ORIGINAL ARTICLE

Spectrum of skeletal dysplasia in short stature children in tertiary care hospital.

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ABSTRACT… Objective: To evaluate the spectrum of skeletal dysplasia in short stature children at National Institute of Child Health (NICH), Pakistan. **Study Design:** Case Series study. **Setting:** Department of Endocrinology, NICH, Karachi, Pakistan. **Period:** January 2022 to November 2023. **Methods:** Short statured (height < -2.0 SD) children of either gender aged between 1 month up to 16 years and diagnosed with skeletal dysplasia were analyzed. At the time enrollment, gender, age, anthropometric measures, antenatal history, and family history were noted. Complete skeletal survey was performed. **Results:** In a total of 131 short statured children with skeletal dysplasia, 77 (58.8%) were male. The mean and median age were 5.54±4.33 and 5.0 (1.5-8) years. Consanguinity was reported in 85 (64.9%) cases whereas siblings were affected among 9 (6.9%) cases. The most frequent presenting complaints and clinical features were joint pain, facial dysmorphism, movement limitations, and infections, reported by 67 (51.1%), 67 (51.1%), 65 (49.6%), and 63 (48.1%) children respectively. Mucopolysaccharidosis (29.0%), achondrodysplasia (13.7%), and osteogenesis imperfecta (10.7%) were the most common types of skeletal dysplasia. **Conclusion:** Mucopolysaccharidosis, achondrodysplasia, and osteogenesis imperfecta were the most frequent types of skeletal dysplasia. The most frequent presenting complaints and clinical features were joint pain, facial dysmorphism, movement limitations, and infections. The high prevalence of consanguinity and familial history emphasizes a probable genetic basis for skeletal dysplasia.

Key words: Achondrodysplasia, Mucopolysaccharidosis, Osteogenesis Imperfecta, Short Stature, Skeletal Dysplasia.

INTRODUCTION

Skeletal dysplasias encompass a diverse group of genetic and clinically varied disorders that impact the growth and development of bone and cartilage, often resulting in disproportionate shortening of limbs and the spine.[1] Skeletal dysplasia affects nearly 1 in 5000 live births, accounting for 5% of children born with a birth defect.[2] In the most recent 2015 version of the "Nosology and Classification of Genetic Skeletal Disorders", there has been a reduction in the overall burden from 456 to 436. However, the number of disorder groups has increased from 40 to 42, and the number of associated genes has risen from 226 to 364 when compared to the 2011 version.[3]

The patients of skeletal dysplasia commonly present with short stature in childhood, however due to its heterogeneity, musculoskeletal effects range in severity from premature arthritis in average height individuals to severe short stature with death in the perinatal period.[4] An accurate diagnosis of a skeletal dysplasia is still based on detailed evaluation of clinical and radiographic findings despite growing role of molecular genetics.[5] A thorough clinical assessment to include family history and available ancestral data are required for the study.[6] A study on spectrum of disproportionate short stature at Tertiary Care Centre in Northern India was conducted in 2017 which concluded that definitive diagnosis of skeletal dysplasia is possible with methodological approach and helps in providing adequate risk of re-occurrence to families and charting adequate management plan. In the study forty cases with disproportionate short stature (median age 3.1 years, 24 males were assessed. Achondroplasia was the commonest (n=9) skeletal dysplasia; conclusive diagnosis was not possible in six

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Time of onset of symptoms helps narrows down the diagnosis as 100 out of more than 450 conditions manifest during perinatal period and achondroplasia often exhibit with identifiable short-stature at birth.[7] In the course of a physical examination, it is recommended to measure body proportions such as the upper-to-lower segment ratio, arm span, and sitting height.[8] However, it is acknowledged that radiographic assessments often provide more accurate quantifications due to potential influences on clinical measurements from factors like skinfolds and bone bowing.[9]

International literature is available but no such local data is on view regarding the spectrum of skeletal dysplasia so this study is thought to assist in shedding light on the different types of skeletal dysplasia and related clinical history and radiographic findings in short statured children visiting one of the leading pediatric child healthcare facility of Pakistan. The aim of this study was to evaluate the spectrum of skeletal dysplasia in short stature children at National Institute of Child Health (NICH), Pakistan.

METHODS
The case series study was conducted at the endocrinology department of NICH, Karachi, Pakistan from January 2022 to November 2023. A sample size of 131 was calculated taking the prevalence of skeletal dysplasia in short stature children as 32.1%[7], with 95% confidence level and 5% precision. Non-probability consecutive sampling technique was adopted. Inclusion criteria were short stature children of either gender aged between 1 month up to 16 years and diagnosed with skeletal dysplasia. Short stature was labeled as height < -2.0 SD below the mean for children of that similar gender and chronological age. Exclusion criteria were Children with constitutional and familial short stature, down syndrome, turner syndrome, or Noonan syndrome. Children with metabolic bone condition such as Rickets or hypophosphatasia or those whose parents/guardians did not want their children to be part of this study were also excluded. This study was commenced after the approval of "Institutional Ethical Review Board (ERB)" of NICH (IERBB-49/2022) (24.2.2023) Informed and written consents were obtained from parents/guardians of all patients.

At the time enrollment, gender, age, anthropometric measures, antenatal history, and family history were noted. Detailed physical examination was performed and medical history was recorded. Relevant laboratory investigations were sent to institutional laboratory. Complete skeletal survey was performed. Skeletal dysplasia is defined as a heterogeneous group of abnormalities affecting growth and development of bone and cartilage characterized by disproportionate shortening of the limbs and/or spine. Disproportionate short stature was divided into short trunk or short limb varieties. Short trunk was labeled as decreased upper/lower segment ratio while a short statured patient with normal trunk and relatively short limbs might had an increased upper/lower segment ratio. Short limb types were Rhizomelia as proximal limb shortening (Humerus / femur), Mesomelia as middle segment shortening (Radius, ulna, tibia, fibula), or Acromelia as distal segment shortening (hand and foot). Arm Span was measured as distance between tips of middle fingers with both arm outstretched. Lower segment (LS) measured from pubic symphysis to heel and UPPER Segment (US) derived by deducting the LS from height.

After collection of the data, analysis was performed using "IBM-SPSS Statistics", version 26.0. Categorical data were shown as frequency and percentages. Numeric variables were present as mean and standard deviation.

RESULTS
In a total of 131 short statured children with skeletal dysplasia, 77 (58.8%) were male. The mean and median age were 5.54 ± 4.33 and 5.0 (1.5-8) years (ranging between 2 months to 16 years). Consanguinity was reported in 85 (64.9%) cases whereas siblings were affected among 9 (6.9%) cases. Table-I is reporting characteristics of skeletal dysplasia cases. Table-II is showing descriptive details about the anthropometry and skeletal parameters.

| Characteristics		Number (%) / Mean±SD
Gender	Male	77 (58.8%)
	Female	54 (41.2%)
Age (years)	<1	18 (13.7%)
	1-5	56 (42.7%)
	6-12	48 (36.6%)
	13-16	9 (6.9%)
Siblings affected		9 (6.9%)
Consanguinity		85 (64.9%)
First recognition of skeletal disorder	At birth	2 (1.5%)
	Prenatally	2 (1.5%)
	Childhood	115 (87.8%)
	Newly diagnosed	12 (9.2%)

Table-I. Characteristics of short statured children with skeletal dysplasia (n=131)

Parameters	Mean±SD
Weight (kg)	12.10±5.84
Height / Length (cm)	84.55±21.04
Sitting height (cm)	48.75±9.05
Head circumference (cm)	47.89±3.97
Height for age standard deviation Z-score	-5.22±2.25
Weight for height standard deviation Z-score	-4.10±2.15
Arm span (cm)	83.29±29.62
Head length (cm)	11.75±2.67
Foot length (cm)	15.32±4.11
Radius or ulna length (cm)	16.29±4.55
Tibia or fibula length (cm)	26.50±8.75
Humerus length (cm)	17.10±6.06
Femur length (cm)	22.33±7.92
Upper / lower ratio	1.27±0.41

Table-II. Descriptive statistics about anthropometry and skeletal parameters

The most frequent presenting complaints and clinical features were joint pain, facial dysmorphism, movement limitations, and infections, reported by 67 (51.1%), 67 (51.1%), 65 (49.6%), and 63 (48.1%) children respectively (Figure-1).

Mucopolysaccharidosis (MPS) (29.0%), achondrodysplasia (13.7%), and osteogenesis imperfecta (10.7%) were the most common types of skeletal dysplasia. The details about the distribution of types of skeletal dysplasia are shown in Table-III.
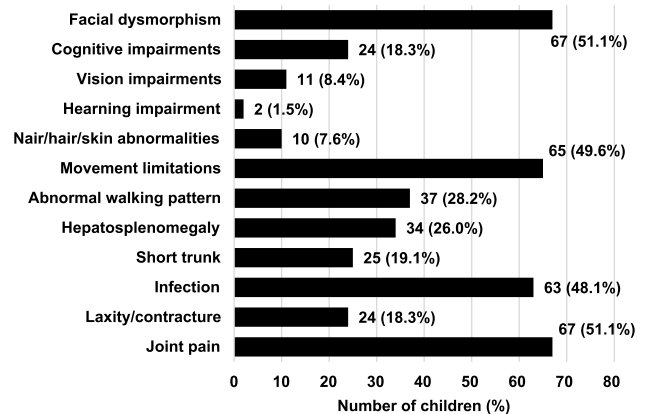
Figure-1. Presenting complaints and clinical features

No.	Skeletal dysplasia	Number (%)
1	Mucopolysaccharidosis (MPS)	38 (29.0%)
2	Achondrodysplasia	18 (13.7%)
3	Osteogenesis imperfecta	14 (10.7%)
4	Pycnodysostosis	9 (6.9%)
5	Spondyloepiphyseal dysplasia	8 (6.1%)
6	Asphyxiating thoracic dystrophy (jeune syndrome)	7 (5.3%)
7	Progressive pseudorheumatoid dysplasia	6 (4.6%)
8	Arthrogryposis multiplex congenita (AMC)	5 (3.8%)
9	Chondroectodermal dysplasia (ellis-van creveld syndrome)	4 (3.1%)
10	Metaphyseal chondrodysplasia	3 (2.3%)
11	Chondrodysplasia punctata	2 (1.5%)
12	Pseudoachondroplasia	2 (1.5%)
13	Sclerosing dysplasia	2 (1.5%)
14	Spodyloepiphyseal congenita	2 (1.5%)
15	Costovertebral dysplasia	1 (0.8%)
16	de Lange Syndrome	1 (0.8%)
17	Lowe syndrome	1 (0.8%)
18	Mandibuloacral dysplasia type A	1 (0.8%)
19	Mesomelic dwarfism	1 (0.8%)
20	Omodysplasia type-2	1 (0.8%)
21	Oral-facial-digital syndrome type 4 (Mohr-Majewski)	1 (0.8%)
22	Progressive pseudo arthopathy	1 (0.8%)
23	Spondylometaphyseal dysplasias	1 (0.8%)
24	Type-1 (hurler syndrome)	1 (0.8%)
25	Type-2 (mohr syndrome)	1 (0.8%)

Table-III. Types of skeletal dysplasia

DISCUSSION

Disproportionate short stature is a hallmark feature in skeletal dysplasias, often assessed through various anthropometric measurements.[10] Evaluating arm span, sitting height, and the ratio of sitting height to total height provides crucial insights into this disproportion. An alternative method involves calculating the upper/lower body segment ratio and comparing it with established references.[11] This approach aids in identifying whether the short stature predominantly affects the limbs' proximal (rhizomelic), middle (mesomelic), or distal (acromelic) segments, depending on which segments—such as the humerus, femur, radius, ulna, tibia, fibula, hand, or foot are notably shortened.[12] This study provides a comprehensive overview of the spectrum of skeletal dysplasia in short-statured children in a tertiary care hospital. Skeletal dysplasia in children presents variety and complex clinical landscape, as evidenced by the diverse range of the conditions observed in this study.

Consanguinity emerged as a notable factor, with a high occurrence (64.9%). The higher prevalence of consanguineous marriages in our region significantly impacts the landscape of genetic disorders, particularly autosomal recessive conditions. This distinctive cultural practice amplifies the frequency of specific genetic entities, making it challenging to extrapolate data from other parts of the world to our population. Total consanguinity rate among parents in a study from Turkey analyzing skeletal dysplasia patients was 53%.[13] The observed prevalence of affected siblings (6.9%) in this research further underscores the familial predisposition to these disorders, necessitating a comprehensive approach to genetic counseling and family screening. These findings further emphasize the potential hereditary nature of skeletal dysplasia, implicating autosomal recessive or dominant inheritance patterns.

Anthropometric measurements revealed profound deviations in height, weight, and other skeletal dimensions, with Z-scores. Previous local data has shown that children with skeletal dysplaisa have significantly low weight and height scores.[14]

These findings highlight the challenges faced by children with skeletal dysplasia in achieving typical growth milestones, emphasizing the importance of early diagnosis and intervention to mitigate potential complications associated with growth and development.[15]

The types of skeletal dysplasia observed in this study encompassed a broad spectrum of conditions. MPS, the most prevalent disorder in this cohort, aligns with its known diverse clinical manifestations and progressive nature. The presence of Achondrodysplasia, Osteogenesis imperfecta, and other relatively less frequent dysplasia further illustrates the heterogeneity within this population. A study from Pakistan by Seema et al revealed achondroplasia, mucopolysaccharidosis, pseudoachondroplasia to be the most frequent types of skeleta dysplasia.[14] The literature describes achondroplasia to be the most common form of skeletal dysplasia[15] and our findings were somewhat different and needs further investigation. Understanding the distinct characteristics and specific clinical presentations associated with each disorder is crucial for accurate diagnosis, appropriate management, and family counseling. A study conducted over six years in North Indian patients with antenatally detected short long bones highlighted significant findings as thanatophoric dysplasia emerged to be the most common type of lethal dysplasia, comprising approximately 20% of the cases, while achondroplasia represented about 27% of the total cases classified as nonlethal dysplasias. This distinction between lethal and nonlethal dysplasias underscores the critical need for accurate prenatal diagnosis to guide appropriate counseling and management decisions for expectant parents.[16]

A separate analysis of fetal autopsies focusing on suspected skeletal dysplasias, identified 15 autopsied fetuses presenting with short-limbed dwarfism. Within the subset, short-rib dysplasia with or without, polydactyly was identified as the most prevalent dysplasia, accounting for approximately 33% of the cases.[17] These findings not only reaffirm the diverse spectrum of skeletal dysplasia but also highlight the prominence of

specific types within the region.[18]

Our findings emphasize the need for heightened clinical suspicion, early recognition, multidisciplinary management, and genetic counseling to optimize the care and outcomes for these children, thereby addressing their complex medical needs comprehensively. Further research bridging the gap between clinical phenotypes and underlying genetic mechanisms holds promise for improved diagnostics, management, and potential therapeutic interventions for these diverse skeletal dysplasia. This study had some limitations including the inability to ascertain causative genetic mutations or molecular characterization due to the scope of the research. Future studies focusing on genotype-phenotype correlations and expanding the understanding of the molecular basis of these dysplasia would offer invaluable insights into their pathogenesis and aid in targeted therapeutic approaches.

CONCLUSION

Mucopolysaccharidosis, achondrodysplasia, and osteogenesis imperfecta were the most frequent types of skeletal dysplasia. The most frequent presenting complaints and clinical features were joint pain, facial dysmorphism, movement limitations, and infections. The high prevalence of consanguinity and familial history emphasizes a probable genetic basis for skeletal dysplasia. Profound deviations in anthropometric measurements highlight the challenges these children face in achieving typical growth milestones. The varying recognition times of skeletal disorders stress the need for improved and early detection strategies. While our study sheds light on the spectrum of skeletal dysplasias, further research exploring genotype-phenotype correlations and molecular characterization is imperative to enhance diagnostics and tailored therapeutic interventions for these complex conditions.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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
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2	Mohsina Noor Ibrahim	Study concept, Methodology, Proof reading, Approval for publication.	
3	Marya Hameed	Critical revisions, Literature review, Discussion, Approval for publication.	