Review of: "Diagnosis of GH Deficiency Without GH Stimulation Tests"

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Potential competing interests: GB has received honoraria for lectures from Ferring, Ipsen, Lilly, Merck Serono, Novo Nordisk, Pfizer and Sandoz as well as for membership in advisory boards from Ferring, Ipsen, Merck Serono, Novo Nordisk, Pfizer and Sandoz. In addition, GB has received a research grant from Novo Nordisk.

To test or not to test - a comment on “Diagnosis of GH deficiency without GH stimulation tests” by Anastasia Ibba and Sandro Loche

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In contrast to the overwhelming literature discussing the validity of GH stimulation tests for the diagnosis of GH deficiency, this brief review paper by Ibba and Loche attempts to define situations and patients that do not require GH stimulation testing for the diagnosis and treatment of GHD.

Health insurance companies and other medical authorities adhere to the dogma that there is no diagnosis of pediatric GHD without GH stimulation testing (1). In fact, this has led to an inflation of GH stimulation testing, even in conditions where these tests are dangerous and lack validated thresholds. Another false assumption resulting from this dogma is that any child with two positive GH stimulation tests is GH deficient and requires rhGH treatment, clearly overestimating the validity of these tests.

Technical limitations of GH stimulation tests

The main argument against GH stimulation tests in the specific group of newborns and infants is technical limitations. A second argument is the high risk of hypoglycemia during fasting for the test. And a third is the questionable validity of traditional GH cut-offs in these very young children.

Ibba and Loche rightly point out the exceptional endocrine condition in the first week of life, characterized by physiological hypersomatropism, which is caused by extensive intrinsic stimulation of GH secretion (2). Here, basal GH concentration provides valid information about GH secretory capacity, even when blood is drawn during troughs of pulsatility. This valuable information is included in every newborn screening card and, if archived, can be retrieved weeks or months later to establish the diagnosis of severe neonatal GHD based on the established cut-off (3). However, when archived newborn screening cards are used, the measured GH content must be corrected for the age of the screening card because GH immunoreactivity decreases over time, even when the cards are stored at 6 degrees Celsius (4). In a recent paper, this correction was not made for cards stored at room temperature, which led to erroneous results (5)

In contrast, the GH concentration of the so-called critical sample taken during hypoglycemia, also mentioned by Ibba and Loche, has been questioned, although many textbooks still refer to it. Retrospective studies suggest that naturally occurring hypoglycemia is not a reliable stimulus for GH, leading to incorrect clinical interpretations (6,7).

No additional evidence with GH stimulation tests

Another argument against GH stimulation testing is the lack of additional evidence provided by the tests in situations where GH deficiency has already been confirmed on other grounds. In general, a medical test should only be used when its result substantially alters the likelihood of disease. Once the diagnosis is confirmed, even a positive test with high validity does not contribute to the diagnosis (8).

In infancy, this evidence is seen outside of GH stimulation tests by Ibba and Loche in the presence of growth failure and low IGFBP-3 associated with multiple pituitary hormone deficiencies or the classical triad of pituitary malformation including ectopia of the neurohypophysis according to recent guidelines (9).

In children, growth failure in combination with congenital or acquired hypothalamic-pituitary defects and one additional pituitary hormone deficiency is considered by the authors sufficient to confirm the diagnosis of GHD without stimulation tests. In the same vein, Clement et al. proposed prediction rules for the diagnosis of GHD without GH testing (10). These rules are based on retrospective analysis of 770 children with suspected GHD, all of whom underwent GH testing and 218 of whom had brain MRI. After artificial intelligence modelling, Clement et al. proposed that GH testing is not required in children that meet the auxological criteria defined in the Growth Hormone Research Society's 2000 summary statement (11) and one of three additional criteria.

The criteria are (a) a specific pituitary malformation on cMRI or (b) ≥ 2 additional anterior pituitary deficiencies. In the presence of only one additional deficiency of the anterior pituitary (c) a complex set of five additional criteria including cranial irradiation or neonatal hypoglycemia is listed by the authors of which one has to be present for the diagnosis of GHD. The first two rules (a and b) fit the argument of the presence of sufficient evidence without endocrine testing. The third rule (c) is more disputable because evidence is weaker. Overall, application of these rules by Clement et al. (10) would dramatically increase the number of cMRI examinations in short children, which today are usually performed only in children with positive GH stimulation tests.

Exclusion of GHD without measuring stimulated GH

An important aspect of GH stimulation testing can be read between the lines of Ibba and Loche´s article, but is important. We should focus more on auxology, on the change in height SDS or height velocity. We should not rush GH testing, but wait and see for 12 months if there is no additional evidence of GHD. We can all increase the pretest probability by rigorously selecting the children tested. This will lead to a reduction in the number of tests and, more importantly, fewer negative and false-positive tests.

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