

Readdressing Short Stature in India: The “Long and the Short” of it

Stature is one of the widely used indices of overall health and well-being in children. Short stature (SS) can be defined either on the basis of comparison with the normal population (less than 2 SD or the 3rd centile) or with respect to the genetic potential (derived from parental stature) of a given individual. Deviation from standard height percentiles using calculated height velocity is one of the earliest indicators of short stature, irrespective of etiology. SS evaluation is one of the most comprehensive assessments in endocrinology and entails detailed history, physical examination, and biochemical, hormonal, radiological investigations, and genetic testing when indicated. It is also the clinical situation with multiple dilemmas, bearing in mind that 25% to 90% of children referred for short stature are not actually short, reassurance is the treatment of choice in nearly half the cases, and the limited scope of the use of growth hormone (GH) therapy in idiopathic short stature (ISS), Turner syndrome (TS), and skeletal dysplasias.^[1,2]

SS is broadly divided into normal variant short stature (NVSS) (which includes constitutional delay of growth and puberty (CDGP) and familial short stature (FSS)) or pathological short stature (causes include endocrine, syndromic, or chronic-disease related). However, FSS is increasingly being classified as a pathological variant with the recognition of hitherto undiagnosed genetic conditions such as GH resistance (GHR), collagenopathies, RASopathies, and aggrecan gene mutations.^[3] RASopathies denote developmental syndromes occurring due to germline mutations in the Ras–RAF–MEK–ERK/mitogen-activated protein kinase signaling pathway and include Noonan, Leopard, and the cardio-facio-cutaneous syndromes.^[4] Aggrecan is a proteoglycan constituent of the growth plate cartilage and mutations in it have been found to be the underlying cause in a proportion of patients with FSS.^[5] Current understanding implicates growth plate chondrocytes as one of the central parameters of both normal growth and normal variations of growth at the intraindividual (pubertal growth spurt) and interindividual (varied normal height in the population) levels. However, there is a lack of evidence on the trends in the etiological spectrum of SS across nationwide studies. Dynamicity in the prevalence and patterns of SS is expected, considering the change in nutritional status, recognition of endocrine causes in primary care settings as well as increasing focus on identifying genetic causes of underlying growth hormone deficiency (GHD) and/or hypopituitarism. Furthermore, whether the age of identification and diagnosis of SS is decreasing, suggesting improved surveillance or awareness of this chronic problem, remains unexplored.

Studies reporting the etiology of SS in community or outpatient settings in India were analyzed and stratified on the basis of duration of study and date of publication. There were four studies in the second decade of the twenty-first century, including our unpublished survey in 2191 school children in the community,^[6-8] and two major studies in the first decade.^[9,10] NVSS accounted for the most number of cases of SS. Hypothyroidism was the most common endocrine cause of SS and the second most common cause overall. This evidence was consistent, irrespective of the geographical location (north and south of the country) of the participants. On the other hand, there was a discrepancy in contemporary reports from north India itself, with one study reporting skeletal dysplasia as the most common etiology of SS, followed by ISS and TS in their cohort. The variance, despite a similar time frame and similar geographic location, is intriguing but may be indicative of the settings of the study (genetic referral clinic).^[8]

Nationwide trends revealed a greater preponderance of pathological SS in the first decade of the twenty-first century, which has transitioned to NVSS over the second decade. The earlier predominance of pathological SS was uniform, irrespective of consecutive admissions or referral for SS.^[11] This shift may possibly be due to increased awareness and access to health care, improved trends in nutrition as well as early diagnosis and management of chronic diseases and endocrinological conditions which are implicated in SS. The overall prevalence of hypopituitarism including GHD has seemingly halved with time, from 22.6% in the twentieth century to under 10% in more recent studies, but there are/is no similar evidence available for Turner's syndrome.^[9,10] Pathological SS is expected to be more discernible owing to greater deviations of height from the normal or clinical features associated with the primary condition (systemic or syndromic disease or hormonal cause). Hence, improved knowledge about the problem may be one of the contributors to this transition. Inherent differences between community-based and clinic-based assessments are expected owing to referral bias, as children with greater severity of SS and pathologic causes are more likely to present in hospital settings. Etiological differences may also mirror the socio-economic and literacy status of the community as malnutrition and chronic diseases are more likely to affect children from the lower strata of society. This impact of nutrition on stature is well-evidenced by the fact that the earlier reported entity of GHR, of which poor nutritional status is a cause, is virtually absent from recent studies.^[10,12] Interestingly, the prevalence of SS has

remained virtually unchanged over the past two decades in India (varying from 2.8% to 3.7%). Furthermore, the variability in growth charts between different studies has not posed a significant effect on the overall prevalence of SS. Despite this reassuring data suggesting a transition to a predominantly physiological etiology of SS, the higher age at presentation in some reports is a cause of concern.^[7]

The authors performed the largest community-based study in the country to generate normative reference range intervals for IGF-1. In this study, stature was assessed among other anthropometric parameters in healthy school-going children in the community between the ages of 5 and 18 years. The final enrolment was 2191 children, with 47.92% (n = 1050) girls. We found a 2.42% (n = 53) prevalence of short stature, as defined by height < 3rd centile on the revised Indian Academy of Pediatrics (IAP) growth charts,^[13] and the mean age of diagnosis of SS was 11.8 ± 4.5 years. Based on gender, the prevalence of SS was 2.54% (n = 28) in boys at a mean age of 10.5 ± 4.4 years and 2.38% (n = 25) in girls at a mean age of 13.3 ± 4.2 years. In this SS cohort, low weight (60.7%) and normal weight (39.3%) was noted in boys, but in girls, the major proportion (72%) was constituted by normal-weight individuals. Prepubertal status was present in 58.6% of the boys and 20.8% of the girls. On analyzing the causes, CDGP was present in 28% of the boys irrespective of the chart used to compute bone age (Greulich Pyle (GP) or Tanner Whitehouse (TW) charts), but the prevalence was 12% in girls when using GP charts and 16% when using TW charts. Familial short stature (FSS) was present in a higher proportion in boys (25%) than in girls with SS (20%) when using the IAP criteria and 14.2% and 8% in boys and girls, respectively, when using the National Institute of Nutrition (NIN) criteria.^[14] Among pathological causes of SS, hypothyroidism was more common in girls (16%) than boys (10.7%). The overall prevalence of celiac disease in the study (defined by IgA anti-TTG) was 1.55% (n = 34), but there were no cases among children with SS. This was most likely attributable to the early pick-up/detection as they were identified in the presymptomatic phase. It may also be due to the fact that the prevalence of the coeliac disease is higher in hospital settings as children with gastrointestinal symptoms or anemia are more likely to seek consultation than in community settings where asymptomatic individuals are much more likely. Its controversial to comment so early as the IGF-1 values mismatch yet to be sorted out soon

Our study provides interesting insights into the transition in the profile and etiology of SS, which is possibly reminiscent of an upsurge in economy, education, and access to basic health care in the country. Though the prevalence of SS has remained reasonably stable, it is the metamorphosis in the etiological profile that deserves attention. The gender difference between the age of SS in the community is also intriguing, with girls getting diagnosed at a more advanced chronological age than boys, probably reflecting the social fabric in the community. Prior studies conducted in hospital settings from the north reported a relative preponderance of celiac disease, also

presenting with SS as a monosymptomatic presentation. The current report of almost similar overall prevalence of celiac disease, but none of them having SS probably points towards early detection or asymptomatic seropositivity, thereby averting long-term complications such as SS in these children. Among endocrine conditions, the prevalence of hypothyroidism has remained unchanged with time. Community-based data such as ours are the true indicators of the burden of the insidious problem of SS and have furnished contemporary evidence on the prevalence and etiological spectrum of SS.

Stature being a continuous accrual and cumulative phenomenon is usually diagnosed later than sooner. One of the early clues for the diagnosis of short stature is a derailment of height velocity, which can be easily obtained from regular anthropometric evaluations in school records. Encouraging and educating schools, institutions, vaccine centers, and primary health care providers about the importance of at least annual anthropometry is another area that may aid in timely diagnosis and referral to tertiary care centers. Furthermore, in children with chronic disease of any etiology, referral to the endocrinologist for further evaluation and ruling out concurrent treatable hormone deficiency such as hypothyroidism, growth hormone deficiency or resistance, can improve final adult height. National policies to target screening for childhood stunting in identified high-risk areas can also be employed.

Financial support and sponsorship

The study received funding from the Endocrine Society of India (ESI) and Society of Endocrine Health Care for Elderly Adolescents and Children (SEHEAC).

Conflicts of interest

There are no conflicts of interest.

KV Raviteja*, **Liza Das***, **Bhanu Malhotra**, **Raman K. Marwaha***, **Pinaki Dutta**

Department of Endocrinology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, ¹Department of Endocrinology, International Life Sciences Institute, New Delhi, India

* These authors are equally contributed to this work

Address for correspondence:

Prof. Pinaki Dutta,
1012, Nehru Extension Block, Department of Endocrinology, PGIMER,
Chandigarh - 160 012, India.
E-mail: pinaki_dutta@hotmail.com

REFERENCES

1. Grote FK, Oostdijk W, Keizer-Schrama SM, Van Dommelen P, Van Buuren S, Dekker FW, *et al.* The diagnostic work up of growth failure in secondary health care; an evaluation of consensus guidelines. *BMC Pediatr* 2008;8:1-9.
2. Song KC, Jin SL, Kwon AR, Chae HW, Ahn JM, Kim DH, *et al.* Etiologies and characteristics of children with chief complaint of short stature. *Ann Pediatr Endocrinol Metab* 2015;20:34-9.
3. Lin YJ, Cheng CF, Wang CH, Liang WM, Tang CH, Tsai LP, *et al.* Genetic architecture associated with familial short stature. *J Clin Endocrinol Metab* 2020;105:1801-13.
4. Gualtieri A, Kyprianou N, Gregory LC, Vignola ML, Nicholson JG, Tan R, *et al.* Activating mutations in BRAF disrupt the hypothalamo-pituitary axis leading to hypopituitarism in mice and

- humans. *Nat Commun* 2021;12:1-8. doi: 10.1038/s41467-021-21712-4.
5. Nilsson O, Guo MH, Dunbar N, Popovic J, Flynn D, Jacobsen C, *et al.* Short stature, accelerated bone maturation, and early growth cessation due to heterozygous aggrecan mutations. *J Clin Endocrinol Metab* 2014;99:E1510-8.
 6. Velayutham K, Selvan SS, Jeyabalaji RV, Balaji S. Prevalence and etiological profile of short stature among school children in a South Indian population. *Indian J Endocrinol Metab* 2017;21:820-2.
 7. Dutta D, Biswas K, Arora R, Barman N, Bhushan D, Bhakhri BK. Profile and height outcomes of children with short stature in north India: An experience from a tertiary care centre. *Indian J Pediatr* 2014;81:205-6.
 8. Kaur A, Phadke SR. Analysis of short stature cases referred for genetic evaluation. *Indian J Pediatr* 2012;79:1597-600.
 9. Bhadada SK, Bhansali A, RaviKumar P, Kochhar R, Nain CK, Dutta P, *et al.* Changing scenario in aetiological profile of short stature in India-growing importance of celiac disease: A study from tertiary care centre. *Indian J Pediatr* 2011;78:41-4.
 10. Zargar AH, Laway BA, Masoodi SR, Wani AI, Salahuddin M. An aetiological profile of short stature in the Indian subcontinent. *J Paediatr Child Health* 1998;34:571-6.
 11. Colaco P, Desai M, Choksi CS. Short stature in Indian children: The extent of the problem. *Indian J Pediatr* 1991;58:57-8.
 12. Desai M, Colaco P, Sanghavi KP, Choksi CS, Vaz FE, Ambedkar MC. Profile of growth hormone deficiency in Bombay. *Indian J Pediatr* 1991;58:33-42.
 13. Khadilkar VV, Khadilkar AV. Revised Indian academy of pediatrics 2015 growth charts for height, weight and body mass index for 5–18-year-old Indian children. *Indian J Endocrinol Metab* 2015;19:470-6.
 14. Mamidi RS, Kulkarni B, Singh A. Secular trends in height in different states of India in relation to socioeconomic characteristics and dietary intakes. *Food Nutr Bull* 2011;32:23-34.

Submitted: 12-Jul-2021

Published: 12-Jan-2022

Accepted: 20-Oct-2021

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online

Quick Response Code:



Website:

www.ijem.in

DOI:

10.4103/ijem.ijem_306_21

How to cite this article: Raviteja KV, Das L, Malhotra B, Marwaha RK, Dutta P. Readdressing short stature in India: The “long and the short” of it. *Indian J Endocr Metab* 2021;25:389-91.

© 2022 Indian Journal of Endocrinology and Metabolism | Published by Wolters Kluwer - Medknow