

# MORPHO-FUNCTIONAL RE-ESTABLISHMENT OF CRANIO-FACIAL GROWTH DISORDERS IN PITUITARY DWARFISM BY RHGH THERAPY

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## Abstract

The present study evaluates the cranio-facial growth disorders in a series of patients suffering from pituitary dwarfism, as a result of the therapy with recombinant human growth hormone (rhGH). Included in the study were 15 children diagnosed with pituitary dwarfism in the Endocrinology Clinics of the "Sf. Spiridon" Hospital of Iasi, subjected to a treatment with rhGH for 2 years. After the application of the therapy, the parameters of general physical development were followed and the dental orthopantomography and profile cephalometry were analyzed. The results obtained confirm a general physical growth of about 1.3 cm/month in the first year of treatment, followed by values around 1.1 cm/month in the second year. Cranio-facial development was improved by the increase of both mandibular vertical branch and facial height. At the level of the dental arches, one could observe improved sagittal and transversal relations at molar level, as well as a regulating tendency of dental eruption. The therapy with rhGH is thus influent at cranio-facial level, favourizing the development of maxillaries, regulation of dental eruption and the aesthetic aspects.

**Keywords:** *craniofacial skeleton, growth hormone deficiency, growth hormone replacement therapy.*

## INTRODUCTION

The different complexity of the cranio-facial manifestations in pituitary dwarfism requires therapeutical solutions capable of correcting not only the disfunctional potential (even if non-validating), but also the aesthetic prejudices, whose importance is increasingly justified.

The diagnosis of the cranio-facial modifications should synthesize an ample action, based on a minute clinical investigation within which these modifications – analyzed in detail – should permit the elaboration of an investigation program favourizing certification, detailing and control of the evolution within a correction therapeutical program.

The differences noticed in the relative increase of the various cranio-facial components have been acknowledged for quite a long time. One of the first investigators to quantify relative facial growth was Hellman, who described the length and depth of the face as uniform along time; at regional level, he measured relative length, relative width and inferior depth. Hellman's cross-sectional comparisons indicated that, even starting with very young ages, facial width may attain maturity more rapidly than facial depth which, in its turn, tends to be more mature than facial depth [1].

In 1979, Baugan *et al.* introduced three types of distinct growth processes, including a cranial pattern for cranium and cranium basis, a facial pattern for the maxillary and the mandible, and a general pattern for the long bones of the body. The cranial basis was characterized as having the lowest relative increase and the least intense pubertary increase, the facial pattern being enlarged with about 1.5-2% per year, while stature grew with 3.5% each year. Four years later, Buschang *et al.* demonstrated that growth of the cranio-facial complex actually represents a mathematical integral over the neural and general curves of Scammon [2]. Buschang *et al.* introduced the notion of gradient of maturity of craniofacial growth (CFGMG), covering the area from head's height up to the anterior cranial basis. Even if the cranio-facial compounds of girls are considered more mature than those of boys, the gradient of variation among sizes does not depend on sex [1,2].

As a result of the general epigenetic effects, GH assures an excellent test for such a

hypothesis. GH has been recognized as a major factor in controlling somatic growth and maturation, its effects depending on the duration of the treatment. However, the impact of GH deficiency or that of its therapeutic supplementation upon the cranio-facial complex has not been thoroughly analyzed with regard to the CFGMG pattern [1,3].

## MATERIALS AND METHOD

The study was performed on a group of 15 children (8 boys and 7 girls) from the region of Moldova, diagnosed with pituitary dwarfism in the Endocrinology Clinics of the "Sf. Spiridon" University Hospital of Iași, and treated with rhGH for 2 years.

Selection of the pituitary dwarfism cases was based on the inclusion criteria recommended by the National Program of treatment with growth hormone, as follows:

- severe cases, showing a deficit exceeding 3DS and which, usually, respond to not very high rhGH doses;
- presumed receptivity of the patient to the treatment;
- evaluation of a bone age of maximum 11 years;
- evidencing of the somatic growth deficit by means of specific provocative tests (the test to arginine, the test to induced hypoglycemia, the test of stimulation with clonidine), subordinated to the principle according to which two concordant tests bear the significance of an inclusion criterion (or of a significant test and of an IGF1 value below the average ones - *i.e.* lower than ½ of them).

The exclusion criteria considered included:

- confirmation of a benign or malignant tumour (including the thyroidian nodule, leukemias and craniopharyngioma);
- bone age older than 11 years, correlated with the occurrence of the secondary sexual features;
- absence of response to the treatment (a growth ratio below 5 cm per year);

- the impossibility of assuring a prothetic ratio;
- QI > 70.

The norms of therapeutical posology refer to an equivalent initial dose of 0.1 UI/kgc/week, with the appreciation of a satisfaction response at a growth ratio of 1 cm/month. For a growth ratio below 0.5 cm/month, double doses have been administered, attainment of a dose > 0.2 UI/kgc/week requiring the identification of the interference factors.

The Genotropin (KabiPharm, 16 UI/f) and Norditropin (Novo-Nordisk) preparations have been employed. The administration schemes were different, with the exception of the 6 days/week one.

Selection, out of the total number of treated cases, of only 15 children, is caused by the scarce available documentation, restricted to the therapeutical start of the cranio-facial evaluations. Also selected were some cases which involved comparable therapeutical intervals (2 years). The children were examined clinically, generally and stomatologically, according to the study patterns, dental orthopantomography and profile cephalometry (figure 1).

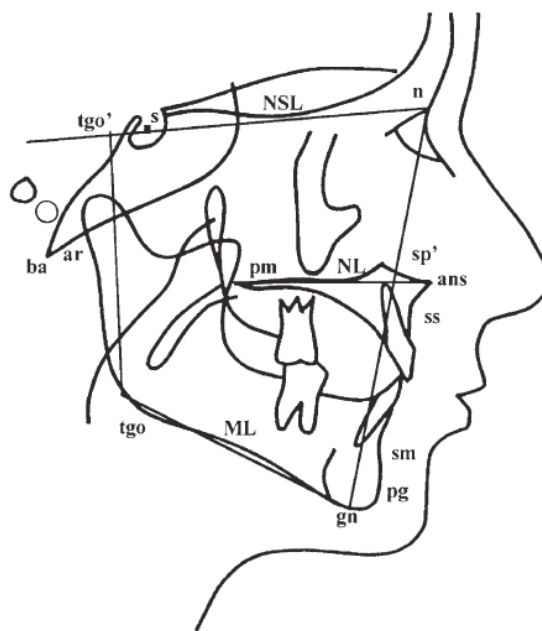
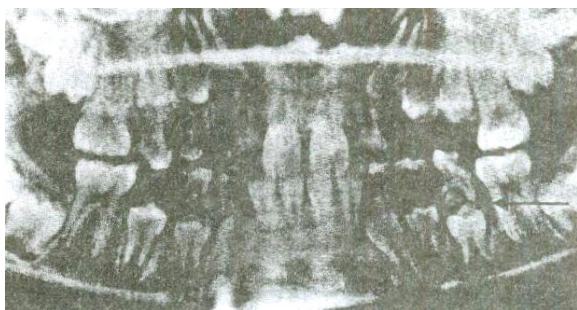


Fig. 1: Landmarks and reference lines used for linear and angular measurements on the profile cephalogram

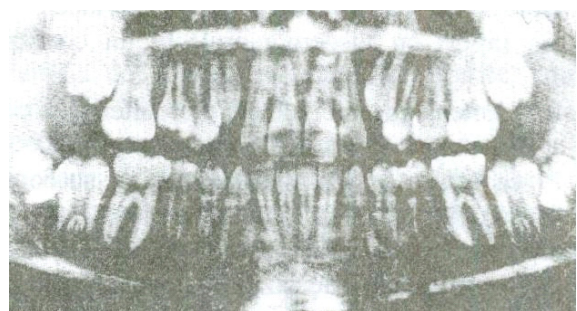
## RESULTS

The general physical development following the treatment with rhGH registered a stature growth of approximately 1.3 cm/month in the first year and of 1.1 cm/month, respectively, in the second year of treatment. Analysis of the profile teleradiographies after 2 years of treatment evidenced improvement of the linear and angular values, comparatively with the standard values, as a function of age, manifested especially by the growth of the horizontal and vertical branches of the mandible, by a minimum growth of the dimensions of the clivus - which cause anterior facial rotation.

The measurements taken at the level of the patterns of study showed an obvious melioration of the sagittal relations at molar level, while the deficit - both the sagittal and the transversal one - is not wholly recovered at the level of the dento-alveolar arches (with an average recovery of approx. 2-3 mm). The orthopantomographies show an accelerated rhythm of dental eruption, so that, after the treatment, the dental age is correlated with the chronological one (figure 2).



*Prior to the treatment with rhGH*



*2 years after the treatment with rhGH*

**Fig. 2: The RC case - Orthopantomographies taken prior to and after the treatment with rhGH**

## DISCUSSION

Cranio-maxillo-facial development in pituitary dwarfism is harmoniously correlated with the hypostature development, the patients generally showing a smaller cephalic brain pan, with a tendency towards brachicephalia. The facies is ovoidal, with the features of a mesoprosopone, with tendency towards euryprosopic face. Mention should be made of an uneven development of the facial zones, both vertically and transversally, while the weakly developed facial massive acquires the "doll aspect", most frequently put into evidence by an "in future" pigmentation of the cheek bones, with an area of oro-nasal paleness. The face is delicate, gracile, these patients preserving a specific childish aspect until reaching adolescence. Later on, the teguments of the face get soon wrinkled, the facies having an aspect of precocious oldness (of the infanto-senescent type). The eyes are expressive, with hypotelorism, oblique, small and round. The nasal pyramid is weakly developed, with small and round nostrils. The mentoniere region is small, dull, with mandibular retrognathism. The profile is convex, with the labial part normal or stressed. The hypoplastic larynx will determine a high-pitched voice [4].

By the insufficient bone development, in general, and facial massive bones, especially, the oral cavity is small, with hypoplastic dental arches and micrognathism, elements induced by the insufficiency of the pituitary growth hormone. This bone structure of the maxillaries will cause dento-alveolar disharmonies, dental malpositions, included teeth. As to the volume, the teeth may be either reduced or normal in size. Apart from the volume anomalies, mention should be also made, in pituitary dwarfism, of anomalies in number, position and structure. Also possible is the dental eruption delayed, on the average, with 3 and even 5 years, and preservation, on the arch, of the temporary teeth up to the adolescent years. Affection of the marginal periodontium is precocious and sometimes severe and, besides the local irritation caused by the oral hygiene, the periodontal inflammation may be also determined by the higher presence of alkaline phosphatases in the gingival mucous membrane [5].

Reports upon the dentition and facial structure in children with deficit of GH (hypopituitarism) have been initiated in the 30'ies and 40'ies. Based on singular cases, they described the delayed dental and facial development. In time, extended analyses demonstrated delays in the dental, facial and cranial base development [5,6].

It was observed that delayed dental development is always less pronounced than that of stature or of the bone age. In a group of 25 patients with GH deficit, Sinikka Pirinen [7] asserted that the deficit of dental development is progressive, varying among 1-6 standard deviations (SD). Dentition appears as harmoniously delayed, so that all components taken into study for dental development (resorption of decidual teeth, formation of permanent teeth and change of dentition) evoke the same delay degrees.

The GH begins to influence the linear growth almost from the 9th month. However, few papers have been devoted to the eruption of decidual teeth in children with deficit of GH. Anamnesticly, an either normal or slight time delay is appreciated.

The observations made on Lewis rats with deficit of GH evidence a small population of odontogenous cells with a reduced number of mitoses.

The children with deficit of GH present a disparity in their neuro- and viscerocranial development (neurocranium with a significant development comparatively with the viscerocranium) at an IQ over the one corresponding to age. Cephalometric studies showed low dimensions of the anterior and posterior zones of the cranium base.

Analyzing 21 cases of either isolated or combined hypophysary deficit, Sinikka Pirinen [7] demonstrated the low sizes of the cranial base and the reduced mandibular posterior height in patients with GH deficit, comparatively with healthy subjects of the same stature from a control group. Within the same group, in a significant number of cases, a comparatively higher height of the face (N-ANS) was also evidenced.

In a study proposed as a master thesis at the University of Michigan, elaborated in 1992, Krista A. Richey communicates the results of the therapeutical effects of GH upon the dento-alveolar development in children with idiopathic hypostature, starting from the suggestion of the

Genentech Joint Group Study, according to which 50% of the ill ones would respond to the human recombinant growth hormone. From this perspective, the author evaluated teeth sizes, the modifications in the sizes of the dental arches and of the dento-alveolar disharmonies along a 5 year-treatment with human recombinant growth hormone on 31 children with idiopathic hypostature, on applying hypopituitarism as a pattern for the approach and analysis of the dental parameters. Negligible differences are recorded between the sizes of arch evaluated pre-therapeutically and immediately after initiation of the treatment and, again, insignificant differences among the latter ones and those re-evaluated one year after the initiation of the treatment with recombinant growth hormone. In spite of the statistically-significant trend, estimated for the relative sizes of the arch during prolonged treatment, the therapeutical effects of the long-term administration are viewed as speculative [8,9].

The dento-alveolar disharmonies of the subjects with hypostature, measured by the occlusal index, are slightly increased during the investigation interval, while the influence of the human recombinant growth hormone upon the modifications of the dento-alveolar unbalance remain uncertain.

## CONCLUSIONS

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The results of the rhGH therapy in pituitary dwarfism confirmed the improvement of the facial traits, materialized in anterior facial rotation and accelerated rhythm of dental eruption, thus counterbalancing the cranio-facial growth disorders, all of them contributing to achieving a really important aesthetic effect.

The restricted number of cases and the control interval during the treatment with growth hormones, added to the different ages of the subjects included in the study in the beginning of the treatment, with which the receptivity to growth hormones is undoubtedly correlated, do not permit drawing of quantifiable conclusions. In the subjects here under investigation, our observations have mainly outlined the main tendencies to be developed and confirmed in future researches.

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