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ORO DENTAL CHANGES IN THE MOST COMMON GROWTH HORMONE PATHOLOGY

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The maxillofacial changes may be generated by pituitary diseases. Excess of growth hormone-GH (acromegaly) and deficit of GH in children could generate oro-dental pathology. Oral manifestations in acromegaly include changes of hard and soft tissues. At the level of hard structures, it can be observed enlargement of maxillary but especially of mandible with prognathism and jaw malocclusion, teeth separation, increased dental mobility, tooth loss. At the level of soft structures, it can be seen enlargement of the lips, tongue (macroglossia) and salivary glands, gingival hypertrophy. The bone growth is not reversible with successful therapy of acromegaly. In acromegalic patients the correction of maxillofacial changes and dental malocclusion should to be achieved after GH and IGF-1 levels have been normalized for at least 6 mounts. Oro-dental pathology in GH deficiency in children included: small size of maxilla and mandible, small dental arches, dental malocclusion, delayed pattern of eruption. The prevalence of oro-dental changes is high in acromegalic patients as well as in patients with GH deficiency. Therefore, besides the treatment of the underlying condition, good collaboration between endocrinologists and dentists it is recommended.

Keywords: oro-dental pathology, acromegaly, growth hormone deficiency in children

INTRODUCTION

The maxillofacial changes could be generated by pituitary disorders. Deficit and excess of GH can generate oro-dental pathology and the most common symptoms and clinical signs in acromegaly and GH deficiency in children will be presented.

GH is a polypeptide of 191 amino acid, synthesized, stored and secreted by specific cells of the anterior pituitary gland. GH exerts its effects by binding to the extracellular domain of the GH receptor, followed by dimerization of receptor, this path being important for signal transduction[1]. Postnatal longitudinal grow and development are dependent on physiological pulsatile GH secretion. Two mechanisms seem to be involved in longitudinal grow:

– activation of the mitogen activated protein kinase (MAPK) pathway through GH which directly stimulates division and multiplication of chondrocytes;

– stimulation of Janus kinase-signal transducer and activator of transduction (JAK-STAT) and secondary synthesis of insulin-like growth factor 1 (IGF-1)[2].

IGF-1 is a proliferative and differentiation factor; is produced in liver and multiple tissues and functions in an endocrine/paracrine and autocrine manner. One such tissue is bone where IGF-1 shows stimulatory effects on osteoblasts and chondrocytes[3]. At the same time GH exhibits metabolic effects: promotes protein synthesis, increases lipolysis, increases the free fatty acids levels, reduces liver uptake of glucose and increases gluconeogenesis in the liver[4]. GH secretion is regulated by the hypothalamic factors (grow hormone-releasing hormone-GHRH and grow hormone-inhibiting hormone-GHIR or somatostatin) and the mediators of GH actions (IGF-1 and ghrelin)[5].

GH EXCESS-ACROMEGALY

Acromegaly is an endocrine disorder characterized by GH hypersecretion which generates multiple

comorbidities and secondary increase in mortality. The incidence of the disease is low and is estimated at 3–4 new cases per million[6]. The affection is determined in most cases by a pituitary adenoma hyper-secreting of GH. In few cases the disease is generated by a hypothalamic tumor that secretes excess of GHRH or ectopic secretion of GHRH.

Clinical manifestations of acromegaly are a consequence to the somatic and metabolic effects of excess GH exposure, and of compression phenomena generated in pituitary mass. The most typical clinical signs are: skin changes, muscle hypertrophy, changes in bones and cartilage that mark the semiology of acromegaly and predominantly affect the extremities, the cephalic extremity, the hands and the legs. Characteristic symptoms of acromegaly are: excessive sweating, joint pains, carpal tunnel and sleep apnea syndrome. The expanding pituitary mass can generate: headache, hypopituitarism, visual impairment, rhinorrhea (if invasion is of the sphenoid sinus)[7]. The facial features are characteristic and may include: skin thickening, frontal bone bossing, zygomatic arch prominence, enlargement of the base of the nasal pyramid, changes in the oral cavity.

Oral manifestations in acromegaly include changes of hard and soft tissues. At the level of hard structures, it can be observed enlargement of maxillary but especially of mandible with prognathism and jaw malocclusion, teeth separation, increased dental mobility, tooth loss. Changes may also interest soft structures of the oral cavity and it can be seen enlargement of the lips, tongue (macroglossia) and salivary glands, gingival hypertrophy[8]. Other manifestations of acromegaly in the oral cavity are: hypertrophy of palatal tissues, the particular disposition of the teeth due to the macroglossia pressure and radiological investigations can highlight taurodontism (large pulps chambers) pathological cementum excess[9]. Changes of hard and soft tissues of the oral cavity in acromegaly are show in Table 1.

The analysis of the frequency of oro-dental pathology in acromegaly has been evaluated by several researchers. Kreitschmann-Andermahr I and collaborators reported that oro-dental pathologies was present in four of five operated patients with acromegaly; the most frequent manifestations were: macroglossia, enlargement of interdental spaces, mandible grow and prognathism[10]. Another study involving 28 acromegaly patients revealed that 96% had an asymmetric movement of mandibula, 86% asymmetric face, 57% prognathism which correlated significantly with the duration of the disorder and 42% diastemas. The authors concluded that "*The high incidence of these manifestations and its relation to the disease duration requires a carefully work-up of oral and maxillofacial examinations in close collaboration with endocrinologists, dentists and dental surgeons*"[11]. In a study in which 16 acromegalic patients and 20 subjects control patients were included, all acromegalic patients presented dental mobility and malocclusion and 93.75% diastemas. Acromegalic patients din not present periodontitis while 10 subjects of control group were diagnosed with this condition[12].

Table 1

Changes of hard and soft tissues of the oral cavity in acromegaly

Oral manifestations in acromegaly
Changes of hard tissues
Mandible overgrowth with prognathism
Jaw malocclusion
Enlargement of interdental spaces, increased dental mobility, tooth loss
Changes of soft tissue
Enlargement of the lips
Enlargement of the tongue (macroglossia)
Enlargement of the salivary glands
Gingival hypertrophy

Diagnosis of acromegaly requires physical examination and laboratory testing (measurement of IGF-1 and glucose–suppressed GH levels). After biochemical diagnosis, further evaluation include: magnetic resonance imaging (MRI) scan of pituitary gland, ophthalmologic examination, evaluation of anterior pituitary function[13]. Diagnosis and evaluation of oro-dental pathology in acromegaly requires: physical examination and radiological explorations (intra-oral and panoramic radiographs, lateral and postero-anterior cephalograms)[11].

Therapeutic options are surgical, medical and radiation therapy. Surgical intervention (pituitary surgery) is the first-line option in patients with micro and macro adenomas with compressive effects on local structures. Medical therapy is as adjuvant treatments in patients with residual disease after surgery. There are 3 classes of drugs: dopamine agonist (the first option), somatostatin analogues and GH receptor agonist. Pituitary radiation therapy is recommended to patients who do not fully respond to the previously mentioned therapies[13]. The treatment of oro-dental changes in acromegaly must consider the stage of evolution of the disease. The following therapies are mentioned in a study conducted by Kreitschmann-Andermahr I and collaborators: dental crowns, dental bridges, dental implant, dental prostheses, orto-dental and

surgical correction of teeth[10]. The bone growth is not reversible with successful therapy. The correction of maxillofacial changes and dental malocclusion should to be achieved after GH and IGF-1 levels have been normalized for the least 6 mounts[13].

GH DEFICIENCY IN CHILDREN

GH deficiency in children is often isolated and described as idiopathic, a term that is useful when the pathological process is not known. The incidence of GH deficiency in children has been estimated to 1/4000[14]. The most characteristic clinical signs are represented by short stature, low growth velocity for age, immature face with prominent forehead and mid-facial hypoplasia[15]. The oro-dental changes in GH deficiency in children have a high prevalence and include: small size of maxilla and mandible, small dental arches, dental malocclusion, delayed pattern of eruption[9]. Other less common clinical signs are agenesis of the upper central incisor and solitary maxillary central incisor[16, 17].

Diagnosis of GH deficiency in children requires auxology, radiological evaluation of bone age, laboratory testing (GH stimulation tests, IGF-1 levels), MRI and genetic testing in certain cases[18]. Some researchers think that auxology and clinical judgment are essential in diagnosis of GH deficiency in children[18,19,20,21]. According to the recommendations of the "*Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone Deficiency in Children and Adolescence"* the evaluation for GH deficiency it's recommended in seven situations:

- height □-3 standard deviation (SD) below the mean;
- height □-1.5 SD below the mid-parental height;
- height □-2 SD below the mean and a height velocity over 1 year □-1 SD below the mean for chronological age, or a decrease in height SD of □-0.5 over 1 year in children over 2 years of age;
- in the absence of short stature, a height velocity □-2 SD below the mean over 1 year or □-1.5 SD sustained over 2 years;
- suggestive signs of an intracranial lesion;
- signs of multiple pituitary hormone deficiency:
- neonatal symptoms and signs of GH deficiency[22].

Radiological investigations include evaluation of bone age and evaluation of central nervous system (MRI). Evaluation of bone age is done routinely through x-ray of the left wrist hand or of the knee and ankle. MRI is recommended to be done in case of suspected or known intracranial tumors, structural and developmental anomaly. Although there are numerous controversies about the significance of the resultant, the validity and reproducibility of GH stimulation tests, they continue to be used in the diagnosis of GH deficiency[18]. The pharmacological agents used are: insulin, glucagon, arginine, clonidine, levodopa but a single test is address for a single pathway in the regular of GH secretion and are poorly reproducible[18, 23]. This is the reason why "*Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents*: *Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency"* published in 2016 in Hormone Research in Pediatrics, suggest establishing a diagnosis of GH deficiency without GH stimulation tests in the following conditions:

- auxological criteria;
- the congenital malformation-the imaging triad: ectopic posterior pituitary, pituitary hypoplasia with abnormal stalk:
- tumor irradiation;
- deficiency of one additional pituitary hormone[24].

It is considered that the IGF 1 level reflects the circulating level of GH but the IGF-I determination is limited by the sensitivity of the assay[18]. Diagnosis and evaluation of oro-dental pathology in GH deficiency requires as with acromegaly, physical and radiological explorations.

Treatment of GH deficiency in children involves administration of exogenous recombinant human GH. Authors of the "*Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents*: *Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency"*, recommends an initial GH dose of 0.16–0.24 mg/kg/week (22–35 μg/kg/day) with individualization of subsequent dosing[24]. Substitution treatment over a long period of time decrease the disproportion in jaw dimensions and prevents malocclusion[25] and positively influences the process of replacement of dentition[26]. The literature does not provide standardized information on the treatment of oro-dental pathology in patients with GH deficiency. Treatment of particular pathology, respectively

solitary maxillary central incisor requires orthodontic, prosthodontic and oral surgical treatment[17].

CONCLUSIONS

Excess and deficiency of GH causes specific changes in the oral cavity. The prevalence of oro-dental changes is high in acromegalic patients as well as in patients with GH deficiency. Therefore, besides the treatment of the underlying condition, good collaboration between endocrinologists and dentists it is recommended.

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REFERENCES

1. de Vos AM, Ultsch M, Kossiakoff AA. Human growth hormone and extracellular domain of its receptor: crystal structure of the complex. *Science,* **1992,** 255(5042):306-12.
2. Binder G, Wittekindt N, Ranke MB. Noonan Syndrome: Genetics and Responsiveness to Growth Hormone Therapy. *Horm Res*, **2007,** 67 (Suppl 1): 45–49.
3. Guntur AR, Rosen CJ. IGF-1 regulation of key signaling pathways in bone. *Bonekey Rep*, **2013,** 2: 437, doi: 10.1038/bonekey.2013.171.
4. Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev*, **2009,** 30(2):152-177.
5. Ayuk J, Sheppard MC. Growth hormone and its disorders. *Postgrad Med J*, **2006,** 82(963): 24–30.
6. Alexander L, Appleton D, Hall R *et al*. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)*, **1980**, 12:71-79.
7. Chanson P, Salenave S. Acromegaly. *Orphanet J Rare Dis*, published online, doi: 0.1186/1750-1172-3-17, **2008**.
8. Manetti L, Bogazzi F, Brogioni S *et al*. Submandibular salivary gland volume is increased in patients with acromegaly. *Clin Endocrinol (Oxf)*, **2002,** 57(1):97-100.
9. Atreja G, Atreja SH, Jain N, Sukhija U. Oral manifestations in growth hormone disorders. *Indian J Endocrinol Metab*, **2012,** 16(3): 381–383.
10. Kreitschmann-Andermahr I, Kohlmann J, Kleist B *et al*. Oral-dental pathologies in acromegaly. *Endocrine,* **2018,** 60(2):323-328.
11. Herrmann BL, Mortsch F, Berg C *et al.* Acromegaly: A Cross-Sectional Analysis of the Oral and Maxillofacial Pathologies. *Exp Clin Endocrinol Diabetes,* **2011,** 119(1): 9-14.
12. Lima DL, Montenegro RM Jr, Vieira AP *et al*. Absence of periodontitis in acromegalic patients. *Clin Oral Investig*, **2009,** 13(2):165-169.
13. AACE Acromegaly Guidelines. *Endocr Pract*, **2011,** 17(Suppl 4), 636-646.
14. Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child*, **2016,** 101(1): 96-100.
15. Shalet AM, Toogood A, Rahim A, Brennan BM. The diagnosis of growth hormone deficiency in children and adults. *Endocr Rev*, **1998,** 19(2): 203-223.
16. Bretéché F, Delaire J, Ginguene Y. Agenesis of the superior central incisor. Its relation to pituitary nanism. *Rev Stomatol Chir Maxillofac*, **1984,** 85(1): 72–74.
17. Hall RK. Solitary median maxillary central incisor (SMMCI) syndrome. *Orphanet J Rare Dis*, **2006,** 9;1:12.
18. Stanley T. Diagnosis of Growth Hormone Deficiency in Childhood. *Curr Opin Endocrinol Diabetes Obes,* **2012,** 19(1): 47-52.
19. Bidlingmaier M, Freda PU. Measurement of human growth hormone by immunoassays: current status, unsolved problems and clinical consequences. *Growth Horm IGF Res*, **2010,** 20(1):19–25.
20. Gandrud LM, Wilson DM. Is growth hormone stimulation testing in children still appropriate? *Growth Horm IGF Res*, **2004,** 14(3):185–194.
21. Frystyk J, Freda P, Clemmons DR. The current status of IGF-I assays--a 2009 update. *Growth Horm IGF Res*, **2010,** 20(1):8–18.
22. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. *J Clin Endocrinol Metab*, **2000,** 85(11): 3990–3993.
23. van Vught AJ, Nieuwenhuizen AG, Gerver WJ *et al.* Pharmacological and physiological growth hormone stimulation tests to predict successful GH therapy in children. *J Pediatr Endocrinol Metab*, **2009,** 22(8):679–694.
24. Grimberg A, DiVall SA, Polychronakos C *et al.* Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr*, **2016,** 86:361-397.
25. Kawala B, Matthews-Brzozowska T, Bieniasz J, Noczyńska A. Dental and skeletal age in children with growth hormone deficiency treated with growth hormone – preliminiary report. *Pediatric Endocrinology, Diabetes and Metabolism,* **2007,** 13(4): 210–212.
26. Partyka M, Chałas R, Dunin-Wilczyńska I *et al*. Influence of growth hormone therapy on selected dental and skeletal system parameters. *Ann Agric Environ Med*, **2018,** 25(1): 60-65.