Growth Hormone Stimulation: An Achilles Heel in the Evaluation of Short Stature

Height has always fascinated the human psychology, and given a choice, every human being wants to be taller than others. Hence, many parents are concerned about the height of their child and consult the endocrinologists for short stature. Short stature is defined as a height below –2 SD of given population and is seen in 2.3% of the population. Clinical and auxological features exclude causes like genetic, bone disorders, systemic diseases, and constitutional delay. Common endocrine disorders like hypothyroidism and Cushing's syndrome are also obvious clinically. Alterations in GH-IGF-1 (growth hormone—insulin like growth factor) axis remain an important treatable cause of short stature. Diseases of GH-IGF-1 axis consist of deficiency and insensitivity of these hormones including acid labile subunit (ALS) deficiency. Deficiency or resistance of IGF-1 system leads to prenatal growth failure whereas growth hormone deficiency (GHD) or insensitivity causes postnatal growth retardation. GHD is an area of intense research and discussion in the last century. It is important to identify GHD, because the condition is completely reversible with the administration of the recombinant GH therapy. GHD affects the psychosocial and developmental aspects of the child and GH replacement has a key role in the optimizing the health in later life. Hence, proper evaluation and interpretation of assessment of GH-IGF-1 axis becomes essential for every endocrinologist.

After discovery of GH from the human pituitary gland by Li and Papkoff in 1956 and its biochemical structure in 1966, the radioimmunoassay for GH estimation was developed by Roos and Thorell in 1968. It was also established by 1968 that a GH level >10 ng/ml was a normal response following insulin induced hypoglycemia.[1] Initially, GH was derived from the human or bovine pituitary sources and was scarcely available, thereby limiting the treatment to children with severe GHD and stringent cutoff values (<3–5 ng/ml). On 19th April 1985, distribution of pituitary GH was suspended due to reports of death of four young adults in the United States with slow viral (prion-mediated) Creuzfeldt Jacob Disease (CJD), who had been treated with GH and use of human pituitary GH rapidly ceased. In the same year (1985), Genentech, brought to market the genetically engineered recombinant GH (rGH). This unlimited commercial supply of rGH led to an ever-growing list of FDA-approved indications for GH use in GHD and non-GHD children with short stature and for additional indications in adults.[2,3] This has revived interest in the GH assessment methods to help in further increasing the indications for the GH therapy.

The diagnosis of GHD is suspected by the auxological characteristics but is required to be confirmed by the GH provocation tests. The imaging and genetic testing have a limited role in the evaluation of GHD, as it is essential to demonstrate failed GH stimulation for the diagnosis. The IGF-1 is a relatively stable compound in the serum without significant variation, making it an attractive alternate option for the diagnosis of GHD.[4] However, the IGF-1 assay is costlier, not widely available and is highly specific, but not sensitive in the diagnosis of GHD. However, a combination of low GH and IGF-1 value below 2 SD of reference ranges standardized for age and sex for the population, which has been recently published for Indian population,[5] strongly suggest GHD.

GH secretion is regulated by multiple physiologic factors like nutritional status, exercise, sleep; hormones and neurotransmitters like GHRH, insulin induced hypoglycemia, amino acid infusion (arginine), catecholamines and dopamine. GH secretion is pulsatile and serum concentrations are low during the daytime. Hence, rather than a single basal GH estimation, provocative tests are required for GH status and assessment. Immunoradiometric assays (IRMAs) are commonly used to determine the level of GH. GHD is defined as a serum peak GH concentration <10 ng/ml on provocation with a combination of at least two separate stimulation tests. GH stimulation tests are performed with various stimuli, such as insulin, L-dopa, arginine, clonidine, glucagon, and growth hormone releasing hormone (GHRH). The test using insulin as a stimulus is classically recommended, but this test has potential risks such as hypoglycemia. In addition, several other investigative methods are in use as analysis of spontaneously secreted 24 h GH estimation, measurements of GH dependent factors (IGF-I, IGFBP-3, ALS), and the biochemical response to exogenous GH (e.g., IGF generation).

GH stimulation tests have many issues concerning their variability, reproducibility, assay methodology, and limited evidence-based cutoff values.[6] There are several limitations of interpretation of data from these tests where there is lack of standardization and lack of normative data even today. The physicians interpreting the GH stimulation results have to tread a narrow path and caution to avoid any potential pitfalls. The lack of diagnosis results in a missed opportunity to treat a completely reversible condition, whereas the overdiagnosis results in subjecting to unnecessary injectable GH replacement for many months or years to a child with substantial financial implications.

Insulin induced hypoglycemia test is considered gold standard and been in use for more half century. It is little cumbersome test and require continuous presence of physician for 2 h. Once clinical and biochemical hypoglycemia is evident, this can be aborted by oral feed and sample can be collected at half hour

intervals for 2 h. Though safe in experienced hand,[7,8] the same is not routinely done in pediatric practice for the possible deleterious complications.[9] Other tests are either not used due to unavailability of testing agents or ambiguity in cutoff values.

The clonidine stimulation test (CST) is the most commonly used provocative test to rule out GHD in the clinical practice. Most of the GH stimulation tests are cumbersome, with repeated collection of the samples. A single GH sample estimation is charged close to thousand rupees and multiple sampling involves a major expenditure in the resource constrained situations. In this regard, Thakur *et al*.; and colleagues have studied, whether a single stimulated GH value could have sufficient sensitivity and specificity to diagnose GHD.[10] Their findings did not support a single sample with necessary sensitivity and specificity, but a combination of 60- and 90-min samples could be the ideal option. The authors have not studied the evaluation of GHD in adults, which is a different subject altogether with a different set of stimulation tests and cutoffs.

Though the study by Thakur *et al*.; is limited by the retrospective design, small sample size and lack of comparison with the gold standard method, it has certain implications for the diagnosis of GHD in our country. First, there is a definite role of discarding the GH sample collection at 30 min after administration of clonidine. None of the previous studies have also shown any significant role of the same in the evaluation of GHD. Second, the baseline GH sample has a limited value in the evaluation of short stature. A random GH measurement may be useful in the diagnosis of GHD in neonates only as reported by Binder and colleagues, with a sensitivity and specificity of 100% and 98%, respectively.[11] Third, the sampling may not be relevant after 90 min as most of the stimulation would have already happened prior to that. Though the authors have not evaluated GH samples beyond 90 min, previous reports suggest that there is no significant additional case detection rate with the inclusion of 120-min sample in the GH stimulation protocol.[12] Lastly, the cutoff was based on the GH estimated using the chemiluminescence assay. Many researchers and institutions still use the IRMA for the estimation of GH and it is important to identify the assay specific cutoff values in the diagnosis of GHD.[13]

The future guidelines concerning the evaluation of short stature should address the issues with the GH stimulation tests and come out with definite protocols. We suggest that the GH stimulation tests should be divided into two tier systems based on the higher sensitivity (tier 1) and higher specificity (tier 2). The GH stimulation protocol should involve doing one each of tier 1 and tier 2 tests prior to the final confirmation of the GHD.

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