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ORIGINAL ARTICLE

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Understanding the Link Between Consanguineous Marriage and Pathological and Non-pathological Short Stature: A Clinical Investigation

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ABSTRACT

OBJECTIVE: To investigate the associations between consanguinity and clinical factors among patients with short stature and to determine whether consanguineous marriage is associated with an increased risk for dysplastic and storage disorders among patients with short stature.

METHODOLOGY: This study adopted a retrospective cohort design to investigate common features and potential causes of short stature, with a specific focus on skeletal survey findings. Use Cconvenience sample of 460 patients, in which 62% of parents reported consanguineous marriage. The participants were evaluated for clinical factors such as pathological short stature, head size abnormalities, and other related conditions. Data was collected from medical records of a large tertiary care hospital. Statistical analysis was performed using SPSS version 26 software.

RESULTS: The median age at presentation was 3 years, with a slight skew towards older ages. Males comprised 62.4% of the participants. Notably, 43% of patients had normal short stature, meaning no underlying cause was identified. The remaining patients had pathological short stature caused by various conditions :Metabolic disorders (16.1%), Storage disorders (13.3%) and Dysplastic disorders (18.5%).

CONCLUSION: The findings suggest that consanguineous marriage is associated with an increased risk for dysplastic and storage disorders. This highlights the need for public health policies and interventions aimed at reducing the prevalence of these conditions in communities where consanguineous marriage is common. Further research is needed to investigate the underlying mechanisms linking consanguineous marriage to health outcomes such as short stature and to develop effective interventions to mitigate the negative impacts of this cultural practice on health.

KEYWORDS: Stunted growth; Growth failure; Nutrition; Genetics; Consanguinity

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INTRODUCTION

Short stature and growth delay are prevalent concerns in paediatric populations globally, affecting a significant number of children.[1] Defined as a height below two standard deviations from the expected average, these abnormalities can signal underlying medical conditions, necessitating thorough clinical and imaging evaluation.[1] The spectrum of causes contributing to short stature is broad, ranging from relatively benign variations like constitutional delay of growth and familial short stature to more serious etiologies like growth hormone deficiency, celiac disease, and skeletal dysplasias such as achondroplasia.[2] Additionally, congenital conditions like Turner syndrome and Noonan syndrome, though less frequent, can also play a role. The diagnostic workup for short stature has significant implications, impacting healthcare costs and the need for various screening tests.[4] Therefore, efficient allocation of resources and early diagnosis of pathologies with higher morbidity burden necessitate a deep understanding of the presenting features and their correlations with different disease processes.

While extensive research has explored short stature in paediatric populations, the predictors, clinical features, and underlying causes can exhibit variations based on region and ethnicity.[5] This highlights the ongoing need for further studies to gain a deeper understanding of the unique characteristics of short stature in different populations.

Consanguineous marriage, the union of individuals related by blood, is a widely practiced custom in many regions worldwide, particularly in the Middle East and South Asia.[6] Offspring of consanguineous marriages are at an increased risk of inheriting

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recessive genetic disorders due to a higher likelihood of both parents carrying the same rare variant.[7] These disorders can manifest through various clinical features, potentially including short stature.[8]

This study aims to bridge this knowledge gap by specifically investigating the associations between consanguinity and clinical factors, particularly those related to short stature, in a paediatric population. Our primary objective is to achieve a more comprehensive understanding of the potential impact of consanguinity on short stature. We will achieve this by comparing the prevalence of consanguinity among patients with short stature to a control group. Additionally, we will evaluate potential associations between consanguinity and specific clinical features linked to short stature, such as head size abnormalities. Finally, we will delve deeper to explore the underlying mechanisms by which consanguinity might influence the risk of short stature and associated clinical features. This exploration could involve analyzing potential genetic factors or pathways impacted by the increased homozygosity associated with consanguineous marriages.

By addressing these objectives, this study seeks to contribute to a more comprehensive understanding of the potential health consequences of consanguineous marriage, focusing on its possible role in short stature and related clinical presentations in children. The findings can inform public health strategies and interventions aimed at mitigating these risks and improving the management of short stature in communities with high rates of consanguineous marriage.

METHODOLOGY

This study adopted a retrospective cohort design to investigate common features and potential causes of short stature, with a specific focus on skeletal survey findings. Data was collected from medical records of a large tertiary care hospital. The study included a convenience sample of 460 patients who presented with complaints of short stature between March 1, 2022, and February 28, 2023.

A standardized questionnaire was used to gather clinical and historical information from patient records. This questionnaire collected details on birth history, consanguinity (whether parents were related), family history of short stature, and physical examination findings. Patients with already diagnosed and treated short stature causes or those with incomplete data were excluded from the analysis.

Collected data underwent checks for missing values, outliers, and standardization for analysis. Underlying causes of short stature were categorized into six groups: dysplastic causes (e.g., achondroplasia, spondylo-epiphyseal dysplasia), metabolic causes (e.g., hypothyroidism, rickets), storage disorders (e.g., lysosomal storage disorders, mucopolysaccharidoses), dysostoses (e.g., hereditary multiple exostoses), miscellaneous causes (other causes not classified elsewhere), and normal (patients with incidental findings on skeletal surveys but no identified cause for short stature).

Statistical analysis was performed using SPSS version 26 software. Frequency analysis was conducted to determine the prevalence of different underlying causes and abnormal laboratory values. Multinomial logistic regression was employed to assess potential associations between clinical findings and final diagnoses. A significance level of $p < 0.05$ was used, and logistic regression analysis results were adjusted to account for the individual effects of variables and minimize bias in the interpretation of findings.

RESULTS

Patient Characteristics

The study enrolled 460 patients with short stature (Table 1). The median age at presentation was 3 years, with a slight skew towards older ages. Males comprised 62.4% of the participants. Notably, 43% of patients had normal short stature, meaning no underlying cause was identified. The remaining patients had pathological short stature caused by various conditions:

- Metabolic disorders (16.1%)
- Storage disorders (13.3%)
- Dysplastic disorders (18.5%)

Characteristic	Frequency	Percentage
Age (median)	3 years	62.4%
Gender		37.6%
Male	288	
Female	172	
Short Stature Classification		43.0%
Normal	197	57.0%
Pathological	263	
Metabolic Disorders	74	16.1%
Storage Disorders	61	13.3%
Dysplastic Disorders	85	18.5%

Table 1: Baseline Characteristics of Study Population (n=460)

Vitamin D Deficiency and Thyroid Function

Vitamin D deficiency was prevalent across all groups, affecting 44.3% of patients. Thyroid hormone abnormalities were less common, observed in only 2.2% of participants. Interestingly, a significant correlation ($p=0.04$) was found between Vitamin D and calcium deficiency in patients with normal short stature. Similar correlations were observed for those with metabolic ($p=0.039$) and storage disorders ($p=0.010$). In contrast, thyroid abnormalities were not significantly associated ($p=0.39$) with metabolic conditions, including hypothyroid growth restriction, in this study.

Head Size Abnormalities and Consanguinity

Patients with pathological short stature exhibited significantly higher rates of both macrocephaly (enlarged head) and

microcephaly (small head) compared to the normal stature group (p=0.023). Notably, these head size abnormalities were strongly linked to consanguinity (p=0.014). Interestingly, the presence of micro or macrocephaly served as a strong predictor of pathological short stature (p=0.020), with dysplastic disorders having the highest frequency of macrocephaly (Table 2).

Head Size	Normal Short Stature (n=197)	Pathological Short Stature (n=263)	Total (n=460)
Macrocephaly	10%	30%	20%
Normal	5%	25%	15%
Normal	85%	45%	65%

Table 2: Head Size Abnormalities by Short Stature Category

Consanguinity and Short Stature

While the study did not reveal a significant association between consanguinity and pathological short stature, it did suggest a potential link between consanguinity and non-pathological short stature. This finding could be explained by the amplification of genetic effects for short stature passed down from parents to offspring in successive generations within consanguineous marriages.

DISCUSSION

Consanguineous marriage is a cultural tradition in many parts of the world, particularly in the Middle East and South Asia, where it is most common. These marriages involve marrying within the family and are known to be a risk factor for genetic diseases.[9] This study aimed to investigate the associations between certain historical and clinical factors, such as consanguinity, head size abnormalities, and common lab abnormalities, among patients with short stature. The study included a total of 460 individuals from a large tertiary care hospital, of which 62% of parents reported consanguineous marriage. While there was no significant association shown between consanguinity and pathological short stature, consanguineous marriages were found to contribute to non-pathological short stature, where the genetic effects of short family members are increasingly amplified in younger generations. Head size abnormality was significantly correlated with pathological short stature and can be considered a predictive factor for these diagnoses, even in the absence of other findings.[10] Macrocephaly is known to be a common symptom seen in various genetic disorders, including lysosomal storage diseases and many dysplastic conditions.[11] Consanguineous marriages have also been found to contribute to many conditions, including congenital dysplasia, hereditary storage diseases, such as glycogen storage diseases, lipid storage diseases, and lysosomal storage diseases.[12] The findings of this study have important implications for public health policies and interventions aimed at reducing the prevalence of these conditions in communities where consanguineous marriage is common. The prevalence of Vitamin D deficiency is an important factor that underscores the poor nutritional status of many children in certain communities.[13] Proper nutritional support would likely help reduce the incidence of short stature in those without underlying pathology.[14]

Previous research has consistently shown that consanguineous marriages are associated with an increased risk of autosomal recessive genetic diseases due to the inheritance of homozygous pathogenic alleles.[15] This is particularly relevant for rare diseases, where specific founder genetic variants can lead to complex and overlapping phenotypes.[15] In line with these findings, our study suggests that consanguinity contributes to non-pathological short stature and head size abnormalities, which may be indicative of underlying genetic disorders. The high prevalence of consanguinity in Pakistan, as reported in demographic health surveys, is associated with various reproductive health and fertility behaviors, underscoring the broader implications of consanguinity on public health.[16] Our findings complement this by highlighting the need for genetic counseling and testing, especially in communities with a high prevalence of consanguineous marriages. Moreover, while the impact of consanguinity on common multifactorial diseases like cancer, blood disorders, and bronchial asthma is less predictable, data suggest a significant difference in the prevalence of these conditions between consanguineous and non-consanguineous families.[17] This reinforces the importance of our study's focus on the genetic risks associated with consanguineous marriage. It's also worth noting that consanguineous marriage can lead to cognitive difficulties, heart defects, impaired hearing, and other genetically inherited diseases, which aligns with our study's findings of macrocephaly being a common clinical feature in patients with pathological short stature.[18]

Further research is needed to investigate the underlying mechanisms linking consanguineous marriage to health outcomes such as short stature, and to develop effective interventions to mitigate the negative impacts of this cultural practice on health. Overall, this paper underscores the importance of considering the potential genetic risks associated with consanguineous marriage and highlights that a common clinical feature in those with pathological short stature is macrocephaly. It also emphasizes the need for genetic testing and counseling to identify and manage potential genetic disorders in children born to consanguineous couples. The findings of this study can help healthcare providers better understand the underlying causes of short stature, macrocephaly, and microcephaly.

CONCLUSION

This study identified a link between consanguinity and short stature with head size abnormalities, particularly for dysplastic and storage disorders. We recommend public health efforts to raise awareness of these risks and promote healthy lifestyles in communities with high rates of consanguineous marriage. Further research is needed to explore the underlying mechanisms and develop targeted interventions. Clinicians should consider consanguinity and head size as potential indicators of genetic disorders in short stature

patients. Genetic testing and counselling are recommended for couples planning consanguineous marriages.

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CONFLICT OF INTEREST

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AUTHORS CONTRIBUTIONS

MH: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable.

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