Genetic counseling in chromosomal abnormalities

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Pure trisomy due to nondysjunction of chromosome 21 is responsible for 96% of Downs with a recurrence risk of less than 1%. Parental karyotype is not required in nondysjunction type of trisomies. Majority of fetuses with Trisomy 13, 18, monosomy XO and triploidy display major malformations on USG. Recurrence for all of the above nondysjunction numerical aberration is low. Hence, pregnancies with previous history of any of the above confirmed on fetal karyotype, can be followed up by serial ultrasound scans. Translocation of chromosome 21 (4% of Downs), the recurrence risk varies between 10-25% if one parent is a carrier of a translocation. The risk of unbalanced translocation in the offspring will depend on the type of translocation in the parents, which parent is involved and whether translocation is between homologous or non homologous chromosome. Once an unbalanced translocation in the fetus / child has been identified, parental karyotype is essential. More than 50% of translocations in fetus occur denovo. So if parents have a normal karyotpe, no matter what the translocation in the fetus, recurrence risk is minimal < 1%.

Introduction

Chromosomal anomalies form the major cause of birth defects and mental retardation. All pregnancies carry a baseline risk of 3-4% for major congenital anomalies.[sup] [1] The etiology for birth defects include chromosomal, single gene or mendelian disorders, multifactorial, teratogenic or environmental effects.

Genetic counseling is the process by which the parents at risk of a hereditary disorder are communicated of its consequences, the probability of its inheritance and the ways in which it may be prevented.[sup][2] In the context of fetal medicine, the disorders that are addressed are mostly those that affect the unborn with conditions which manifest either before or after birth and counselees are usually prospective mothers, and her partners.[sup] [3] Genetic counseling ideally should be provided by a team of professionals that include physician, geneticist, genetic counselor and psychologist. But most counseling in relation to prenatal diagnosis in developing countries is inevitably carried out by obstetricians. This places a heavy responsibility on the obstetrician to be knowledgeable about the modern advances, to identify women at risk, to choose properly the tests required and if need to refer her to appropriate specialist.

The time is not far when the female giving birth to an abnormal baby may take the obstetrician to a consumers court for failing to recognize and inform her of the risk she had and the way in which this could have been avoided. This article will try to cover common chromosomal abnormalities which clinicians encounter in their day to day practice and their management.

Before describing the risk in specific groups of chromosomal disorders, two fundamental facts that the clinician should bear in mind are:

*Majority of chromosomal disorder have an extremely low risk of recurrence in a family, especially where no abnormalities is present in the parents. *The majority of disorders following Mendelian inheritance show no visible chromosomal abnormality.The incidence of recognizable chromosomal abnormality in unselected newborns is 9.2 per 1000 of which 75% have autosomal and 25% has sex chromosomal abnormalities.[sup] [4]

Classification of Chromosomal Aberration

Abnormalities of chromosomes are classified as structural and numerical involving both autosomes and sex chromosomes.

Numerical aberrations are further classified as:

Aneuploidy when there is a loss or gain of one chromosome.

Gain of one chromosome is referred to as Trisomy, when three copies of a chromosome are present instead of the normal pair. Common trisomies are 13, 18, and 21. Trisomy 13 and 18 usually present on prenatal ultrasound as multiple congenital malformations or a still birth. Trisomy 21, the most common and best known of chromosomal disorders, is most elusive on ultrasound and may survive postnatally with mental retardation.

Monosomy, when there is a loss of a chromosome, is uniformly lethal if it involves autosomal chromosome. Monosomy X, commonly known as Turner Syndrome survives with residual dysfunction.

Polyploidy is the gain of a whole set of chromosome such that the cell contains multiples of haploid chromosomes (Triploidy 3 N, Tetraploidy 4 N). Outcome with polyploidy is either a spontaneous miscarriage, still birth or a vesicular mole.

Mechanism of numerical aberration Meiotic nondysjunction is the most frequent mechanism responsible for numerical aberration. It is the failure of separation of two homologous chromosome which migrate to the same gamete during the process of meiosis I or II. This diploid gamete when unite with a normal gamete results in a zygote with trisomy [Figure 1]. Aging ova in the mothers with advanced maternal age predisposes to such meiotic nondysjunction.[sup] [5] Most commonly encountered nondysjunction trisomy is Downs Syndrome.

Down's Syndrome

Presence of an extra chromosome 21 lead to Down's syndrome. There are 3 types

*Pure trisomy due to nondysjunction of chromosome 21 is responsible for 96% of Downs with a recurrence risk of less than 1%. Risk increases with increasing maternal age. *Translocation of chromosome 21 (4% of Downs), the recurrence risk varies between 10-25% if one parent is a carrier of a translocation. *Mosaic Downs in which 2 cell lines, one with normal chromosome and other with trisomy is present in the same individual. Recurrence risk again is low. Case 1: Nondysjunction downs 26 years old female, G2P1 L1 with previous baby having pure Trisomy 21 came with ongoing pregnancy of 10 weeks of gestation. Karyotype and clinical picture of the previous affected individual is as shown [Figure 2]. Since the recurrence risk with nondysjunction trisomy is < 1%, the plan for this pregnancy was measurement of Nuchal Translucency at 10-14 weeks. Patient maybe given an option of first trimester screen at 10-14 weeks which will give the risk prediction for Downs or an amniocentesis at 16 weeks which rules out chromosomal abnormality. Screen if negative or normal karyotype on amniocentesis, can be followed up with a targeted scan at 18 weeks. Parental karyotype is not required in non dysjunction type of trisomies.

Majority of fetuses with Trisomy 13, 18, monosomy XO and triploidy display major multisystem malformation sonographically [Figure 3]. Recurrence for all of the above nondysjunction numerical aberration is low. Hence pregnancies with previous history of any of them proved on fetal karyotype can be followed up by serial scans. The vital issue is that previous index case should have been worked up and confirmed by karyotype on fetal blood sampling / amniocentesis.

Structural aberration This arises from a chromosomal breakage, followed by an abnormal rearrangement. They may be

*Translocations *Deletions *Duplications *Inversion *IsochromesSince translocations are responsible for a major fraction of structural aberration, we will discuss them in more detail.

Chromosomal translocation is the transfer of genetic material between 2 chromosomes. It is considered balanced if there is no loss of genetic material. Unbalanced translocation occurs when material is either gained or lost resulting in partial / complete, monosomy / trisomy.

Balanced Translocation [Figure 4]

Robertsonian translocation occurs among acrocentric chromosomes (Group D 13 - 15, Group G 21 -22) which fuse together at their centromere. This may occur between similar pair of chromosome (homologous translocation) or different chromosomes (non homologous).

Reciprocal translocation is an exchange of genetic material between two nonhomologous chromosomes. It occurs among metacentric or submetacentric chromosomes. Since there is no loss of genetic material in balanced translocations it produces no phenotypic effect and the individual is called a healthy carrier. But it causes increased risk of producing unbalanced translocations in their offspring.

The risk of unbalanced translocation in the offspring will depend on the type of translocation in the parents, which parent is involved and whether translocation is between homologous or non homologous chromosome. Theoretical risk in the offspring for unbalanced translocation Downs is 1:3 [Figure 5]. In fact the actual risk if mother is a carrier is 10% and 2.5% if father is a carrier of 14:21 or 21:22 translocation. But if one of the parents is a balanced translocation carrier of 21:21 chromosome risk to the offspring is 100% [Figure 6].

More than 50% of translocations in fetus occur denovo. So if parents have a normal karyotpe, no matter what the translocation in the fetus, recurrence risk is minimal < 1%.[sup] [6]

Case 2 Patient R, married for 2 1/2 years, non consanguineous marriage. Scan at 19 weeks in her first pregnancy showed increased nuchal fold thickness, bilateral cleft lip and palate, vermian agenesis, enlarged echogenic kidneys and AVSD [Figure 7]. Ultrasound guided fetal blood sampling was done which showed unbalanced translocation Trisomy 13. Pregnancy was terminated and autopsy confirmed the findings of ultrasound along with postaxial polydactyly in all 4 limbs [Figure 8].

To predict the recurrence risk in her next pregnancy, parental karyotype was done. Father's karyotype was normal and mother was a

carrier of balanced robertsonian translocation involving chromosome 13 and 14. Recurrence risk given during counseling was 10-15% and was advised prenatal diagnosis by CVS/ amniocentesis in each subsequent pregnancy. In her next pregnancy, scan at 16 weeks showed bilateral cleft lip and palate, echogenic small bowel, hypoplastic left heart syndrome and polydactyly. Features were similar to the previous pregnancy, hence amniocentesis was not done and pregnancy terminated. Autopsy confirmed the ultrasound findings [Figure 9].

Case 3 Mrs. A, 26 years, G2P1L1, married for 4 years, non consanguineous marriage, came with an ongoing pregnancy at 13 weeks. Previous 3 year old sibling, weighed 3kg at birth, born by LSCS for breech presentation with no antenatal or intrapartum complication, had delayed milestones. On examination the child had features suggestive of Downs syndrome with hypertelorism, epicanthic fold, upslant eyes and low set ears. Karyotype done outside was reported normal. We repeated the karyotype on a strong suspicion of Downs which showed unbalanced Robertsonian translocation of 21:21 chromosomes [Figure 10].

This homologous translocation has a 100% recurrence risk if one of the parent is a carrier. Parental karyotype for future risk assessment was done and found normal. So the parents were reassured that it was a denovo translocation in the first child with low recurrence risk in this pregnancy. Amniocentesis at 16 weeks was done and karyotype was normal for the fetus.

Case 4 Mrs. M, P0A4, married for 2 years, non consanguineous marriage came for a prepregnancy counseling for recurrent pregnancy losses. Her sugars, thyroid profile, antiphospholipid antibody screening, pelvis ultrasound all were normal. Parental karyotype was done where the husband's karyotype showed 46XY, 9qh+ i.e. increase in the length of q arm of chromosome 9 which is a normal variant. Patient had a balanced reciprocal translocation of chromosome 8 and 9. We were able to find out her cause for recurrence pregnancy loss with risk of 10-25% for subsequent abortions. If pregnancy continues beyond 16 weeks, prenatal diagnosis for fetal karyotype is mandatory to rule out unbalanced translocation Pre implantation diagnosis may help such parents. Balanced chromosomal rearrangements have been found with an increased frequency in couples with recurrent pregnancy losses.[sup] [7]

Case 5 Mrs. P married for 41/2 years, 3rd degree consanguineous marriage, G2 P1L1 came with an ongoing pregnancy at 22-23 weeks. Previous child 2.1kg at birth developed seizures at 2 months of life. Now 31/2 years with no head control, microcephaly, dysmorphic facies with micrognathia, upturned nostril, pectum excavatum, inguinal hernia and hypospadias. Karyotype showed partial monosomy of short arm of chromosome 4 [Figure 11]. Mother's karyotpe was normal and father had a balanced reciprocal translocation between chromosome 2 and 4. Recurrence risk in ongoing pregnancy is high so a fetal blood sampling has been offered.

Conclusion

*Nondysjunction trisomy has a recurrence risk of < 1%. *Once an unbalanced translocation in the fetus / child has been identified, parental karyotype is essential. *If parents are carriers of balanced translocation, risk for unbalanced translocation in the fetus is high and all subsequent pregnancies require prenatal sampling. *Recurrence risk is low if neither parents are carriers of balanced translocation. Hence there is no need for invasive testing.

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