'Growth hormone deficiency' or rather 'short stature unresponsive to stimulation tests'?

Gianluca Tornese

Short stature is one of the most common causes of parental concern and referral to paediatric endocrinologists.¹ An appropriate diagnosis of short stature should be performed as early as possible and personalised treatment should be started promptly. Until recent years, the dominant conceptual frame for understanding short stature has been centred on the growth hormone (GH)-insulin-like growth factor 1 (IGF-1) axis; however, we now know that the growth plate could be the primary site of growth disturbances in contrast to the classic endocrine hormonal pathways, even in the absence of evident skeletal dysplasia.²

GH deficiency (GHD) is rare in childhood, with an estimated prevalence between 1 in 3500 and 1 in 10000 children, also depending on cut-off levels used at stimulation tests used for the diagnosis. As a matter of fact, these provocative tests of GH secretion using pharmacological stimuli are required—together with auxological criteria—to diagnose GHD, but the lack of any 'gold standard' test has led to the development of somewhat arbitrary cut-off levels that varied over time and among countries.³

Apart from cut-off levels, several issues have been raised regarding the reliability of stimulation tests:

- ▶ the problems with variability and reproducibility of the tests that are non-physiologic³;
- ▶ the scarce correlation between IGF-1 levels and a low response to stimulation tests⁴;
- ▶ the existence of a consistent part (13%–36%) of GHD poor responders to GH treatment⁵;
- ▶ the high rate (up to 81%) of normal re-testing at the end of growth (questioning a false-positive diagnosis at the beginning)⁶;
- ▶ the presence of pathological stimulation tests in conditions where a problem in GH secretion is not

supposed to be the cause (such as Turner syndrome⁷ or Noonan syndrome⁸ or *SHOX* deficiency⁹;

- ▶ the normal stimulation tests found in children with genetically confirmed isolated GHD due to mutations in the *GH-1* gene.^{10 11}

Recently, it has been calculated that the probability of a true positive result for a stimulation test in a child with short stature is about 1 in 36 cases.¹²

For all these reasons, we can assume that the test is practical only to distinguish to whom we can prescribe somatropin (recombinant human GH (rhGH)) treatment. Nevertheless, we know the clinical and cost-effectiveness of somatropin treatment (compared with treatment strategies without somatropin) for children with GHD and other conditions resulting in growth failure.¹³

I, therefore, suggest that until we do not have a proper 'gold standard' in biochemical diagnosis of GHD, we should limit the use of 'GHD' diagnosis only for:

- ▶ genetic diagnosis of isolated GHD (*GH1*, *GHRHR* and *RNPC3*);
- ▶ multiple pituitary combined deficiencies;
- ▶ presence of abnormalities within the hypothalamus-pituitary axis at MRI;
- ▶ acquired damage (brain trauma, central nervous system infection, tumours of the hypothalamus or pituitary, radiation therapy, infiltrative diseases).

In all other cases of short children with inadequate response at GH stimulation tests, since the suspicion of GHD is high but—for the reported reasons—we cannot identify these children any further as having a GHD, I suggest using another classification, such as 'Short stature Unresponsive to Stimulation tests' (SUS).

This name change, which merely defines what we are facing, would avoid labelling children with a condition we are not entirely sure they have, with all the clinical sequelae that an individual with GHD may expect over the years (eg, evolution of subsequent multiple pituitary hormone deficiencies, altered body composition, decreased bone mineral density).

In any case, rhGH treatment should continue to be offered to children with SUS.¹³ Since the first-year response is a critical determinant of the total treatment height outcome in growth disorders besides GHD,¹⁴ a re-evaluation of results after 1 year of treatment could also be helpful in SUS to decide whether to discontinue the therapy. On the other hand, a good response to rhGH treatment is non-specific and should not be used to define the aetiology of short stature,¹² as it can be found in several conditions, sometimes misdiagnosed at first as having GHD (eg, *IHH*, *SHOX*, *PTPN11*).¹⁵

Further research is needed to understand whether short children with SUS respond differently to somatropin treatment than other categories (eg, idiopathic short stature, small for gestational age).

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ORCID iD
Gianluca Tornese <http://orcid.org/0000-0002-4395-3915>

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Institute for maternal and child health IRCCS 'Burlo Garofolo', Trieste, Italy

Correspondence to Dr Gianluca Tornese, IRCCS Materno Infantile Burlo Garofolo, Trieste 34137, Italy; gianluca.tornese@burlo.trieste.it

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