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CYTOGENETIC EVALUATION OF CHILDREN WITH DISORDERS OF SEX DEVELOPMENT- A RETROSPECTIVE STUDY

Genetics

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ABSTRACT

The present study was carried out to find out the incidence and types of chromosomal abnormalities in children referred to Cytogenetic Laboratory with Disorders of Sex Development (DSD) from Department of Paediatrics, Institute of Maternal and Child Health (IMCH), Government Medical college, Kozhikode, which is a Tertiary Care Centre of North Kerala.

Study settings and design: A retrospective study of Karyotypes of 88 children was done over a period of 6 years and 6 months(January 2014 to July 2020)

Methods : Peripheral blood lymphocyte culture was done according to standard protocol and chromosomal analysis was carried out using Cytovision Software version 7

Results: The results of present study shows that children with DSD showed a predominance of 46,XY karyotype (56.81%) followed by 46,XX (15.9%). Numerical or structural anomalies of sex chromosomes were found in less than 10% . Trisomy 21 (3.4%), Trisomy 13 (1.4%) and Trisomy 18(1.14%) were also detected.

Conclusion: Children with DSD or genital ambiguity represent a medical and social problem that must be solved quickly and accurately by a multidisciplinary team. Early identification of genetic cause of DSD will help in efficient management of children with more focused endocrine and surgical interventions.

KEYWORDS

Disorders of Sex Development (DSD)

INTRODUCTION

The discordance between genetic, gonadal or anatomic sex is collectively known as disorders of sex development (DSD)[1]. DSD are classified based on the affected individual's karyotype as follows [2,3] **.(Table 1)**

A. Sex chromosome DSD
B. 46,XY DSD
C. 46, XX DSD

Table1. Clinical classification and causes of DSD

Type	Causes
a. Sex chromosome DSD	a) 45,X: Turner syndrome and variants b) 47,XXY: Klinefelter Syndrome and variants c) 45,X/46,XY: Mixed gonadal dysgenesis and ovotesticular DSD d) 46,XX/46,XY: Chimeric and ovotesticular DSD
b. 46,XY DSD	a) Disorders of gonadal development b) Defect of androgen biosynthesis or action
c. 46,XX DSD	a) Disorders of gonadal development b) Disorders of androgen excess c) Anatomical and syndromic disorders

The disorders of sexual development can be associated with variations in genes, developmental programming and hormones [4] . This leads to atypical development of internal and external genital structures.

Affected individuals are usually recognized at birth due to ambiguous external genitalia. Some patients present later with postnatal virilization, delayed onset of puberty, primary amenorrhoea or infertility.

The frequency of genital ambiguity is in the range of 1:2000-1:4500 [5]

Embryology

Normal sex development is dependent on the synergistic action of genes, hormones and developmental programming. Sex determination is governed by sex chromosomes X and Y.

The sex Determining Region on the Y chromosome (SRY) is the main factor that initiates the indifferent gonads and external genitalia to develop into the male types [6]. The relevance of testosterone for male sexual differentiation was performed and emphasized by Dr. Alfred Jost.

The urogenital ridges develop in the embryo during 4-6 weeks of intra uterine life as out growths of coelomic epithelium. These ridges give rise to the kidneys, adrenal cortices, gonads and reproductive tracts.

Initially, both Wolffian and Mullerian ducts develop. The Wolffian ducts give rise to the epididymis, vas deferens, ejaculatory duct and seminal vesicles, under the influence of testosterone. Testosterone also promotes the descent of testis into the scrotum. Anti Mullerian Hormone(AMH) secreted by Sertoli cells of fetal testis suppresses the development of uterus and fallopian tubes.

In the absence of SRY gene, the indifferent gonad develops into ovary. In the absence of testosterone and dihydrotestosterone, the external genitalia develop into clitoris, vagina and labia.

Dihydrotestosterone promotes the formation of the corpus spongiosum, corpora cavernosa, penile urethra and scrotum.

Genetic Testing in DSD

It plays an important role in the evaluation of a new born with DSD. Knowing the genetic etiology can be utilized in predicting the phenotype and to focus on endocrine as well as radiological investigations. It also helps in medical and surgical management of the affected child.

Results of Cytogenetic Analysis

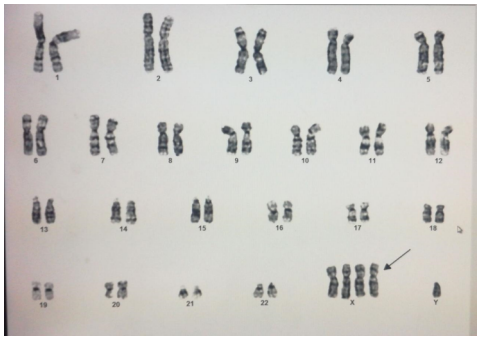
A total of 88 cases were evaluated for chromosomal abnormalities over a period of 6 years and 6 months, The Karyotypes and percentage of different types obtained in our study are given in **Table 2**

Table 2: Cytogenetic analysis of children with DSD

Sl No	Karyotype	No: of Cases	Percentage(%)
1	46, XY	50	56.81
2	46, XX	14	15.90
3	47, XXY	05	5.68
4	45, X	03	3.40
5	mos 45,X/46,XY	02	2.28
6	Trisomy 21(2 males, one female)	03	3.40
7	Trisomy 13	01	1.14
8	Trisomy 18	01	1.14
9	48,XXYY	01	1.14
10	49,XXXXY	01	1.14
11	46,XX,del(13)(q21)	01	1.14

12	46,XX with male external genitalia and undescended testis	02	2.28
13	Polymorphic variants (1qh+,9qh+,1qh-)	04	4.55
	TOTAL	**88**	100

Fig 1. Karyotype of a child with 49 XXXXY



DISCUSSION

The birth of a child with ambiguous genitalia is a medical and social emergency, as the child may have other life threatening congenital anomalies and endocrine disorders. A multidisciplinary team consisting of a Paediatrician, Paediatric Endocrinologist, Paediatric Surgeon, Geneticist and Radiologist should assess the newborn child or adolescent with DSD. The parents also should be included in discussions regarding sex of rearing the child.

Estimation of serum electrolytes, 17-hydroxyprogesterone, testosterone, FSH, LH, AMH, Plasma renin activity and androstenedione may be done. Karyotyping and additional genetic testing are essential. USG to assess the presence of uterus and position of undescended testes can be helpful. Ovaries are too small to be visualized in a newborn; so, the lack of visualization of the ovaries does not indicate that the ovaries are absent.

In our Institution, as a part of evaluation of a newborn with DSD, we work as a team and blood sample is sent for karyotyping immediately. Other tests such as electrolyte - hormonal assay are also done simultaneously. A shared decision is taken by the experts' team which takes into consideration the well being of the patient as well as the wishes, beliefs, social and cultural traditions of the parents.

Karyotyping forms one of the first essential steps in the evaluation of children with DSD. Early identification of the genetic cause of DSD will help in the clinical management of the affected individual.

Cytogenetic studies are conducted in children with DSD in various centers of the world. Results from all these centers show that 46,XY karyotype was the most frequent in DSD cases. **Table 3** shows the comparison of studies conducted in five centres.

Table3 : Comparison of Cytogenetic studies in DSD

SLNo:	Authors	Percentage of 46, XY	Percentage of 46, XX	Percentage of other anomalies
1	Soheir S [8] *etal*	50	37.5	12.5
2	Silkar [9] *etal*	51.4	34.9	13.7
3	Georgette Beatriz [10] *etal*	61.3	30.4	10
4	Rodrigo[11] *etal*	71	19	10
5	Present Study	56.8	15.9	27.3

Over six years and six months, 88 cases of DSDs were studied in our center retrospectively. There was a predominance of 46,XY karyotype (56.8%), followed by 46,XX (15.9%). Numerical and structural anomalies of sex chromosomes, mosaics comprised of 27.3%

Our results regarding the frequency of 46,XY karyotype were similar to those obtained by Soheir *et al*, Silkar and Georgette Beatriz. The percentage of 46,XX karyotype is consistent with the finding of Rodrigo *et al.*

The frequency of other chromosomal anomalies detected in our study is higher than the values obtained in other centres. Georgette Beatriz *et al* have reported sex chromosome aneuploidy, mosaics, structural anomalies of X chromosomes. Our findings are given in **Table 1**

CONCLUSION

It can be concluded that the 46,XY karyotype was the most frequent among DSD cases. Children born with DSD require special attention by a multidisciplinary team to rule out other congenital anomalies, electrolyte imbalance and endrocrine disorders. This team can help in assigning an appropriate sex of rearing to the new born child based on the etiology and to detect any other life threatening disorders if present.

Parents of children with DSDs should be given proper guidance and education about long term outcomes. Several websites and organizations exist for the guidance of affected individuals and their families, so that they can exchange information and provide suitable strategies with better understanding and acceptance of the child's condition, optimal growth and overall development of a child born with DSD.

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