Drug-Induced Gingival Overgrowth – An Overview Andcurrent Concepts.

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ABSTRACT
Drug-induced gingival over growth is a condition caused by undesired effects due to the intake of certain drugs. The most commonly involved drugs are anti-convulsants, calcium channel blockers and immunosuppressants. Understanding the patho-physiological changes and reaction of gingival fibroblasts is more important however an exact pathological explanation is still not completely understood in many cases. Genetic predisposition and oral hygiene plays a major role in DIGO. The management of DIGO includes ruling out the causative agent and proper assesment of the gingival tissue, and an effective treatment which differs to each individual is established.

KEY WORDS : Drug-induced Gingival Overgrowth (DIGO), Anti-convulsants, Immunosuppressants, Calcium Channel blockers.

INTRODUCTION

Drug-induced gingival overgrowth (DIGO), is also called as drug-induced gingival enlargement. Previously it was called as drug induced gingival hyperplasia. This is a side effect of certain drugs; where the gingival tissue is not the targeted organ. It is a side effect of anti-convulsants, immunosuppressant and mostly the calcium channel blockers. The side effect of phenytoin (PHT) an anti-convulsant was first reported by Kimball in the year 1939. This Over growth can cause cosmetic problem, disturbs eating and speech, affects effective teeth cleaning and causes teeth non-alignment.This seems to exacerbate and accelerate one another in patients with gingival and periodontal enlargement.The factors such as; age,presence of pre-existing plaque, genetic predisposition,and gingival inflammation affects the relationship betweenthe gingival tissueand the drugs. The causative drug regimen can not be altered in some patients as it is essential for maintaining the patient's health. Such patients require a different treatment and care.[1]
There's been no clear cut literature which could state the pathogenesis, clinical changes, and the treatment for affected patients. There is a need for us to refine our knowledge about known drugs and familiarise with the latest drugs.

COMMON DRUGS THAT CAUSE GINGIVAL OVERGROWTH

Drugs that are commonly involved in gingival overgrowth are-

1. Anticonvulsants
2. Immunosuppressants
3. Calcium channel blockers.[2]

1. **Anticonvulsants**
   Phenytoin (PHT, or 5,5-diphenylhydantion), sodium valproate, phenobarbitone, vigabatrin, primidone, mephenytoin, and ethosuximide are some of the drugs that causes gingival overgrowth. Drugs like PHT, phenobarbitone, and primidone are metabolised to 5-(4-hydroxyphenyl) 5-phenyl hydantion (4-HPPH), responsible for the overgrowth of the gingival tissue. Phenytoin is the anticonvulsant most commonly associated with gingival enlargements.[3]

2. **Immunosuppressants**
   Cyclosporin, tacrolimus, and sirolimus are immunosuppressants connected to gingival growth, and cyclosporin is the most well-known of these. The occurrences of gingival over growth has been found in almost 53%of patients taking cyclosporin after renal transfer.[4]Tacrolimus is less harmful than cyclosporin, causing less hepatic and renal harmfulness and less extreme gingival over growth than cyclosporin.[3][7][8][9]

3. **Calcium Channel Blockers**
   The calcium channel blockers such as nifedipine, nitrendipine, felodipine, amlodipine, nisodipine, verapamil and diltiazem are used for treatment of hypertension, angina pectoris, peripheral vascular diseases. The effect of these drugs on gingiva is more when the former drugs are given in combination as they act synergistically.[10]

Epidemiology
The drug-induced gingival overgrowth is most frequently found in Male children and the adolescents and is most prevalently located in the gingival tissue anteriorly. Geneticpredisposition plays an important role, and the degree and extend of over growth is based on the drugs.[11]

Drug	Prevalence rate
Phenytoin	50%
Cyclosporin	30%
Nifedipine	20%

PATHOPHYSIOLOGY
Seymour et al. gave the theory of genetic predisposition as the important factor for Drug-induced gingival overgrowth In 1996.[2] This is supported by the fact that some individuals develop gingival overgrowth while some do not while taking the same drug. Theinflammatory response of gingival fibroblasts and the proliferation of connective tissue matrix, doesinfluences the genetic character of the individual's gingival fibroblasts in response to the drugs. [3]

1. **Gingival Fibroblasts And Cellular Folate Uptake**
   Inducing drugs go about as a trigger for the initiation and multiplication of gingival fibroblasts, causing an expanded connective tissue creation of GAGs (glycosaminoglycans).
   These drugs decrease cellular uptake of folate by genetically predispose fibroblastsDiminished intracellular folate converts into a reduction in the blend or initiation of MMPs (grid metalloproteinases), which are needed to change idle collagenase over to dynamic collagenase, permitting an abundance of connective tissue develop.

2. **Matrix Metalloproteinases**
   These are in excess of 20 compounds that achieve the corruption of connective tissue constantly rebuilding. These incorporate collagenases, gelatinases, and stromelysins. Restraint of enactment of these can bring about the amassing of extracellular framework and collagen and cause DIGO.

3. **Inflammatory Cytokines**
There are more than 20 mixes that accomplish the defilement of connective tissue continually reconstructing. These consolidate collagenases, gelatinases, and stromelysins. Restriction of authorization of these can achieve the hoarding of extracellular structure and collagen and cause DIGO. Kindled gingival tissue displays more elevated levels of interleukin-1 beta (IL-1beta), a proinflammatory cytokine.[3]

4. **Na+/ Ca2+ ion Flux Drug Mechanisms**
Fugi and Kobayashi (1990) detailed hindrance of Ca2+ take-up inside gingival fibroblasts by PHT and a few calcium channel blockers (CCBAs). Thomas and Petrou (2013) detailed a decrease in Na+ channel accessibility and, subsequently, a reduction in the activity likely sufficiency. This causes diminished Ca2+ section, and a decline in Ca2+ enacted K+ channels.

5. **Plaque Buildup**
The moved medication in crevicular gingival liquid or bacterial plaque applies a direct poisonous impact on the gingival tissue. Dental plaque incites irritation, which causes gingival abundance. Irritation causes the upregulation of changing development factor-beta 1 (TGF-beta 1). Henceforth, control of dental plaque is required in the treatment and anticipation of DIGO over the long run.

Histopathology
In DIGO, the pathology lies in the connective tissue and not the epithelial cells of the gingiva. There is an unreasonable collection of extracellular grid like collagen with fluctuating measures of incendiary invades, prevalently plasma cells. Fibroblastic expansion may not be apparent. Unpredictable segments of collagen strands are seen blended with entering epithelial edges.[3]

Clinical Features
Patients with DIGO commonly gives gingival hypertrophy, torment during rumination, and restorative deformation one to a quarter of a year subsequent to beginning treatment with one of the medications related with the sickness. They will report a previous clinical history of hypertension, angina, epilepsy, or have gotten an organ relocate as of late.[16]

Clinical Findings
1. Firm, easy, nodular growth of the interdental papilla, restricted to the keratinized segments of the gingiva and reaching out to the facial and lingual gingival edges.

2. In extreme cases, a colossal overlap of hypertrophied gingival tissue is noticed covering the crowns.

3. At occasions, it shows up firm and pale pink with minute lobulations, sulking from underneath the gingival edge, outlined by a depression of tissue which doesn't seep on contact.

4. If auxiliary aggravation exists, the gingiva seems smooth, and the augmentation is more prominent in the maxillary and front mandibular areas.

5. Typically, it isn't seen in edentulous zones of the gingiva.

As per histological and histomorphometric investigations, phenytoin-instigated sores are the most fibrotic. Cyclosporin-actuated sores are more kindled and show a low fibrotic part, and nifedipine sores are blended.[16]

EVALUATION
The determination of medication actuated gingival excess is made by clinical assessment and the patient's previous clinical history.
1. A periodontal assessment is important to assess for the presence of periodontal illness.

2. Full mouth periapical radiographs and orthopantomography are to be taken prior to starting any treatment to preclude periodontal illness.
3. Scaling and root arranging must be done.
4. Complete blood count (CBC) is shown in patients with gingival amplification if there is a presence of plentiful gingival draining regardless of whether it is drug-incited to preclude pallor and leukemia.
5. Tissue biopsy ought to be completed in the event that the introduction of the illness is irregular.
6. Histopathological assessment of continuing excesses is compulsory to assess threatening changes.[17]

TREATMENT AND MANAGEMENT

The point of treatment in DIGO is to lighten the patient's uneasiness, to have the option to do basic acts like eating and biting torment free, treat the aggravation, decrease the swelling, and give a superior corrective appearance to the gingiva.

Ceasing or changing the drug must be put getting looked at.[11] An option in contrast to phenytoin incorporates carbamazepine and valproic corrosive, which have indicated a lower sway in gingival overgrowth . Diltiazem and verapamil display lower pervasiveness of gingival broadening contrasted with nifedipine. Cyclosporin can be subbed by tacrolimus, and the utilization of azithromycin in blend with cyclosporin has demonstrated a lessening in the seriousness of DIGO.[2] Plaque control should be the initial phase in the treatment of DIGO, proper oral cleanliness, and expert plaque expulsion, including tooth surface cleaning and occasional scaling, which are fundamental.Control of irritation, including non-steroidal mitigating specialists, anti-microbials to control disease, and skin antifungal medicine like nystatin and folate supplementation may likewise be used.

The careful techniques incorporate gingivectomy and periodontal fold surgery.Electrocautery might be utilized in troublesome cases, youngsters, or where the gingiva is delicate and prone to drain.

The CO2 laser has a frequency of 10600 nm; henceforth, it is promptly consumed by water and consequently is successful in the medical procedure of delicate tissues with high water content like the gingiva.A laser is favored over the surgical tool as it has solid bactericidal and hemostatic impacts.[13]

DIFFERENTIAL DIAGNOSIS

1. False development of gingival tissue: This is pseudo-augmentation of the gingiva.
2. Inflammation: Chronically kindled gingival tissue is red or violaceous smooth and seeps on contact.
3. Familial or innate: The propensity runs in the family.
4. Physiological states: Puberty and pregnancy are related with gingival growth.
5. Scurvy: Vitamin C inadequacy can deliver exceptionally delicate draining gingiva.
6. Systemic infections: Leukemias, tuberculosis, sarcoidosis.[14]

In every one of these conditions, an intensive history, actual assessment, and examinations, including biopsy, might be needed to affirm the etiology.

PROGNOSIS

The gingival growth can continue, regardless of medication replacement and great plaque control, and for this situation, careful administration to reestablish typical gingival shapes is performed. The repeat of DIGO in carefully treated cases, which are normal, may show up when three to a half year after the method. As a rule, the outcomes keep going for in any event a year.[15]

PATIENT EDUCATION

The patients must be instructed about sufficient brushing and flossing procedures that might be joined by chlorhexidine gluconate flushes to control the degrees of bacterial plaque. Ordinary meetings with their dental specialist must be refined to perform proficient cleaning of the teeth. These measures can forestall or diminish the rate and the degree at which repeat happens.[15]

CONCLUSION

Drug induced gingival overgrowth is one of the most inescapable undesirable impact of foundational medicine on the periodontal tissues. Subsequently, it is appropriate to recognise and investigate conceivable danger factors identifying with both pervasiveness and seriousness of medication instigated gingival abundance. Fresher atomic methodologies are expected to obviously build up the pathogenesis of gingival excess and to give novel data to the plan of future preventive and helpful modalities.

REFERENCE:

1. Marshall RI, Bartold PM. Medication induced gingival overgrowth. Oral Dis. 1998 Jun;4(2):130-51
2. Seymour RA, Thomason JM, Ellis JS. The pathogenesis of drug-induced gingival overgrowth. J ClinPeriodontol. 1996 Mar;23(3 Pt 1):165-75.
3. Dongari-Bagtzoglou A., Research, Science and Therapy Committee, American Academy of Periodontology. Drug-associated gingival enlargement. J Periodontol. 2004 Oct;75(10):1424-31.
4. Greenberg KV, Armitage GC, Shiboski CH. Gingival enlargement among renal transplant recipients in the era of new-generation immunosuppressants. J Periodontol. 2008 Mar;79(3):453-60.
5. Sekiguchi RT, Paixão CG, Saraiva L, Romito GA, Pannuti CM, Lotufo RF. Incidence of tacrolimus-induced gingival overgrowth in the absence of calcium channel blockers: a short-term study. J ClinPeriodontol. 2007 Jul;34(7):545-50.
6. Nassar CA, Nassar PO, Andia DC, Guimarães MR, Spolidorio LC. The effects of up to 240 days of tacrolimus therapy on the gingival tissues of rats--a morphological evaluation. Oral Dis. 2008 Jan;14(1):67-72.
7. Cota LO, Oliveira AP, Costa JE, Cortelli SC, Costa FO. Gingival status of Brazilian renal transplant recipients under sirolimus-based regimens. J Periodontol. 2008 Nov;79(11):2060-8.
8. Cota LO, Aquino DR, Franco GC, Cortelli JR, Cortelli SC, Costa FO. Gingival overgrowth in subjects under immunosuppressive regimens based on cyclosporine, tacrolimus, or sirolimus. J ClinPeriodontol. 2010 Oct;37(10):894-902.
9. Cota LO, Viana MB, Moreira PR, Gomez RS, Cortelli JR, Cortelli SC, Costa FO. Gingival overgrowth in cyclosporine, tacrolimus, or sirolimus-based immunosuppressive regimens and the single nucleotide IL-6 (-174 G/C) gene polymorphism. Arch Oral Biol. 2010 Jul;55(7):494-501.
10. Lafzi A, Farahani RM, Shoja MA. Amlodipine-induced gingival hyperplasia. Med Oral Patol Oral Cir Bucal. 2006 Nov 01;11(6):E480-2.
11. Doufexi A, Mina M, Ioannidou E. Gingival overgrowth in children: epidemiology, pathogenesis, and complications. A literature review. J Periodontol. 2005 Jan;76(1):3-10.
12. Diesel A, Moriello K. Medical Management of Cyclosporine-Induced Gingival Overgrowth Using Oral Azithromycin in Six Dogs. Vet Sci. 2015 Feb 05;2(1):13-22.
13. Mavrogiannis M, Ellis JS, Thomason JM, Seymour RA. The management of drug-induced gingival overgrowth. J ClinPeriodontol. 2006 Jun;33(6):434-9.
14. Agrawal AA. Gingival enlargements: Differential diagnosis and review of literature. World J Clin Cases. 2015 Sep 16;3(9):779-88.
15. Camargo PM, Melnick PR, Pirih FQ, Lagos R, Takei HH. Treatment of drug-induced gingival enlargement: aesthetic and functional considerations. Periodontol 2000. 2001;27:131-8.
16. Bharti V, Bansal C. Drug-induced gingival overgrowth: The nemesis of gingiva unravelled. J Indian SocPeriodontol. 2013 Mar;17(2):182-7.

17. Samudrala P, Chava VK, Chandana TS, Suresh R. Drug-induced gingival overgrowth: A critical insight into case reports from over two decades. J Indian SocPeriodontol. 2016 Sep-Oct;20(5):496-502.