Significance of IGF-I generation test in diagnosing primary and non-primary IGF-I deficiency – clinical considerations

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Introduction

In current classifications, primary insulin-like growth factor-I (IGF-I) deficiency (IGFD) is considered to be a synonymous of growth hormone (GH) insensitivity, while secondary IGF-I deficiency is equivalent to GH deficiency (GHD) [1]. According to previous recommendations, the diagnosis of severe primary IGFD in a patient with normal GH peak in stimulation tests (stimGH) required to perform IGF-I generation test (IGF-GT) with exogenous GH administration and to demonstrate IGF-I increase <15.0 ng/ml during this test [2].

Recently the significance of IGF-GT has been questioned by some researchers [3-5] who have suggested that children with short stature, normal stimGH and severe IGFD should be diagnosed as ones with primary IGFD and treated with mecasermin with no necessity to perform IGF-GT in them. However, other authors still consider IGF-GT as necessary to differentiate primary IGFD from other diseases [6,7].

In our previous study [8], a high variability of stimGH in the tests repeated twice in the same patient with IGFD within a few months interval was observed, despite the relative stability of simultaneously measured IGF-I concentrations. Thus, the same patient could be diagnosed once with primary IGFD and once with secondary IGFD. In some of such patients with *de facto* unclear diagnosis, GH therapy was administered after exclusion primary IGFD by documenting significant IGF-I increase in IGF-GT.

Objectives

The aim of the study was an evaluation of the significance and clinical utility of IGF-GT in children with normal stimGH and IGFD, with respect to the efficacy of growth-promoting therapies.

Methods

Analysis comprised 110 children with height SDS (hSDS) <-2.0, normal stimGH (>10.0 ng/ml) and IGF-I SDS for age and sex <-1.0.

In all the patients IGF-GT was performed during 7 days with daily GH dose 0.033 mg/kg. At least doubling the initial IGF-I concentration, leading to its normalization, was considered to be evidence of GH sensitivity.

In most cases, stimGH in repeated tests was <10.0 ng/ml, thus allowing the diagnosis of GHD and these children were subjected to GH therapy.

Results

In the subgroup of 24 children with hSDS <-3.0 and IGF-I SDS <-2.5, who could be diagnosed with severe primary IGFD, according to the criteria proposed by Savage [3], the increase of IGF-I ranged from 25 to 357 ng/ml. So, none of them fulfilled the standard criteria of severe primary IGFD, including IGF-I increase IGF-GT <15.0 ng/ml (see Figure 1).

Only one patient from this group, with the lowest IGF-I increase in IGF-GT (from 129 to 154, *i.e.* 25 ng/ml), was treated with mecasermin up to final height (FH) with hSDS increase from -3.69 to -1.67.

Other 10 of these 24 ones, in whom stimGH in repeated tests was <10.0 ng/ml, were treated with GH up to FH, with hSDS increase from -3.60±0.41 to -1.26±0.60 (see Table 1).

Without performing IGF-GT, these patients would be diagnosed with primary IGFD and could be subjected only to mecasermin therapy, despite the fact that they turned out to be GH-sensitive.

In 3 other patients with hSDS < 3.0 and IGF-I SDS <-1.5, increasing in IGF-GT by 23-39 ng/ml, currently treated with mecasermin, height velocity (HV) increased also significantly (at least doubled).

In other 60 children with hSDS<-2.0 and IGF-I SDS <-1.0, increasing in IGF-GT by 51-514 ng/ml, subjected to GH therapy, HV during 1st year of treatment increased from 3.7±0.9 to 8.7±2.6 cm/year (see Figure 2); 55 out of them completed GH therapy with hSDS increase from -3.01±0.67 to -1.37±0.87.

Figure 1

Table 1

Pat. N°	sex	stim GH [ng/ml]	IGF-GT start [ng/ml]	IGF-GT start IGF-I SDS	IGF-GT 7 days [ng/ml]	IGF-GT 7 days IGF-I SDS	IGF-I increase [ng/ml]	height SDS start	final height SDS	height SDS increase	pre-GH HV [cm/yr]	1st yr HV [cm/yr]
1	f	13.6	58	-2.83	219	0.52	220	-3.01	-0.55	2.46	4.1	9.4
2	m	12.8	83	-3.04	440	0.90	443	-3.64	-2.50	1.14	3.9	8.5
3	m	40.0	77	-2.58	190	-0.48	192	-3.66	-2.00	1.66	4.0	9.7
4	m	11.6	51	-4.90	204	-1.56	206	-4.04	-1.83	2.20	3.5	7.0
5	m	13.0	181	-2.65	510	0,,05	511	-3.42	-1.25	2.17	5.4	9.3
6	m	12.8	89	-3.58	258	-0.99	259	-3.24	-1.00	2.24	4.1	8.6
7	m	10.1	133	-2.59	293	-0,68	294	-3.26	-0.92	2.34	2.0	7.1
8	m	12.2	49	-5.68	176	-2.47	177	-4.52	-0.90	3.62	4.4	14.8
9	m	11.7	28	-5.00	89	-2.26	90	-3.73	-0.87	2.87	3.0	4.5
10	m	10.0	126	-3.31	242	-1.67	243	-3.49	-0.73	2.76	3.8	11.5

Figure 2

Conclusions

The diagnosis of primary IGFD should be confirmed by the poor response to GH administration in IGF-GT, as some children with severe IGFD benefit during GH therapy despite normal stimGH. This speaks strongly against the diagnosis of GH insensitivity (*i.e.* primary IGFD) in them. It seems that such patients should also not be diagnosed with idiopathic short stature, as in fact they have IGFD that responds well to exogenous GH administration. We would like to propose a diagnosis of non-primary IGFD for such cases. The specific criteria of this diagnosis should be defined after conducting further studies on this issue, while our results are – to some extent – preliminary.

It seems also reasonable to increase cut-off level of basal IGF-I and of IGF-I increase in IGF-GT for qualifying children to mecasermin therapy.
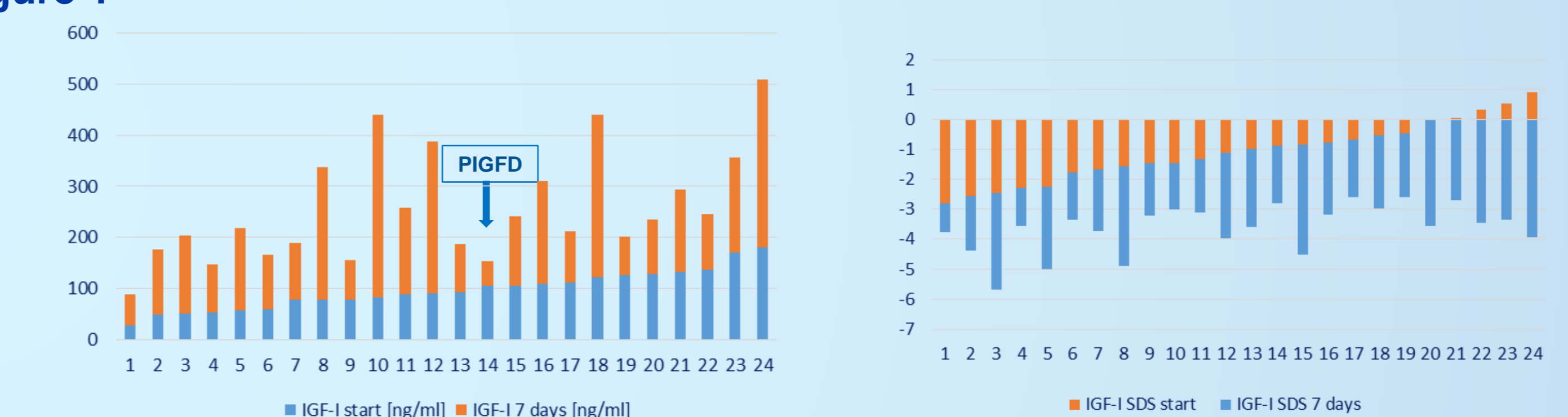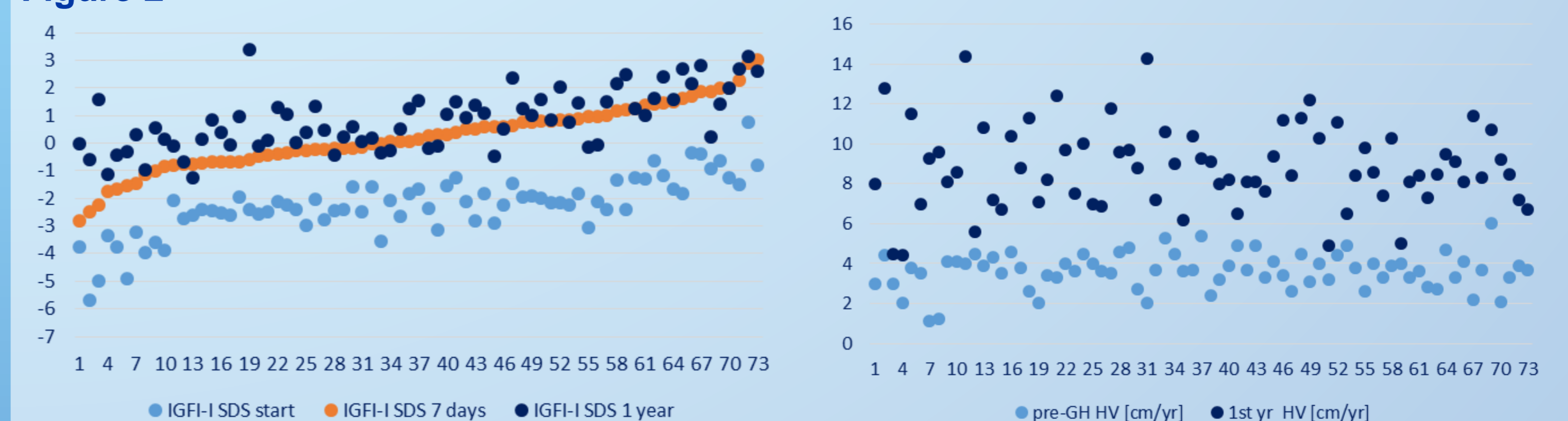
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