Review of: "Clinical Characteristics of Short-Stature Patients With Collagen Gene Mutation and the Therapeutic Response to rhGH"

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We really appreciated the article published by Chen *et al.*[1], describing so meticulously possible clinical features of patients affected by collagen-enconding genes mutations causing short stature.

It is increasingly evident how the world of short stature, as we have known it until a few years ago, is undergoing a real revolution mainly due to the recent exponential advancement in genetic technology: starting from the first descriptions of possible genes influencing adult height in 2010[2], we currently know multiple genes (e.g.*ACAN, IHH, NPR2...*), most of whom inherited in an autosomal dominant manner, potentially accounting for many of the historically so-called Familiar Short Stature (FSS) cases. These findings have therefore enabled us to shift attention from the classical GH-IGF1 axis to the growth plate as the main site of growth disturbances[3].

The article allows us to carry out two types of reflections: the first of a diagnostic nature, the second of a therapeutic nature.

First, in the study were enrolled children who possessed short stature but also skeletal abnormalities, in some cases very phenotypically expressed. However, from literature it is known how many of these conditions affecting the growth plate may be genetically present but clinically manifesting exclusively with an isolated short stature, in the absence of noticeable bone dysplasia[3]. We believe that, due to the enormous potential benefit that can derive and the increasing accessibility, the time has come to adopt a genetic screening in the context of all pediatric short stature. Specifically, we would consider appropriate to add FSS among the factors that increase the possibility of a monogenic cause of short stature, in addition to the criteria suggested by Dauber in 2014[4][5]. The benefit of such genetic screening does not only concern a diagnostic aspect but also the possible role of recombinant human GH (rhGH) therapy in such conditions. And this is where the second reflection comes in: the study enrolled patients in whom other known causes of short stature have been excluded, including growth hormone deficiency (GHD). However, 9 patients with mutations regarding collagen genes received rhGH with a benefit on their growth, consistent with what has already been demonstrated in a cohort of patients affected by these mutations[6], but more generally consistently with what already highlighted in other growth plate-related syndromic short stature (e.g. *ACAN* [7], *IHH*[8]). Consequently, we believe that it is clearly needed to overcome the anachronistic concept of GHD, for several reasons: firstly, for the rarity in pediatrics of primary GHD (prevalence estimated between 1 in 3,500 and 1 in 10,000, with many established controversies related to the different cut-offs used and arbitrarily decided[9]), probably much rarer than the emerging genetic defects related to the growth plate. Secondly, and perhaps even more important, because it has convincingly been proven that a normal GH secretion pattern on

stimulus tests does not necessarily rule out a condition of short stature that could equally benefit from rhGH therapy, as already happens in specific conditions, such as Noonan syndrome[10] or SHOX deficiency[11].

In conclusion, in our opinion the path that is emerging is a path in which short stature will be soon divided into two categories: forms responsive to therapy with rhGH (based no longer on stimulus tests but on the results of genetic screening) and those not responsive. The term GHD, moreover, should be reserved only to specific conditions: 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). While waiting to understand what the fate of stimulus tests will be in the near future, in the meantime for all other short stature with an inadequate response at GH stimulation we propose to adopt the term “Short stature Unresponsive to Stimulation tests” (SUS)[12]. Treatment with rhGH should continue to be offered to patients presenting SUS: however, they should ideally receive at the same time genetic testing, in order to create a potential correlation between genetic mutation and response or non-response to therapy. It is evident that further studies are needed to understand how to best manage short stature, which represents one of the main reasons for concern for patients and parents and one of the most common clinical conditions that the pediatric endocrinologist has to face in his daily routine[13].

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