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İlaca Bağlı Dişeti Büyümeleri ve Tedavi Yaklaşımları

Drug-induced Gingival Enlargement and Treatment Modalities

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ÖZET
Antikonvülsanlar, kalsiyum kanal blokerleri ve immünosupresanlar dişeti büyümesine neden olan temel ilaç gruplarındandır. İlaca bağlı dişeti büyümelerinin nasıl meydana geldiği tam olarak bilinmese de yaş, genetik ve ilaçların farmakokinetik özellikleri gibi birçok faktörün dişeti büyümesi patogenezinde rol oynayabildiği bildirilmiştir. Bireyin genetik özelliklerine bağlı olarak, ilacın dişeti üzerine etkisi değişebilmektedir. Bu makale, ilaca bağlı dişeti büyümelerinin prevalansı, risk faktörleri, patogenezi ve tedavi yöntemleri ile ilgili bir derlemedir.
Anahtar Kelimeler: ilaca bağlı dişeti büyümeleri, antikolvülsan, kalsiyum kanal blokeri, immünosupresan

ABSTRACT
Anticonvulsants, calcium channel blockers and immunosuppressants are the main drug groups that may lead to gingival enlargement. Although the underlying mechanism of drug-induced gingival enlargement is uncertain, it has been reported several factors such as age, genetics and pharmacokinetic properties of the drugs can play role in pathogenesis of gingival enlargement. The effect of drug on gingiva can vary depending on the genetic characteristics of individuals. This article is about the prevalence, risk factors, pathogenesis, and clinical management of drug-induced gingival enlargement.
Keywords: *drug-induced gingival overgrowth, anticonvulsant, calcium channel blocker, immunosuppressant*

INTRODUCTION

Hyperplasia is defined as the increase in the volume of an organ or part of it which is resulted from the increase of the number of the cells in the regarding tissue. Hypertrophy on the other hand, is growth of the tissue due to the volume enlargement of its component cells. Drug-induced gingival enlargements are hyperplastic in their nature. They make plaque control difficult along with esthetic problems, formation of pseudopockets and increase in the microbial activation of the periodontal pocket which results in destruction of the periodontal tissues.[1, 2] Anticonvulsant, immunosuppressant and calcium channel blockers are the main drug groups that lead to gingival enlargement which is proved in several studies.[3-5] Clinically, drug-induced gingival enlargements can impede the oral functions of the patients, pave the way for periodontal destruction, increase plaque accumulation, lead to halitosis and cause psychological problems by affecting esthetics and phonetics.[6] In addition, oral infections originated from gingival enlargement can affect the systemic health of the patient.[7] This situation mostly appears on organ transplanted patients who are under cyclosporine A treatment and have gingival enlargements due to those drugs.

Drug-induced gingival enlargement has been associated with phenytoin for the first time by Kimball in 1939.[8] Up to now three different group of drugs has been linked with gingival enlargement. These are; Anticonvulsants, immunosuppressants and calcium channel blockers.[9] Despite the fact that the drugs that cause gingival enlargement have different pharmacologic effects, they all exhibit common histopathologic findings in the connective tissue.[10]

Types of pharmacologic agents

a. Anticonvulsants

The major drug in this group is phenytoin, a derivative of hydantoin. Other derivatives of hydantoin, which causes gingival enlargement, are ethotoin, mephenytoin, succinimide, methsuxinimide and valproic acid.[10] Phenytoin is an antiepileptic drug that is used since 1938 for treatment of grand mal and temporal lobe type epilepsies. It is used for some type of neuralgias and cardiac arrhytmia, too. Phenytoin usually is used per os and absorbed slowly by the gastrointestinal system. It is 90 % bounded to the plasma proteins and metabolized in liver by CYP 450 enzyme. [11, 12]

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b. Immunosuppressants

Immunosuppressive drugs cause suppression or selective inhibition on several components of the immune system. Most of these drugs are used for the treatment of transplant rejection reactions created by CD4 type lymphocytes, diseases leading to development of autoimmunity (rheumatoid arthritis, systemic lupus erythematosus etc.), psoriasis and atopic dermatitis. They prevent acute allograft reactions strongly. Immunosuppressants enhanced the success ratio of organ transplantation and their usage became routine in the last 40 years. However, their effects on subsequently developing chronic rejection reaction are low yet. They are used in high doses to prevent rejection reactions in initial period that has higher risk of rejection and in lower doses for maintanance treatment in following several years. The most significant disadvantages of immunosuppressive drugs are impairment of the immune system against infections and malignancy and increasing the risk of neoplasm development (30-40% of transplanted patients in 30 years) in long-term users.

The drugs that cause immunosuppression are mainly glucocorticoids, antiproliferative drugs and calcineurin inhibitors.[13]

Cyclosporine A, which is one of the calcineurin inhibitors, that is obtained from a fungi called Tolypocladium inflatum gams. Because its effect on immunosuppression is proved in lots of experimental models about tissue and organ transplantation, cyclosporine A is used common in clinical practice nearly 30 years.[14] It is a selective immunosuppressant. It impedes IL-2 secretion from helper T-lymphocytes. As a result of insufficient production of IL-2, formation of cytotoxic T-lymphocytes is avoided selectively. In addition, it blocks IL-2 receptors located on cytotoxic T-lymphocytes. Thus, the activity of cytotoxic T-lymphocytes, which cause the rejection of transplanted graftis blocked. While helper and cytotoxic T-lymphocytes are susceptible to cyclosporine A; suppressor T-lymphocytes are resistant. Cyclosporine A does not disrupt the function of suppressor T-lymphocytes. In this way, acceptance of transplanted graft is achieved.[15] Rateitschak-Plüss et al has shown the side-effect of the drug on gingival enlargement in 1983.[16] There are many studies reporting varying degrees of gingival enlargement develops because of the usage of cyclosporine A.[17, 18, 19]

c. Calcium channel blockers

Calcium channel blockers are drugs that are used for treatment of hypertension, vasospastic angina, supraventricular arrhythmia and myocardial infarction.[13, 20] They stop calcium intake into the cells by blocking the slow calcium channels. They especially block calcium entrance into the cardiac and smooth muscle cells. Consequently, a decrease in contractility and oxygen consumption of cardiac muscle occurs.[21]

Drugs that are defined as calcium channel blockers are grouped as below [22]:

Derivatives of dihydropyridine (nifedipine, nicardipine, felodipine, amlodipine, nitrendipine, isradipine etc.)

Derivatives of phenylalkylamine (verapamil, gallopamil etc.)

Benzodiazepines (diltiazem)

Pathogenesis of Drug-induced Gingival Enlargements

Although the clinical symptoms and prognosis of the gingival enlargement are well-known; its pathogenesis is not clarified yet.[4] Several factors play role in pathogenesis of gingival enlargement. These can be listed as age, genetics, pharmacokinetic properties of the drugs, changes occuring in the connective tissue of the gingiva due to drugs, histopathological, structural and inflammatory changes, and the effects of these drugs on the growth factors.[23] (Figure-1) Drugs that induce gingival enlargement do not show the same impact on every patient. In the patients who are taking the drug and exhibit gingival enlargement; a susceptible fibroblast population might be involved.[24, 25] Furthermore, polymorphisms in the genes of cytochrome P450 enzyme and variety of human lymphocyte antigen (HLA) phenotypes, may be other reasons of the difference between patients.[17, 9]

Some of the research mention that the severity of the gingival growth is dependent on the dose of the drug, their concentrations in the plasma, saliva and gingival sulcus and duration.[26, 27] (Figure-1) In contrast, some of the research does not support the same relationship.[28, 29] Different degrees of inflammation can be observed in drug-induced gingival enlargement. The degree of the inflammation depends on the dosage, type and usage time of the drug, oral hygiene habits of the patient, environmental factors and individual susceptibility determined by genetic factors.[6, 30]

Histopathology of Drug-induced Gingival Enlargements

The common histopathologic finding of all drug-induced gingival enlargements is the increase in connective tissue matrix. In several cell culture studies it has been outlined that collagen synthesis from fibroblasts induced by drugs is important in terms of pathogenesis of gingival enlargement. However, the differences in the results can be based on the variety of the experiment techniques and heterogeneity of fibroblasts extracted from the gingiva.[23]

Histologically both epithelium and the connective tissue modify drug induced gingival enlargement cases. Epithelium shows different degrees of acanthosis. Thin and long retepegs can be observed. Main alterations in lamina propria are proliferation of fibroblasts and the increase in collagen synthesis.[31] In patients with phenytoin induced gingival enlargement, *the connective tissue* contains much more non-collagen matrix than collagen matrix. This non-collagen matrix consists of proteoglycan and glycosaminoglycan. The level of non-collagen matrix in phenytoin using patients is high

compared to normal gingival tissue.[31-33] In gingival fibroblasts of patients with phenytoin induced gingival enlargement huge amount of sulfate mucopolysaccharide and large secretory granules are seen.[33, 34] Kato et al.[35] showed that phenytoin doesn't affect the proliferation of gingival fibroblasts, yet by repressing matrix metalloproteinase (MMP)-1, MMP-2 and MMP-3, and inducing matrix metalloproteinase tissue inhibitor-1, impedes collagen destruction.

Histochemically, nifedipine induced gingival growth and phenytoine induced one are similar to each other. Gingival fibroblasts obtained from both of them, contains sulfate mucopolysaccharides in large quantities and large secretory granules.[35]

Prevalence

Phenytoin induced gingival enlargement is observed approximately in 50% of the patients (within the range of 0% to 84,5%) using the drug.[11, 12, 36, 37, 38] Similar to phenytoine, gingival enlargement is not observed in every nifedipine using patient, incidence of gingival growth is approximately 20%.[20]

Most of the organ transplant patients use nifedipine too together with cyclosporines. It is found that, when these two drugs are used combined, the incidence of gingival enlargement increase. [12, 39, 40] (Figure-1) In kidney transplant patients, the incidence of gingival enlargement is 8% when cyclosporines are used alone, while it is 51% when two drugs are used combined.[39] The other calcium channel blockers such as amlodipine, nitrendipine, felodipine and verapamilde also cause gingival enlargement. However, the incidence of gingival growth caused by those drugs is pretty lower than nifedipine induced growth.[41]

Clinical manifestations

Drug-induced gingival enlargements are mostly seen in the anterior region on the buccal aspects of the teeth. They usually appear early in life, following 3-6 months of drug usage. Lesions usually initiate from the gingival papilla without any pain and in 12 months they reach their maximum severity. At that level, the lesions in the gingival margin and the papilla can unite and turn into a mass that covers the coronal part of the teeth. In the beginning, hyperplastic tissue does not bleed easily, seems pale pink, nodular and fibrotic, however; in case of inflammation erythema, edema and bleeding may be observed in the tissue. Although it can be seen in all around the mouth, labial surfaces of *maxillary* and mandibular anterior teeth are more common. Periodontal tissue damage is not seen in most of the cases.[42]

The incidence and severity of gingival enlargement due to phenytoin usage is maximum in labial surfaces of mandibular and *maxillary* anterior teeth.[36] (Figure-2) Three months after initiation of the treatment, the enlargement begins to occur and makes its peak in the first year.[43] First findings of the growth are seen in papilla region as swellings. Afterwards, gingiva expands and gains a nodular appereance. The nodules extend in both labiolingual and coronal directions. They diminish as they get closer to mucogingival junction.[38] The color of gingiva changes from dusty-rose to bluish red, due to presence of inflammation.

Nifedipine induced gingival enlargement was first reported in 1984. Gingival growth starts soon after drug usage and regresses as soon as quitting the drugs. Gingival enlargement is especially obvious in labial surfaces of maxillary and mandibular anterior teeth, and it doesn't occur in edentulous regions.[3] The gingival growth looks like phenytoin induced growth as color, stiffness and contour. Generally it starts from interdental papilla. These enlargements can be edematous or fibrotic depending on the degree of inflammation caused by local factors.[11] Fibrotic enlargements are generally limited; however growth towards coronal can be observed, too. This can effect both the function of mastication and oral care habits which may lead to periodontal disease as well as creating esthetic problems.[44] (Figure-3)

Drug induced gingival enlargement in the oral cavity due to immunosuppressants usage starts within 6 months after the transplantation, it can be in varying sizes, from a slight change of interdental papilla to surrounding all the dental crown. Gingival enlargement generally is located on vestibule surfaces of the teeth. (Figure-4) Consequently, disorder in speaking and occlusion, difficulty in mastication occurs. These lead to undernutrition and change in dentition chronology especially in children. Gingival enlargement also impairs oral care. And this may result as formation of oral sepsis foci, which can cause serious outcomes, especially in patients whose immune systems are suppressed.

Risk factors

It has not been clarified yet why gingival enlargement is observed in some patients while it's not in others.[45, 46] Lack of good plaque control and the presence of gingivitis, independently from the drugs used, aggravate the drug-induced gingival enlargements. [11, 47, 48] Most of the evidence about the relationship between bacterial plaque and gingival enlargement was obtained from cross-sectional studies. It is not clear exactly whether plaque is an aggravating factor of gingival enlargement or forms as a result of morphological changes in the gingiva.[9]

Treatment of Drug-induced Gingival Enlargements

In treatment of drug-induced gingival enlargements, the first step is to improve the level of oral care. Although quitting the drug or reducing the usage is the definite treatment, it is not always possible in most of the patients. When the prevalence and severity of gingival enlargement is high, surgical treatment is inevitable. Gingivectomy and other operational tecniques can be considered as surgical treatment. Regardless of the preferred surgical approach, recurrence is observed after a period of time, depending upon the drugs used.[2]

Treatment can be arranged in 3 steps:

Step 1: First of all, the patient's physician should be consulted about stopping of replacing the drug. Quitting the drug is not possible usually, but it can be replaced with another one. Carbamazepine and valproic acid, as an alternative to phenytoine, cause very little gingival enlargement. As an alternative to nifedipine, diltiazem or verapamil, which are calcium channel blockers that cause gingival enlargement less often, can be preferred. Rather than calcium channel blockers, other antihypertensive drugs, that do not result in gingival growth, can be utilized. Replacing cyclosporine A with other drugs is very limited. Recently, some studies, that show regression in gingival growth when cyclosporine A is replaced with tacrolimus, are published.[49]

Step 2: The physician should emphasize the importance of plaque control. In drug-induced gingival enlargement cases, pseudo pocket can be formed and this situation, that facilitates the accumulation of plaque, raises the probability of occurrence of periodontitis. A good plaque control also helps in the prevention of the recurrence of the growth in surgically treated cases.

Step 3: In some cases, despite all the recommendations above, gingival enlargement continues. These type of cases should be treated surgically. Two surgical methods are used for this purpose: gingivectomy and flap operations. The selection of appropriate technique depends on the severity of the growth and tissue structure. If gingiva is still soft and fragile after the initial periodontal treatment, gingivectomy is performed. Gingivectomy is an extremely effective method of treatment in cases without attachment or bone loss. On the other hand, if gingivectomy technique will create mucogingival problems, then flap technique should be preferred.[50] The advantages of flap surgery are lack of large wound surface left for secondary wound healing and less postoperativebleedingand discomfort.[51] Second alternative to conventional gingivectomy in drug-induced gingival enlargement cases is laser-assisted gingivectomy. Advantages of laser applications are; sterilization of the operation area, less bleeding during the excision, faster healing potential, and minimal post- operative discomfort.[52]

Generally, recurrence is often unavoidable in drug-induced gingival enlargement cases although the surgical procedure and ensuring post-operative hygiene. In a study performed by İlgenli et al, in 18 months following the active treatment, 40% recurrence of cyclosporine A or nifedipine induced gingival enlargement is observed after periodontal surgery. Gingivectomy should be repeated periodically in individuals constantly using drugs and with severe gingival enlargement because of the repetitive nature of the drug-induced gingival growth.[53]

Conclusion

Anticonvulsants, immunosuppressants and calcium channel blockers are the main drug groups that lead to gingival enlargement. Phenytoin-induced gingival enlargement is observed approximately in 50% of patients using the drug whereas cyclosporin and calcium channel blocker-induced gingival enlargement seem to be less common, ranging from 20-45% and 20% respectively. Although the mechanisms that trigger drug-induced gingival enlargement have not been completely understood, it has been demonstrated that several factors such as genetics and pharmacokinetic properties of the drugs may play role. The gingival enlargements are more severe in the maxillary and mandibular anterior regions and often result in aesthetic disfigurement.

The treatment of drug-induced gingival overgrowth should be planned carefully by considering the patient's systemic condition as a priority. Consultation with patient's physician to replace the drug with another one if possible, should be the first step of treatment. Following nonsurgical therapy when necessary, surgical treatment should be performed. Periodic periodontal maintenance is also crucial to minimize the recurrency.

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