ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 7, Issue – 2, April – 2024, Page No. : 94 - 101

Drug Induced Gingival Enlargement

[1]Dr. Anil Melath, Professor and H.O.D, Department of Periodontics, Mahe Institute of Dental Science & Hospital.

[2]Dr. Subair.K, Professor, Department of Periodontics, Mahe Institute of Dental Science & Hospital.

[3]Dr. Arjun M.R, Reader, Department of Periodontics, Mahe Institute of Dental Science & Hospital.

[4]Dr.Indrajith.D, Post Graduate, Department of Periodontics, Mahe Institute of Dental Science & Hospital.

[5]Angelin Arulselvam, Final BDS , Mahe Institute of Dental Science & Hospital.

[6]Yogesh Aridhas, Final BDS, Mahe Institute of Dental Science & Hospital.

Corresponding Author: Dr Indrajith D, Mahe Institute of Dental Sciences & Hospital.

Citation of this Article: Dr Anil Melath, Dr Subair K, Dr Arjun MR, Dr Indrajith D, Angelin Arulselvam, Yogesh Aridhas, "Drug Induced Gingival Enlargement", IJDSIR- April – 2024, Volume –7, Issue - 2, P. No. 94 – 101.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Introduction

Drug induced Gingival Enlargement also known as Drug Induced Gingival Over growth, was previously known as Drug Induced Gingival Hyperplasia.

It is a side effect of certain drug classes such as anticonvulsants, immunosuppressants and calcium channel blockers, where the gingival tissue is not the intended target organ.(1)

Gingival overgrowth hinders proper dental hygiene apart from cosmetic damage, causes painful chewing & eating. There is a variable gingival response in taking drugs. Within a group of patients, there appears to be variability in the severity and extend of gingival changes.(2)

Etiology

Drugs are the most common cause for gingival enlargement. DIGO is aside effect seen is patient's taking drugs such as anticonvulsants, immunosuppressants, or calcium channel blockers. DIGO is associated with patient genetic predisposition and presence of gingival inflammatory existing plaque.(3,4)

Anticonvulsants

Phenytoin (PHT, or 5, 5- diphenylhydantoin), sodium valproate, phenobarbitone, vigabatrin, primidone, mephenytoin and ethosuximide are some of the drugs that cause gingival enlargement. It is indicated for treating temporal lobe, tonic – clonic and psychomotor seizures.(4)

Drugs causing gingival overgrowth:-

Category: Pharmacologic agent

Anticonvulsants

- Phenytoin
- Sodium Valproate
- Phenobarbitone
- Vigabatrin
- Primidone

- Mephenytoin
- Ethosuximide
- Ethotoin
- Methosuxinimide

Immunosuppressants

- Cyclosporin
- Tacrolimus
- Sirolimus

Calcium channel blockers

Nifedipine	Nitrendipine	Felodipine
Nicardipine	Manidipine	Amlodipine
Nimodipine	Nisoldipine	Verapamil
Diltiazem		

Immunosuppressants

Immunosuppressants are prescribed after organ transplantation to prevent organ transplant rejection. It is also used to treat some autoimmune disorders like rheumatoid arthritis.[5]

Cyclosporin, Tacrolimus, Sirolimusare immunosuppressants linked to gingival enlargement. Cyclosorin is the most frequently prescribed immunosuppressive drugs after organ transplant and the incidence of gingival enlargement have been found in approximately 53% of patients.[6]

Sirolimus shows predisposition to gingival enlargement. ([7,8,9])

Calcium Channel Blocker

Calcium channel blockers are used for treating hypertension,Angina pectoris and peripheral vascular disease[4]

The drugs includes nifedipine, nitrendipine, felodipine, amlodipine, misodipine, verapamil and diltiazem. In 1994, Seymoul etal reported the first case of gingival enlargement attributed to amlodipine.[9] Renal transplant patients who are under immunosuppresants like cyclosporin shows greater chances of developing gingival hypertrophy when put on nifedipine or diltiazem. However the extent of hypertrophy is more noticed with cyclosporin.[4]

Epidemology

Drug induced gingival hypertrophy is commonly seen in male children and adolescents ; more prevalence in the anterior gingival tissue. The genotype of the individual have an effect on development of DIGO[10].

It is estimated that 50% of adults treated with phenytoin suffer from gingival enlargement, 30% with cyclosporine and 20% with nifedipine.[11]

Pathophysiology

Drug induced gingival enlargement is multifactorial[2,12,4]Severity of gingival enlargement in patients taking medications correlate with poor plaque control and is categorized as plaque induced gingival diseases modified by medications under recent classification system for periodontal diseases.[4]

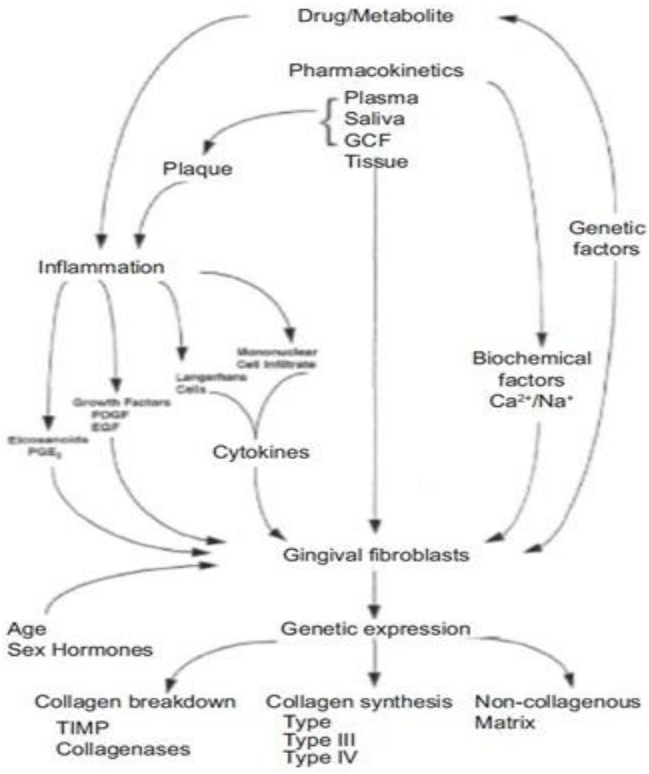

Figure 1

Schematic diagram to illustrate the potential multifactorial features and interactions involved in the pathogenesis of drug-induced gingival overgrowth.

Mechanism of DIGE

The mechanism behind DIGE is divided into non inflammatory(biochemical)and inflammatory pathways .[13,14]Non inflammatory pathways include 1) inhibitory effect of sodium /calcium ion flux upon cation channel mechanism and2) defective collagenase activity due to decreased uptake of folic acid.[15]The inflammatory pathways include, alteration in the production of inflammatory cytokines and interaction of chemotactic factors and immunological changes and inflammatory process.[16,17,18,19]

Clinical manifestations

Clinical manifestations of gingival enlargement frequently appears within 1-3 months after initiation of treatment with the associated medications.[4]

Growth starts as a painless, bead like enlargement of the interdental papilla, and extends to the facial and lingual gingival margins. As the condition progress, the marginal and papillary enlargements unite; they may develop into a massive tissue fold covering a considerable portion of crowns.[20]

Firm, painless, nodular enlargement of the interdental papilla, limited to the keratinized portions of the gingiva and extending to the facial and lingual gingival margins.

In severe cases, a huge fold of hypertrophied gingival tissue is observed covering the crowns.

If no secondary inflammation is present, it appears firm and pale pink with minute lobulations, pouting from underneath the gingival margin, delineated by a groove of tissue that does not bleed on touch.

If secondary inflammation exists, the gingiva appears smooth, and red or bluish-red.

The enlargement is generalized, but it is usually greater in the anterior regions.

Typically, it is not seen in edentulous areas.

The gingival overgrowth disappears when teeth are extracted.[21]

Phenytoin-induced gingival overgrowth generally begins in the anterior interdental gingival papillae, often within 1 month after initiation of the drug.[22]

As the gingival changes gradually become more pronounced, the marginal tissues that often extend to cover portions of the clinical crowns of the teeth become involved (Fig. 1). This involvement tends to be more pronounced on the facial than on the lingual surface of the teeth. Histologically, phenytoin-induced gingival overgrowth usually demonstrates increases in connective tissue, with no change in vascularity, and a relative decrease in epithelial thickness in comparison with normal gingiva.

Chronic inflammatory cells, mainly lymphocytes and plasma cells, may be found as gingival inflammation arises as a result of increased plaque retention.[23]

Figure 2: Phenytoin-associated gingival overgrowth. Note near-complete coverage of clinical crown.

Cyclosporine-induced gingival overgrowth is similar to phenytoin-induced gingival overgrowth.

Initially, the anterior labial interproximal gingiva becomes involved. Subsequently, the marginal gingiva,

which increases in dimension to cover portions of the clinical crowns of the teeth, becomes involved.[24]

Figure 3

Calcium channel blocker-related gingival overgrowth (Fig. 3) closely resembles phenytoin-induced overgrowth. Usually, it becomes apparent 1 to 3 months after initiation of the drug.

Specific dose or plasma levels have been associated with this type of gingival overgrowth in animal models but have not been demonstrated in humans.

One theory is that plaque accumulation as a result of inadequate oral hygiene may add to the severity of this type of overgrowth.

This relationship has been questioned by some investigators.[25,26,27,28,29]

Figure 4

Treatment / Management

The aim of treatment in DIGO is to alleviate the patients' discomfort, enabling them to do simple acts like eating and chewing pain-free, treat the inflammation, reduce the swelling, and give a better cosmetic appearance to the gingiva.

The modalities of treatment are medical and surgical. Medical management is the first line of therapy, whereas surgery is reserved for recurrences or cases that persist despite good medical treatment. Discontinuing or changing the medication must be placed under consideration.[30,31]

An alternative to phenytoin includes carbamazepine and valproic acid, which have shown a lower rate of gingival enlargement. Diltiazem and verapamil exhibit a lower prevalence of gingival enlargement compared to nifedipine. Cyclosporin substitution is more complicated because there are limited options available. Cyclosporin can be substituted by tacrolimus, and the use of azithromycin in combination with cyclosporin has shown a decrease in the severity of DIGO.[32]Plaque control should be the first step in the treatment of DIGO, correct oral hygiene, and professional plaque removal, including tooth surface cleaning and periodic scaling.[33,34]Control of inflammation, including non-steroidal anti-inflammatory agents, antibiotics to control infection, and topical antifungal medication like nystatin, may also be utilized. Folate supplementation has also been used.[35]

The primary aim of nonsurgical approaches is to reduce the inflammatory component in the gingival tissues and thereby avoid the need for surgery. Meticulous removal of plaque on a frequent basis helps in the maintenance of attachment levels. Patients at risk from, or who have developed drug-induced gingival overgrowth will benefit from effective oral hygiene measures, professional tooth cleaning, scaling, and root surface instrumentation. For some patients these measures alone could reduce the gingival overgrowth to acceptable

levels, for others, it could make surgical correction easier.[36,37,38]

Chronically immunosuppressed patients, papillary lesions present on the surface of the enlarged gingiva have been reported to resolve using topical antifungal medications (e.g. nystatin lozenges)[4].

A review of clinical trials suggests that there are some benefits associated with the use of systemic azithromycin in the management of gingival overgrowth. Lu et al. considered that drug-induced gingival overgrowth may be either prevented or treated through a pharmaceutical strategy using nonsteroidal anti-inflammatory agents to control IL-1-mediated inflammation, or by treatment with a reassuringly safe profile of low dose androgen receptor antagonists to block the androgen receptor CTGF/CCN2-collagen cascade and decrease collagen production.[39] Gingival enlargement may persist, despite drug substitution attempts and good plaque control. These cases need to be treated by periodontal surgery. Before any surgical procedure, precautions and consultations with physician regarding underlying systemic disease should be taken into consideration. The surgical management of drug-induced gingival overgrowth includes the scalpel gingivectomy, periodontal flap surgery, electrosurgery, and laser excision. The clinician's decision to choose gingivectomy or periodontal flap surgical techniques must be made on a case-by-case basis and should take into consideration the extent of area to be involved in surgery, the presence of periodontitis, the presence of osseous defects combined with the gingival enlargement lesions, and the position of the bases of the pockets in relation to the existing mucogingival junction. Nevertheless, surgical intervention using conventional means (scalpel) may sometimes be technically difficult and/or impractical for example in children or mentally handicapped, or in patients suffering from impaired hemostasis. In these situations the use of electrosurgery may be advantageous. The use of lasers has shown some utility for reducing gingival enlargement, an approach which provides rapid postoperative hemostasis.[40]

Differential diagnosis

False enlargement of gingival tissue: pseudo-enlargement of the gingiva, caused by an enlarged underlying bony tissue. The gingiva here has no abnormality.

Inflammation: chronically inflamed gingival tissue is red or violaceous, smooth, and tends to bleed on the touch.

Familial or hereditary conditions: examples include familial fibromatosis, idiopathic fibromatosis, gingivomatosis, and hereditary gingival hyperplasia. The gingiva is pink, non-tender, involves the attached gingiva, the gingival margin, and the interdental papillae, and has a firm and leathery consistency.

Physiological states: puberty and pregnancy are associated with gingival enlargement.

Scurvy: vitamin C deficiency can produce very tender bleeding gingiva.

Systemic diseases: leukemia, tuberculosis, sarcoidosis – their diagnosis can be corroborated hematologically.

Conditions similar to gingival enlargement

Fibrous epulis/peripheral fibrom

Angiogranuloma/Pyogenic granuloma

Gingival cysts

Neoplasms.[41]

Prognosis

If the medication inducing the gingival overgrowth can be changed to a drug that is less associated with this complication, the gingival tissue may return to normal with the aid of adequate plaque control. The gingival enlargement can persist, despite drug substitution and

good plaque control, and in this case, surgical management to restore normal gingival contours is required. These modalities of treatment, although effective, do not always prevent the recurrence of the enlargement. DIGO recurrence in surgically treated cases may appear as soon as three to six months after the procedure. In general, the results last for at least twelve months.[40]

Maintenance

Chlorhexidine gluconaterinses and professional cleaning can decrease the rate and the degree at which recurrence occurs. A hard, natural rubber, fitted bite guard worn at night may also assist in the control of recurrence. Recurrence may occur as early as 3-6 months after the surgical treatment, but in general, surgical results are maintained for at least 12 months.[40]

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