

Original Research Article

Having a common ancestor; significance of consanguinity and genetic diseases

Madhurasree Nelanthala, Brahmpreet Kaur, Vinod Ingale, Suvarna Magar*, Pradnya Joshi

Department of Pediatrics, MGM Medical College, Aurangabad, Maharashtra, India

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***Correspondence:**

Dr. Suvarna Magar,

E-mail: drsuvnamagar@gmail.com

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ABSTRACT

Background: Consanguinity is prevalent in India, which is one of the high-risk factors for increased risk of single gene diseases. Global developmental delay is heterogeneous group of genetic diseases which includes chromosomal and single gene diseases. The aim of the study is to determine impact of consanguinity on these 2 groups of diseases.

Methods: A retrospective review of children coming to genetic OPD with global developmental delay (GDD) and children who were proven inborn errors of metabolism (IEM) was done. Presence of consanguinity or its absence was noted in all the children in both groups.

Results: Out of 194 cases visited to genetic OPD, 103 (54%) of the patients were product of consanguineous marriage and 91 (46%) were product of non-consanguineous marriage. Out of 103 cases born of consanguineous marriage, 59 (57.3%) were GDD and out of 91 children who were born of non-consanguineous, 70 (68.35%) were having GDD. The difference was statistically significant with p value of 0.003. Out of 103 cases which were product of consanguineous marriage 44 (42.7%) were IEMs and out of 91 children who were product of non-consanguineous, 21 (23%) were having IEMs. The difference was statistically significant with p value of 0.004.

Conclusions: Genetic drift or founder mutations need to be considered in Indian communities, where small sub-communities are genetically isolated pools and can have distinct genetic diseases belonging to particular communities not having impacted by consanguinity. Consanguinity increases risk of autosomal recessive diseases like inborn errors of metabolism.

Keywords: Consanguinity, Inborn errors of metabolism, Global developmental delay

INTRODUCTION

As per clinical genetics, consanguineous marriage is defined as a union between two individuals with same ancestor. In first degree consanguineous marriage there is 50% sharing of DNA, in 2nd degree 25% in 3rd degree 12.5% sharing of DNA occurs.¹ There are many studies that mention about deleterious effects on off-spring, right from fetal growth compromise to even reproductive loss.^{2,3} Consanguineous marriages are very common throughout the world, especially marriage between 1st cousins is most common. A study done at Qatar suggests

a significant role of consanguinity in increasing the prevalence of genetic disorders, mainly autosomal recessive diseases.⁴ The risk increases more when there are multiple consanguineous marriages within the same kindred. This study is done to know the impact of consanguinity on two group of diseases i.e. first group being global developmental delay and another being inborn errors of metabolism. We chose inborn errors of metabolism as another comparative group because most of them are autosomal recessive diseases which are known to have definite increase in incidence of occurrence than non-consanguineous group.

Hence further study may help in decreasing prevalence of genetic disorders by prevention in form of curtailing down consanguineous marriages by public awareness.

METHODS

This is a retrospective observational study done in department of pediatrics, MGM medical college, Aurangabad. Data was collected for period of 24 months from February 2018 to January 2020. Ethical clearance was obtained for the study from ethical committee, MGM MCH, Aurangabad. Cases included are patients visiting pediatrics genetic clinic with genetic disorders like global developmental delay and inborn error of metabolism.

In our study we tried to study the role of consanguinity in two subsets. We included two groups to see if the impact of consanguinity is different on heterogenous group of global developmental delay and a homogenous group of single gene diseases like inborn errors of metabolism. We choose inborn errors of metabolism as most of them are autosomal recessive diseases and consanguinity has been noted to be the risk factors in previous studies. Hence, we categorized population into two groups-GDD which included both heterogeneous population with genetic causes including chromosomal, single gene defects which may also include undiagnosed inborn errors of metabolism, cerebral dysgenesis, and perinatal asphyxia, cerebral palsy etc. which may be genetic or non-genetic and second group of Inborn error of metabolism.

Definitive diagnosis was done by doing all necessary investigation as per standard protocol with use of tandem mass spectrometry (TMS), urine gas chromatography mass spectrometry (GCMS), magnetic resonance imaging

(MRI) brain, enzyme assays for lysosomal storage diseases, karyotyping, chromosomal micro array and next generation sequencing etc. Demographic variables are expressed in the form of frequency and percentage. Chi square test was used to check the association between study variables and demographic variables. All statistical analysis is done by using SPSS 21.

RESULTS

A total number of 194 patients visited the genetic clinic during the study period. Out of which 119 (61.34%) were males and 75 (38.65%) were female. The age group distribution showed 52 (26.80%) children were less than 1-year age group, 95 children were (48.96%) in 1 to 5 years of age group and 47 (24.22%) children were more than 5 years of age group. Out of 194 cases 103 (53.09%) of the patients were product of consanguineous marriage and 91 (46.90%) were product of non-consanguineous marriage. All the consanguineous marriages were of 3rd degree consanguinity. In 194 cases, 129 (66.5%) were of GDD and 65 (33.5%) were IEMs. Out of 103 cases which were product of consanguineous marriage 59 (57.3%) were GDD and out of 91 children who were product of non-consanguineous, 70 (68.35%) were having GDD. The difference was statistically significant with p value of 0.003 (Table 1). This indicated that consanguinity was not having impact on GDD group. Out of 103 cases which were product of consanguineous marriage 44 (42.7%) were IEMs and out of 91 children who were product of non-consanguineous, 21 (23%) were having IEMs. The difference was statistically significant with p value of 0.004 (Table 2). This indicated that consanguinity was significantly high in confirmed single gene diseases IEMs which are autosomal recessive and following Mendelian pattern of inheritance.

Table 1: Consanguineous marriages and GDD.

GDD	Consanguineous marriages				χ ² value	P value
	Yes	No				
	Number	Percentage (%)	Number	Percentage (%)		
Yes	59	54.3	70	68.2	8.38	0.003 Sig. p<0.05
No	44	45.7	21	31.8		
Total	103	100	91	100		

Table 2: Consanguineous marriages and IEMs.

IEMs	Consanguineous marriages				χ ² value	P value
	Yes	No				
	Number	Percentage (%)	Number	Percentage (%)		
Yes	44	67.7	21	23	8.077	0.004 p<0.01
No	59	32.3	70	77		
Total	103	100	91	100		

DISCUSSION

Consanguineous marriages are favored by different populations usually bound to traditional customs, beliefs

and to keep property in united form within the family. It is well known now that this marriage system has been reported as an important factor in the appearance of autosomal recessive diseases and congenital anomalies

etc. Consanguineous marriages are practiced widely, especially in India. In Indian setting, Nalini et al reported the role of consanguinity (46.4%) in causing dysferlinopathy in 28 patients.⁵ Further Bindu et al reported the role of consanguinity (61.5%) as an etiological factor for Hallervorden-Spatz syndrome (HSS), a rare autosomal recessive neurodegenerative disorder of childhood.⁶

In our study we made two groups and compared. One group was global developmental delay as it includes chromosomal causes, microdeletion/microduplication syndromes, single gene defects, and non-genetic causes like teratogens, perinatal asphyxia, prematurity etc. which could also be because of underlying unproven genetic mechanisms. This heterogenous group showed statistically significant number of children belonging to the non-consanguineously married couples. This indicates that if we take all kinds of causes for one of the common clinical presentations of genetic diseases, consanguinity does not increase risk for the occurrence of these genetic diseases. There is genetic drift or founder effect having community specific genetic diseases because of repeated inbreeding in same community which may cause genetic diseases be present though non consanguineously married.⁷ There is an Indian study on increased occurrence of congenital heart diseases in children of consanguineously married couples, which are group of congenital malformations of heterogenous etiologies.⁸

Our study showed statistically significant number of inborn errors of metabolism diagnosed in children born to consanguineously married couples. Single gene defects with autosomal recessive patterns of inheritance definitely have increased risk in endogamy. Study done at Denmark by El Mouzan et al confirmed the increased risk of IEM in offspring of consanguineous marriage⁹

A study was done at Scotland by Waters et al in which they compiled all the studies done worldwide related to IEM and enlisted the causes and drawbacks in diagnosis of IEM. Study also showed that cases of IEM are correlating in areas where there is higher prevalence of consanguineous marriage.¹⁰

Our study was planned to know the role of consanguinity in global developmental delay and IEM from our region. This genetically isolated region must be having founder effect or genetic drift mechanism to have no impact of inbreeding on global developmental delay group.

Limitations of study are such that, the sample size can definitely be more, for precise calculations to extrapolate on general population. The cases need to be genetically proven and genetic mutation data of population must be present, to find out about founder mutation or genetic drift phenomenon in Indian sub communities. This will require funding and focus on genetic research.

CONCLUSION

Genetic drift or founder mutations need to be considered in Indian communities, where small sub-communities are genetically isolated pools and can have distinct genetic diseases belonging to particular community. Genetic evaluation of global developmental delay group may unravel newer causes of community specific genetic diseases. So, further studies need to be done to find out more about region specific genetic diseases especially for India.

Consanguinity definitely plays role in autosomal recessive diseases like inborn errors of metabolism where risk is increased. So, any consanguineously married couple must undergo pre-conception genetic counselling, especially if history of suspected or diagnosed genetic disease in family.

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