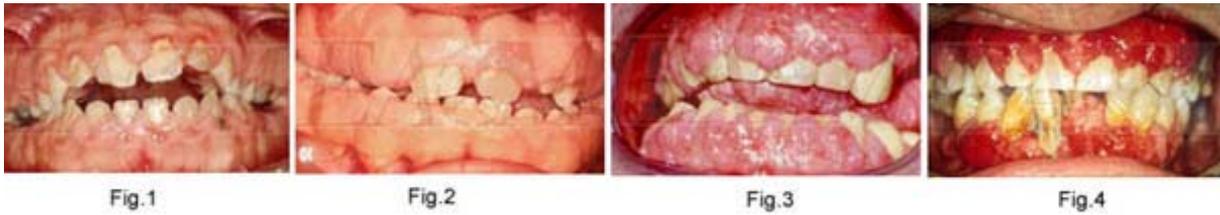


DRUG-INDUCED GINGIVAL OVERGROWTH



Definition

Many terms have been used to describe gingival overgrowth. The expression *gingival hyperplasia* (“abnormal increase in the number of normal cells in a normal arrangement in an organ or tissue, which increase in volume”) and *gingival hypertrophy* (“enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells”) have been also used, although gingival overgrowth is the general term that better describes this iatrogenic condition.

Drug-induced gingival overgrowth occurs as a side effect of some systemic medications. The pharmacological agents mainly associated with gingival overgrowth are:



- phenytoin (Fig.1 and Fig.2), a drug used for the management of epilepsy, and other anticonvulsants such as sodium valproate, phenobarbital, vigabatrin;



- ciclosporin (Fig.3), an immunosuppressant drug used to reduce organ transplant rejection;



- calcium-channel blockers (Fig.4) (nifedipine, verapamil, diltiazem, oxodipine, amlodipine), a group of anti-hypertensive drugs.

Other drugs, such as antibiotics (erythromycin) and hormones, have been also associated with this side effect.

Epidemiology

Not all the patients using these agents are affected by gingival overgrowth, and the extent and severity are variable in such patients.

Phenytoin-induced overgrowth may be present in 50 to 100% of patients treated with such drug, whereas ciclosporin and calcium channel blocker-induced overgrowths seem to be less common, ranging from 15-85% and 10-30% respectively.

Although gender and age may not be relevant risk factors for phenytoin-induced overgrowth, among patients taking ciclosporin and/or nifedipine, males may be at higher risk than female.

The relationship between age and gingival overgrowth is uncertain; some authors have described young age as risk factor, but other studies have not confirmed such finding. Age is not an applicable risk factor for the calcium channel blockers since the use of the drugs is usually confined to the middle aged and older adult. Nevertheless, in patients treated with both ciclosporin and calcium channel blockers, age has been identified as a risk factor.

A correlation with dosage, duration, drug concentrations (in blood and whole saliva) and severity/extent of gingival enlargement has also been suggested, but so many variables (sampling technique, pharmacokinetic factors) can influence this aspect, that it remains controversial. However, it has been recently reported that patients treated with ciclosporin solution experience earlier onset of gingival changes and more extensive overgrowth than patients using capsules.

Clinical presentation

The gingival overgrowth usually starts from the papillary regions. As the process develops, the papillae increases in size and the margins and gingival attachment may also become involved. The anterior segments and the labial gingiva are most commonly involved, but the enlargement may also be observed in the molar regions, particularly in the late stages of disease. Some case reports have also described overgrowth of edentulous ridges and elsewhere.

Clinical features of the gingival overgrowths are very similar, independent of the drug implicated. However small differences have been described: in cases due to anti-epileptic drugs, gingivae are firm and pale because of the conspicuous fibrous component, while other drug-induced gingival enlargements are characterised by a nodular lobulated spongy aspect and secondary inflammation that may induce oedema, ulcerations and bleeding on brushing.

Etiopathogenesis

The pathogenesis of drug-induced gingival overgrowths is still not completely understood. It has been demonstrated that gingival enlargement has a multifactorial nature and is affected by factors such as age, demographic variables, genetic predisposition, oral hygiene status, pharmacokinetic variables and molecular and cellular changes in gingival tissues. Ciclosporin, phenytoin and calcium-channels blockers can influence the metabolism of some age-dependent hormones (i.e. testosterone) which could have a direct effect on gingival cells populations.

Some studies have demonstrated that patients developing gingival lesions have high frequency of particular HLA antigens and genetic markers (cytochrome P450, HLA-DR2,) and this appears to be related to a genetic predisposition for this pathology. Furthermore, it has also been reported that patients who expressed genetic markers such as HLA-B37 or HLA-DR1, are afforded some degree of protection against gingival overgrowth.

Changes in gingival contour seen in drug-induced gingival overgrowth may also be exacerbated by plaque-induced gingival inflammation, through a mechanism of mechanical and chemical chronic irritation.

Even drug variables such as dose, duration of therapy, serum and salivary concentration appear to be related to the pathogenesis of gingival enlargement.

Concomitant use of drugs implicated in gingival overgrowth is likely to increase the incidence and degree of gingival lesions, although controversy still exists. A direct effect of ciclosporin, phenytoin and nifedipine (or metabolites) on the activity of some gingival cells (i.e. fibroblasts) has been demonstrated. Enhance of cells growth and of production of proteins as collagens has been observed in cultures of human gingival cells directly stimulated with these drugs.

Diagnosis

The diagnosis of drug-induced gingival overgrowth is mainly based on the clinical appearance of the gingivae and on the medical history.

The histopathological features of the phenytoin drug-induced gingival enlargements are mainly characterised by proliferation of morphologically normal fibroblasts and by an increased amount of collagen.

The histopathological features of the other drug-induced gingival enlargements are similar and characterised by a collagenous connective tissue with little or no inflammatory exudates. The connective tissue is highly vascularised and there are focal accumulations of inflammatory infiltrates dominated by plasma cells, that may be suggestive of a neoplastic process.

Treatment

Treatment of drug-induced gingival overgrowth includes surgical and/or non-surgical therapies.

Non-surgical treatment, where it is possible, is based on the interruption, modification of the dosage or replacement of the drugs.

In patients treated with ciclosporin, it seems that the contemporary use of the antibiotic azithromycin may decrease the severity of gingival overgrowth. Furthermore, in adult organ transplant patients, dosages of both prednisolone and azathioprine appeared to afford the patients some degree of "protection" against gingival overgrowth and may also reduce the severity of this side effect.

Good oral hygiene associated with the use of chlorhexidine oral rinses and frequent plaque and calculus removal procedures, could help to reduce the degree of gingival overgrowth. After the interruption of therapy or the replacement of drugs, follow-up of 6-12 months is important to evaluate the resolution of gingival overgrowth and/or the necessity of a surgical treatment.

Surgical treatment consists of removing gingival hyperplastic tissues with periodontal surgical techniques of gingivectomy and/or periodontal flaps. Gingivectomy is the treatment preferred when the gingival overgrowth involves small areas (up to six teeth), there is no evidence of attachment loss and there is at least 3 mm of keratinized tissue. The periodontal flap is preferred when the gingival overgrowth involves larger areas (more than six teeth) and there is evidence of attachment loss combined with osseous defects. CO₂ or argon-laser surgery has been proposed as surgical treatment of gingival overgrowth because of decreased surgical time and rapid post-operative haemostasis. Good oral hygiene for preventing or retarding the recurrence of the gingival overgrowth is important after surgery.

Prognosis and complications

Recurrences are frequent, particularly in patients with less than optimal plaque control and when the drug regimens cannot be modified or reduced.

As reported above, the presence of dental plaque, orthodontic and prosthetic appliances, or imperfect restorations may contribute to increase the inflammatory changes of the gingivae.

The enlarged gingivae are not only aesthetically displeasing but can occasionally interfere with occlusion, mastication and speech.

Prevention

Good oral hygiene may help to prevent the onset and development of gingival enlargement.

Further reading

- 1) Marshall RI, Bartold PM. Medication induced gingival overgrowth. *Oral Diseases*, 1998; 4:130-151.
- 2) Camargo PM, Melnick PR, Pirih FQM, Lagos R, Takei HH. Treatment of drug-induced gingival enlargement: aesthetic and functional considerations. *Periodontology* 2000, 2001; 27:131-138.
- 3) Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. *J Clin Periodontol* 2000; 27:217-223.
- 4) Seymour RA, Thomason JM, Ellis JS. The pathogenesis of drug-induced gingival overgrowth. *J Clin Periodontol* 1996; 23:165-175.
- 5) Vescovi P, Meleti M, Manfredi M, Bonanini M. Pathogenesis of cyclosporin induced gingival overgrowth. *Min Stomatol* 2003; 52:219-229.

Links

http://www.mchoralhealth.org/PediatricOH/mod7_3_6.htm

<http://www.perio.org/consumer/nifedipine.htm>

<http://www.ncl.ac.uk/dental/research/oral/periodontal.htm>