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Genetic Counseling of Prenatally Detected Sex Chromosome Anomalies

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Abstract:

Prenatal screening tests are being universally employed in the current era to identify women at risk of fetal aneuploidies. This unveils a high proportion of unanticipated findings amongst which sex chromosome abnormalities are frequently encountered. It is imperative that geneticists and fetal medicine specialists have sufficient knowledge about these anomalies in order to provide appropriate genetic counseling and assist the couples in decision making during pregnancy. In the article, we briefly discuss the outcomes and counseling approach for the prenatally detected common sex chromosome abnormalities.

Keywords: Sex chromosome anomalies, prenatal screening,Turner syndrome, Klinefelter syndrome, genetic counseling.

Introduction

Sex chromosome abnormalities (SCAs) are the most frequently encountered chromosomal abnormalities both prenatally and at birth. These are due to the presence of an extra or missing X or Y chromosome and most commonly include 45,X; 47,XXX; 47,XXY; and 47,XYY. The prevalence of SCAs is estimated to be around one in 500 newborns, twice as common at birth as trisomy 21. The frequency at prenatal diagnosis is much greater and ranges from 1 in 250 to 300 (Linden et al., 2002). Though not a primary target for detection in prenatal diagnosis, incidental findings like SCAs cannot be avoided. With expanding use of population wide screening for chromosomal anomalies by novel genomic technologies like non-invasive prenatal screening (NIPS), such problems will be more commonly seen in the near future. Being an unexpected finding in prenatal testing, SCAs pose significant challenge to the genetic counselor in terms of counseling and dilemma for the family. The outcome varies greatly from normal phenotype to those with significant phenotypic abnormalities. Individuals with SCA usually do not have significant intellectual disability. Hypogonadism and infertility remain the major issues; both of which have solutions in the form of hormone replacement therapy (HRT) and assisted reproductive techniques (ART). The difficulties in decision making are obvious as uncertainties about the phenotype are not strong enough to consider termination of pregnancy. The decision depends upon parents' family history and their perspectives to look at the problem. The parents' thinking gets influenced by what is conveyed to them by health care professionals involved in prenatal diagnosis and counseling. Hence, it is essential that accurate and up-to-date information about the likely outcomes is communicated to the family in a simplified manner. Through this article, we describe the outcomes of various prenatally detected SCAs and the issues in counseling for the same.

The following case scenarios present some common problems faced by the clinicians and families and perspectives in approaching them:

Case scenario 1: *A 32-year-old G2P1+0L1 mother who has a previous child with Down syndrome (Trisomy 21) visits us at 16 weeks of gestation for prenatal counseling. After pre-test counseling regarding the risk of recurrence of 1% for trisomy 21 in the current pregnancy, she opts for prenatal testing. Amniocentesis followed by quantitative fluorescent polymerase chain reaction (QFPCR) reveals 47,XXY and this finding is confirmed by karyotyping.*

Case scenario 2: *A 35-year-old G3P0+2, with previous two abortions, presents with history of two IVF (in vitro fertilisation) failures and consults us in view of non-invasive prenatal screening (NIPS) test showing high risk for monosomy X. This finding is*

confirmed by chromosomal analysis from amniotic fluid. Ultrasonography evaluation at 18 weeks is normal.

Case scenario 3: *A 30-year-old G3P2 mother with previous two healthy children, visits us at 17 weeks for counseling regarding high risk for trisomy 21 (1:151) on quadruple marker testing. Pre-test counseling is provided. Options of NIPS and invasive testing are given and she opts for invasive testing. Amniocentesis followed by QFPCR and karyotype is suggestive of 47,XXX chromosome complement.*

Counseling for the above-mentioned cases requires in-depth knowledge about the clinical phenotypes of SCAs, variability in presentation and availability of management options for hypogonadism and infertility. As these situations are not infrequent, it is important that clinical geneticists, fetal medicine specialists and counselors acquire adequate knowledge to provide prospective parents with sufficient and unbiased information regarding these SCAs and guide them in decision making.

Pre–test Counseling

Pre-test counseling for prenatal procedures done for varied indications should always include discussion about the various disorders which can be detected by the test. A brief discussion on the outcome of these disorders in general which would result in mental or physical abnormalities should be discussed. The counseling must include the possibility of detection of unrelated abnormalities including SCAs, unbalanced autosomal abnormalities other than the intended ones, and mosaic forms. Many of these may have variable outcomes. Some groups even suggest that obtaining consent from couples, as to whether to include or exclude the results of these incidental findings, is essential (Herlihy et al., 2010).

Post–test counseling

Post-test counseling should mainly focus on the specific disorder which has been diagnosed. The following points have to be kept in mind when providing information and counseling to the couples:

- couple should be made aware of the frequency of the condition in the general population;
- the occurrence of SCAs is a random event;
- incidentally detected sex chromosome aneuploidies are more often associated with normal to mildly affected phenotypes than postnatally detected SCAs (Pieters et al., 2011);
- the possibility of spontaneous abortion of pregnancy especially in fetuses with 45,X should also be mentioned;
- variability in the phenotype of the condition can exist and the inability to provide a precise individual prognosis must be discussed;
- uncertainty and complexity in providing counseling in case of mosaicism for SCAs should be discussed;
- role of other autosomal genes and environmental factors altering a child's prognosis should be stressed upon;
- written material providing comprehensive information about the relevant karyotype will be useful;
- if possible, showing selected photographs of individuals with SCAs and talking to other parents of children with SCAs can be reassuring and helpful;
- finally, the issue of disclosure of SCA diagnosis by parents to others and the consequences of the same should be addressed at the time of diagnosis;
- if the couple decides to continue with the pregnancy, they should be adequately counseled regarding when and how to anticipate the problems and to seek medical care;
- the couple should be informed of the available postnatal interventions. The potential benefit of knowledge of the condition to facilitate early intervention should be highlighted; and
- it is important to be aware that in addition to phenotypic outcome, the obstetric history of the woman will play an important role in taking decision about the fate of the current pregnancy. This can be perceived in the case scenarios discussed above.

Apart from the above-mentioned points for general counseling, the major point that has to be highlighted in the discussion of these SCAs should be its impact on the reproductive

Table 1 The prenatal and postnatal outcome of few of the commonly detected sex chromosome anomalies.

	45,X (Morgan, 2007)	47,XXY (Girardin & Van Vliet, 2011)	47,XXX (Wigby et al., 2016)	47,XYY (Bardsley et al., 2013)
Prevalence	1:2500-3000 live born girls	1:500-1000 live born males	1:1000 live born females	1:1000 live born males
Risk factor	None	Advanced maternal age	None	None
Prenatal outcome	99% get aborted spontaneously; increased nuchal translucency (NT), cystic hygroma or hydrops	High rates of preterm deliveries; no specific antenatal malformations	No specific antenatal malformations	No specific antenatal malformations
Intelligence	Normal but 15-20 points below controls and siblings	Normal but 15-20 points below controls and siblings	Normal but 15-20 points below controls and siblings	Normal
Characteristic features	Short stature (>95%), webbed neck, low posterior hairline, narrow palate with crowded teeth, broad chest with widely spaced nipples, cubitus valgus, multiple pigmented nevi	Tall stature, small testes, gynecomastia in late puberty, sparse body hair	Tall stature	Tall stature, macrocephaly, macrodontia, scoliosis
Associated abnormalities	Cardiac malformation (coarctation of aorta or bicuspid aortic valve in 75%) sensorineural hearing loss, recurrent otitis media, renal malformation (e.g., horseshoe kidney, duplicated or cleft renal pelvis), autoimmune thyroiditis, celiac disease, scoliosis	Diabetes, metabolic syndrome, osteoporosis and cardiovascular diseases in adulthood	Rare	Hand tremors or other involuntary movements (motor tics), seizures, and asthma
Development	At risk of mild delay in acquiring nonverbal, social, and psychomotor skills	Reduction in speech, language abilities, verbal processing speed and school performance	Mild motor delay, language difficulties and decreased school performance	At risk for mild speech/language and motor delays, learning disabilities

Psychiatric ailment#	Prone for shyness, anxiety, low self-esteem and depression	Depression, paraphilia, autistic and obsessive-compulsive are common	Psychotic illness like cyclothymic and labile personality disorder common (38%)	Attention deficit (50%), autism spectrum disorder (29%) and anxiety (26%)
Puberty	Absent*	Normal (hypogonadism occurs later)	Normal	Normal
Reproduction	Infertile*	Infertile (options like sperm extraction and cryo-conservation available)	Fertile (4% develop premature ovarian failure)	Normal
Management & follow up	Echocardiogram & renal ultrasound at birth; annual physical, psychological, cardiac, thyroid, bone and blood pressure evaluation; hormonal therapy at adolescence	Annual physical and psychological evaluation; endocrinological evaluation at adolescence; testosterone therapy during adolescence	Annual physical & neuropsychological evaluation; ovarian function assessment during early adulthood	Annual physical & neuropsychological evaluation
Risk of recurrence	Rare	Rare	Rare	Rare

*Normal menstruation and fertility seen in 2-5% mosaic individuals
May be seen more frequently than in the general population

and neurocognitive outcomes. These issues are discussed briefly in Table 1. Though not always foolproof, the following issues can be discussed in brief in selected scenarios.

1. ***45,X (Turner syndrome):***

    - Mental development and cognition are usually normal.
    - Major concern for this condition is hypogonadism and primary amenorrhea. Hormone replacement therapy (HRT) is indicated to initiate and maintain secondary sexual characters.
    - Short stature is common. Early growth hormone therapy can help to improve short stature.
    - Associated abnormalities in cardiovascular system and renal system should be mentioned. Some of the cardiac anomalies can be detected by prenatal echocardiography but coarctation of aorta, commonly seen in girls with Turner syndrome is difficult to diagnose prenatally.
    - Risk of infertility is high. With the help of assisted reproductive techniques, pregnancy can be achieved in some women with Turner syndrome.

2. ***47, XXY (Klinefelter syndrome):***

    - These individuals may have mild cognitive and psychiatric disturbances.
    - Major issue is male hypogonadism. Treatment with sex hormones for hypogonadism is indicated.
    - Infertility is common but reproductive options like testicular sperm extraction (TESE) and cryo-conservation are possible to improve reproductive outcomes.

3. ***47,XXX and 47,XYY:***

    - The reproductive and cognitive outcome is usually satisfactory.

- The psychological and behavioural problems reported in studies are usually mild and these individuals have a slightly increased prevalence when compared to normal individuals but ascertainment bias behind these studies should be kept in mind.

Previously, phenotypes of SCAs were known only for postnatally detected cases as they are the only ones who seek medical attention for phenotypic abnormalities. This ascertainment bias reflected in counseling for SCAs where incidentally detected SCAs during prenatal tests led to termination of most of these pregnancies. This issue was compounded by lack of adequate information about long term follow up of children with SCAs who were diagnosed prenatally. However, eliminating such ascertainment bias, recent studies have proved that incidentally detected prenatal diagnosis of SCAs is associated with normal to mildly affected phenotypes when compared to postnatal cases (Pieters et al., 2011).

Studies have evaluated parental attitude towards terminating or continuing a SCA-affected pregnancy and have found that factors like specific type of SCA, parental age, gestational week at diagnosis, counselor's genetic expertise, number of children in the family, previous experience of the family with children having birth defects or genetic disorders, socioeconomic status, and ethnicity and religious beliefs, influenced the decision to continue or abort the pregnancy. History of infertility or previous child with developmental delay may also complicate the decision-making process. This also gets largely influenced by the information one receives from a health professional (Operto et al., 2019; Shaw et al., 2008; Jeon et al., 2012). In recent times, there has been an emerging trend towards continuation of pregnancy of a fetus with SCAs due to improved counseling efforts and availability of adequate information on prognosis of these SCAs. Simultaneous progress in the field of ART has also totally changed the reproductive outcome of these individuals with SCAs.

Genetic counseling for sex chromosomal mosaicism

Mosaicism is defined as the presence of two or more cell lines derived from a single zygote but with different chromosomal complements in an individual. Genetic counseling becomes complex in such cases due to variability in phenotypic expression due to variable degree of mosaicism in different tissues. These factors pose uncertainty about the postnatal outcome of such disorders.

In prenatally detected 45, X/46, XY mosaicism, a normal male phenotype was present in 90% of cases (Telvi et al., 1999). However, the dilemma in counseling exists as in 10% of cases, the phenotypic spectrum can vary from females with Turner syndrome to males with infertility or individuals with ambiguous genitalia. The neurodevelopmental and reproductive outcome will also be highly variable in these individuals posing significant challenges in counseling.

A favourable prognosis exists for mosaic Turner syndrome (45,X/46,XX) who tend to have fewer signs and health problems like near normal stature and may have normal reproductive capabilities and no cardiovascular complications (Tuke et al., 2019). Similarly, mosaic Klinefelter syndrome are well androgenized and have better reproductive capability than their non-mosaic counterparts (Samplaski et al., 2013).

Genetic counseling for structural aberration of sex chromosomes

Structural aberrations involving X chromosome commonly include isochromosome Xq and ring chromosome. For such structural aberrations involving one X chromosome, the counseling is similar to that for Turner syndrome. However, ring X chromosome may be associated with more severe intellectual disability.

Cytogenetically visible structural aberrations of Y chromosome include deletions, translocations, rings, inversions and isochromosomes. Structural aberrations of Y chromosome usually result in mosaicism due to its predisposition to subsequent chromosome instability and loss of the abnormal Y chromosome, thereby causing mosaic 45,X. The phenotypes in such case can vary from females with Turner syndrome to males with infertility or ambiguous genitalia based on number of cells lines with 45,X and abnormal Y chromosome (Patsalis et al., 2005). Counseling in these cases is challenging as a definite prediction of phenotype is impossible and this uncertainty is likely to cause dilemma in decision-making for the family.

Not all structural aberrations are pathogenic. Pericentric inversions involving Y chromosome are mostly familial and not associated with any

phenotypic manifestations or fertility issues except in rare cases when genes determining sex in the inverted area are disrupted (Motos Guirao, 1989).

For other rare and complex aberrations, a comprehensive use of cytogenetic, microarray and fluorescent in situ hybridisation techniques are required for accurate identification of such abnormalities. The counseling for these rare SCAs varies on a case-to-case basis and is beyond the scope of this article.

Other rare SCAs

Chromosomal abnormalities where there is presence of more than two X chromosomes-

48,XXY or 49,XXXXY: They are more severely affected in terms of neurocognitive and behavioural function. The phenotype progressively deviates from normal as the number of X chromosome increases. These individuals have been shown to function at a lower cognitive level and with more immature and maladaptive behaviours as compared to individuals with fewer X chromosomes (Visootsak et al., 2007). Infertility and inadequate virilization are anticipated.

Conclusion

The chances of encountering SCAs are high with widespread availability of prenatal tests and especially after widespread use of NIPS in obstetric practice. It is therefore crucial that geneticists and counselors acquire adequate knowledge regarding the implications of SCAs and develop structured pre-test and post-test counseling strategies. This in turn would help prospective parents to take a personalized and autonomous decision regarding the pregnancy.

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