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Analysis of Therapies Applied to Gorham-Stout Syndrome: emphasis on dentistry

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Abstract: Rationale: The Gorham-Stout syndrome is a rare disease whose studies are not yet conclusive, requiring the dentist-surgeon to know the main signs and symptoms and characterization of radiological and laboratory tests to obtain data that supports a correct diagnosis. General objective: a second essay on Gorham-Stout Syndrome focused on basic supports for Dentist Surgeon on the diagnosis and evolution of treatment of this pathology, having seen its importance in musculoskeletal system and that can be occur also in the skull and jaw, they require a differentiated and well-founded diagnosis. Specific objectives: identify the signs and symptoms of Gorham-Stout Syndrome; and, to know the evolution of the treatment of this pathology. Methodology: bibliographic review performed on the main health platforms provided by Virtual Health Library (VHL), using the descriptors Gorham-Stout / + / Syndrome, Idiopathic Massive Osteolysis and Phantom Bones / + / Syndrome, without time definition, in the languages: English, Portuguese, French, Spanish and Italian; from the results obtained, a screening was made to select the articles of interest for this research. Conclusion: In the literature there are no treatments indicated for all cases, varying in situation and degree of bone loss, therefore, more studies should be performed to provide scientific support for effective treatments and bases for meta-analyzes; As it is a rare syndrome that can also affect the skull and jaw regions, it is of great importance that the dentist is able to diagnose and work in a multidisciplinary team of studies for the treatment of this pathology.

Keywords: Gorham-Stout Syndrome – maxillofacial region, Idiopathic Osteolysis Massive – maxillofacial region, Gorham-Stout Syndrome – therapies. Rare diseases

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I. Introduction

Several pathologies have conditions to be rare, among these: Hereditary Angioedema, Takayasu's arteritis, Spinal Muscular Atrophy, Cluster Headache, Rett Syndrome, Gaucher's disease, 5p- Syndrome (Cri-Du-Chat), Epidermolysis bullosa, Marburg Haemorrhagic Fever, Noonan syndrome, Roussy-Lévy Syndrome, Osteogenesis Imperfecta and Gorham-Stout Syndrome, between about 7000 to 8000.

The World Health Organization - WHO considers rare diseases when, affects 65 people per 100,000, that is, 1.3 per 2000 people[1]. It is Noted, Gorham-Stout Syndrome was only reported about 200 to 250 cases worldwide in the last 100 years, which can be considered as a very rare pathology.

Gorham-Stout Syndrome, which also receives other names such as, massive idiopathic osteolysis, acute spontaneous bone absorption, phantom bone syndrome, bone disappearance disease, evanescent bone disease, Type IV Osteolysis in Torg Classification and colleagues, among other denominations. There has been little discussion in dentistry, both because of its rarity of cases and because there is little research in orthopedics and dentistry identified in the main health platforms (Lilacs, Bireme, MEDLINE) in english, spanish and portuguese[2].

Gorham, Stout (1955, 985) with regard to the rarity of this pathology, they say at the time that: One may search through the standard textbooks of medicine, surgery, orthopaedics, roentgenology, and pathology without finding a single reference to this unusual condition. Even French's Index of Differential Diagnosis, a storehouse of information on medical curiosities, fails to mention it. The most comprehensive discussion of the subject in English appeared in Coley's classical monograph, Neoplasms of Bone. This author stated that acute spontaneous absorption of bone is ‘A little understood and extremely rare condition’, that it has been described also as ‘phantom bone’ or ‘disappearing bone’, and that only three cases had been reported before 1946. Coley presented a table of four published and three unpublished cases[3].

Gorham-Stout syndrome is a rare and peculiar musculoskeletal disorder, in which the affected bone virtually disintegrates and is replaced by fibrous vascular connective tissue. The etiology is speculative. The clinical presentation is very variable and its naturais history has an unpredictable prognosis[4].

Gorham, Stout (1955, 992) affirm through bibliographic research that: The milder cases show the absorption of part of a single bone, while the severer cases progress until almost all of the osseous tissue of one or more bones has disappeared, with only a fibrous band left as a residuum. Regeneration of bone to any notable extent has not occurred[3].

The objective of this article is an essay on Gorham-Stout Syndrome aimed at providing the Dental Surgeon with basic knowledge about the diagnosis and the evolution of the treatment of this pathology, due to its musculoskeletal importance, which also occurs in the mandible and other parts of the skull, and the first knowledge is important for a differential diagnosis. The specific objectives are: to lead the professional to identify the signs and symptoms of Gorham-Stout Syndrome; To know the evolution of the treatment of this pathology, providing the first paths towards the patient.

The methodology was a bibliographic review, with searches on the main health platforms provided by the Virtual Health Library (VHL), using the descriptors Gorham-Stout /+/ Syndrome, Idiopathic Mass Osteolysis and Phantom Bones /+/ Syndrome, without definition of time, requesting results in the following languages: English, Portuguese, French, Spanish and Italian. Of the results obtained in the screening were selecting the artiitems of most interest to this research.

II. Epidemiology and symptomatology

The skull is among the least common sites of involvement, and its occurrence in the jaws is very rare[5]. 30% of affected patients, maxillofacial involvement is noted, with the mandible being most frequently affected. Simultaneous maxilla and mandible involvement may occur[6]. Mandibular involvement usually begins with the alveolar bone, then extends to the basal bone and subsequently surrounds the branches and condyle and can even spread to the base of the skull[7].

The syndrome has been described in patients as young as 1-month to as old as 75 years. The bones of the upper extremity and the maxillofacial region are the predominant osseous locations of the disease. Approximately, around 60% of all cases with vanishing bone disease occur in men[5].

The signs and symptoms are, asthenia, localized pain accentuated by palpation, mobility and tooth loss in the region, edema, some cases purulent secretions, pathological bone fractures (in many cases similar to glass bone syndrome) resulting in malocclusion, deformity of the region, radiography showing massive bone resorption, involvement of the joints in the region involved, presence of small angiomatosis composed of hemangioma and lymphogioma in the TMJ (temporomandibular joint), hyperemia, gingivorrhagia, trismus, significant presence of osteoclasts in histopathological exams, gradual replacement of bone and cartilage tissue by fibrous vascular connective tissue resulting in radiographs with significant radiolucency in the mandible and / or maxilla region, sometimes presenting bone necrosis in the head of the condyle, the signs and symptoms varying according to the region and type of joint involved[2].

Regarding the mandible and maxila the sign and symptoms include mobile teeth, pain, malocclusion, deviation of mandible and clinically obvious facial deformity. Obstructive sleep apnea syndrome has been noted secondary to posterior mandibular displacement after extensive osteolysis. Pathologic fracture of mandible may also occur. Involvement of temporomandibular joint (TMJ) by Gorham syndrome can be mistaken for TMJ dysfunction[8].

The pathological process is characterized by the replacement of normal bone with non-neoplastic vascular tissue, with an aggressive behavior, similar to a hemangioma / lymphangioma. In the early stage of the lesion, the bone is reabsorbed and replaced by hypervascular fibrous connective tissue and/or angiomatous. Histologically, the presence of vessels with thin walls is verified, which can be capillary, sinusoidal or cavernous. In late stages, there is a progressive destruction of bone, with the appearance of fibrotic tissue and massive osteolysis[4].

III. Diagnostic

The phenomenon of the extensive disappearance of an entire bone, such as the clavicle, scapula, or humerus, is quite distinct from the thinning of bone which occurs in atrophy from disuse. It also differs from the acute inflammatory atrophy associated with trauma described by Sudeck and from lytic processes in bone due to tumor, hyperparathyroidism, and other knowts causes. Osteolysis of notable degree has been observed in rheumatoid arthritis, leprosy, malum perforans pedis, and congenital pseud arthrosis, but in these cases a considerable portion of the affected bone remains, and the disease does not lead to complete disappearance of a bone by concentric atrophy, with only a fibrous-tissue band left as a residuum[3].

It is necessary to make a differential diagnosis, so that there is no conflict with other pathologies that may present bone loss, such as: angiosarcoma, fibrous dysplasia, Von Recklinghausen disease

(neurofibromatosis), bone hemangioma, hyperparathyroidism, eosinophilic granuloma, hereditary osteolysis, bacterial or fungal osteomyelitis, osteopenia, osteoporosis, osteosarcoma, severe periodontitis, Winchester syndrome, glass bone syndrome, bone tuberculosis, among others[2].

Radiological examinations, notably X-rays, computed tomography (CT) and magnetic resonance imaging (MRI), associated with bone biopsy, are essential in the differential diagnosis of this rare pathology[4].

Radiographically, the precocious alterations consist of foci of intramedullary radiolucency of varying sizes and ill-defined margins. These coalesce, becoming larger and involving the cortical bone. Eventually, large portions of the bone involved disappear. As the process evolves, new areas of involvement demonstrate loss of lamina dura and narrowing of the cortical plaques before the development of obvious radiolucency. In some cases the destruction can mimic periodontitis or periapical inflammatory disease[6].

During the initial stage of the lesion, radiolucent foci appear in the intramedullary or subcortical regions, resembling findings seen in patchy osteoporosis. Subsequently, slowly progressive atrophy, dissolution, fracture, fragmentation and disappearance of a portion of the bone occur with tapering or "pointing" of the remaining osseous tissue and atrophy of soft tissues. Panoramic radiograph shows resorption and decreased vertical height of the mandibular body with the resorption extended towards the basal bone[8].

In histological review Gorham and Stout (1955) always report the partial dilation of the spinal cord (when it still remains), with the filling of red blood cells with dilated capillaries (both large and small), usually with thin walls and the presence of red blood cells, spaces with free anastomosis, with swollen endothelial cells and bone remains in dilated spaces[3].

Regarding the mandible in the histological reviews carried out by Gorham and Stout (1955, p. 1000), they show a case that: A woman, thirty-six years old, with no definite history of injury, complained of pain in her jaw. Roentgenograms showed total absorption of the mandible, with extension to the maxilla and to the palatine and sphenoid bones. No definite diagnosis was made, but 'connective tissue and capillariesâ' were noted in the biopsy specimen of the maxilla (...) Re-examination of the slide showed only a small amount of the maxillary bone. There had been a marked proliferation of thick-walled vessels, some of which appeared to be arterioles and venules in the gum which impinges upon the alveolar process. Most of these contained few red blood cells or none. In only one marrow space did dilated thin-walled capillaries filled with red blood cells appear"[3].

As for Gorham-Stout syndrome in mandible, a final diagnosis of Gorham- Stout syndrome is difficult. Laboratory findings are not specific and are of no value in the diagnostic procedure. Radiographs provide the most significant clues for obtaining a diagnosis. In early X- rays, Johnson and McClure noted evidence of one or multiple centromedullary and subcortical radiolucencies, usually with indistinct margins and no sclerotic borders. Later, these lesions may enlarge and fuse together, causing a disruption of the cortex and then intraosseous and extraosseous resorption. CT scanning and three-dimensional reconstruction are more useful for accurately assessing the range of bone destruction at the time of diagnosis. MRI is used to define the extent of vascular formation and the involvement of the adjacent soft tissue. The histological findings depend on the phase in which the disease is diagnosed. In the first of the two phases, the bone-displacing fibrous tissue section exhibits a higher concentration of blood vessels, whereas only fibrous tissue is detected in the second phase[9].

IV. Evolution of treatments

The therapies are very varied, depending on the time of pathological manifestation, type of diagnosis, line of action of the team, among others. Below is a table, as a suggestion for differences in treatment lines between authors and a graph for better visualization of the frequency of therapeutics indications.

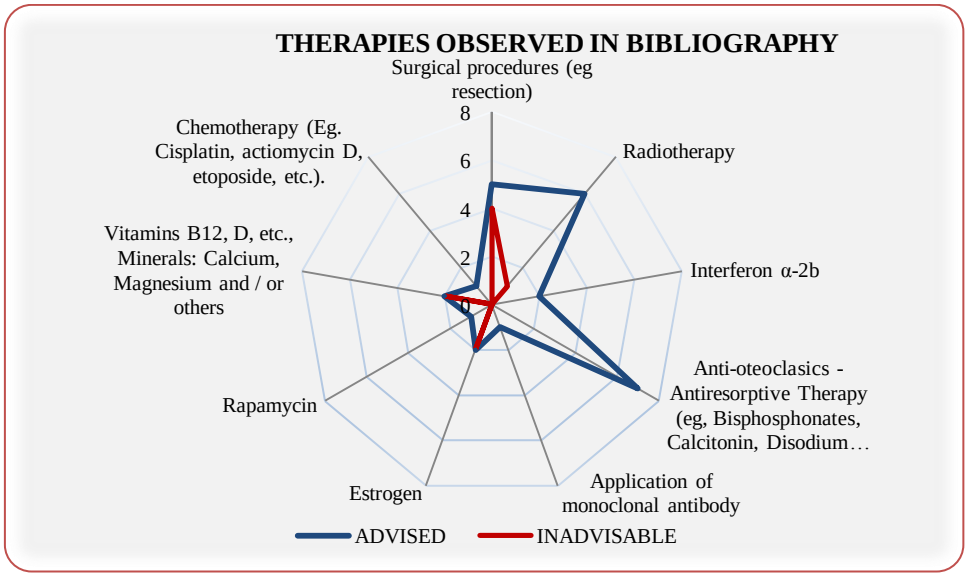
EVOLUTION OF THERAPIES

Authors	**Treatment (recommendations or citation)**	**Not recommended**
Gorham, Stout (1955, 985) *apud* Leriche (1937)[3,10]	Periarterial sympathectomy produces an extraordinary curative effect [3,10]	
Möller (1999)[11]	(505) "It seems reasonable to suggest that antiresorptive therapy, for example with bisphosphonates or calcitonin, started in an early phase of the disease, could lead to a dramatic improvement in the treatment of progressive osteolytic changes"[11].	502 "(...) treatment by local resection, with or without replacement by a prosthesis, radiotherapy or even amputation has been tried. Curettage with incomplete resection rarely cures the disease. Bone grafts will be resorbed. Radiotherapy using total doses from 30 Gy up to 45 Gy has been reported to arrest the osteolysis, but not

		all cases respond. Immobilisation of the affected bone does not influence the prognosis. Improvement did not occur after the administration of oestrogen, androgen, magnesium, calcium fluoride, adrenal extracts, vitamin D, aluminium acetate solution, ultraviolet radiation, ionised calcium, somatotrophin, placental extracts, vitamin B12, amino acids, or transfusions of placental blood or blood from growing young children"[11].
Benhalima (2001)[12]	(38) Surgical intervention and radiation therapy are suggested methods of treatment. Radiotherapy provided better results in selected cases, with a total dose of 35 to 45 Gy. But the possibility of spontaneous recession anticipates any conclusion as to the efficiency of irradiation. Surgical reconstruction should always be performed in the inactive phase, as homologous grafts can also undergo resorption[12].	(38) Removal of pathological angiomatous tissue was generally inefficient [12].
Patel (2005)[13]	(70) Various therapeutics modalities have been used in the treatment of Gorham-Stout Syndrome. Non-surgical options include radiotherapy, anti-osteoclastic medication (bisphosphonates), and interferon alfa-2b. Operative options include: surgical resection, reconstruction with bone graft, or prosthesis [13].	(70) The success rate after using a bone graft is low. Most surgeons, based on their personal experience, have observed that the bone graft undergoes dissolution. In recent years, most patients have been treated with surgery and / or radiation therapy [13].
Neville, Damm, Allen, Bouquot (2009)[6]	(625) Reported therapies include: estrogens, magnesium, calcium, vitamin D, fluorine, calcitonin, interferon alfa-2b and chemotherapeutic agents (eg cisplatin, actinomycin D, etoposide). Surgical intervention has limited success. When surgical removal is combined with bone graft placed undergoes new bone osteolysis. Radiotherapy is the most successful and widely accepted mode of therapy, but failures can occur. In addition, this therapy exposes the patient to a risk of post-irradiation sarcoma. In a limited number of patients, disease stabilization has been reported after bisphosphonate therapy, although long-term studies are needed to evaluate this treatment modality [6].	(625) Treatment is not particularly satisfactory. (625) The effectiveness of any therapeutic intervention is difficult to assess, not only because the syndrome is very rare, but also because the condition can stop spontaneously in some patients [6].
El Kouba et alii (2010)[14]	(619) Treatment should be instituted when the process is progressive and osteolysis is extensive. It is based on local resection, with or without prosthesis, radiotherapy or amputation. (622) It seems sensible to treat patients with this disease with anti-resorptive therapy such as bisphosphonates and calcitonin, which should be started at an early stage in an attempt to reduce the progression of the osteolytic process. However, there is still a lack of studies proving these data due to the rarity of	(619) Incomplete resection of the lesion is rarely curative, and the bone lysis process is perpetuated. Immobilization does not alter the prognosis, as does the administration of estrogen, androgen, magnesium, calcium, adrenergic extracts, vitamin D, aluminum solution, ultraviolet radiation, somatotrophin, placental extracts, vitamin B12, amino acids or blood transfusion of growing children[14].

	the syndrome [14].	
Coelho, Graça, Caseiro-Alves (2013)[7]	(42) The treatment of Gorham-Stout Syndrome is controversial, and there are no validated therapies, however, there are some publications reporting advantages in the use of interferon a-2b, bisphosphonates, steroids and low-dose radiotherapy. Surgical treatment is also an option, and includes locais resections of the affected bone, with or without placement of prostheses or bone grafts[7].	(42) Recurrence is common, with resorption in bone grafts, they should be used only after complete stabilization of the osteolytic process[7].
Dong, Zhang, Sun,Guo (2013)[9]	(162) "Radiotherapy and etidronate therapy were proposed to the patient...[9]"	
Guruprasad, Prabhakar, Hemavathy, Chauhan (2014)[5]:	(169) Most patients were treated with surgery and / or radiotherapy [5].	
SÁ et alii (2015)[4]	(241) Most patients are treated with radiotherapy and surgical procedures [4].	(241) There is no established effective therapy [4].
Bocchialini, Ferrari, Burlini (2017)[15]	(113) "In our case, the patient initially underwent pharmacological therapy with vitamin D, calcium, and bisphosphonates. Due to the extent of the lesion, and because the disease is often self-limiting, conservative treatment appeared to be an appropriate choice in our case"[15].	
Lova (2018)[16]	(100) Moderate dose radiotherapy (40-45 Gy in fractions of 2 Gy) also proved to be effective. Current clinical trials are evaluating the effectiveness of rapamycin [16].	(100) Surgical intervention with bone grafts or prostheses is also done widely, but with limited success[16].
Hassani (2019)[17]	(2) "Recently, a new treatment method has been introduced that applies monoclonal antibody against vascular endothelial growth factor" (3) "Our treatment with an oral bisphosphonate (alendronate 70mg per week) for four months not only stopped the bone osteolysis but also improved her symptoms and bone quality"[17].	

The graph below shows an analysis of the bibliography with emphasis on the therapies observed, to facilitate the understanding of the various treatments of Gorham-Stout Syndrome.



Surgery is not indicated until the pathological process has stabilized, especially with regard to any type of graft, as they are usually lost. The bibliography shows that surgery to remove angiomatous tissue is not successful. It is worth mentioning that in some situations total or partial arthroplasty is necessary, however, as already mentioned, only when the pathology stabilizes.

There is still a great indication for radiotherapy, where different types of dosages appear in the bibliography. Antiosteoclastics as anti-resorptive therapy were also widely indicated as inhibitors of bone resorption, being indicated: bisphosphonates (main recommendation), calcitonin and disodium etidronate, varying the indication between the authors.

It is worth mentioning that rapamycin is being studied for its role as an inhibitor of T lymphocytes, however, research is still inconclusive due to the rarity of Gorham-Stout Syndrome. Also, therapy with monoclonal antibodies is being studied.

In all cases, where surgery does or does not occur, appropriate physiotherapy is advised, especially in the case of surgeries, which, consequently, should be referred to physiotherapy, pre and post surgery.

Regarding physiotherapy this syndrome seriously compromises hard tissues to the point of disintegration, the physiotherapy procedure has to be very well decided and planned with the team, especially with regard to the maxilla and mandible. In this case, the decision depends on the stage of the syndrome. It is worth mentioning that, just as in medicine and dentistry, there are no proven efficient therapies, the same applies to physiotherapy, due to the rarity of Gorham-Stout syndrome [2].

The action of physiotherapy in the initial phase should be aimed at stretching and muscle strengthening before the total disappearance of the mandible or maxilla bone. It is suggested cryotherapy, moist heat, laser therapy, if there is drainage edema, stretching of the muscles that involve the jaw with projection, retraction and lateralization movements, raising and lowering the jaw, active exercises, among others. It is also important to stretch and strengthen the muscles responsible for supporting the head[18].

The stretching of these muscles can be done with hydrotherapy, for example Watson, due to having some movements that facilitate the patient's adaptation to passive movements. In the most serious situations when the disappearance of the mandibular and / or maxilar bones has already occurred, damaging the joint, since it will inevitably reach the head of the mandible, damaging the TMJ, at this stage there is a need for arthroplasty, in many cases, with replacement of the mandible or hemimandible by an arthrodesis of the TMJ with prosthesis of the mandible and / or maxilla, needing to start the postoperative physiotherapy as soon as possible[18].

Physiotherapy should intervene giving guidance for daily life activities, protect joints and promote range of motion, mitigate the stage of inflammation by promoting analgesia and edema reduction, maintaining and / or strengthening muscles, among others, which can be done through cryotherapy, laser therapy, lymphatic drainage, kinesiotherapy, proprioceptive exercises, among other procedures. In analgesia procedures, cryotherapy can be the choice, as well as lymphatic drainage to decrease post-surgical edema. Infrared heat therapy can also be a great help in this procedure and can be used at the end of the session, but never followed by cryotherapy. It is worth mentioning that ice packs must be applied with a protective wrap in the region and must not exceed 20 minutes of application. If necessary, for longer periods, opt criocruff. Laser therapy, therapeutic ultrasound, galvanic current and transcutaneous electrical neurostimulation (TENS) in the region

close to the prosthesis are not recommended, as they cause energy and heat and can heat the prosthesis, causing internal burns [2,18].

It cannot be forgotten the strengthening of other muscles involved Temporomandibular movements depend on the synergy of several muscles, where they stand out: masseter, medial and lateral, temporal, pterygoids, in addition to the digastric, sternohyoid, sternothyroid, styloid, geniohyoid, infrahyoid, mylohyoid, omohyoid, suprahyoid and thyrohyoid[19].

It should be noted that there is still no drug or surgical therapy, observed in the international literature, which can be indicated for all cases of Gorham-Stout syndrome, due to its rarity. However, in terms of current events, radiotherapy, antiosteoclasts and rapamycin have stood out. However, in all cases physiotherapy is indicated to strengthen the muscles involved, which was treated in the first trial by Guedes, Guedes II and Guedes (2018).

V. Conclusion

As it is a very rare syndrome that can also affect regions of the skull and jaw, it is of great importance that the dental surgeon is able to diagnose Gorham-Stout syndrome and be able to work in a multidisciplinary study and treatment team. this pathology.

In the research carried out, no effective treatment was identified in the literature that can be indicated in all cases, varying from the situation and the degree of bone loss, thus requiring further scientific studies on this pathology. However, there were strong trends in surgery, radiotherapy and treatment with various types of bisphosphonates. However, in recent years there have been trends in innovative treatments such as: application of monoclonal antibodies, rapamycin and associated treatments.

Further studies should be carried out to increase the bibliography of this pathology and to provide scientific support for efficient and effective treatments and bases for meta-analysis.

NOTE: The health area is very dynamic, so many procedures mentioned here can change, requiring the reader to update periodically.

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