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Drug-induced Gingival Enlargement – Part II
Antiepileptic Drugs: Not Only Phenytoin is Involved

Katia Lin, Laura M. F. F. Guilhoto, Elza Márcia Targas Yacubian

Associação Brasileira de Epilepsia

ABSTRACT

Introduction: Gingival enlargement is the term now used to describe medication-related gingival overgrowth or gingival hyperplasia, a common reactionary phenomenon that occurs with the use of several types of therapeutic agents, including antiepileptic drugs. This disorder has been recognized since 1939, shortly after the introduction of phenytoin. **Methods:** Review of literature concerning etiology, pathogenesis and management of antiepileptic drug induced gingival enlargement. **Conclusions:** It is important that neurologists become aware of the potential etiologic agents of antiepileptic drug induced gingival enlargement and its characteristic features in order to be able to prevent, diagnose and successfully manage it.

Key words: gingival enlargement, phenytoin, antiepileptic drugs, adverse effects.

RESUMO

Hipertrofia gengival medicamentosa – Parte II. Drogas antiepilépticas: não exclusividade da fenitoína

Introdução: Hipertrofia gengival é o termo usado na atualidade para descrever aumento gengival ou hiperplasia gengival, um fenômeno comum que ocorre com o uso de vários tipos de agentes terapêuticos, incluindo drogas antiepilépticas. Este distúrbio foi descrito em 1939, logo após a introdução da fenitoína. **Metódos:** Revisão da literatura em relação a etiologia, patogênese e manejo da hipertrofia gengival induzida por drogas antiepilépticas. **Conclusões:** É importante que neurologistas estejam conscientes dos agentes etiológicos em potencial da hipertrofia gengival induzida por drogas antiepilépticas e de suas características a fim de preveni-la, diagnosticá-la e tratá-la de modo satisfatório.

Unitermos: hipertrofia gengival, fenitoína, drogas antiepilépticas, efeitos adversos.

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INTRODUCTION

"Gingival enlargement" is the term now used to describe medication-related gingival overgrowth or gingival hyperplasia and can be defined as an abnormal growth of the periodontal tissue.[1] The term "gingival hyperplasia" is an inappropriate term because enlargement is not the result of an increase in the number of cells, but rather an increase in extracellular tissue volume.[2]

Gingival enlargement produces aesthetic changes and clinical symptoms including pain, tenderness, bleeding, speech disturbances, abnormal tooth movement, dental occlusion problems, enhancement of caries development and periodontal disorders.[3] It may be caused by medications, including antiepileptic drugs (AED)[4-7], genetic abnormalities, such as hereditary gingival fibromatosis,[8] proliferative lesions, etc.[9]

This article reviews the etiology, pathogenesis and AED associated with gingival overgrowth, in addition to its multidisciplinary management and prevention.

PERIODONTAL ANATOMY

The periodontium comprises the tissues that surround and support the teeth, including the gum and tooth anchorage: the periodontal ligament, tooth cementum, and the alveolar bone.[3]

The gum is a mucous membrane that covers the dental arches, extending between the teeth to which it is adhered closely. Histologically, the gum consists of an epithelium, connective tissue with fibroblasts and the extracellular matrix (largely made up of collagen fibers and ground substance – sulfated glycosaminoglycans).[3]

The regulating cell of the gingival connective tissue is the fibroblast, which synthesizes and breaks down the collagen fibers and the ground substance. The *periodontal ligament* is a connective tissue structure that surrounds the dental root and connects it to the alveolar bone, with insertional, remodeling, nutritive and sensorial functions. The *tooth cementum* is a hard structure, similar to bone tissue, whose function is to maintain the size of the root and guarantee the anchorage of the tooth. Finally, the *alveolar bone* is the structural tissue, to which the fibers of the periodontal ligament are anchored.[3]

PATHOGENESIS OF GINGIVAL ENLARGEMENT – AN HISTORICAL PERSPECTIVE

Drug-induced gingival enlargement (DIGE) associated with chronic use of the AED phenytoin was first reported in 1939 by Kimball.[10] In the same year, Faurbye and in 1959, Strean & Leoni suggested that the alkalinity of phenytoin might be the cause of the gingival side effect.[11,12] In 1948, Brandon hypothesized that phenytoin had a direct action on the gingival tissues.[13] In 1975, Angelopoulos argued that phenytoin induced degranulation of mast cells which resulted in the generation of a substance that increased collagen formation.[14] Larmas, in 1976, suggested that phenytoin had a proliferating effect primarily on the basal cell layer of the oral epithelium thus increasing the epithelium-connective tissue interface area, which was confirmed by Hassel et al.[15,16] Furthermore, the oral epithelium may have an inducing effect on the underlying fibroblasts, in which specifically alkaline phosphatase may be involved.[15] In 1977, Vogel speculated that phenytoin-induced gingival enlargement was due to an end-organ folic acid deficiency, which could lead the gingival tissues susceptible to inflammation by causing degenerative changes in the gingival sulcular epithelium, the main physical barrier against local irritants.[17]

Gingival enlargement is associated with multiple factors including inflammatory (acute and chronic), idiopathic, drug-induced, neoplasia (benign and malignant tumors), hormonal disturbances, ascorbic acid (vitamin C) deficiency and with dental eruption.[3] After that, gingival hypertrophy related to phenytoin, has been described as one of the DIGE. Currently, more than 15 drugs have been identified as possible causative agents, including oral contraceptives.[18,19] However, there are 3 classes of drugs that are well-established causes of gingival enlargement, being responsible for most cases: AED, antihypertensive calcium antagonists and immunosuppressant cyclosporine. One property that is common to these 3 classes of drugs is that they all directly affect cellular calcium metabolism. Since cellular production of collagenase is modulated by calcium influx, fibroblasts from patients treated with these drugs may produce an inactive form of collagenase, being responsible for an increase in extracellular matrix.[3]

The precise mechanism by which drug-induced gingival enlargement occurs is still not completely understood, although a number of hypothesis have been suggested.[14] Phenytoin probably interacts with a subtype of susceptible fibroblasts, cyclosporine affects the metabolism of these cells and nifedipine enhances this effect reducing their metabolism.[9,18] Several factors may influence the relationship between the various implicated drugs and components of the gingival tissues, including: age, genetic predisposition, pharmacokinetic variables, drug-induced alterations in gingival connective tissue homeostasis, ultra structural factors and inflammatory changes, drug-induced action on growth factors, etc.[20]

Three significant factors which are important in the expression of these gingival changes can be considered: drug variables, plaque-induced inflammatory changes in the gingival tissues and genetic factors – the latter determining the heterogeneity of the gingival fibroblasts.[20] Some drugs induce a direct effect on a subgroup of

fibroblasts, named "responders", that are apparently genetically determined to be sensitive to the drug causing gingival growth. Such drugs produce a decrease in calcium influx (due to alterations in calcium-sodium exchange), which causes a decrease in cellular folic acid uptake (producing a localized folate deficiency) thus, limiting the production of the collagenase-activating enzyme (the active form of collagenase). Also, since the presence of inflammation secondary to dental plaque causes proliferative increases in connective tissue, the catabolic ability of collagenase is saturated, and the inhibited degradation of the extra cellular matrix causes a local accumulation of this matrix.[3,21]

There is an inconclusive relationship between the severity of the gingival enlargement and drug dose, duration of therapy and drug concentrations in serum, saliva and gingival crevicular fluid.[22]

Several other factors may be involved in DIGE such as androgenic hormones.[23] Brown et al. (1991) have pointed out in this entity several factors: increase of sulphatid glicosamines, immunoglobulins, epithelial growing factor; calcium and sodium rupture efflux in fibroblasts, folic acid and colagenase deficiency.[21] Saito et al. (1996) have shown by immunohistochemistry studies in gingival enlargement caused by phenytoin and nifedipine that the increase in β growing factor, basic growing fibroblasts factor, its receptors and glicosaminoglicans heparan sulphate are involved; this was confirmed in other studies.[24,25] The clinical presentation of gingival hypertrophic and inflamed tissues is associated with specific macrophagic phenotypic picture that express β citocine IL-1 in tissues or platelet growing factor. Iacopino et al. (1997) and Saito et al. (1999) have speculated that p53 protein expression in DIGE suggests that its pathogenesis is involved with DNA abnormalities.[26-7]

Reduction of IgA salivary levels was accounted for the cause of gingival enlargement induced by phenytoin but it was not confirmed, as well as alteration of subgingival microflora.[28-32]

CLINICAL AND HISTOLOGICAL PRESENTATION

The onset of gingival overgrowth may occur after the first month of treatment but it usually occurs not earlier than 3 months following the initiation of therapy, with a tendency to affect the gingival tissues around the labial surfaces of the anterior teeth.[33] Clinically, enlargement of the gingival tissues characteristically begins in the region of the interdental papillae, which gradually increases in size and extends laterally until adjacent papillae coalesce. If plaque control is good there will be minimal bleeding and the enlarged tissues will be of a firm consistency with a healthy pink color, but the gingival lesion will be red if inflammation is present (Figure 1). There is significant correlation between the incidence and/or severity of gingival overgrowth and the level of plaque and calculus accumulation.[19] The extension of gingival enlargement may be related to dose, duration and plasmatic levels of the drug, but there is no consensus in the subject. Growth is slow, but in severe cases it can increase to the point of full-tooth coverage and may result in gross displacement of teeth.[2]

Clinical and histopathological features do not differ greatly between the different classes of DIGE, which is characterized by excessive accumulation of extracellular matrix proteins and ground substance, with a parakeratinised epithelial layer and deep ridges penetrating into the underlying connective tissue (Figure 2). As with non-enlarged gingiva, the level of inflammatory cell infiltrate varies widely.[3,19,33]

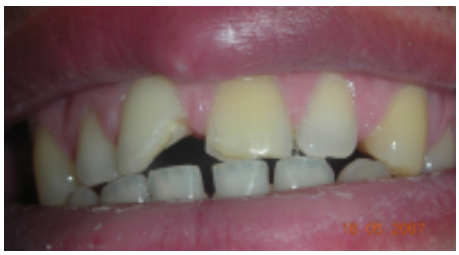

Figure 1. Clinical presentation of phenytoin induced gingival enlargement.

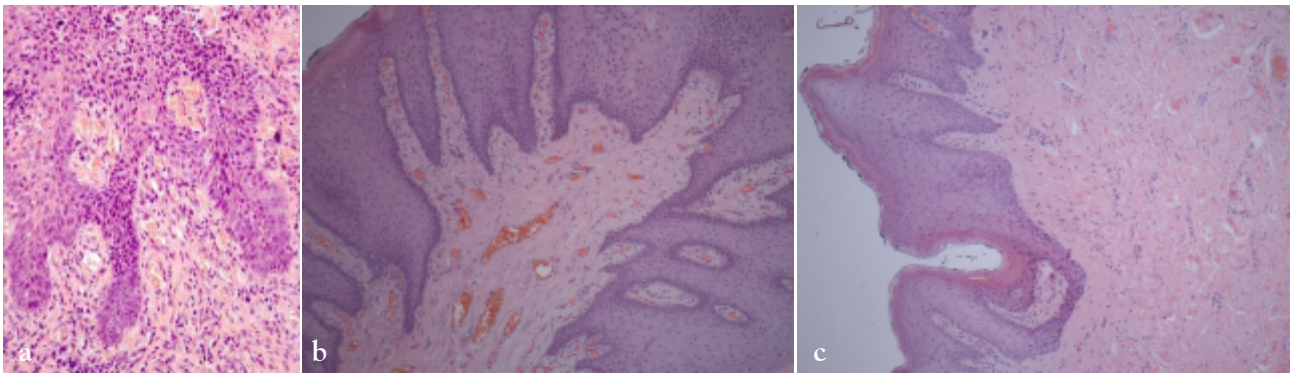

Figure 2. Hystopathologic presentation of gingival enlargement: **a** - irregular acanthosis with lymphomononuclear infiltrate; **b** - irregular acanthosis with capillary congestion and chorion fibrosis; **c** - chronic form: irregular acanthosis with mild parakeratosis and papillomatosis with chorion fibrosis.

DIGE has only been reported occasionally in edentulous patients and in primary dentitions, but has been documented adjacent to titanium dental implants with phenytoin use.[35-6]

ANTIEPILEPTIC DRUGS THAT CAUSE GINGIVAL ENLARGEMENT

In 1938, Merritt and Putnam published their noteworthy data using phenytoin to treat major, absence and psychomotor seizures.[37] Since that time, phenytoin has been demonstrated to be a highly effective anticonvulsant. Phenytoin has been investigated as a treatment for more than 100 diseases. In dermatology, phenytoin has been investigated to treat ulcers, epidermolysis bullosa, and inflammatory conditions due to its inhibitory effect over collagenase, facilitating collagen deposition; stimulation of fibroblast proliferation and antibacterial activity, facilitating the healing of ulcers; also has complex effects on the immune system, in particular an induction of a T-helper-2-type response, which might underlie its common induction of eruptions and immunologic effects.[38]

Gingival enlargement is one of the most frequent adverse effects associated with the administration of phenytoin. Incidence rates have ranged from 3 to 93%, but about 50% of patients on long-term phenytoin therapy develop gingival enlargement.[39-43]

Long-term phenytoin can also lead to a coarsening of the face, enlargement of the lips, and thickening of the scalp and face.[39] Both genders and all races are susceptible to phenytoin-induced gingival enlargement. Those affected are largely adolescents and young adults, and less frequently, the elderly.[3] Gingival enlargement becomes clinically noticeable within 2 to 3 months after initial administration of phenytoin and reaches its maximal severity after 12 to 18 months.[38]

Other AED have also been linked to gingival overgrowth, specifically valproic acid and phenobarbital. However, prevalence rates have been not studied.[44-52] There have been rare reports on primidone and vigabatrin.[53,54] Zonisamide and phenytoin have been described to alter dentin formation and bone mineral density of the mandible in growing rats.[55]

TREATMENT AND PREVENTION

Ideally, the treatment of choice for medically induced gingival overgrowth would be discontinuation of the associated medication. Nevertheless, this approach is often not possible.[56-7]

Effective treatment of a condition such as this generally focuses on correction of the aesthetic and/or functional problems that result, and can be divided into either nonsurgical or surgical alternatives.[19]

Nonsurgical therapy

Given the significance of plaque and calculus as a risk factor for exacerbation of gingival overgrowth, initial periodontal therapy should be aimed at reducing the inflammatory component comprising comprehensive oral hygiene advice to ensure optimal home care along with regular professional debridement. Prophylaxis includes oral hygiene instructions with frequent and correct brushing of teeth, and use of floss and rinses. The use of a 0.2% chlorhexidine mouthwash has been shown to be a highly beneficial adjunctive regimen to mechanical oral hygiene methods. The administration of folic acid (topical and/or oral) could ameliorate gingival overgrowth in some cases, but its specific role has not clearly been established.[3,19]

Spontaneous remission of DIGE has been shown to take place following a change in medication to one that is not associated with gingival changes combined with presence of good oral hygiene.[19] Dahllof et al. found that bucco-lingual overgrowth decreased significantly within one month of phenytoin withdrawal, and by 6 months was reduced 30% in the absence of professional prophylaxis; however, unfortunately not all patients respond to this mode of treatment, especially when the gingival lesions have been long-standing.[33,43]

Surgical therapy

Definitive treatment involves surgical elimination of the excess gingival tissue through implementation of either the gingivectomy procedure or periodontal flap approach. The clinician's decision to choose between these two surgical techniques should be made on an individual basis, encompassing careful consideration of the following aspects: the extent of area requiring surgery; the presence of periodontitis and osseous defects; the amount of keratinized gingival, and the position of the base of the pockets in relation to the existing mucogingival junction; the use of carbon dioxide laser surgical therapy is also becoming more common in treatment of gingival overgrowth due to its advantages in postoperative haemostasis.[1]

Although recurrence can occur in some cases, meticulous home care, chlorhexidine gluconate rinses, and close 3-monthly maintenance and professional debridement following surgery will minimize this possibility. Relapse may occur 3-6 months after surgical treatment, but in general maintenance of surgical results for at least 12 months are reported.[19]

CONCLUSION

DIGE may occur in patients taking therapeutic dosages of AED, mainly, but not only phenytoin. Its clinical appearance is similar in most cases and the comprehensive management may be challenging and multidisciplinary in nature.

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Endereço para correspondência:
Associação Brasileira de Epilepsia
Rua Botucatu, 740 – Vila Clementino
CEP 04023-900, São Paulo, SP, Brasil
Tel.: (11) 5549-3819
E-mail: abe@epilepsiabrasil.org.br