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Skeletal growth and maturation in children afflicted with major endocrine disorders

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SUMMARY

Orthodontic and dentofacial orthopedic strategies depend on both skeletal growth and maturation stages. In children, various parameters such as growth curves shown in the child's health record, pubertal changes, or skeletal maturation (using the vertebral maturation method) need to be evaluated. These elements allow the practitioner to choose the optimal moment to start treatment or to discontinue it. Endocrine disorders such as growth hormone variations, thyroid disorders, and pubertal issues could modify skeletal growth and maturation. Diagnoses and treatment of these pathologies affect maxillofacial growth and development. Thus, these pathologies should be taken into consideration during orthodontic and dentofacial orthopedic treatment in children.

KEYWORDS

Growth, skeletal maturation, CVM, orthodontics, dentofacial orthopedics, endocrine disorders, growth hormone

INTRODUCTION

Pediatric care differs from adult treatment because children show ongoing bone growth along with continuous changes in cartilage growth and the accompanying bone maturation.

In DFO, most of the patients are children or adolescents. They are therefore experiencing a growth phase. As such, most orthodontic treatments aim to modify this growth, both in its direction and its potential. For example, orthopedic therapies are aimed at redirecting condylar growth to treat a skeletal class II. However, there are individual, physiological, or pathological variations in bone growth and maturation. Endocrine disorders modify these parameters and must therefore be considered while planning orthodontic treatments.

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EVALUATING GROWTH AND BONE MATURATION

Growth

There are different measurement parameters to assess the growth of children. These are systematically observed by the attending physicians and pediatricians who monitor the children during follow-up. Any deviations from the norm is, at the very least, cause for concern, and these should be addressed by a specialist (pediatrician or pediatric endocrinologist) if required.

- Height: up to 4 years (or 100 cm), height can be measured using a measuring tape with the child lying down; however, beyond 100 cm, the child's height will be measured in the standing position with the head turned to one side and with a measuring tape attached to the wall.
- The growth rate is calculated by the increase in height in centimeters per year.
- Target height is calculated by calculating the average height of the parents and adding 6.5 cm for boys and subtracting 6.5 cm for girls.
- Weight: measured with a measuring scale after the child is undressed.
- The body mass index or BMI (weight in kg/the square of height in meters).
- The cranial circumference: measured with a measuring tape at the largest cephalic circumference.
- Additional measurements include the following: the brachial circumference and the relationship between the brachial and cranial circumferences and the upper segment/lower segment ratio and arm span-height difference.
- To analyze these circumferences, they must be plotted on curves. In France, these curves are presented on health cards. In instances of complex orthodontic treatment, it may be advisable to note these elements in the health record to assess the overall growth potential of the child.
- In France, the weight, height, and cranial circumference are analyzed at birth using the curves by Usher and Mac Lean. More recently the AUDIPOG curves were introduced and can be used from 0 to 22 years of age. There are also curves developed by Sempé and Pédron (Fig. 1). These curves differ according to the sex of the patient.
- In France, BMI is assessed using the Rolland–Cachera curves (Fig. 2), which also differ according to sex.

Bone Maturation

In DFO, cervical vertebrae maturation (CVM) is currently used. This technique is easily accessible because it can be performed on any profile radiograph. The cervical spine is observed by analyzing cervical vertebrae C2, C3, and C4. Its main benefit is not having to add wrist X-rays, thereby avoiding radiation. Cervical spine radiographs are already being used when making diagnoses in DFO. Moreover, there is a good correlation between carpal bone age, mandibular growth, and the pubertal growth peak[6,7,11]. There are six stages of maturation. (Fig. 3).

- Stage 1 (CS1): the lower edges of the vertebrae C2, C3, and C4 are

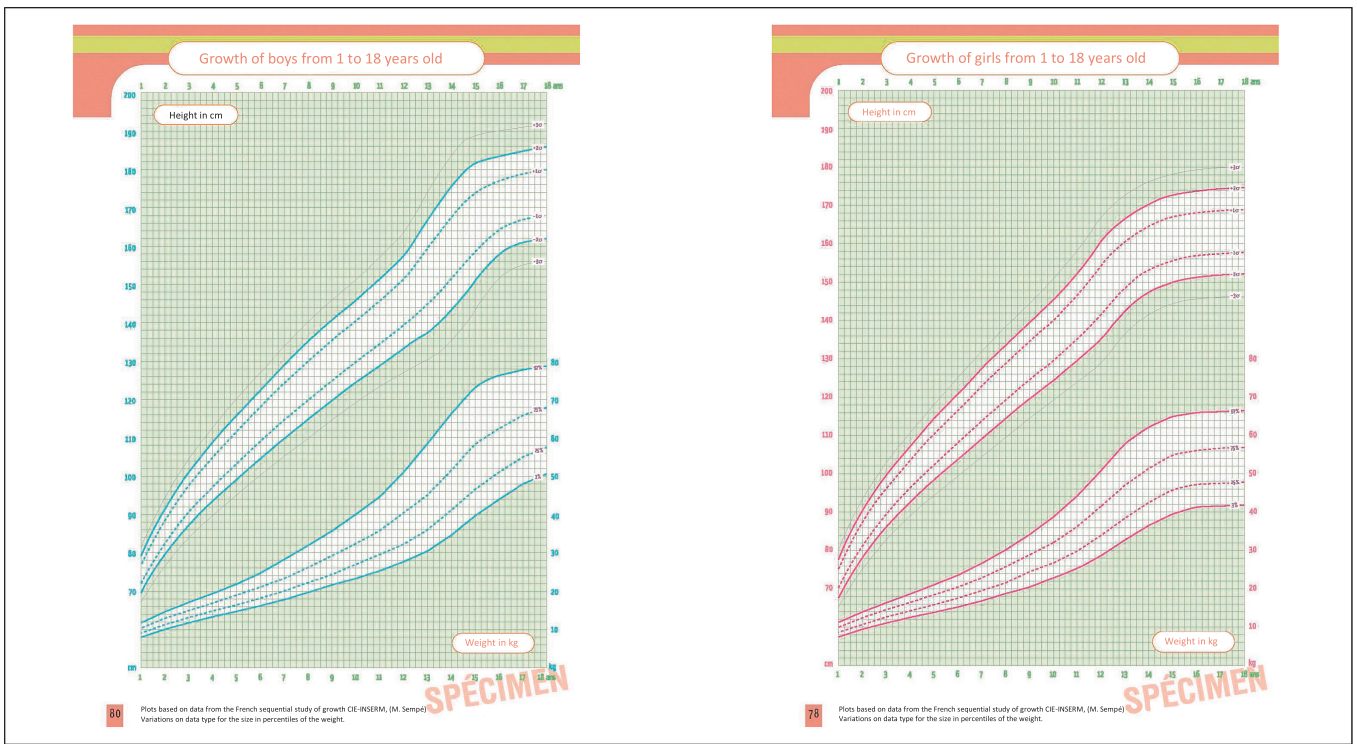

Figure 1
Curves by Sempé and Pédron.

flat, the upper edges are tapered from the back toward the front and to the trapezoidal vertebral bodies. This stage takes place 2 months before the peak in pubertal growth.

- Stage 2 (CS2): a concavity is formed at the lower edge of C2, and the anterior height of the vertebral bodies increases. This stage generally occurs 1 year before the pubertal peak.
- Stage 3 (CS3): a concavity is formed at the lower edge of C3. The pubertal peak occurs 1 year later.
- Stage 4 (CS4): a concavity is formed at the lower edge of C4. The vertebral bodies become rectangular. There is a pubertal peak in mandibular growth between CS3 and CS4.
- Stage 5 (CS5): concavities at the lower edges of the cervical vertebrae are more pronounced, the square vertebral bodies and the intervertebral spaces are decreased. This stage comes 1 year after the pubertal peak.
- Body Mass Index (BMI) = Weight (kg)/Height (m).
- Stage 6 (CS6): all the concavities appear deeper; the vertebral bodies are longer than they are wide. This stage occurs 2 years after the peak, signaling the end of pubertal mandibular growth. Other methods of bone maturation analysis exist, but they are seldom used in DFO.
- Bone maturation can be evaluated by conducting a bone age analysis

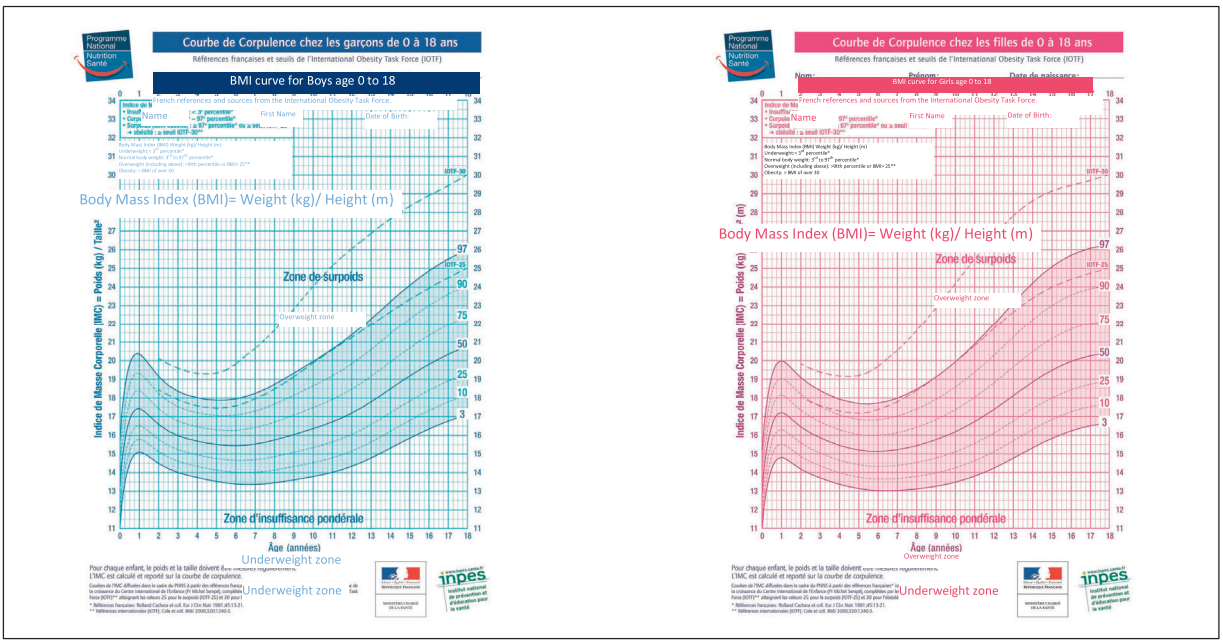

Figure 2
BMI curves by Rolland–Cachera

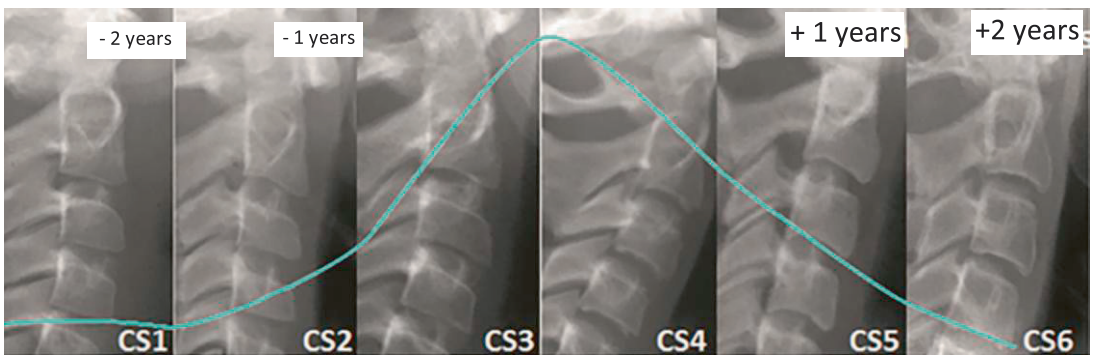

Figure 3
Location of the pubertal peak in mandibular growth over the six stages of cervical vertebral maturation according to Baccetti et al.[3]

(via radiographs of the hand, and the frontal side of the left wrist). These radiographs then analyzed by comparing the X-ray with the Greulich and Pyle atlas, which is a series of hand and wrist models, each reproduction corresponding to an average feature of the chronological age according to the sex[1]. Calcification and hand bone cartilage growth are analyzed.

- When growth is complete, the Risser test can be used particularly within the context of

scoliosis where the therapeutic indications depend on the degree of maturation. An X-ray of the frontal view of the pelvis analyzes growth in the cartilage of the iliac crests. The complete fusion of the ossification nucleus of the iliac crests marks the end of bone maturation.

- **Tooth maturation**, by quantitative or qualitative radiological analysis, is poorly correlated with overall bone maturation and is therefore a poor evaluation tool.

NORMAL GROWTH IN CHILDREN

Growth is deemed "normal" when it is situated on the curves between –2 and +2 standard deviations (SD) or between the 3rd and the 97th percentile (BMI curves), without slowing or breaking this growth.

Antenatal growth is assessed by antenatal ultrasound and neonatal measurements.

There are three phases in normal postnatal growth in childhood.

- Phase 1: early childhood (0-4 years): phase of rapid growth (+25 cm in the first year or 75 cm by age 1, years + 10 cm in the 2nd year, or 85 cm by age 2 years).
- Phase 2: childhood (age 4 years to pubertal period): growth rate slowed to 5–6 cm per year.
- Phase 3: puberty: accelerated growth rate and bone maturation, pubertal gain of about 20–25 cm for girls and 25–30 cm for boys.

The response to orthodontic treatment is better in phases 2 and 3, especially with respect to mandibular growth[3,4]. It is therefore necessary to analyze children's growth phases both clinically and radiologically. Clinical analyses look for recent accelerations in growth or signs of puberty such as breast development and hair growth. Radiological assessments optimize the start of orthodontic treatment. Growth has officially ended when the growth rate is <2cm per year and when the bone age is >15 years for girls and >16 years for boys.

Growth is **stunted** when it measures <–2 SD and severely retarded when it is <–4 SD.

Any slowdowns or breaks in the growth rate constitute cause for alarm as well as deviations of >1.5 SD between the actual height of the patient and the average height.

FEATURES OF THE MAJOR ENDOCRINE DISORDERS

It should be noted that two-thirds of the growth retardations or slowdowns are in fact linked to slower but nonpathological maturations; these are sometimes familial.

Growth Hormone (GH)

Growth Hormone Deficiency or GHD can be either congenital or acquired.

- Neonatal findings for congenital forms: GH is not essential for intrauterine growth and birth size is usually normal. Afterward, growth is slowed because of various retarding factors, such as a chubby face with a marked saddle nose deformity, obesity, and micropenis (in boys). Among the etiologies found were genetic anomalies, syndromes caused by pituitary stalk interruption, and idiopathic GHD.
- Acquired signs: the clinical signs are delayed and are caused by cerebral tumors (mainly craniopharyngioma) but also the cranial trauma, histiocytosis, and cerebral radiotherapy; in 70% cases, the cause is idiopathic.

GHD diagnosis is made after the conduct of two growth hormone stimulation tests on the growth hormones which have been deemed deficient (GH <20 IU/L). The diagnosis of the etiology is made systematically with a cerebral and pituitary MRI. The diagnosis can in no way be based on the analysis of the sella turcica on the cervicocranial X-rays.

Bone maturation and growth are greatly delayed in the case of GHD and are directly related to the severity of GHD and its etiology.

The occurrence of excess growth hormone is called acromegaly. This excess growth hormone results from a pituitary adenoma, visible during a pituitary MRI. It can be isolated, genetically or otherwise, or integrated into a multiple endocrine neoplasia type 1 (NEM 1).

Thyroid hormone abnormalities

- Congenital hypothyroidism has been linked to a missing thyroid gland, an ectopic thyroid gland, or hormone replacement dysfunction. This causes delayed growth and bone maturation associated with thermal regulation disorders, hypotonia, asthenia, and delayed neurological development. The incidence of a child having a severe clinical issue has become rare because the introduction of neonatal screening which allows the early introduction of thyroid hormone supplementation. The severity of congenital hypothyroidism can be assessed at birth by skeletal X-rays. The absence of ossification points is a sign of profound hypothyroidism.
- Persons should be sufficiently trained in the diagnosis of congenital hypothyroidism in countries where there is no screening for growth retardation associated with mental retardation or even macroglossia with delayed dentition[5].
- Hyperthyroidism is very rare in children especially younger children and has little effect on growth. In the case of a late diagnosis, there is accelerated growth rate and rapid bone maturation.

Pubertal Disorders

The sex hormones (estrogen and testosterone) are involved in growth through the ossification of conjugated

cartilage and increased muscle mass. The date of the onset of puberty affects skeletal maturation.

Early-onset puberty occurs before the age of 8 years for girls and before the age of 10 years for boys, with an accelerated growth rate and premature bone maturation. Because this occurs during the rapid acquisition of the pubertal growth peak, the patient is at risk of being "small in stature." Cases of early-onset puberty can be slowed down by administering monthly intramuscular injections of GnRH.

In girls, **delayed puberty** is evidenced by the absence of breast development at age of 13 years and the absence of increased testicular volume by the age of 14 years in boys. Some pubertal delays are pathological and should be investigated in a bid to try to identify Turner syndrome, the hypogonadotropic hypogonadism typical of Kallman syndrome, Klinefelter syndrome, etc. However, most retardations are termed "simple pubertal delays" because there may be a family history of late pubertal development. It is, therefore, necessary to take note of the mother's age of first menstruation as well as the age of the father's pubertal growth spurt. In this case, there may be a growth retardation because of the lack of a pubertal growth peak, but the child's final height will be normal. Bone maturation will also be delayed.

WHAT TO MONITOR IN THE ORTHODONTIST'S OFFICE?

Cases of Growth Hormone Deficiency

Dentofacial malformations are found in certain congenital pituitary deficits (syndromic or genetic), such as dental ageneses, enamel abnormalities, supernumerary incisors, and facial mass abnormalities (labiopalatal or velopalatal cleft, choanal atresia)[8,10].

Although more discreet, in cases where there is a GH deficiency, there is a decrease in mandibular growth and the posterior skull base, in addition to a delay in the development of the middle tier. Dental calcification is slowed and the appearance of permanent teeth is delayed[2].

Growth hormone treatment normalizes mandibular growth (the ascending ramus becomes larger) as well as posterior skull base growth and therefore reestablishes the normal proportions of the face[9]. It should be noted that maxillomandibular imbalances can increase during the duration of treatment hence the need for an orthodontic follow-up every 6 months[12].

Cases of excess growth hormones

The exaggerated growth of the mandible leads to prognathism, which is typical of acromegaly. The damage is both functional and esthetic. The teeth retain their normal size, resulting in a dentomaxillary disharmony with diastema distributed over the arch and difficulty chewing. Once the excess growth hormone is controlled, either by pituitary surgery or drug therapy, a surgical correction can be performed. Macroglossia

is frequently found in acromegaly but does not require surgical treatment.

Cases of congenital hypothyroidism

Macroglossia, traditionally present at birth, regresses with thyroid hormone supplementation.

The nose, mandible, and maxillae undergo premature ossification.

Dental eruption is delayed because of the delayed formation of tooth buds. The teeth display morphological abnormalities such as discrepancies between normal-sized teeth which appear to be too large for the very short dental arches, irregular teeth, and sometimes supernumerary teeth or even double rows of teeth. The frequency of cavities and gingival lesions is increased[13].

Cases of hyperthyroidism

There is accelerated growth and two dentitions. In adults, there are also multiple cavities and alveolar bone lysis evolving into periodontal disease. The teeth are not modified. If the treatment plan is adapted and properly conducted, the thyroid assessment is normalized, as such there are no contraindications of orthodontic treatment.

Treating hyperthyroidism with synthetic antithyroid drugs may cause agranulocytosis. The main cause of death is opportunistic germ infection right at the buccal opening. The onset of a fever with oral ulcers and a sore throat mandates an immediate blood count and the termination of drugs.

Cases of simple pubertal delay

The craniofacial dimensions, i.e., the total mandibular length, the length of the mandibular ramus, and facial height, are below average in patients who experience pubertal delay.

Low-dose testosterone therapy helps accelerate postural and craniofacial growth[14].

CONCLUSION

When treating children, DFO treatments must include growth analysis to optimize treatment initiation.

To this end, analyses must be supported by the growth curves found in the health record, and the cervical vertebral maturation index must be predominantly used.

Endocrine pathologies and treatments can modify growth and maxillofacial bone maturation and must, therefore, be considered.

Conflict of interest: The authors have declared that they do not have any conflict of interest.

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