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Original Article

CORRELATION OF CONSANGUINITY WITH PREVALENCE OF CHROMOSOMAL ANOMALIES IN PATIENTS OF AMBIGUOUS GENITALIA: A CYTOGENETIC STUDY

Anushree Pandey[1], Rakesh Kumar Verma[2], Dewanshi Mishra[3], Archana Rani[2], Navneet Kumar[2]

1. Maharshi Vishwamitra Autonomous State Medical College Ghazipur, India
2. Department of Anatomy, KGMU, Lucknow, India
3. Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India

ABSTRACT

Introduction: The condition when the sex of the baby can't be determined and there is variation of genitalia from normal is known as ambiguous genitalia. Consanguinity can be defined as blood relationship that exists among individuals that descend from a common ancestor. If two individuals who are in close blood relation get married there is high chance that any single copy of gene which is present in common ancestor gets doubled in the subsequent generation. A recessive gene may thus come to light for the first time in subsequent generation. The aim of the present study was to see the correlation of consanguinity with prevalence of chromosomal anomalies in patients of ambiguous genitalia.

Materials and Methods: Study was conducted in the cytogenetic laboratory of the Department of Anatomy, King George's Medical University UP, Lucknow. The patients were screened in the Department of Paediatrics and Paediatric Surgery and blood samples were taken. Cytogenetic analysis was done.

Results: Consanguinity was traced in 4 (18.2%) cases, of whom 3 (75%) had chromosomal anomalies. Out of remaining 18 (81.2%) cases, chromosomal anomalies were seen in 4 (22.2%) cases.

Conclusions: The proportion of cases with anomalies was higher in those positive for consanguinity as compared to those without consanguinity.

Keywords : Consanguinity, Ambiguous genitalia, Chromosomal anomalies

Address for Correspondence:
Dr. Anushree Pandey, Assistant Professor, Department of Anatomy, Maharshi Vishwamitra Autonomous State Medical College, Ghazipur, India
Email: anu031103@gmail.com Mob: 8318660751

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INTRODUCTION

Consanguinity is a very common cultural practice socially accepted by nearly 20% of the world's population living in Afro-Eurasia and by people migrating from these regions to other areas. These populations have their own reasons to promote consanguineous marriages. However, there are many drawbacks associated with these marriages, such as higher fertility rates, stillbirths, and slightly elevated infant mortality rates, along with a birth defect frequency that is around 2-3% higher. Autosomal recessive disorders become more apparent in individuals who are offspring of closely blood-related parents, but the offspring of such parents don't show any variation in the frequency of X-linked recessive disorders or autosomal dominant disorders [1, 2, 3, 4]. Therefore, consanguineous marriages are a matter of concern for all geneticists.

When the marriage is between second cousins or closer, with an inbreeding coefficient (F) of ≥0.0156, it is interpreted as a consanguineous marriage [6]. Here, (F) represents a measure of the proportion of loci at which the offspring of a consanguineous union is expected to inherit identical gene copies from both parents. The inbreeding coefficient is even higher when marriage occurs between double first cousins or uncle-niece pairs [3].

Due to the effect of consanguinity, alleles with abnormalities are concentrated in society because closely blood-related individuals have many alleles that are more or less similar, and if mating occurs, the chances of defective alleles in offspring are enhanced, leading to increased morbidity and mortality due to various genetic diseases. Consanguinity produces many ailments, one of which is ambiguous genitalia.

Previously, various terms were used to define this variation of genitalia from normal, such as intersex, hermaphrodite, pseudo-hermaphrodite, etc., but this was very disappointing to many families [7, 8]. Therefore, it was decided to use a better term in place of intersex, hermaphroditism, and pseudo-hermaphroditism [9-10]. Experts from various fields gathered in Chicago in 2005 (the Chicago Consensus) to coin better terminology and treatment recommendations for this issue, and they proposed a new and more respectful term: disorders of sex differentiation (DSDs). Now, the term DSD is used in place of various confusing terms.

Diagnosis of these cases is done by various methods, one of which is cytogenetics, an emerging field of science in which chromosomal structures are observed and analyzed, along with their properties and actions during cell division, whether in somatic cells or germ cells, and their roles in mitosis and meiosis. This helps to understand how chromosomes, or specifically, genes, influence the phenotype of an individual.

MATERIAL AND METHODS

The study was of a descriptive type. The review board of King George's Medical University UP, Lucknow, approved it. Ethical clearance was also granted by the Ethical Clearance Board of King George's Medical University UP, Lucknow, with vide letter number 2083/Ethics/R.Cell-17. The study was conducted in the Anatomy Department Cytogenetic Lab in collaboration with the Pediatric Surgery Department of King George's Medical University UP, Lucknow. Screening of patients was performed in the OPD of the Pediatric Surgery Department. Patients with a clinical diagnosis of ambiguous genitalia, made by the pediatrician and pediatric surgeon, were included in the study.

The criteria for inclusion in the study were patients who provided consent. Patients who declined to give consent were excluded from the study. A detailed history of patients was obtained, considering various factors that influence the development of Disorders of Sex Differentiation (DSD), and samples of suspected cases were collected from there. Peripheral blood samples were taken, and the samples were analyzed in the cytogenetic laboratory; a karyogram was prepared, and evaluation was conducted..

RESULTS

A total of 24 children with suspected ambiguous genitalia lying in sampling frame were included in the study to solve our

Type	No. of cases	Percentage
Consanguinity	4	16.7
No consanguinity	20	83.3

Table 1. Incidence of consanguinity in study population (n=24)

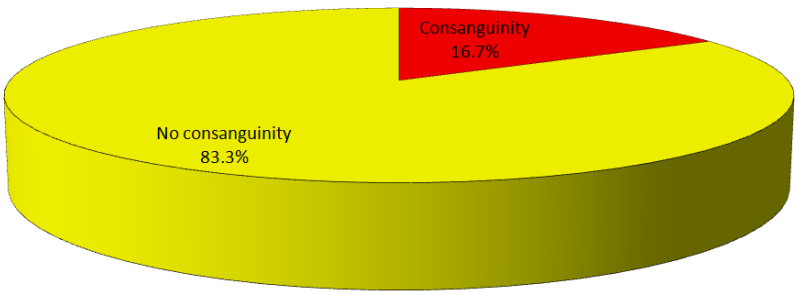

Fig. 1. Pie diagram representing incidence of consanguinity in study population (n=24)

purpose. After history taking and karyotyping following results were found.

Consanguinity was found in four (18.2%) cases, of whom three (75%) had some sort of anomaly in their chromosomes. Among the rest of the 18 (81.2%) cases, a chromosomal anomaly was found in four (22.2%) cases (Table 1 & 2, Fig. 1 & 2). Though the proportion of those with anomalies was higher in those positive for consanguinity compared to those without consanguinity, this difference was not statistically significant (p=0.077). A total of 20 (83.3%) cases did not involve consanguinity. A consanguineous relationship was reported in 4 (16.7%) cases. Among the 4 consanguineous cases, 3 (75%) had different genotypes and phenotypes, while 1 (25%) had the same genotype and phenotype. There were no structural or chromosomal anomalies found among the consanguineous cases (Table 3, Fig. 3).

The occurrence of different genotypes and phenotypes was relatively higher (75%) in consanguineous cases compared to non-consanguineous cases (20%). However, this was not statistically significant (Table 4, Fig. 4).

Consanguinity	**Total**	**With anomalies (n=7)**		**Without anomalies (n=15)**	
		No.	**%**	**No.**	**%**
Yes	4	3	75.0	1	25.0
No	18	4	22.2	14	77.8
		p=0.077 (Fisher exact test)			

Table 2. Association between prevalence of chromosomal anomalies and consanguinity (n=22)

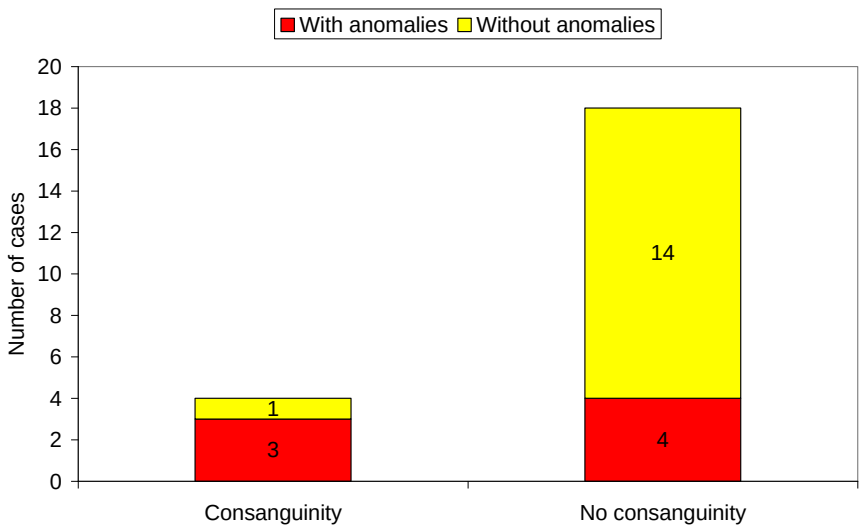

Fig. 2. Bar diagram depicting association between prevalence of chromosomal anomalies and consanguinity

Type	No. of cases	Percentage (%)
Same genotype & phenotype	1	25
Different genotype & phenotype	3	75
Numerical anomalies	0	0
Structural Anomalies	0	0

Table 3. Distribution of anomalies in consanguineous cases (n=4)

Type	Consanguineous cases		Non-consanguineous cases	
	Number	Percentage	Number	Percentage
Same genotype & phenotype	1	25	14	70
Different genotype & phenotype	3	75	4	20
Numerical anomalies	0	0	1	5
Structural Anomalies	0	0	1	5

Table 4. Correlation of types of anomalies found in consanguineous and non-consanguineous cases (n=24)

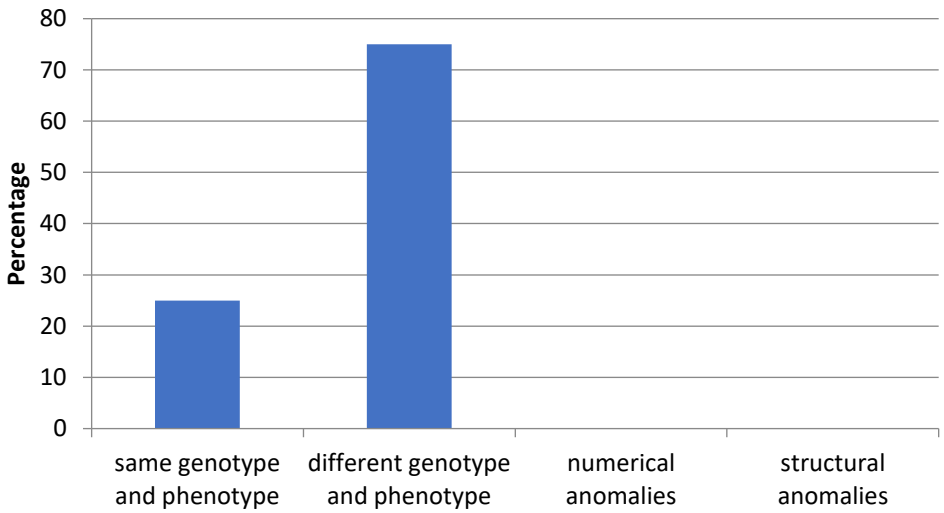

Fig. 3. Bar diagram showing distribution of anomalies in consanguineous cases (n=4)

DISCUSSION

The actual effect of consanguineous marriage on chromosomal abnormalities is still to be meticulously researched and observed, but for autosomal recessive conditions, it can be said that the risk tends to be higher [11]. Many studies have been conducted in different parts of the world by various researchers to determine the exact correlation between consanguinity and various chromosomal abnormalities. During these studies, it was found that in Western countries where consanguineous marriage is less common, the incidence of true ambiguous genitalia was estimated to be 1:5000 births, while in countries where consanguinity was common, the incidence of ambiguous genitalia was higher. In Egypt, it was found to be 1:3000, and in Saudi Arabia, it was found to be 1:2500 [12].

Among 24 patients, we found 4 (16.7%) cases with consanguinity. Our study runs parallel to many other studies but differs from some others. Al-Mutair et al. (2004) retrospectively reviewed a total of 120 medical records of suspected cases of ambiguous genitalia between 1989 and 1999 in Riyadh, Saudi Arabia. They found consanguinity ranged between 60% and 100% in various types of endocrine and congenital developmental defects [13]. Our study differed from this study possibly due to different geographical areas and sample sizes.

Joshi et al. (2006) reviewed 109 patients presenting with ambiguous genitalia over 10 years (1995-2004) at B.J. Wadia Hospital for Children, Parel, Mumbai, India. They found consanguinity in 27 (24.7%) cases [14]. Our study was not entirely consistent with this study but was nearly close to it; the difference might be due to the large sample size and long duration of their study.

Pandith et al. (2015) carried out a study on 50 cases of ambiguous genitalia in the Jammu Kashmir region and found consanguinity in 10 (20%) cases. The result of our study is nearly similar to theirs [15].

Shojaei et al. (2017) conducted a study on 37 patients in Tehran, Iran, and consanguinity was found in 21% of cases. This may be due to the high rate of consanguineous marriages in the Iranian population [16]. Our study is consistent with the results of this study, showing a similar percentage of consanguinity.

CONCLUSION

Consanguinity was found in 16.7% of cases. Among cases born due to consanguineous marriage, 75% had chromosomal anomalies. On comparison with other studies, we noted that consanguinity is one of the important risk factors for the development of ambiguous genitalia, and the rate of chromosomal anomalies was also high. Further studies with better techniques are

needed, and associated chromosomal anomalies need to be investigated. However, accurate diagnosis is burdensome and a big-budget task, so we need to find ways through which we can easily make the diagnosis, and that too on a low budget.

Apart from monetary problems and ease of diagnosis in these cases of ambiguous genitalia, we have to face many religious, social, and cultural factors. Besides diagnostic issues, we also need to educate society about the effects of consanguineous marriages.

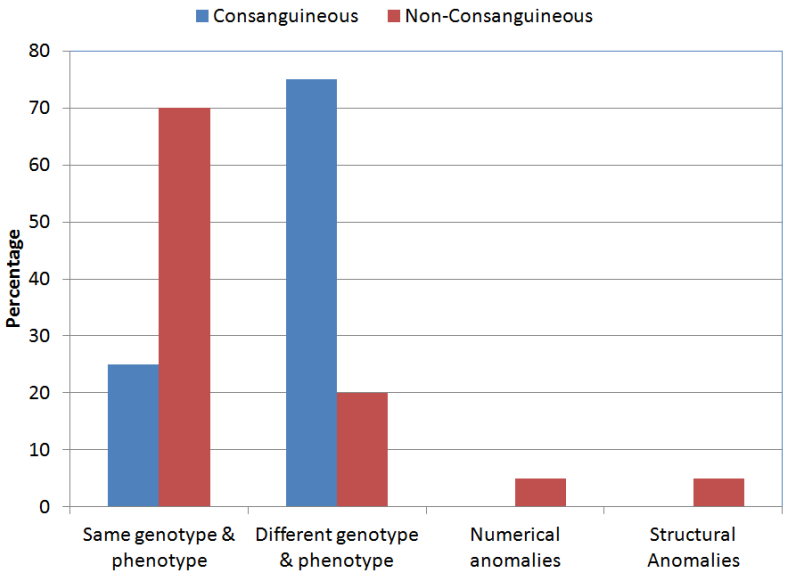

Fig. 4. Bar diagram showing correlation of types of anomalies found in consanguineous and non-consanguineous cases

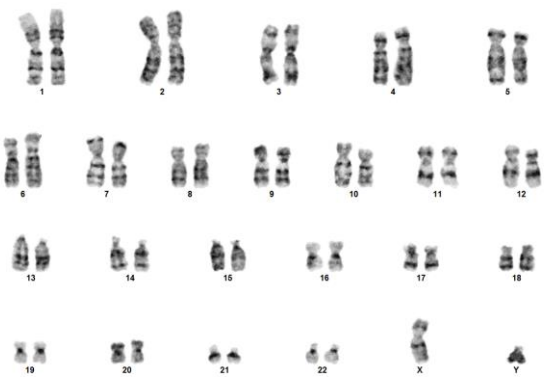

Fig. 5. Karyogram of phenotypic female with male genotype

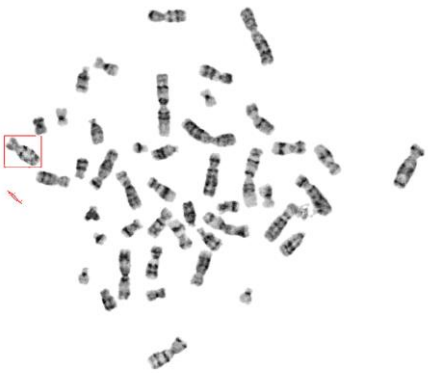

Fig. 6. Metaphase of phenotypic female with male genotype

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