

Insulin like growth factor 1 in healthy Algerian children

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Abstract:- The Insulin like Growth Factors (IGFs = essentially IGF1 and IGF2) play a key role in many physiological processes. Therefore, they are involved in numerous pathologies including stunting. A comparative study on the determination of IGF1 was made between a group of healthy normal sized Algerian children (n = 266) and a group of Algerian children with a deficit in growth hormone (n = 107) and another Western healthy normal size children group (Rosenfeld Series). The results are as follows: Before 04 years, there is a large overlap of results between IGF1 of deficient children in GH and Algerian control subjects. After 04 years, the IGF1 rates are significantly reduced for different age groups of GH deficient patients compared to Algerian control group. The values found in the Algerian IGF1 control group were significantly lower than those of western healthy children. This parameter should be interpreted carefully when exploring a stature in Algeria and must be integrated into all clinical and laboratory patient elements. It is necessary to establish Algerian standards for the analysis of this assay. The introduction of the IGFBP3 is not yet available in our country, seems to be more interesting given the poor nutritional status.

Keywords: Delay stature, GH deficiency, IGF1, IGFBP3, Nutrition

I. Introduction

The IGF1 secretion, particularly in the liver, is closely dependent on growth hormone as well as nutritional factors. Blood levels of IGF1 increases gradually from birth to the end of puberty, then declines to stabilize in adulthood and decline again with senescence¹. Many anabolic effects of the growth hormone are mediated by IGF1 a mitogen polypeptide with a structural similarities with insulin². The dosing of IGF1 is thus an indicator of GH secretion in the deficit as in hypersécrétion. Plasma concentration of IGF1 will vary depending nutritional status, metabolic condition and pathologies present. In acromegaly, IGF1 is elevated significantly. For the diagnosis of GH deficiencies of the child, the interpretation of IGF1 assays is more complex because it is difficult to assign a lower limit of normal in children before the age of 5-6 years old³. Large studies show that if more than 80% of children considered as bearers of GH deficiency, according to the criteria provided by GH stimulation tests, have low IGF1. The results will be further reduced if there is a dietary deficiency^{4,5}.

The aim of this work is to study the IGF1 variations in Algerian healthy children and to compare results obtained with those of a group of European healthy children.

Population And Methodology:

This is an analytical comparative study of 266 children of normal size and free from any condition that may sound on GH/IGF1 axis, were taken for the determination of IGF1 (G1). The samples were grouped according to age and pubertal status based on Tanner staging⁶. The hormonal assay was performed by radioimmunoassay (cis). The results were compared with those of 107 Algerian patients with growth hormone deficiency (GHD) and those of healthy children Rosenfield western group (G2)⁷. The diagnosis of GHD was established on a beam of clinical and paraclinical arguments⁸

- The anamnestic data and clinical characteristics of GH failure.
- The low rate of IGF1 and the negative response to both pharmacological tests of GH stimulation (insulin tolerance test and glucagon)
- The radiological assessments (X ray of the left wrist, magnetic résonance imaging of the hypothalamic pituitary région)

II. Results

Before the age of 04 years there is an overlap of IGF1 results between GHD children (n = 5) and IGF1 child witnesses (G1) of the same age.

After 04 years IGF1 rates are significantly reduced for the different age groups of GHD subjects compared to the control group (G1) whatever the pubertal stage. Only one patient, who started puberty at the

time of study, in which the evaluation of IGF1 was possible, had a normal rate of pubertal age (Table I). IGF1 values found in the G1 group consisting of healthy children as controls in our study are significantly lower than those of European normal sized healthy children with the exception of the age group (8-10 years) where IGF1 values from our witnesses are not different from those of healthy children (Table II).

Table I: IGF1 results of GHD patients, comparison with G1 controls

GHD Average ± SD ng/ml Borders médian (numbers)	Control group (G1) Average ± SD ng/ml Borders median (numbers)	P
30,13 ± 12,502 (21,29 - 38,97) (2)	41,966 ± 20,834 14,39 - 95,58 40,38 (73)	-
31,873 ± 21,354 (24,95) (3)	76,437 ± 20,879 (15,430 - 137,860) 77,545 (50)	-
35,37 ± 19,73 (15,69 - 80) 28,195 (22)	127,170 ± 27,91 (89,38 - 195,85) 120,41 (27)	< 4.10 ⁻⁴
23,944 ± 14,75 (12 - 61,61) 19 (9)	144,030 ± 31,490 (102,740 - 244,72) 133 ,89 (30)	< 10 ⁻⁶
37,006 ± 37,16 (15 - 226,6 21,95 (49)	165,875 ±29,887 (125,930 - 264,38) 156,990 (37)	< 10 ⁻⁶
81,668 ± 58,8 (17,53 - 183,49) 78,29 (10)	200,740 ± 50,772 (110,39 - 299,830) 197,490 (29)	< 10 ⁻⁶
53,01 (1) (0)	244,791 ± 58,558 (118,620 - 310,260) 259,140 (19) 338,849 ± 90,044 (178,830 - 571,310) 346,470 (15)	-
59,503 ± 48,827 (14,23 - 151,910) 31,03 (11)	319,422 ± 100,9 (202,46 - 495,98) 302,08 (15)	< 10 ⁻⁶

Table II: I GFI Results group G2, comparison with an international reference

Pubertal stage/(Age) [1]	Algerians children of normal size(G2) Average ng/ml (nb)	Western children normal sizeAverage ng/ml (nb) (G2) [7]	P
TANNER I (< 2)	41,966 ± 20,834 (n = 73)	104,5 ± 44,14 (n = 20) WESTERN CHILDREN NORMAL SIZE AVERAGE ng / ml (nb) (G2)	< 0,025
TANNER I (2 - 4)	76,437 ± 20,87 (n = 50)	213,25 ± 152,8 (n = 24)	< 0,026
TANNER I (4 - 8)	127,170 ± 27 ,91 (n = 27)	260,71 ± 135,83 (n = 35)	< 0,005
TANNER I (8 - 10)	144,030 ± 31,490 (n = 30)	130,46 ± 136,56 (n = 26)	Not significant
TANNER II (12 - 14)	200,746 ± 50,772 (n = 37)	488,34 ± 361,31 (n = 64)	< 0,03
TANNER > II	296,430 ± 85,91 (n = 49)	490 ± 140 (n = 28)	< 0,002

III. Discussion

Growth hormone ensures growth of skeletal and cells via growth factors (IGFs or somatomedins). They are synthesized primarily by the liver under the control of main hGH but also insulin and nutrients. These hormones are transported in the blood by specific binding proteins (BPs). The most important is the BP3. Their role is to ensure the setting aside of IGFS in the blood and distribution to target cells^{3,2}.

The measurement of IGF1 which is the main factor postnatal growth assesses the somatotrophic function.^{9,10} The values found should be interpreted according to age, pubertal stage and nutritional status. In normal subjects and properly fed, the rate is progressively increasing during childhood and reaches a maximum during the pubertal growth spurt². Several factors are known to cause variation in the levels of GH and IGF1 in the circulation. They include an individual's genetic make-up, the time of day, age, sex, exercise status, stress levels, nutrition level, body mass index (BMI), disease state, race, estrogen status, and xenobiotic intake¹¹ Patients with impaired growth hormone have very low levels. In children with nutritional deficiency, chronic liver disease and in particular in those with idiopathic short stature, the IGF1 average rate is moderately reduced.^{3,10}

By comparing the results of IGF1 in G1 control in our study to those of Rosenfeld (G2)⁷ we find that IGF1 values of Algerian witnesses are lower than those of Western normal children. Indeed, the mean values of IGF1 were significantly lowered in healthy control subjects in all Algeria pubertal stages except at the prepubescent stage (8-10 years) where there is no significant difference. It should also be noted that for very young children under the age of 05 years a significant difference ($p < 0.025$) was noted.

These results can be explained by the ethnic differences between the two populations but also by the nutritional status of the Algerian child which still insufficient since IGF1 is highly dependent on nutrition. Indeed, IGF1 is an important mediator of balanced growth in most body tissues and may be an important link between nutrition and growth. In addition to the endocrine mechanism of action, this peptide acts by autocrine and paracrine mechanisms. Nutrient intakes and nutritional status are key regulators of plasma concentrations of IGF1. The modulation of the IGF1 secretion as a function of the nutritional intake involves changes in response to GH at its receptor and its post-receptor^{12,13}. A fasting of 10 days in healthy volunteers leads in a 70% decrease in IGF1 plasma concentrations.¹⁴ The decrease in plasma IGF-I concentration is correlated to the decrease in excretion of urea suggesting that the extent of IGF1 in plasma is a good indicator of the nitrogen loss.

These low values of serum IGF1, during the fasting in man, are not due to a decreased secretion of GH, because it is observed, in parallel, an increase of the peak frequency of GH, an increase of the total cumulative concentration of 24 hours and an increase of the peaks amplitude.¹⁵ The disparity between GH and IGF1 suggests that individuals subjected to fasting have a resistance to GH hypothesis supported by the observation that GH administration in healthy volunteers subjected to a three-day fasting leads to an increase IGF-I in serum equal only to twice the normal, when she reached ten times the normal when GH is administered to GH-deficient subjects but subject to a normal diet.¹⁶ Serum IGF1 is decreased in patients with protein-energy malnutrition but serum GH is often high in malnourished patients, suggesting that those have a resistance to GH.^{12,17,18}

Dietary restrictions also lead to lower insulin which may be involved in reducing IGF1 plasma. A high value of GH with a low value of IGF1 and insulin may promote lipolysis and constitute an adaptive mechanism increasing the availability of fatty acids for peripheral tissues.¹⁹ The regulation of IGF1 with insulin concentrations is probably modified by changes in the liver of GH binding.²⁰ Insulin also potentiates the stimulatory effect of GH and the amino acids on the IGF1 generation.²¹ A regulation by the nutrients of the synthesis of IGF1 may also be exerted at the translational level, since differences were observed between the serum IGF1 values and the concentrations of IGF1 mRNA liver.^{22,23} In addition to the liver, it has been observed, during deficiency regimes, decreased levels of IGF1 mRNA in most other organs (lung, kidney, muscle, stomach, brain, testes).²⁴

From these findings we can say that it is particularly necessary in our country, to integrate the results of IGF1 to all clinical and laboratory data during the exploration of growth retardation in a child. This is all the more important that IGF1 normal children with constitutional and / or family short stature values would certainly further reduced if they were to measure, and a large overlap exists between the most likely rate of these children and those of genuine GHD.

It would be more appropriate to consider the IGFBP3 in the exploration of the small size in Algeria. Unfortunately, this assay is not yet available, so it has not been assessed in this study. IGFBP 3 is particularly interesting in our opinion, that this parameter is normal in healthy children with short stature, and unlike IGF1, does not need an extraction at the dosage.^{3,4,25} These normal values are comparatively higher during infancy and are perfectly discriminative.^{3,2,26}

Thus, it is a very important parameter for assessing the somatotrophic axis especially in very young children. However, it should also be noted that as IGF1, it is not enough only to certainty diagnose. It may be normal in irradiated patients^{27,28} and in genuine GHD.^{29,30,31}

IV. Conclusion

The values of IGF1 found in the Algerian healthy subjects are significantly lower than those found in the healthy children in the west. So this parameter must be interpreted carefully when investigating a delay of growth in Algerian and must take into account the biological and clinical context of the patient. It is necessary to establish Algerian IGF1 standards. The introduction of IGFBP3 not yet available, would be more interesting in our context.

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