THE ROLE OF ENDOGENOUS FACTORS IN DEVELOPMENT AND GROWTH

RODICA MIHĂILĂ[1], I. G. TOTOIANU[2], ELENA RESIGA [3], R. MIHĂILĂ[4]

[1,3]DPH Sibiu, [2,4] „Lucian Blaga"University of Sibiu

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Abstract: *A height lower by 2 SD to the one considered normal defines a retard in growth. It should be acknowledged even since childhood when it could undergo treatment; otherwise this might lead to a short stature in adulthood. The internal factors of the human body that have implications regarding children's embryonic, foetal and postnatal development shall be examined. Genetic factors control the pace of individual growth. The genetic disorders of the metabolism of some aminoacids determine serious development disorders, especially at the level of the nervous system. The influences of the secretion tonus of various endocrine glands will be examined some having a stimulatory, other an inhibitive role for the final height of the individual.*

Cuvinte cheie: *dezvoltarea organismului, creşterea, înălţimea, greutatea corporală*

Rezumat: *O talie inferioară cu 2 DS celei considerate normale defineşte retardul creşterii. El trebuie recunoscut în copilărie, când este accesibil unui tratament; altfel, poate conduce la o talie mică la adult. Sunt examinaţi factorii interni ai organismului uman care au implicaţii privind dezvoltarea embrionară, fetală şi postnatală a copiilor. Factorii genetici controlează ritmul creşterii individuale. Tulburările genetice ale metabolismului unor aminoacizi determină tulburări grave ale dezvoltării, mai ales la nivelul sistemului nervos. Sunt examinate infuenţele tonusului secretor al diverselor glande endocrine, unele cu rol stimulator, altele cu rol inhibitor, asupra taliei definitive a individului.*

SCIENTIFICAL ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

The child's growth is normal if the height-weight parameters evaluate parallel with the reference curves ranging between +2 and –2 standard deviation or between 3° and 97° percentile. Consequently, it is considered that children whose height is lower by 2 SD have a retard in growth.

It is very important to acknowledge growth retardation during childhood, because this might lead to a short stature in adulthood. The growth retard may be the expression of a pathological process, of which the child's vital or functional prognosis may depend on. Disregarding some type of retard, means not finding out an accessible potential situation leading to a treatment, this would allow the amelioration or the normalisation of the height (1).

The stages of growth: between 0-2 years, nutrition has an essential role, between 2-12 years the growth hormone is of primary importance; between 12-18 years, the sexual steroids and the growth hormones have the main effect.

The internal factors of the maternal body are important for the children's embryonic, foetal, postnatal development: the malformations of the uterus, the pressure caused by uterine tumours or by the shape of a narrow pelvis, defects of the placenta, the presence of diabetes, hypothyroidism, severe pulmonary and cardiovascular diseases, severe anaemia, the disorders of the placenta, the insulin administration, sexual and suprarenal hormones may trigger development disorders (2). The pregnant woman's nutrition disorders, its exposure to X-rays, the intake of some teratogenic drugs during pregnancy (thalidomide, vitamin A overdose), abortive ones (aminopterins, quinine, sulphamides, some antibiotics), some viral infections (rubella, herpes viruses, flu, neural viruses) streptococcus, staphylococcus infections, toxoplasmosis, malaria, the pregnant woman's syphilis may affect the intrauterine development of the baby. During the pregnancy complicated by asthma bronchitis, there is a sexually specific effect for the immune maternal body, with side effects on the placental function and on the growth of the foetuses of feminine gender. The use of steroids taken by inhalations by women suffering from asthma bronchitis was beneficial for the growth of foetuses of feminine gender due to the control of their maternal systemic inflammation (3). The children of younger mothers, babies from first pregnancies, the babies of mothers with a lower height have lower height and weight at birth as compared to those of older, multiparous mothers or those with a better physical development. In over 90 % of the cases, the children with a retard in growth will normalise their height in the first 2 years after birth. The treatment with somatotropine hormone (0.4mg/kg/day dosed in 7 weekly injections) must be followed for 3 years and may be interrupted, or extended depending on its results on the height (4). In a multicentric study in which somatotropine hormone was given in a 66 micrograms/ kg/ day dose at children with a low height at birth as compared to gestational age, their height significantly increased after 3 years (from -3.0 SD to -1.3 SD). At the control group (untreated) the growth in height was very little (from -3.2 SD to -2.9 SD) (5, 6, 7).

Genetic factors

Girls have an advance as regards skeletal maturation during growth; their ossification of growth cartilage ends 2 years earlier than boys'. Genetic factors control the pace of individual growth. There is pathology of development which is genetically transmitted to offspring: pituitary dwarfism, pituitary gigantism and hereditary dwarfism. Also the basic characteristics of the morphology of the various human races are transmitted.

[1]Corresponding Author: Rodica Mihăilă, Public Health Direction of Sibiu, 1-3 Gheorghe Barițiu street, Sibiu, România; E-mail: mihaila_rodica@yahoo.com; tel +40-(269) 210071

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For instance the Turner syndrome is accompanied by growth retardation existing even since birth in 1 of 2 cases, which progressively aggravates, over the years, it becomes more accentuated at puberty, due to the absence of the pubertal growth rate in such a way that the final height in the absence of any treatment and despite late growth is on average 142+/-5cm (8). The treatment of height retardation is today mainly performed with somatotropine hormone in a 0.35mg/ kg/ week doses assigned in 7 injections. The treatment of the absence of puberty entails the administration of estrogens for its triggering followed by estroprogestative (9).

The genetic malformation syndrome is accompanied by a precocious retard in height, a mental retard and a dimorphic syndrome of the face and limbs. It has a wide aetiology: the Rubinstein, Taybi Prader Willi, Cornelia de Lange syndromes (10).

The constitutional bone disease of the skeleton is diagnosed with the aid of radiography which shows epiphyseal, metaphyseal, vertebral malformations (10, 21). There are: achondroplasia, skeletal dysplasia, pychodysostosis (1).

Metabolic factors

The genetic disorders of the metabolism of some aminoacids trigger serious development disorders, especially at the level of the nervous system (phenylketonuria with phenylketonuric mental retardation) but also at the level of the plasmatic protein synthesis, of the carbon hydrates and the plasmatic lipids metabolism; there can be enzymatic deficits in the synthesis of the thyroid hormones of suprarenal steroids, hemoglobin synthesis disorders (hemoglobinopathies and thalassemia) metal, sulphur and potassium metabolism disorders (2). It is necessary the early identification of these disorders and the immediate start of therapy to prevent serious symptoms of genetically determined growth pathology.

Endocrine factors

The final waist of the individual may be influenced more or less by the secretor tonus of various endocrine glands, some with stimulatory some with an inhibitory role.

The pituitary growth hormone (STH) stimulates linear growth through its predominantly condrogenetic and less osteogenetic role. The STH stimulation of the growth cartilage is made with the aid of some sulfactation factors (somatomedines). STH has a tissular construction protein synthesis and morphogenetic role action stimulating the DNA and RNA synthesis. A somatomedine named insulin-like growth factor I (IGF -1) entitled somatomedine A or C, was purified out of human plasma and it was proved that it reacted with specific cellular receptors. A similar substance – IGF-II was also purified out of human plasma, but it is less dependent on STH and less active on the cartilage. The levels of IGF-1 reflect the levels of STH: they are high in acromegaly and low in pituitary dwarfism. IGF has a stimulatory effect on the synthesis of collagen by osteoblasts and has a less specific effect on the proliferation of bone cells. It has also been demonstrated that STH has direct effects on the cartilage.

Idiopathic short stature is particular to patients with a height more than 2 SD below average, normal or slowed growth pace, normal weight according to their age, the absence of any specific obvious chronic physical or psychological disorder. Children have usually short stature at birth and insufficient growth during the first 2 or 3 years of life, afterwards the growth rate becomes normal. Global bone age is equal to height age during the first years, and then during puberty it is accelerated to reach actual age. Puberty commonly takes place at a normal age, and despite pubertal growth, the final adult height remains short as compared to their parents. Endocrine tests are normal. Some patients with idiopathic short stature might have anomalies of the STH-TGF-I accompanied by a certain degree of STH insensitivity. The levels of IGF-I of these children may be below the value average of normal children (14, 15, 16).

Evocative clinical symptoms of STH deficiency are excess weight around the trunk area, small limbs, round forehead, doll-like face, the presence of a micropenis and bouts of hypoglycemia; these are inconstant ant frequently growth failure appears sparsely.

The growth curve indicates a slowdown, leading to a modification of the growth chart. The deficiency diagnosis is made based on the deficit or lack of the STH secretion after stimulation. STH deficit is considered when the level after stimulation is lower than 10 ng/ml. The observance of a STH deficit leads to the examination of another pituitary deficit or a possible lesion to the hypothalamus-pituitary area through CT scan or magnetic resonance imaging (10, 17).

It is allowed that about 1 out of 100 children may be thought of having idiopathic short stature, but not all are candidates are advised to follow STH therapy. U.S Food and Drug Administration endorsed in July 2003 the use of somatrotropine for the treatment of idiopathic short stature. STH treatment should not be administered only to get a higher stature; it has been observed that height is associated with success (men with average height earn more than the short or the taller ones). STH therapy is efficient only after the ossification of growth cartilages. If the treatment starts from the age of 5, it will probably last 5 to 8 years. The treatment consists in administering growth synthesis hormones in a 0.25/mg/kg/day, dose divided in 7 weekly injections. It must be followed until the end of the growth period and of puberty. If there are other pituitary disorders, they will be treated in a parallel way (10, 17).

Insulin is a hormone with a protein synthesis and cellular multiplication role, stimulating growth. Newborn of diabetic mothers are overweight at birth and have the height superior to the normal average and children suffering from Type 2 diabetes have at the onset of the disease a height superior to the normal one and an excess of insulin levels.

Thyroid hormones stimulate the growth and maturation of the growth cartilage and of the muscle cells; their action in bone maturation is predominantly osteogenetic. They act synergic with STH on somatic growth. Children with congenital myxedema have a slower growth rate. At the age of 20, they reach 1 meter height retardation, thus the disharmonious thyroid dwarfism is produced. The dosage of thyroid hormones (the T3 and T4 parts) allows the confirmation of thyroid insufficiency disorder diagnosis. TSH evaluation allows the distinction between primary hyperthyroidism (elevated TSH) and secondary ones (low or normal TSH). The treatment is of hormone replacement and it is made with Levothyroxine 6-8 microg/kg at birth then 100 microg/sm (1).

Androgen hormones have a protein synthesis effect; they stimulate the STH production and act directly on growth cartilages. In moderate doses, they stimulate both linear growth and bone maturation, through condrogenetic and osteogenetic action. Estrogen hormones stimulate somatic growth, having a synergic action with that of STH. They favour osteogenesis and they have a calcipexic action, of calcium fixation at the level of the bone.

Glucocorticoid hormones have an inhibitory effect on somatic growth, favouring protein catabolism; they have an antagonist competitive action with STH at the level of growth cartilage. The Cushing syndrome is exceptional at children. It associates growth retardation, a defect in the repartition of adipose tissue predominantly on the face and trunk area, hirsutism, muscular atrophy, seborea and acne (18). The

diagnosis is based on the evaluation of free urinary cortisol. At children who undergo the administration of glucocorticoids (iatrogenic hypercortisolism) a slower growth rate was observed, leading to cortisol determined dwarfism (1).

The thymus, until its involution which appears at the onset of puberty, has an activating stimulatory effect on growth by increasing STH action and though its intervention in the glucid and calcium metabolism (12).

BIBLIOGRAPHY

1. Naima E, Gaouzi A, Benhamou B, Msefer-Alaoui F. Le retard de croissance statural chez l'enfant. www:santemaghreb.com. Le guide de la médicine et de la santé au Maroc, Mai 2004.
2. Tănăsescu G. Dezvoltarea fizică şi neuropsihică a copiilor şi adolescenţilor. Factori care influenţează dezvoltarea umană. În: Tratat de Igienă, Vol III, sub red Mănescu S, Ed Medicală, Bucureşti, 1986: 27-115.
3. BarclayL. Maternal asthma untreated with steroids linked to reduced female fetal growth. Am J Respir Crit Care Med. 2003; 168: 1317-1323.
4. Simon D. Y-a-t-il des indications pour l'hormone de croissance? Archives de Pédiatrie 9, Suppl 4; 2002: 454s-455s.
5. Arends N J T, Boonstra V H, Mulder P G H, Odink R J H et al. GH treatment and ist effect on bone mineral density, bone maturation and growth in short children born small for gestational age: 3-year results of a randomized, controlled GH trial. Clin Endorinol 2003; 59: 779-787.
6. Hokken-Koelega A C, De Ridder M A, Lemmen R J, Den Hartog H et al. Children born small for gestational age: do they catch up? Pediatric Research 1995; 38: 267-271.
7. Job J C, Rolland A. Natural history of intrauterine growth retardation: pubertal growth and adult height. Archives Françaises de Pédiatrie 1986; 43: 301-306.
8. Saenger P, Albertsson-Wikland K, Conway G S, Davenport M et al. Recommendations for the diagnosis and management of Turner syndrome. J Clin Endorinol Metab 2001; 86: 3061-3069.
9. Chernausek S D, Attie K M, Cata J F, Rosenfeild R G et al. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. J Clin Endorinol Metab 2000; 85: 2439-2445.
10. Kasse M C. Retard de croissance staturale. Impact Internat, Dec 1994: 175-182.
11. Maroteaux P. Les chondrodysplasies. In: DavidM. Coor Endocrinologie-croissance, Simep (David m, Floret D), Pediatrie 1984; 2: 222-229.
12. Popa M. Dezvoltarea fizică – indicator al stării de sănătate la copii şi tineri. În: Compendiu de Igienă, sub red. Ionuţ C, Ed Med Universitară „Iuliu Haţieganu", Cluj-Napoca, 2004: 553-573.
13. Brauner R. Conduite pratique devant une anomalie de la croissance staturale. Encycl Méd Chir (Elsevier, Paris), Pédiatrie 4-005-A-10; 1999: 7.
14. BlairJ C, Camacho-Hubner C, Miraki-Moud F, Rosberg S et al. Standard and low-dose IGF-I generation tests and spontaneous growth hormone secretion in children with idiopathic short stature. Clin Endocrinol 2004; 60: 163-168.
15. Ghico E, Aimaretti G, Maccario M, Fanciulli G et al. Dose-response study of GH effects on cirulating IGF-I and IGFBP-3 levels in healthy young men and women. American J Physiol 1999; 276: E1009-E1013.
16. Talange N K, Price D A, Gill M S, Whatmore A J et al. IGFBP-3 generation; an index of GH insensitivity. Pediatirc Res 1996; 39: 849-855.
17. Lecornu M. Les insuffisances antehypophysaires. In: david M, coor Endocrinologie-croissance, Simep, 1984 (David M, Floret D), Pediatrie 2: 320-326.
18. Raux-Demay M C. Pathologie des corticosurrenales chez l'enfant. Encycl Méd Chir (Editions scientifiques et Médicales Elsevier SAS, Paris), Pédiatrie 2001; 4-107-A-10: 27.