Endocrine regulation of craniofacial growth

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Pirinen S. Endocrine regulation of craniofacial growth. Acta Odontol Scand 1995;53:179–185. Oslo. ISSN 0001–6357.

This paper presents an updated review of the role of endocrine factors in craniofacial and dental development. Some unpublished results of the author's own studies are presented. Longitudinal growth studies have shown the similarity of facial and somatic growth rates, whereas dental development has been found to be independent. The increased therapeutic use of the growth hormone (GH) has focused attention on the dental and craniofacial effects of GH. Whereas delayed and advanced cranial base and facial growth is obvious in conditions with either lack or excess of GH, the effect of GH on the dentition is less clear. Thyroid hormones seem to be necessary for the eruptive movement of teeth. Sex steroids clearly have an effect on facial and cranial base growth and are also odontogenic, but the effects have not been much studied. The growth-inhibiting effect of corticosteroids is explained partly by the reduced response of cartilage cells to insulin-like growth factor-1. Experimentally, the effect is also seen in the condylar cartilage, but clinical studies have not been published. In tooth eruption an accelerating effect has been noted in experimental animals. The role of androgenic hormones in mandibular growth stimulation is discussed.
☐ *Glucocorticoids; growth hormone; human; sex steroids; thyroid hormones*

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Generally, it can be assumed that facial growth and general somatic growth are under the same endocrine control. This has been demonstrated in longitudinal studies comparing facial growth rates with those of somatic growth (1–3). Inside the craniofacial system, however, other growth mechanisms modify the timing and result of growth. Neural, lymphoid, and dental growth and the growth of upper airways follow their own course within the craniofacial bones, complicating the study of growth in the craniofacial area.

Endocrine regulation of growth has been studied by observing patients with endocrine disorders, analyzing samples from growing healthy children, and with animal experiments. Molecular biology techniques have opened new perspectives for this research and contributed significantly to the present understanding of growth regulation.

Growth hormone

Growth hormone (GH) is a peptide hormone secreted by the somatotropic cells in the anterior lobe of the pituitary gland. Human growth hormone (hGH) differs from that of all other species. GH secretion is pulsatile, and the secretory bursts occur especially at early hours of sleep and throughout the night (4). The genes of the GH family are assigned to chromosome 17q23–q24 (5). The biologic actions of GH are mediated by its binding to a specific receptor located on the cells of target tissues. The GH receptor gene has also been characterized (6). GH has no specific target organ. It is an anabolic hormone to which every organ system responds. However, it has a profound effect on cartilage growth. Many of its effects on bone and linear growth are believed to be mediated by insulin-like growth factors (IGFs) (7). The IGF-1 gene is located in chromosome 10 and is produced in the liver but also locally in tissues. Recently Ohlsson et al. (8) confirmed that GH is a primary and IGF-1 a secondary stimulatory effector in cartilage growth and maturation. GH is the main regulator of childhood and adolescent growth. Small children secrete less GH than tall ones (9). The GH pulse amplitude is increased in growth spurts. Plasma IGF-1 concentrations increase simultaneously.

Since 1985 hGH has been biosynthesized (rhGH) and, although very expensive, is available for the treatment of various growth disorders.

Reports on the dentition and facial structure of children who were GH-deficient (hypopituitary) started to appear in the dental literature in the 1930s and 1940s (10, 11). These reports, based on single cases, described delayed dental and facial development. Later, larger samples were analyzed, and delayed dental, facial, and cranial base development was demonstrated (12–14). Dental delay is always less pronounced than delay in height or bone age. In a group of 25 patients with growth hormone deficiency (GHD) we showed that the lag in dental development is progressive and varies between −1 SD and −6 SD (SD of dental age) (15). The dentition seems to be harmoniously delayed, so that all studied components of dental development (deciduous tooth resorption, permanent tooth formation, and eruptive movement) display the same degree

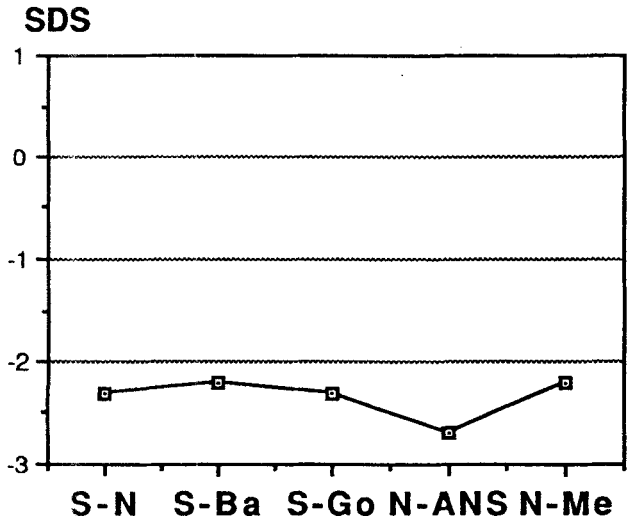

Fig. 1. Mean craniofacial pattern profile of 13 untreated patients with isolated or combined growth hormone deficiency. Mean age, 9.8 years. Age- and sex-specific means and standard deviations used in calculation of the standard deviation scores (SDS) by Bhatia & Leighton (60).

of retardation. GH starts to influence linear growth from about 9 months of age (16). Very little, therefore, is known about deciduous tooth eruption in GHD children. On the basis of our anamnestic findings, it appears to follow a normal or a slightly delayed timing. It is not yet clear whether treatment with GH influences dental development (15, 17, 18), but the results point towards a slight accelerating effect during the first years of treatment. The crown and root lengths are reduced in the hypopituitary dwarf mouse (19, 20). In the Snell mouse (19) all anterior pituitary hormones are lacking. The Lewis GHD dwarf rat displayed smaller populations of odontogenic cells and less mitoses in these cells (21). This experimental animal has very low GH production, whereas its other anterior pituitary hormone levels are normal.

Children with GHD are described as having a big skull and babyish face, which contrasts strongly with their intelligence, which is average for age. They are progressively shorter than their peers and often have a rich subcutaneous fat layer (16). Cephalometric studies have demonstrated small size of anterior and posterior cranial bases and small mandibular dimensions (13, 22). Our own analysis (23) of 21 patients with isolated or combined pituitary deficiency demonstrated small cranial base dimensions, small posterior facial height, and small posterior mandibular height, even when GHD patients were compared with healthy controls of the same height. In our group of 13 untreated patients (Fig. 1) with pituitary deficiency, the relatively smallest dimension in age-matched comparison was upper face height (N-ANS).

Excessive GH secretion leads to gigantism in the young and to acromegaly in adults. An intermediate form of patients, tall acromegalics, is also recognized. GH hypersecretion is usually caused by a pituitary adenoma. We have described the craniofacial condition of two female patients (heights, 190 cm and 205 cm) with gigantism due to an excess of GH (23). Anterior facial heights were relatively the largest cephalometric dimensions (+6.8 and +3.3 SD), followed by posterior facial heights (+3.7 and +4.9 SD). Posterior cranial bases were long, but anterior cranial bases were of normal size. The faces of these female patients were broad, and the zygomatic arches pronounced. Cervical vertebrae were excessively high. Both had relatively normal dental occlusions.

Acromegaly is also rare but more common than gigantism. The serum IGF-1 levels of these patients are very high; the mean value of IGF-1 is reported to be tenfold higher than in normal adults (24). In this condition the hands, feet, and face grow characteristically at adult age. Mandibular growth is gradual and often noted by the dentist when crossbite has developed. The calvarium, hands, and feet grow by bone apposition. The skin and subcutaneous tissue thickens, reflecting the effect of GH in the connective tissue. The tongue grows, and general visceral overgrowth has been documented. Cartilaginous tissues enlarge, ribs thicken, and costochondral cartilage has been shown to be hypertrophic (25). Hypertrophic articular cartilage and the growth of chondrocytes in the articular cartilage may give rise to acromegalic arthropathy (26). It can be assumed that mandibular growth in acromegaly results from both appositional growth and hypertrophic changes in the condylar cartilage.

The treatment of different groups of patients with recombinant human growth hormone (rhGH) will in time give more evidence on dental and craniofacial growth in these patients, and orthodontists should therefore follow closely the results of these treatment studies. It will take some time before the final effect of GH treatment on craniofacial growth can be evaluated. A recent article, however, mentions acromegaloid features as one of the side effects of hGH treatment (27).

Thyroid hormones

Thyroid hormones (TH) lack a specific target organ; they affect every organ and system and every biologic process. Thyroid disorders are common, and their effects on craniofacial and dental structures are widely described in the literature. In prenatal hypothyroidism linear growth at birth is normal, but the development of bone and teeth is retarded (28). Later, enamel defects are seen in prenatally developed teeth. After birth hypothyroidism (HT) disturbs normal growth, resulting in growth retardation or complete cessation of growth in athyroidism. The development and growth of the central

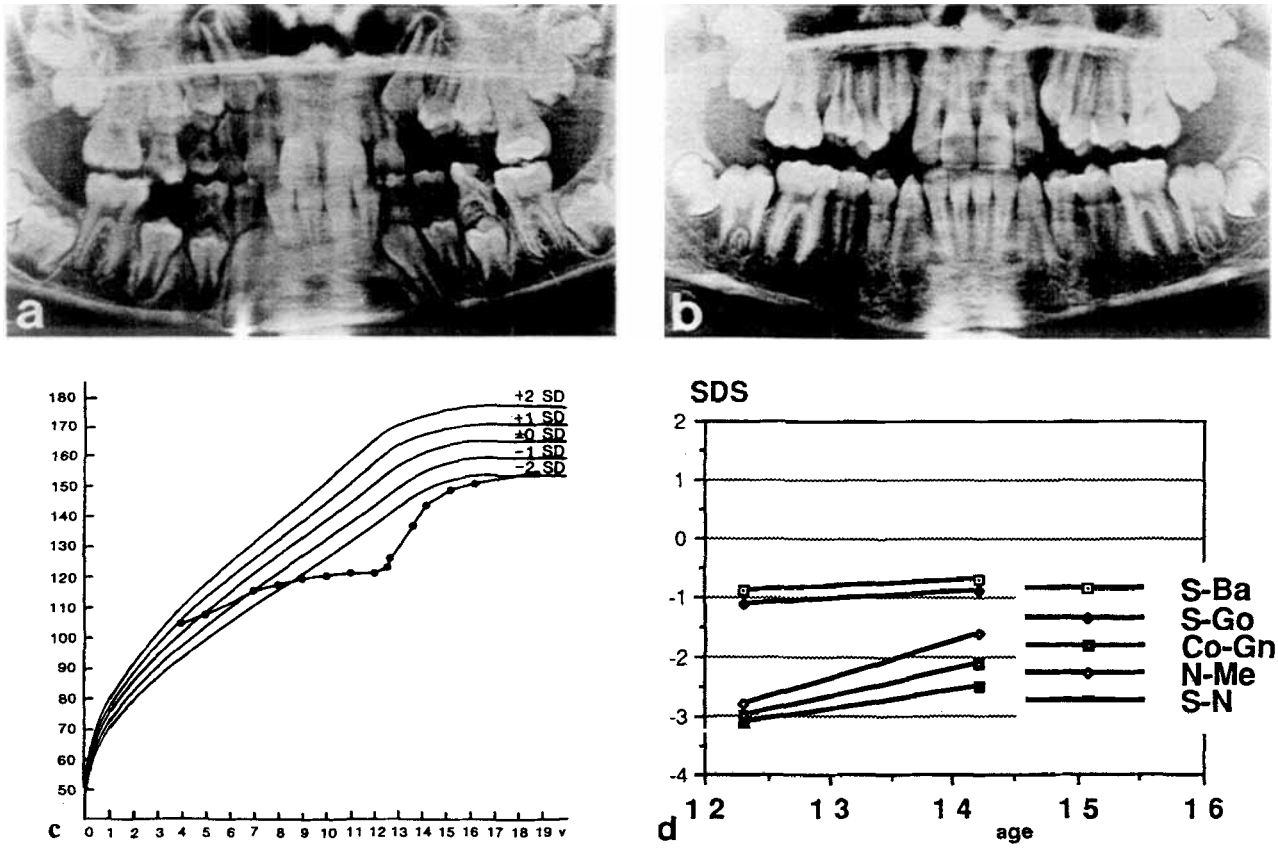

Fig. 2. Panoramic radiograph of a girl with hypothyroidism at diagnosis (12.2 years) (a) and after 14 months of replacement therapy (13.3 years) (b). Dental development is delayed; dental age based on tooth formation (61, 62) is 10.2 years (−2.2 SD) and 11.3 years (−2.0 SD). Eruption is more delayed than formation: permanent canines and premolars show two-thirds root development without corresponding eruptive movement or resorption of deciduous teeth. Note rapid recovery with therapy. 2c) Growth curve of the patient. 2d) Craniofacial dimensions at start and after 2 years of replacement therapy.

nervous system is seriously damaged. Growth of the cranium is retarded, and characteristic brachycephalic facies develops (29). Dental age is less delayed than bone age (13, 14). Rapid recovery of dental delay has been seen when treatment with thyroid hormone has been instituted (Fig. 2a,b) (30).

The presence of thyroid hormones is important in the synthesis of IGF-1. It is likely that thyroid hormone enhances cartilage growth through IGF-1 and by directly accelerating the differentiation of chondrocytes (31). The dental and craniofacial retardation found in hypothyroid conditions of longer duration differs somewhat from that seen in isolated lack of GH. The main difference is in the cranial vault, which shows a growth retardation in HT. Reduced facial height is typical in children with untreated HT of long duration (Fig. 2d). While retardation of tooth formation is of the same order in the two endocrinopathies, arrested tooth eruption is seen in HT. It has been suggested that this effect might be related to the epidermal growth factor (EGF) or EGF receptors (32, 33).

Some old textbooks show pictures of children with hyperthyroidism and demonstrate very early tooth eruption (34), whereas some reports (14) indicate delayed dental development.

Sex steroids

A slight increase in growth rate is seen at the age of 6–8 years in most children (the mid-childhood growth spurt). This is thought to be due to increased GH and IGF-1 production, which is stimulated by adrenal androgens. At puberty an increase in GH production is seen in boys and girls. Several lines of evidence indicate that this increase is sex-steroid-dependent. The sex steroids here are adrenal and ovarian androgens and ovarian and testicular estrogens. Plasma concentrations of IGF-1 show a similar increase (35). In addition to the increase in GH and IGF-1 levels, sex steroids display a small, direct effect on linear growth. This effect is especially seen as vertebral growth (36).

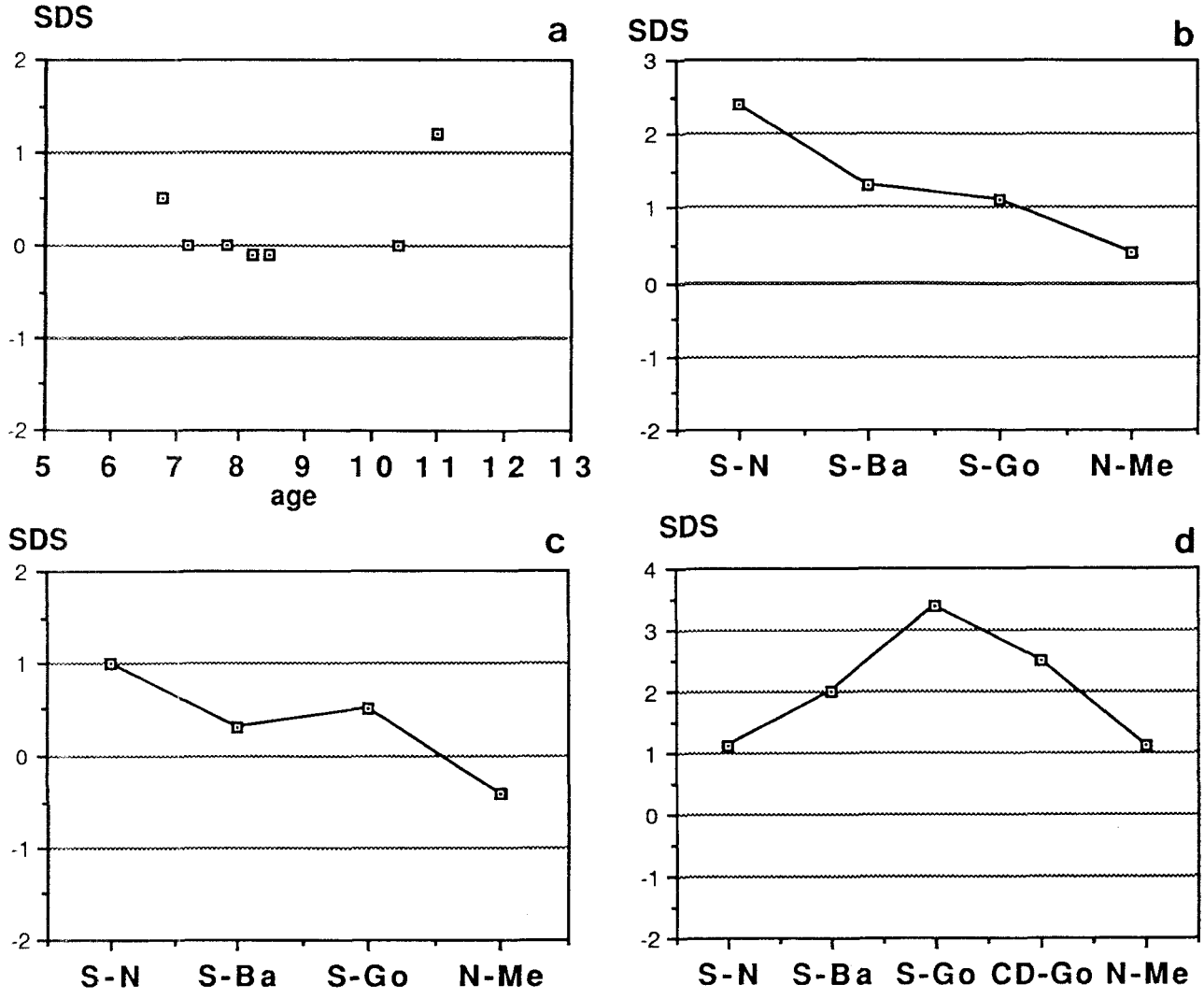

Fig. 3a) Standard deviation scores (SDS) of dental ages of seven patients with precocious puberty (six girls, one boy, aged 7.2 years). 3b) Average craniofacial pattern profile of the four younger girls (bone ages 11, 11.5, 12, and 11 years). 3c) The two older girls (bone age, 16 years) and 3d) the boy (bone age, 13 years). Cranial base and facial height dimensions are advanced in the younger girls and in the young boy and also in the boy's mandibular size, suggesting androgen sensitivity in mandibular growth regulation.

Again, valuable information on the role of sex steroids in dental and craniofacial development has been obtained by studying children with disorders of puberty. In normal, but extremely early or late-maturing children, dental development showed a slight deviation to early or late development, correspondingly (13). On the basis of these observations, Garn et al. (12) noted some sex steroid dependence in late-forming teeth. This finding has not been uniformly confirmed by others, but it reminds us that the different components of the dentition and their development should perhaps be analyzed separately to fully understand the regulation of dental development.

In true sexual precocities a slight advancement of dental age is reported (14). Too far-reaching conclusions should not be drawn on these endocrinopathies as they are seldom of long duration (Fig. 3a).

Advanced facial and cranial base growth has been noted in cases of sexual precocity (Fig. 3b-d). This advancement has, however, been less pronounced than advancement of bone age (13). Correspondingly, delayed facial growth has been demonstrated in delayed puberty and hypogonadism.

In congenital adrenal hyperplasia, increased adrenal androgen secretion causes advanced craniofacial growth. Advanced dental development is also seen (12–14, 37). However, the dentition is always much less advanced than bone age.

Animal experiments with anabolic steroids have demonstrated a clear effect on craniofacial growth,

mainly as overgrowth and rotation of the maxilla (38, 39). Barrett & Harris (38) present the assumption that misuse of anabolic steroids by adolescents and athletes may produce changes also in their craniofacial structures.

Thus, orthodontists should be alert also in following up research related to anabolic steroids and their therapeutic use and abuse.

Corticosteroids

Hyperglucocorticoidism leads to short stature and delayed bone maturation but increases relative weight (40). Very small amounts of cortisol given as medication can decrease growth rate. The mechanism is explained on the basis of lowered GH secretion, and the response of cartilage cells to IGF-1 is also lowered. Moreover, skeletal IGF-1 synthesis is decreased by cortisol, which has an inhibitory effect on bone collagen synthesis (41). In animal and tissue culture experiments mandibular condylar cartilage seems to respond to cortisol in a manner similar to the growth plates of long bones (42–44). Tissues in which cells continuously and rapidly reform (intestinal mucosa, testes, spleen, bone marrow) are more resistant to the 'glucocorticoid retarding effect' (45).

In the process of tooth eruption, however, cortisone has a special effect (46). Eruption rate is accelerated, but the mechanism behind this phenomenon is still uncharacterized. When studying the rat incisor, Teng et al. (47) noted accelerated tooth eruption after cortisone administration only if the fundus of the erupting tooth was left intact.

There seem to be no controlled clinical studies of facial growth or tooth eruption rate in lack or excess of cortisone. There could be an effect, for example, when children with juvenile rheumatoid arthritis are treated with systemic cortisol, when local treatment with cortisone for severe eczema is used, or in connection with inhalation medication for asthma (48; Westphal, personal communication, 1994). The adjustment of doses to an alternate-day regimen has reduced the growth-inhibiting effect of pharmacologic cortisone treatment (49).

Discussion

All in all, facial growth is very much under general growth control, and GH seems to be an important factor also in facial growth.

The determinants of dental development are less clear and hardly to be found by studying classical hormones. GH and TH no doubt, have an obvious effect on dental development. The lack of these two hormones seems to affect the timing of development of the dentition, whereas it is unclear whether an excess of GH or TH has an effect on dental development. The effect may be related to the general mitogenic effects of GH and IGF-1. TH seems to have some role of its own in the eruptive movement of teeth. When experimental work is evaluated, it must be kept in mind that the effects of TH on GH gene expression and GH synthesis vary significantly among mammalian species (50).

Adrenal androgens seem to be odontogenic, but the phenomenon and the mechanism behind it should be better studied.

Clearly, mandibular growth is controlled by GH. Several lines of evidence suggest that mandibular growth is also sensitive to direct androgen stimulation, in addition to the fact that sex steroids exert their effect by increasing GH secretion. Studies clearly demonstrate a pronounced mid-childhood spurt in mandibular growth (1, 3, 51–53), whereas growth in height is only slightly accelerated (54). The mid-childhood growth spurt is produced by adrenal androgens in boys and girls. At puberty mandibular growth peaks a little later than height. A considerable part of the height gain at puberty results from the rapid growth of the vertebrae (55). The peak height velocity (PHV) for sitting height comes later than the PHV for leg length. Vertebral growth is said to be under direct androgen influence, and the later timing of maximal mandibular growth could also reflect the same dependency. Vertebral growth continues slowly to the third decade of life. The timing suggests that androgenic hormones may be of importance in maintaining this growth (55). The mandible also grows slowly during adult life (56). The third line of evidence suggesting androgen sensitivity in mandibular growth control is the obvious sexual dimorphism in human facial dimensions. The male mandibular ramus is on the average 14% longer than the female ramus, whereas other facial dimensions have approximately an 8% sex difference (57).

Orthodontists should carefully follow the new developments in pharmacologic growth stimulation, treatments with classical hormones, and local treatment with GH, IGF-1, and other growth factors (58, 59). When the problem of the local application of hGH and growth factors is successfully solved, new possibilities for the treatment of craniofacial growth problems will open.

Acknowledgements.—The author presents her warm thanks to Professor Jaakko Perheentupa and Dr. Hanna-Liisa Lenko, Children's Hospital, University of Helsinki, Division of Pediatric Endocrinology, for cooperation and guidance.

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