carried out by one of the two apparently healthy parents. An abnormal chromosome complement (aneuploidy) contributes significantly to foetal loss during pregnancy. The contribution of chromosomal abnormalities to foetal loss decreases as pregnancy continues. An estimated 50% of first trimester spontaneous abortions result from chromosomal abnormalities, but these abnormalities are responsible for only 5% of stillbirths (after 28 weeks of gestation).

Recurrent miscarriage due to sporadic chromosomal abnormalities may simply be a consequence of the dramatic increase of trisomic conceptions with increased maternal age. A number of foetal chromosomal abnormalities are related to advanced maternal age. These include autosomal trisomies, sex chromosomal polyploidies (XXY and XXX). However, it is also possible that some couples are at increased risk of abnormalities as a result of gonadal mosaicism, factors affecting chromosome structure and segregation, increased sperm aneuploidy in the male partner, or accelerated “aging” of the ovaries. Among the chromosomal anomalies seen in these foetuses autosomal trisomies leads the list (61.6%) followed by triploidy (16%), monosomies (10.6%) and tetraploidy (4.4%). Thus, cytogenetic analysis of the abortus, particularly in cases of recurrent abortion is of great help to arrive at an aetiological diagnosis.

When a Robertsonian translocation causing DS is inherited, the recurrence risk in the future pregnancy depends on the parental sex. In presence of paternal carrier status for t (21;22) the recurrence risk is 5%. It increases further to 10% if mother is a carrier. Over two-thirds of the DS conceptions miscarry spontaneously or are stillborn. A number of tests including screening tests for DS have been devised over last few decades for the prenatal diagnosis of various genetic diseases. Later includes α-fetoprotein levels, unconjugated estriol, serum human chorionic gonadotropin, pregnancy associated protein-A levels and ultrasonography (signs like shortening of humerus and femur, thickening of nuchal fold and renal pyelectasis). They serve as useful markers and indicate need for undertaking prenatal cytogenetic analysis. Foetal karyotype using amniocentesis or chorionic villus biopsy remains the gold standard for the prenatal diagnosis of DS.

Prenatal diagnosis of partial trisomy 21, 46 XX der (21) t (21q;22q) identified using amniotic fluid cell culture associated with balanced translocation in a phenotypically normal mother is reported.
Incidentally in our case mother was also found to have PIC9, a chromosomal abnormality that is so common that few cytogenetists consider it to be a normal variant. However, this view is being challenged. Table 1 shows a short summary of certain large series’ of clinical investigations involving PIC9. An increasing number of investigators have shown increased incidence of “sub-fertility” in adult carriers of PIC9. Whether these represent a true reflection of “sub-fertility” in this group or a selective bias towards the older “sub-fertile” females who conceive at an older age and thus utilise the antenatal diagnostic workup, remains a matter of debate. Earlier claims of increased incidence of schizophrenia in subjects with PIC9 are disproved by others. ^7,16 Congenital myotonic dystrophy, cerebral cyst, phenotypic abnormalities have all been reported with PIC9. ^5,8,17 At the present stage it is difficult to establish if a true relationship exists between these abnormalities and PIC9, as the data is limited. The role of PIC9 still remains a clinical mystery.

References

Table 1: Studies reporting abnormalities associated with inversion of chromosome 9 (PIC9)

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Sample size</th>
<th>Study group</th>
<th>Incidence of PIC9</th>
<th>Important findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kodama Y, 1982</td>
<td>197</td>
<td>Institutionalised severe mental and physical handicap cases</td>
<td>4.56%</td>
<td>Incidence was 4.2 times higher than that in general Japanese population.</td>
</tr>
<tr>
<td>Makino T et al, 1990</td>
<td>1278</td>
<td>Couples with recurrent pregnancy losses</td>
<td>2.34%</td>
<td>32 (5%) had major chromosomal anomalies, 23 (3.6%) had minor chromosomal anomalies. These couples had abortion rate of 90:1%. 3 fold increased risk of offspring with DS in couples with PIC9.</td>
</tr>
<tr>
<td>Serra A et al, 1990</td>
<td>300</td>
<td>DS families</td>
<td>5.66%</td>
<td>PIC9 observed with increasing frequency in habitual and spontaneous abortion groups. Female carrier rate was twice the male carrier rate.</td>
</tr>
<tr>
<td>Yamada K, 1992</td>
<td>4367</td>
<td>Couples with habitual abortions, spontaneous abortions, Cases with DS, XXY complement and normal control</td>
<td>1.65% of normal controls, 1.52% of DS cases, Habitual and spontaneous abortion group had incidence twice the normal control</td>
<td></td>
</tr>
<tr>
<td>Ko TM et al, 1992</td>
<td>1350</td>
<td>Chinese foetus</td>
<td>1.2%</td>
<td>All affected had normal phenotype.</td>
</tr>
<tr>
<td>Teo SH et al, 1995</td>
<td>3506</td>
<td>2448 Antenatal screening samples (ASS) and 1088 peripheral blood leucocyte culture (PBLC)</td>
<td>Overall incidence was 1.07% (1.2% in ASS group and 0.8% in PBLC group).</td>
<td>Increased incidence in schizophrenics. Susceptibility locus hypothesised to be located at break point of inversion 9. Incidence did not differ significantly from reported incidence of 1.7-2.1% in general Japanese population.</td>
</tr>
<tr>
<td>Kunugi H et al, 1999</td>
<td>250</td>
<td>Schizophrenia cases</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>Toyota T et al, 2001</td>
<td>161</td>
<td>Schizophrenia cases</td>
<td>2.5%</td>
<td></td>
</tr>
</tbody>
</table>

DS-Down syndrome