Spectrum of Disproportionate Short Stature at a Tertiary-care Center in Northern India

Forty cases with disproportionate short stature (median age 3.1 y; 24 males) from genetic clinic of Lok Nayak Hospital, Delhi were assessed in this study. Achondroplasia was the commonest (*n*=9) skeletal dysplasia; conclusive diagnosis was not possible in six children. Molecular confirmation of clinicoradiological phenotype was done in 18 of 40 cases. Genetic study of all achondroplasia cases revealed c. 1138 G>A, p. Gly380Arg mutation in hot spot.

Key words: *Achondroplasia, Genetics, Mutation, Stunting*

Disproportionate short stature is a diagnostic challenge to treating clinicians. Evaluation of short stature at a genetic clinic in northern India reported skeletal dysplasia in 32.1% of the cases [1]. Another study from southern India reported experience of 514 cases over 8 years at a tertiary hospital [2]. This indicates high burden of skeletal dysplasias at specialized centers. This report is an attempt to reach a diagnosis with simple tools in cases with disproportionate short stature.

Ethical clearance was obtained from Institute Ethical Committee of Maulana Azad Medical College for this descriptive study conducted between July 2011 to September 2013. Every child with disproportionate short stature was subjected to detailed clinical and radiological evaluation. Clinical and radiological details were used to reach the most likely diagnosis with the help of London Dymorphology Database (LDB), Online Mendelian Inheritance in Man (OMIM), Atlas of Genetic Disorders of Skeletal Development, and online consultation with experts in the field of skeletal dysplasia. Cases, for which diagnosis was not made, were further submitted to panel of experts in European Skeletal Dysplasia Registry. Cases were further subjected for molecular analysis for confirming the diagnosis. Molecular diagnoses of all achondroplasia cases were done using a standard protocol [3]. Molecular testing in other cases was done based on hot spots in case of common mutation and gene sequencing in cases with multiple mutation.

We enrolled 40 cases (median age 3.1y; 24 males) in this study.Majority (35/40) presented with skeletal deformity. ***Web Table*** **I** shows phenotype of all cases: molecular diagnosis was possible in 18 of 40 cases. Achondroplasia was the commonest skeletal dysplasia, constituting 22.5 percent of the total cases enrolled in study. Genetic study of all Achondroplasia cases found c. 1138 G>A, p. Gly380Arg mutation in hot spot.

Achondroplasia as the commonest short limbed dwarfism has been previously reported [4, 5]. The mutation in achondroplasia as found in our study is also reported in earlier studies [6-8]. Most common short trunk dwarfism was Morquio syndrome. Genetic analysis of three cases revealed two pathogenic mutations in *GALNS* gene, which were also reported by Bidchol, *et al.* [9]. c.155C>T, p.Pro52Leu mutation was reported first time from India. Congenital hypothyroidism was found in five cases. Our study highlights that definitive diagnosis of skeletal dysplasia is possible with robust methodological approach. It helps in providing adequate risk of reoccurrence to families and charting adequate management plan.

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WEB TABLE I PHENOTYPE, GENOTYPE AND FINAL DIAGNOSIS OF CHILDREN WITH DISPROPORTIONATE SHORT STATURE (*N*=40)

Phenotype	*Genotype (N: Number of patients)*	*Gene*	*Final diagnosis (number of cases)*	*Clue to diagnosis*
Large head, proximal shortening of limbs, mid face hypoplasia, brachydactyly, trident hand, progressive narrowing of interpediculate distance in lumbar spine	c. 1138 G>A, p. Gly380Arg (9 cases)	FGFR3	Achondroplasia (9)	Large head, proximal shortening of long bones
Joint immobility, short trunk, pectus carinatum, dysostosis multiplex in radiograph	c.155C>T, p.Pro52Leu (2 cases); [c.3G>A; p.1Met>lle] [c.452 C> T ; p.Pro151Leu] (1 case)	GALNS	Morquio Syndrome (7)	Dysostosis multiplex
Coarse facies , dull look, infantile proportion (short limb dwarfism)	Not done		Congenital hypothyroidism (5)	
Short limb dwarfism, round face, flat nasal bridge, advance bone age, monkey wrench deformity of femoral head, short metacarpals, short metatarsals	c.C467T p.Ser156Ph (3)	CANT1	Desbuquois dysplasia (3)	Monkey wrench deformity of femoral head, advanced carpal age
Ovoid vertebrae, metaphyseal flaring, epiphyseal flaring, joint laxity, onset of disease after 2 years of age, Normal shape of body unlike achomdroplasia.	c.1554C>G ; p.Asp518Glu (1)	COMP;	Psuedoachondroplasia (2)	Onset of disease after 2 years of age
Short trunk dwarfism, block/hemivertebrae (thorasic), multiple rib defects (fused) , absence of finger anomalies	Not done		Spondylocostal dysostosis IV(1)	Involvement of thorasic spine and ribs (asymmetrical)
Short trunk dwarfism, block / hemivertebrae (thorasic), no intrinsic rib defects, absence of finger anomalies, ribs are fused symmetrically to the spine posteriorly (crab like chest deformity)	Not done		Spondylothorasic dysplasia (1)	Involvement of spine and ribs (symmetrical)> crab like chest deformity
Short trunk dwarfism , microcephaly, severe mental retardation, wavy iliac crest (pathogonomic)	c.1923del,p.(Tyr642 Metfs*78)(1)	DYM, Dymeclin	Dyggve Mechoir Clausen disease (1)	Wavy iliac crest and mental retardation
Small thorax, rhizomelia, proximally placed thumb, talipes equinovarus, bifid distal humerus	Not done		Atelosteogenesis II (1)	Bifid distal humerus
Short trunk dwarfism, block / hemivertebrae (thorasic), multiple rib defects (fused) , absence of finger anomalies	Not done		Spondylocostal dysostosis (1)	Involvement of thorasic spine and ribs (asymmetrical)

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Phenotype	*Genotype (N: Number of patients)*	*Gene*	*Final diagnosis (number of cases)*	*Clue to diagnosis*
Short limb dwarfism, fine hair, brittle hair, metaphyseal involvement	g.69dupG,r.69dupG(1)	RMRP	Cartilage Hair hypoplasia (1)	Fine hair, only metaphyseal flaringin long bones
Short limb dwarfism, narrow thorax, long coccyx, coccygeal tail, delayed bone age	Not done		Metatropic dysplasia (1)	Presence of coccygeal tail
Short limb dwarfism (acral and mesomelia) , loose and redundant skin on fingers, meta-physeal flaring, ovoid vertebrae	Not done		Acromesomelic dysplasia (1)	Acral and mesomelic parts of long bones are severely affected.
Short limb and short trunk, metaphyseal flaring, ovoid vertebrae	Not done		Unclassified (6)	Needs whole exome/ genome sequencing.