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"Consanguinity as a Risk Factor in the Etiology of Inborn Errors of Metabolism- An Observational Study"

[1]Mrs.Varsha Pramodh, [2]Dr. Gowri Ramesh, [3]Dr.Sujatha Jagadeesh
[1]Senior Research Fellow, Women's Christian College, Chennai.
[2]Research Supervisor and Assistant Professor, Women's Christian College Chennai.
[3]Head of the Department, Department of Genetics, Mediscan Systems, Chennai.

Abstract

Objective: The objective of the present study was to assess the practice of consanguinity among parents of individuals identified with inborn errors of metabolism.

Materials and Methods: Purposive sampling was used to enroll 135 participants (82 males and 55 females)between the age groups of 0 and 50 yearsin this study. Participants were classified based on the broad diagnosis of disorders of Lysosomal storage disease and disorders affecting energy metabolism. The design of the study comprised of a cross-sectional design. A questionnaire was used to collect information pertaining to demographic, socio-economic and consanguinity status of parents of the study participants. The study was conducted over a period of three months at Mediscan Systems, Department of Genetics in a Fetal Care, Genetics and Perinatal pathology Centre, Chennai, India. Descriptive statistics was used to analyze the data.

Results: 76.3 % of the study participants had been affected with Lysosomal storage disorders and 23.7% with disorders affecting energy metabolism. 89% of the participants' parentswere found to have a history of consanguineous marriages. Out of these, 31% of the parents had married their first cousins. 32.5% of the parents belonged to the lower socio-economic strata. With respect to education, 20 % of the parents had completed their middle school education.

Conclusion: In this study, a majority of the parents were found to have a consanguineous marriage. Therefore, consanguinity could also be considered important along with other risk factors in the etiology of inborn errors of metabolism.

Key Words: Consanguinity, Inborn errors of Metabolism.

I. Background

Inborn errors of metabolism are defined as a group of heterogeneous genetic disorders resulting from either absence or monogenetic defects and mutations in thesecretion of important enzymes in metabolic pathways.Sometimes the intermediate metabolites in the pathways get accumulated in vital organs such as the brain, eyes, lungs, liverandleads to toxic conditions. However,these diseases are rare in nature, and extremely difficult to diagnose (1).

The Global birth prevalence estimates of inborn errors according to a study done in 2018 was 50.9 per 1,00,000 live births(2). In the Indian Population, the prevalence is one in 2497 newborns with an incidence rate of 1 in 1000 worldwide. The overall under-five

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mortality rate due to inborn errors is estimated to beseven per cent(3). About 28 types ofinborn errors can be diagnosed at birth by a simple and cost-effective heel prick Universal neonatal screening test. In case of no new born screening, children may develop symptoms such as acidosis, severe vomiting, dehydration, seizures, sucking or feeding problems, and compromised immunity within the first month of life(4).If left undiagnosed, the prognosis is very poor and may lead to hypotonia, hypoxia, coma and death in children with inborn errors. These risk factors may cause irreversible changes in the body and therefore, pose challenges for treatment or management of these conditions (5).

Studies have implicated factors such as residing in rural regions, premature births, consanguinity, geographical distribution, endogamy, ethnicity and genetic mutations to be risk factors in the development of inborn errors of metabolism (6,7). These factors may lead to deleterious complications during pregnancy and also affect fetal outcomes. In some studies,craniofacial defects and 3 methyl crotonyl Co-A carboxylase deficiency were observed in participants who had a history ofconsanguineous marriage(8).

Consanguineous marriages not only cause homozygosity but they pose a fatal and detrimental impact on postnatal and fetal outcomes (9). The risk factors associated with consanguinity are neural tube defects, physical and mental disabilities, still births, sudden infant death syndrome, cleft lip, cleft palate, and inborn errors of metabolism(10,11).

The global incidence of consanguinity is 1 in 1.1 billion and about one in 3 marriages has been found to be consanguineous (9). India is a diverse country with multiple ethnicities and religions residing together.The current populationis 138 crores, which is 17.7% of the World’s population. 65% of the Indian people are found to reside in rural and semi-urban regions(13).One half of the Indian population is a staunch believer and practitioner of consanguineous marriages. This homozygosity that increases with consanguineous marriages also increases the chances of contracting genetic and irreversible disorders by manifold times (14,15).

Studies conducted on data obtained from the National Family Health Survey (NFHS)-4 conducted in 2015-16 reveal the highest practice of consanguinity in 23% of South Indians. This is the largest percentage of populationin India who still followthe custom of consanguineous marriages. In terms of type of consanguinity, there is a higher prevalence of about 8.7 % of marriages between first cousins. However, in this survey, it was also suggested that women with higher literacy levels have reduced or stopped this practice (16).

With this perspective, the aim of this study was to understand the role of consanguinity as a risk factor in the etiology of inborn errors of metabolism.Since these disorders can only be prevented or managedand cannot be reversed, it is important to create awareness in the community about the perils of risk factors such as endogamy, consanguinity and poor maternal health to help prevent premature births or inborn errors of metabolism in the new born.

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II. Materials and Methods

Objective of the Study-The aim of this study was to assess consanguinity in parents of the participants affected with inborn errors of metabolism, and to determine if this could be considered as a risk factor for these conditions.

Design of the Study-The design comprised of a cross-sectionalstudy design.

Site of the Study-This study was conducted at Mediscan Systems, Department of Genetics at a Fetal care, Genetics and Perinatal pathology Centre in Chennai, Tamil Nadu.

Selection of Sample-The study started with identification of 257 patients with a confirmed diagnosis of IEM from across the Country who attended the Genetic counseling clinic between October 2019 and August 2020. Purposive sampling was used to select 135 participants. Out of the 135 participants, there were 82 males and 55 females who met with the inclusion criteria for the study. The participants were in the age group of 0and50 years, and were grouped according to their type of inborn errors. These participants had also undergone tandem mass spectroscopy and genetic mutation analysis with a confirmed diagnosis of inborn errors of metabolism. Classification of disorders surveyed among the participants has been presented in Table 1.

Table 1- Classification of Disorders Surveyed

Disorders Affecting Lysosomal Storage	Disorders Affecting Energy Metabolism
Mucopolysaccharidosis I [MPS I]	Phenylketoneuria
Mucopolysaccharidosis II [MPS II]	Methyl malonic acidemia
Mucopolysaccharidosis III[MPS III]	Propionic aciduria
Mucopolysaccharidosis IV[MPS IV]	Glutaric aciduria
Mucopolysaccharidosis V [MPS V]	3 methyl crotonyl deficiency
Mucopolysaccharidosis VI [MPS VI]	Argininosuccinate lyase (ASL) deficiency
Gaucher's Disease	Succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency
Pompe's Disease	Homocystinuria
Fabry's Disease	Citrullinemia
	Non- ketotichypoglycininemia
	Glycogen storage disease
	Tyrosinemia
	B- Ketothiolase deficiency
	Non- ketotichypoglycininemia
	Urea- cycle disorder
	Maple syrup urine disease (MSUD)
	Isovaleric acidemia

Inclusion criteria for the Study-After obtaining an informed consent either from the participants, their parents or the caregivers, theywere included in the study. Participants over

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50 years of age, andnot willing to participate or with disabilities were excluded from the study.

Tools used for the Study-A questionnaire was used to collect details about the participants' Socio- Demographic data, type of marriage of the parents, Occupation and Literacy levels. These were then classified according to the Kuppusamy scale for Socio-economic status (17).

Statistics-Arithmetic mean, standard deviation and frequency distribution was used to analyze the data.

III. Results

Of the 135 participants enrolled for the study, 60 and 40 percent were males and females respectively. Mean age of the participants was found to be 13.7 ± 8.4 years.

The most common disorder observed was Mucopolysaccharidosis (MPS) with 43.3 % of the study participants being diagnosed with MPS. Out of all the types of MPS, MPS–I(15%) was the highest in the study population. 23.7% participants werediagnosed with disorders involving energy metabolism, with Phenylketonuria (PKU) being the most common.Percentage distribution of participants based on their diagnosis is presented in Table 2.

Table 2- Distribution of Participants Based on their Diagnosis

Disorders	Number of participants[n= 135]		Percentage [%]
	Female [n= 54]	Male [n= 81]	
MPS I	7	14	15.5
MPS II	0	8	6
MPS III	3	6	7
MPS IV	1	9	7.4
MPS VI	4	6	7.4
TOTAL MPS PARTICIPANTS	15	43	MPS= 43.3
GAUCHER'S	15	16	22.9
POMPE'S	5	5	7.4
FABRY'S	0	4	3
DISORDERS AFFECTING ENERGY METABOLISM	19	13	23.7

*MPS- MUCOPOLYSACCHARIDOSIS

The study results revealed that a majority of the parents of participants affected with inborn errors of metabolism had a history of consanguinity. We observed that with reference to consanguinity, 89% of participants were married to their first cousins, second cousins and close relatives. About 35% of the participants were falling under 3rd degree consanguinity and hadmarried their second cousins, followed by 2nd degree consanguinity of 31% who had

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married their 1st cousins, and 23 % of participants followed 4th degree consanguinity by marrying amongst close relatives. Only 11% of the participants had a non-consanguineous marriage. These results suggest that consanguinity that is highly prevalent amongst the Indian Population can be a potential risk factor for the occurrence of inborn errors of metabolism. These results are in agreement with the results produced by a study done by Saleem etal. (2016) in rural villages of Tamil Nadu to examine consanguinity. The authors observed 61% of first cousins to be married in their study population(18). The study also found correlations between consanguineous marriages and poor prenatal or fetal outcomes including birth defects.

From the Socio-demographic survey, it was observed that a majority of the parents were literate and about 27% of parents had completed their graduation, whereas about 25% could complete their high school certification. The remaining 19% parents had completed their diploma and 20 % had attended up to middle school. There were only 5% of the parents who could not continue their education beyond primary class. These results are conclusive with the Indian literacy rate census of 2001 and 2020, wherein about 75% of the Indians have become literates and maximum number of people are able to complete their high school(19).

Occupation of all the participants fathers was surveyed and classified according to the different levels of occupation. The most common occupation of small businesses, farming and clerical jobs amounted to about 32.5%, followed by 31% of semi-skilled workers. A majority of the mothers were found to be homemakers. Studies that examined the relationship between occupation, literacy level and consanguinity have found that parents with lower levels of literacy had higher practice of informal occupation and consanguinity (20).

IV. Discussion

The practice of consanguinity is high in India dueto various religions and ethnicities. This gives rise to higher practice of endogamy and inbreeding (21). Many studies have reported a high inbreeding coefficient along with consanguinity and when checked for fetal outcomes, a higher percentage of birth defects and inborn errors were observed in such populations(22).

Various studies have examined the ill effects of first cousin marriages and strong practice of consanguinity, leading to poor prenatal and fetal outcomes. Conditions like inherited metabolic disorders, bleeding disorders, still births, birth defects, congenital malformations, neural tube defects, physical and mental retardation, cleft lip and palate, and sudden infant death syndrome (SIDS) have been reported as a consequence of consanguinity (22). Studies conducted worldwide in various countries have postulated a strong correlation between consanguinity and fetal anomalies (23,24). In this study, a majority of the participant's parents had a history of consanguinity.

The paternal literacy levels and occupation have been examined in this study to understand a link between literacy and consanguinity. The study has shown a that a very low percentage of them were able to pursue beyond high school and may have had to opt for unskilled, semi-skilled or small-scale shops as a means of livelihood. Reasons for this are

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lower socio-economic status and lower literacy levels. Many of the mothers chose to stay at home to take care of their wards. Studies conducted in Britain, Jordan and many other countries suggest that people with a higher literacy level have a better occupation, and also do not prefer consanguineous marriages as they are more aware of the health risks involved(25–27).

Apart from the physical and mental deterioration, inborn errors of metabolism cause stunted growth, poor cognition, organ damage, oculomotor changes and organ failure. These are all contributory factors to poor quality of life among both the affected individuals and their caregivers. These monogenic, highly morbid and mortal disorders are very difficult to manage, cannot be completely cured and are irreversible in nature. So, all the risk factors associated with the disorder must be avoided,includingconsanguineous marriages(22,28,29).

In conclusion, consanguinity could be considered as an important risk factor in the etiologyof inborn errors.Awareness about consanguineous marriages in pre-marital clinics or education programs on causes and consequences of inborn errors of metabolism may help prevent birth defects (30,31). This will improve child mortality rates, and also contribute to a good quality of life for the child and the entire family.

V. Conflict of interest

The authors have no conflict of interest.

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