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RESEARCH ARTICLE

CLINICAL AND BIOCHEMICAL PROFILE OF CHILDREN WITH SHORT STATURE PRESENTING TO A TERTIARY CARE CENTRE: A 3 YEARS PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objective: To evaluate the clinical and biochemical profile and Growth hormone receptor Polymorphism of children presenting with short stature to a tertiary care centre, and also to study the molecular players/polymorphism that might give us an insight into good response to a relatively expensive modality of treatment. This would thus be directing resources to patients with GH deficiency who would respond best to it.

Materials and Methods: This was an observational study on short stature children presenting to a tertiary care hospital over a period of 3 years. Short stature was defined as height or length less than -2 SD of age and sex matched population using reference WHO growth charts and or growth velocity lower than the 25th percentile for age for at least 1 year or lower than the 10th percentile for age for at least 6 months. All children enrolled underwent extensive baseline work up to investigate for causes of short stature like Endocrine causes (Hypothyroidism, Laron's syndrome), malnutrition, chronic diseases (Thalassemia, chronic kidney disease and renal tubular acidosis), celiac disease, syndromic association, Skeletal dysplasia, Familial short stature, Constitutional short stature and Idiopathic short stature. In children with pathological short stature in whom an identifiable cause of short stature was not found on routine investigations, serum growth hormone (GH), IGF-1 and IGFBP-3 levels were estimated using 2 different pharmacological stimuli.GH value of less than 10 mg/L were considered to be GH deficient. Children with Growth Hormone Deficiency (GHD) were subjected to analysis of the GHD3 exon deletion status. For the genotyping of GHR exon 3 locus, the frequency of GHR transcript variants with retention (GHRfl) or exclusion (GHRd3) of exon 3 was tested by the multiplex PCR assay. This was performed with primers G1, G2, and G3 with a well defined protocol.

Result: A total of 473 children with a median age of 3.65 years (Range 2-18 years) were enrolled. Twenty three percent of the children each were diagnosed as Growth hormone deficient and Idiopathic short stature. Celiac disease also contributed significantly in 18% of cases. The other causes seen were skeletal dysplasia (7%), syndromic (12%) and malnutrition (2%). Amongst children with endocrine disorders, 40% children had hypothyroidism, panhypopituitarism was seen in 10% children and 50% had Laron's syndrome. In Children with chronic disorders, 72% were diagnosed with Thalassemia, 21% with chronic kidney disease and 1 child had renal tubular acidosis. Constitutional and familial short stature were seen in 6% and 2% children respectively. Amongst patients with GHD, 60.7% had wild type (GHRfl/fl), 19.2% were heterozygous (GHRfl/GHRd3) and 20.1% were homozygous (GHRd3/d3), whereas for idiopathic short stature they were 67.5%, 14.5% and 18% respectively.

Conclusion: With high index of suspicion, availability of testing and following an algorithmic approach, diagnosis could be attained in 85% of cases. Our data indicates the changes in profile from those reported earlier in our country. Growth hormone deficiency and celiac disease contribute significantly even though majority are normal variants. Also, genotyping done would help in prediction of response to recombinant GH therapy in a resource constraint resulting in appropriation of finances which could be utilized for a higher priority area.

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INTRODUCTION

Short stature forms a significant cause of psychological affliction in childhood and adolescence. It presents as a continuum of phenotypes ranging from isolated short stature to being a part of a genetic syndrome, sequence or malformation. The paradigm of referrals has changed over time. The major etiologic causes previously were protein energy malnutrition, chronic systemic diseases along with constitutional short stature and growth hormone deficiency (Colaco *et al.,* 1991; Kaur and Phadke, 2012; Soliman *et al.,* 1986). Withimproving knowledge and recognition ofawareness for referral to specialty clinics, it has changed to include many more causes. The estimated prevalence of short stature from India was 5.6% as reported by Colaco *et al.,* 1991. However, the actual prevalence of the problem is difficult to estimate as a large part of the burden of the disease remains undiagnosed and needs to be validated by larger population based studies. This study was intended to evaluate the clinical and biochemical profile of children presenting with short stature. Since growth hormone deficiency constitutes a large proportion of short stature and is

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not easily affordable it was also intended to study the molecular players or polymorphisms that might give as insight into good response to a relatively expensive modality of treatment. This would thus be directing resources to patients with GH deficiency who would respond best to it.

MATERIALS AND METHODS

This was a prospective observational study conducted in a Tertiary care centre in North India over a period of 3 years. Short stature was defined as height or length less than -2 SD of age and sex matched population using reference WHO growth charts and/or growth velocity lower than the 25th percentile for age for at least 1 year or lower than the 10th percentile for age for at least 6 months. Ethical clearance was obtained from institutional ethics committee. After enrolment each child was evaluated as per a predesigned Performa which included the weight and height of the child, height of both parents with calculation of mid parental height. Skeletal radiographs of wrist or elbow as per Gruelich and Pyle atlas estimated bone age. Two observers independently reviewed this. Routine hematological investigations like hemoglobin, MCV and peripheral smear, biochemical investigations like liver and kidney function tests, thyroid function tests were done in all enrolled patients.

The estimated bone age and the relationship between chronological age, bone age and height age were computed and the categorization of familial and constitutional short stature was made. All children were screened for celiac disease that was confirmed by modified ESPGHAN criteria (duodenal biopsy histopathology showing either partial or total villous atrophy, with increased intraepithelial lymphocytes and/or crypt hyperplasia), unequivocal response to gluten free diet and a positive serology (auto antibodies to tissue transglutaminase or anti endomysial antibodies) (Revised Criteria for diagnosis of celiac disease, 1990). Karyotype was done in all female patients with or without a suggestive phenotype in which chronic disorders were excluded. Detailed skeletal evaluation was done when the phenotype was suggestive of a skeletal dysplasia. In children with pathological short stature in whom an identifiable cause of short stature was not found on routine investigations,serum growth hormone (GH), IGF-1 and IGFBP-3 levels were estimated.Isolated GHD was categorized when there was no evidence of panhypopituirism on biochemical investigations and imaging of pituitary fossa on MRI brain was normal.

All short children with obvious dysmorphology were assessed using the London Dysmorphology Database and POSSUM database. The diagnosis in these disorders was confirmed by a database search after evaluation by 2 senior independent reviewers trained in dysmorphology blinded agreed to each other's diagnosis. Based on the above evaluation all children were classified into various categories of short stature. Syndromic short stature which included Noonan, Turner, Russel Silver, Prader Willi, Williams, Costello and Autoimmune Polyendocrinopathy syndrome apart from rare conditions. The others were categorized as endocrinopathies excluding growth hormone deficiency, Celiac disease, short stature due to chronic systemic disease, skeletal dysplasia,and Idiopathic short stature. Endocrine causes like hypothyroidism and Laron's syndrome (growth hormone insensitivity) and diabetes mellitus (type 1) were also ruled out. Diagnosis of Idiopathic short stature was made after exclusion of all obvious causes of short stature outlined above. Constitutional delay and familial short stature were excluded before proceeding for evaluation of the GH-IGF2 axis. Syndromic children included well-delineated syndromes like RAS/MAPK2 pathway was considered in children who fulfilled the score of dysmorphology.

Growth Hormone estimation was done utilizing a sandwich assay using immunoflurometric method (DRG International, Inc., USA. Sex-steroid priming was done for boys using a single intramuscular injection of testosterone enanthate 100 mg given 3–5 days prior to testing and for girls by oral ethinyloestradiol 100 mg for 3 days before testing. After overnight fasting, oral clonidine (5 mg/kg) was administered. Samples were taken at basal, 30, 60, 90,120 minutes of administration of clonidine or insulin in fasting state. Retesting was done with the pharmacological stimulus. GH value of less than 10 mg/L were considered to be GH deficient IGF 1 and IGFBP3 estimationwas done with morning blood samples (2 mL) obtained from all subjects. Samples were separated by centrifugation and stored at -20°C until analysis. Serum IGF-1 and serum IGFBP-3 levels were measured with commercially available enzyme-linked immunosorbent assay (DRG International, Inc., USA) IGFBP-3 (Oscar India), respectively, in accordance with the manufacturer's recommendations. IGF-1 and IGFBP-3 values were expressed in ng/ml.

Samples of patients with Idiopathic short stature andgrowth hormone deficiency were further subjected for analysis of the polymorphism in the GHR gene. For the genotyping of GHR exon 3 locus,the frequency of GHR transcript variants with retention (GHRfl) or exclusion (GHRd3) of exon 3 was tested by the multiplex PCR assay described by Pantel *et al*., 2000 This was performed with primers G1, G2, and G3 (GenBank accession no. AF155912) with a well defined protocol: initial step of denaturation of 3 min at 95 C, followed by 25 cycles consisting of 30 sec at 95 C, 1 min at 64 C, 1 min at 72 C, followed by an extension period at 72 C for 5 min. Amplification of DNA fragments was analyzed by electrophoresis on a 1.5% agarose gel stained with ethidium bromide. A 935-bp band represented the GHRfl allele, and a 532-bp fragment represented the GHRd3 allele (Fig 1). The expected distribution of genotypes at the GHR exon3 locus was determined by means of Hardy and Weinberg law. Age sex and ethnic matched siblings of children accompanying patients for minor ailments were recruited as controls for IGF-1, IGFBP-3 and GHD3 analysis Data was entered in SPSS version (10.0). Descriptive statistics were applied. Mean and standard deviation for age were computed. Frequency of various causes of short stature (Constitutional delay, Familial short stature, GHD,malnutrition, celiac disease, hypothyroidism, genetic syndromes, chronic diseases) was calculated.

RESULTS

Total of 473 children with amedian age of 3.65 years (Range 2-18 years) were enrolled in this period. Males were twice common than females with an altered ratio suggesting existing

gender bias. History of consanguinity was seen in 10 % of population and 11(3%) children had family history of similarly affected siblings

Demographic profile of children with short stature

The age distribution at entry for short stature tended to show 2 peaks (4-6 years & 10 years). Children with skeletal dysplasia presented as early as 3.5 years whereas the mean age of presentation of children with syndromic association and pathological short stature was 6 years due to their characteristically different phenotype. Children with growth hormone deficiency presented around 6.6 years, whereas the mean age of children presenting with hypothyroidism and growth hormone insensitivity was 6.8 years. Children with celiac disease presented as late as 10 years of age. Demographic profile of the patients is depicted in Table 1.

Table 1. Demographic profile of study population

Variable	N=473
Age (y)	2-18 Years
Age Median (IQR)	3.65 years
Sex M:F	2:1
Height (cms)	118.4±20.5(Mean ± SD)
Mid parental height	158.25 ± 6.9(Mean ± SD)

The mean (±SD) height of all the children enrolled was 118.4± 20.5 cms and the mean (±SD) mid parental height was 158.25±6.9 cms. Children with skeletal dysplasias were most severely stunted and had an average height of 75 cms whereas mean height at presentation in the syndromic group with suspected involvement of the RAS/MAPK2 pathway was 97.5 cms. Children with celiac disease fared best in their height at presentation which was 114 cms.

Etiological Profile of children with Short Stature

A significant number of children with short stature were diagnosed as growth hormone deficient (109/473, 23%). Twenty three percent (107/473) children were classified as idiopathic short stature, where as constitutional and familial short stature were seen in 6% (30/473) and 2% (11/473) children respectively. The non- endocrinal disorders attributing to short stature were celiac disease in 18% (83/473),skeletal dysplasia in 7% (31/473), syndromic association in 12% (58/473) and malnutrition seen in only 2% (10/473) of cases. Amongst children with endocrine disorders, hypothyroidism was found in 8 (40%) children, panhypopituitarism in 2 (10%) children and 10 (50%) had Laron's syndrome. Children with chronic disorders, 10 (72%) were diagnosed with Thalassemia, 3 (21%) had chronic kidney disease and 1 child had renal tubular acidosis. The causes are depicted in Table2.

Profile of children with short stature diagnosed as skeletal dysplasia and syndromicassociation

The most common skeletal dysplasia diagnosed with pathological short stature was Achondroplasia (10/31, 32%) followed by pseudochondroplasia (8/31, 25%). The other skeletal dysplasias diagnosed are depicted in Table 3.

Turner's syndrome (25/58, 43%), RASopathy (Noonan syndrome, Costello, 12/58, 21%) and Down syndrome (13/58, 22%) were most commonly seen syndromes associated with short stature. Two children were diagnosed with Williams's syndrome and one child with PraderWilli syndrome. Other syndromes with short stature are depicted in Table 4.

Table 2. Etiological Profile of children (n=473) presenting as Short Stature

Total short stature	N=473 (%)
Syndromic	58 (12)
Idiopathic	107 (23)
Growth hormone deficient	109 (23)
Protein energy malnutrition	10 (2)
Constitutional	30 (6)
Familial	11 (2)
Endocrine	20 (4)
Hypothyroidism	*8 (40)*
Panhypopituitarism	*2 (10)*
Laron's syndrome	*10 (50)*
Celiac n (%)	83 (18)
Diarrheal	*44 (53)*
Nondiarrheal	*39 (47)*
Chronic diseases	14 (3)
Chronic kidney disease	*3 (21)*
Renal tubular acidosis	*1 (7)*
Thallesemia	*10 (71)*
Skeletal dysplasia	31(7)

Table 3. Profile of children presented with skeletal dysplasia

Total Skeletal dysplasia	N=31
1.Achondroplasia	10
2. Pseudoachondroplasia/Hypochondroplasia	07
3.Desbuquois dysplasia	03
4.Morquios's syndrome	06
5.Spondyloepiphyseal dysplasia	01
6.Cartilage hair hypoplasia	01
7.Atelosteogenesis	01
8.Diastrophic dysplasia	01
9.Metatropic dysplasia	01

Table 4. Profile of children with short stature having syndromic association

Syndromic short stature		N=58
1.	Noonan/Costello syndrome (RASopathy)	12
2.	Down's syndrome	13
3.	William' syndrome	02
4.	Prader Willi syndrome	01
5.	Russell viper syndrome	01
6.	Turner's syndrome	25
7.	Fanconi anemia	01
8.	Microdeletion (18q)	01
9.	Arskog/Shawl scrotum syndrome	01
10.	Autoimmune Polyendocrinopathy (APECED)	01

Biochemical Profile in patients

The IGF1 and IGF BP3 values were analysed in all the groups and compared with the controls. Patients with Growth hormone deficiency (mean (±SD) of IGF1 3.5±2.12 and IGF BP3 2.3±1.5, $p < 0.001$) and Thallesemia (mean (±SD) of IGF1 13.2±6.7 and IGF BP3 3.9±1.9, p=0.01) were found to have statistically significant low values as compared to the other groups.

The Growth Hormone-IGF-1 Axis in Patients other than Growth Hormone Deficiency

The growth hormone deficiency was found in 90% of the Thalassemic patient evaluated. The serum IGF-1 and IGFBP-3 levels were also found to be low in patients with transfusion dependent thalassemia major. Whereas, variable response was found in syndromic patients like Downs, William's nearly all but 1 DS patient demonstrating a blunted response, the rest had a normal response to the GHRH. Amongst patients with RASMAPK2, 25% of the Noonan's shows reduced response towards GHRH.

Distribution of GHRd3 and GHRfl in the population sample

We have evaluated the allele frequencies of GHRd3 and GHRfl, by simple multiplex PCR assay based on the use of three primers: antisense primer G3 located in exon3, and primer set G1 and G2, which brackets both the single LTR element of GHRd3 alleles and the two repeated elements of GHRfl. Under the specific experimental conditions primers G1 and G2 allowed the amplification of GHRd3 alleles only, whereas primers G1 and G3 amplified the GHRfl alleles, thereby allowing the accurate discrimination the three possible genotypes at this locus (i.e homozygous fl/fl, heterozygous fl/d3, homozygous GHRd3/GHRd3). The distribution of genotypes, which is presented in table 5,6 followed the Hardy-Weinberg equilibrium (X^2= 29.2P value 0.00 for GHD and X^2=0.25 p value 0.00 for ISS), with the allele frequencies for GHRfl/fl, GHRfl/GHRd3, GHRd3/d3 60.7%, 19.2% and 20.1% respectively for a growth hormone deficiency and 67.5, 14.5 and 18 for idiopathic short stature.

DISCUSSION

Short stature or reduced growth velocity is a known cause of concern of many parents referred for pediatric consultation. Short stature is known to affect their psychosocial wellbeing with presence of social disengagement like avoiding socializing with friends, teasing or bullying in school, lack of self confidencealong with numerous physical challenges (Johansen *et al.,* 2007; Voss, 2001). There are very few studies published evaluating etiological and biochemical profile of children presenting with short stature. Early identification and treatment of medical disorders like celiac disease, thalassemia, and congenital heart defects, tuberculosis, chronic kidney disease and malnutrition helps in child's well being and normalizing growth. Children with hormonal disorders like hypothyroidism and growth hormone deficiency show marked improvement and growth after hormone replacement (Lee *et al.,* 2009; Ross *et al.,* 2004; Sandberg, 2011; Coste *et al.,* 2012). Our study demonstrated that from 473 children with short stature, median age of presentation of children was 3.65 years with the range 2-18 years. The age distribution at entry tended to show 2 peaks at 4-6 years & 10 years of age. Children with skeletal dysplasia's were referred early at a mean age of 3.5 years due to significant reduction in height for age as compared to their peers and also presence of strikingly evident dysmorphic features. The mean age of presentation of children with syndromic association and pathological short stature was 6 years due to their characteristically different phenotype. This still seems to reflect a significant delay in referral of these children. Children with growth hormone deficiency presented around 6.6 years, whereas the mean age of children presenting with hypothyroidism and growth hormone insensitivity was 6-8 years. This needs to be stressed, as these children are potentially amenable to therapy. Children with celiac disease presented as late as 10 years of age in our study. Late presentation of celiac could be attributed to low index of suspicion among primary care physicians and height being one of the parameters to be affected later in the course of the disease.

Our main etiologic cause of short stature was growth hormone deficiency followed by idiopathic short stature. This was in consonance with (Colaco *et al.,* 1991), he found endocrinal disorders to be the major cause of short stature. (Kaur *et al.,* 2012) also analysed 137 children with short stature and found skeletal dysplasia as the most common cause of short stature followed by Turner's syndrome and endocrinal abnormalities. There are several studies conducted in the past which have shown non endocrinal disorders as the most common cause of short stature in children (Sultan *et al.,* 2008; Shu *et al.,* 2002; Zargar *et al.,* 1998). This difference in observation could be due the referral bias as our centre is a Genetics referral centre therefore cannot extrapolate to the general population. Also since we offer growth hormone testing in house, there were a large proportion of children referred to us for evaluation of this cause after the common causes had been excluded.

Constitutional growth delay (CGD) and familial short stature (FSS) still contribute to a proportion of referred cases constituting 6% and 2% in our population. CGD and FSS have been reported in earlier studies constituting 9%, 16% and 38% (Bhadada *et al.,* 2011; Bhadada *et al.,* 2003; Dutta *et al.,* 2014) published in the past. Over the years, the etiology of short stature has demonstrated a shift from primarily nutritional causes to endocrine, genetic and chromosomal disorders being important causes of pathological short stature. The same finding is observed in our study. This paradigm shift appears to be influenced by improvement in per capita income and increased emphasis on child nutrition. Availability of and recommendations for the use of recombinant Growth hormone therapy has also altered the fulcrum of case ascertainment as medical attention is frequently sought due to the hope that definite treatment may improve the morbidity associated.

Amongst the non endocrinal disorders, celiac disease acted as a major contributor followed by skeletal dysplasia and syndromic association. Malnutrition was seen in only 2% of cases attributing to increased awareness of parents towards child nutrition. Children with chronic disorders, 10 (72%) were diagnosed with Thalassemia, 3 (21%) had chronic kidney disease and 1 child had renal tubular acidosis. We admit that a disproportionate referral was due to a concommitant evaluation of endocrine disorders in children with Thalassemia. Childrenwith celiac disease with atypical presentation (non-diarrhoeal) form also constituted to a major proportion of the group.Celiac disease is emerging as one of the major non endocrinal causes of short stature is markedly evident over the span of last 3 decades due to the widespread availability of diagnostic facilities at various referral centres, increased awareness of the disease and its manifestations among the general population. It is also seen that children on gluten free

diet have reduced levels of insulin like growth factor 1 (IGF1) and poor growth hormone secretion on stimulatory tests (Assiri, 2010). The limitation of our study was that our being a referral centre the profile of children referred could be skewed. Diagnosis of uncommon syndromes was made on the basis of LDDB search only and disorders of the RAS/MAPK2 pathway were elucidated on the basis of a clinical score. They could not be confirmed by investigations as there are limited facilities for targeted panel for this pathway. Another limitation of our study was unavailable follow up of these children to see the ultimate height outcomes achieved in various sub groups. In short children, a polymorphism in the GH receptor (GHR) gene leading to the deletion of exon 3 (d3-GHR) has recently been linked to the growth response to GH therapy (Dos Santos *et al.,* 2004). The deletion of exon 3 results in the loss of one potential glycosylation site and the amino acid substitution A6D at the N-terminal part of the extracellular receptor domain (Pantel *et al.,* 2000). The d3-GHR isoform shows increased receptor activity, probably due to subtle conformational changes in the extracellular domain that facilitate hormone-triggered activation. Some studies in children with GHD, idiopathic short stature, and those born small for gestational age (Jorge *et al.,* 2006; Raz *et al*., 2008; Tauber *et al*., 2007) have found a better response in height velocity to GH therapy in patients with at least one d3-GHR allele than those bearing two wild-type alleles (fl/fl-GHR). Further an attempt to define the subgroup of GH most likely to benefit by the analysis of the GHD3 exon helps in appropriation of resources currently limited to numerous children. Amongst our subgroup of ptients with iolated growth hormone therapy. This might provide a cost effective delineation of a subgroup which is most rewarding from our study.

Conclusion

Most children with short stature are normal variant short stature. But, growth hormone deficiency and celiac disease also contribute significantly. Early diagnosis and treatment can significantly reduce the morbidity. Increase awareness amongst care taker care and early referrals by health givers would significantly improve outcome and ensure better height gain of children.

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