Drug induced gingival overgrowth – a retrospective study

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Abstract

Aims: The aim of this study was to determine the presence of drug-induced gingival overgrowth in patients admitted to one clinic between 2003 and 2007, and to explore whether the patients' gender and age affected the likelihood of drug induced gingival overgrowth. ***Methods:*** The clinical charts of patients who were treated in a clinic between 2003 and 2007 were reviewed to identify how many patients presented with drug induced gingival overgrowth. The patients' gender and age were recorded as well. ***Results:*** A total of 26 patients presented with gingival overgrowth between 2003 and 2007. Eleven of these patients were diagnosed with drug-induced gingival overgrowth (six due to phenytoin; five due to nifedipine; no patient with cyclosporine A-induced gingival overgrowth). Gingival lesions were more likely to be found in male patients who had taken phenytoin (five males vs. one female patient). No significant differences were found in the ages at which gingival overgrowth occured. Phenytoin-induced gingival overgrowth occurred on average 24 months after phenytoin treatment was initiated and nifedipine-induced gingival overgrowth after 60 months. Oral hygiene was poor in all 11 patients. In the remaining 15 patients, gingival overgrowth was caused by bacterial plaque, leukemia, and pregnancy. The number of patients with nifedipine- and phenytoin-induced gingival overgrowth (N=11) was close to the number of patients with gingival overgrowth due to other factors (N=15), namely due exclusively to bacterial plaque (N=12), leukemia (N=1), and pregnancy (N=1). ***Conclusion:*** The long-term administration of phenytoin and nifedipine for the treatment of various disorders in combination with poor oral hygiene can cause generalized gingival overgrowth. Surgical treatment and change of medication are necessary when gingival manifestations cause functional disorders.

Key words: phenytoin, nifedipine, drug induced, gingival overgrowth, reshaping, side effects.

Introduction

Gingival overgrowth is a disorder with multiple causes. Its pathogenesis and causal mechanisms are not well defined. Over the years, several terms have been used to describe this phenomenon. The most commonly used terms are gingival hyperplasia and gingival hypertrophy. Gingival hyperplasia is a term used when an exaggerated growth of gingival tissue takes place because of an increase in the number of cells, but without changes in cell size. The term gingival hypertrophy is used when an exaggerated growth of gingival tissue is due to an increase in the size of its constituent cells. However, both terms do not accurately reflect the gross and histological appearances of gingival overgrowth [1].

Gingival overgrowth can be caused by a variety of factors. However, it is always exacerbated by the local accumulation of bacterial plaque. Gingival overgrowth can be hereditary, idiopathic, associated with systemic diseases, or drug induced. Drugs causing gingival overgrowth are phenytoin which is an anticonvulsant, cyclosporine A which is an immunosuppressant, and some dihydropyridine derivatives of calcium channel blockers such as nifedipine.

The anticonvulsant phenytoin has been used since 1938. The reported prevalence of phenytoin-induced gingival overgrowth has ranged from 13 to 50% of the patients studied. The calcium channel blocker nifedipine is frequently used in the treatment of hypertension. Gingival overgrowth secondary to nifedipine therapy was first reported in the early 1980s, and was found in 15 to 20% of the cases [2]. Diltiazem, verapamil, and in some cases amlodipine and felodipine, have also been reported to potentially cause gingival overgrowth [3]. Immunosuppressive drugs are used both in the treatment of autoimmune disorders and for preventing rejection in organ transplant recipients. Cyclosporine A has been the drug of choice since the first kidney transplant in humans in 1965. The prevalence of cyclosporin A-induced gingival over-

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growth depends on an individual's susceptibility which is present in over 70% of the adult patients receiving a transplant [2].

Aims

The aim of this study was to determine the incidence of gingival overgrowth caused by two of these three types of drugs (nifedipine and phenytoin) in patients admitted to a clinic between 2003 and 2007, and to explore how the patients' age, gender, treatment duration, and oral hygiene was related to gingival overgrowth. All patients with drug-induced gingival overgrowth received surgical treatment.

Methods

This study was a retrospective analysis of the charts of patients treated at the Department of Oral and Maxillofacial Surgery, St Spiridon Hospital, Iasi, Romania between 2003 and 2007. During these five years, 12.408 patients were admitted to this clinic of which 268 patients (2.15%) presented with gingival benign/malignant lesions. Twenty-six of these 268 patients (9.70%) presented with gingival overgrowth due to various causes, with 11 of the 26 patients (42.30%) presenting with drug-induced gingival overgrowth. The gingival overgrowth of the remaining 15 patients was due to bacterial plaque (12 cases), pregnancy (one case), and leukemia (one case).

Results

Of the 11 patients with drug-induced gingival overgrowth, the lesions were caused in six cases by phenytoin, and in five cases by nifedipine. No case of cyclosporine A-induced gingival growth was recorded. *Table 1* shows that most cases, namely five cases, were admitted in 2003**.**

An analysis of the gender of the patients with drug-induced gingival overgrowth showed that seven patients were male and four patients were female *(see Table 2).* Five of the six patients with phenytoin-induced overgrowth were male, while the gender distribution among the patients with nifedipine-induced overgrowth was more equal. The age distribution of the cases showed that drug-induced gingival overgrowth was not more frequent in patients in different age groups *(Table 2).*

The gingival manifestations secondary to phenytoin use occurred on average two years after the initiation of therapy, while those secondary to nifedipine administration on average occurred five years after the therapy began.

An analysis of the oral hygiene status of these patients based on the presence of bacterial plaque, calculus deposits as well as the presence of multiple non-recoverable radicular remnants in the dental arches showed that four patients in each group had unsatisfactory oral hygiene. In the patients with phenytoin-induced gingival overgrowth, the gums were pale, brilliant, of firm consistency, while the gums of the patients with nifedipine-induced gingival overgrowth had a spongy, nodular appearance, secondary to the inflammation that caused oedema, ulcerations and bleeding upon tooth brushing.

The degree of gingival overgrowth was assessed with McGaw and Lam's measurement system in which grade 0 indicates the absence of gingival overgrowth, grade I gingival growth at the level of interdental papillae, grade II gingival overgrowth at the level of interdental papillae and gingival edges, and grade III a generalized gingival overgrowth covering over 3/4 of dental crowns. All five cases of nifidipine-induced and all six cases of phenytoin-induced gingival overgrowth were rated as grade III gingival overgrowth.

All patients presenting with generalized gingi-

Table 1. *Overview of the number and percentages of patients with drug-induced gingival overgrowth by year*

Year	**Drug-induced gingival overgrowth cause by:**					
	Phenytoin		**Nifedipine**		**Total**	
	Frequency	**%***	**Frequency**	**%**	**Frequency**	**%**
2003	2	7.69%	3	11.54%	**5**	19.23%
2004	2	7.69%	0	0%	2	7.69%
2005	1	3.85%	0	0%	1	3.85%
2006	0	0%	1	3.85%	1	3.85%
2007	1	3.85%	1	3.85%	2	7.69%
TOTAL	**6**	23.08%	**5**	19.24%	**11**	42.31%

Legend: * The reported percentages are computed based on the total number of patients with gingival overgrowth admitted between 2003 to 2007 (N=26).

Table 2. *Age and sex distribution of the patients with drug-induced gingival overgrowth*

Age	Phenytoin				Nifedipine			
	Women	Men	Total		Women	Men	Total	
	Number of cases	Number of cases	Number of cases	%*	Number of cases	Number of cases	Number of cases	%
0–10 years	0	0	0	0%	0	0	0	0%
11–20 years	0	0	0	0%	0	0	0	0%
21–30 years	1	1	2	7.69%	0	0	0	0%
31–40 years	0	1	1	3.85%	0	0	0	0%
41–50 years	0	1	1	3.85%	1	0	1	3.85%
51–60 years	0	1	1	3.85%	1	0	1	3.85%
61–70 years	0	0	0	0%	0	1	1	3.85%
71–80 years	0	1	1	3.85%	1	1	2	7.69%
Total	**1**	**5**	**6**	**23.1%**	**3**	**2**	**5**	**19.25%**

Legend: * The reported percentages are computed based on the total number of patients with gingival overgrowth admitted between 2003 to 2007 (N=26).

val overgrowth were treated with gingivectomies and gingivoplasties. Oral rinsing with antiseptic solutions was administered, and the change of the medication inducing gingival overgrowth was recommended.

Discussion

Gingival overgrowth is a side effect of certain systemic drugs (anticonvulsants, antihypertensives, and immunosuppressants). In this study, the specific drugs identified as causing gingival overgrowth were nifedipine and phenytoin. Despite the fact that the pharmacological effects of these classes of drugs are different and the primary target tissues are not the same, the secondary target seems to be the connective gingival tissue [4, 5]. In the case of phenytoin, most pathogenic theories focus on gingival fibroblasts, which interact with phenytoin and/or its metabolites [4, 6]. Thus, it is believed that phenytoin selects sub-populations of fibroblasts that stimulate protein synthesis and collagen production [4, 7]. Other authors point out the role of intracellular calcium in the pathogenesis of phenytoin-induced gingival overgrowth [8, 9].

Nifedipine also induces gingival overgrowth. The true incidence of nifedipine-induced gingival overgrowth is unknown because most publications on this topic are case reports. The pathogenesis of gingival overgrowth associated with the chronic administration of nifedipine is not fully understood. Barak et al. 1987 [10] suggested that it is caused by changes in Ca^{+2} metabolism, while Glefand et al. 1986 [11] argued that nifedipine can act indirectly by stimulating the production of IL-2 trough T cells or testosterone metabolites [12].

The interaction between calcium channel blockers and other drugs, such as phenytoin and cyclosporine A or their metabolites, and gingival fibroblasts are calcium-dependent. These drugs, which affect the calcium metabolism of transport, might stimulate - in some patients - the hyperplasia of extracellular matrix constituents such as the accumulation of glycosaminoglycans [4, 13].

Despite all this research evidence, the pathogenesis of these gingival lesions is still unclear. It is more than likely that it is multifactorial. Periodontal variables, inflammatory cytokines, growth factors, pharmacokinetic variables, and genetic predisposition can all play a role in the occurrence of drug-induced gingival overgrowth [14]. In addition, risk factors such as age, gender, oral hygiene, and the duration of the systemic therapy administration should be included in research as well [15]. In spite of studies confirming the relationship of age with gingival overgrowth, this relationship is still not clearly supported by all evidence [16].

In this study, the age distribution of the patients with gingival overgrowth showed that five patients with nifedipine treatment were over 50 years of age. This finding is not surprising because antihypertensive medication is largely recommended for the treatment of middle-aged and older adults. On the other hand, of the six patients receiving phenytoin for seizures, four were in the third and fourth decade of life. Thus, age does not seem to be an important risk factor for nifedipine or phenytoin-induced gingival overgrowth.

As to the gender, some studies have demonstrated a certain predilection either for the male [16] or female sex [17].

Guncu et al. (2007) [18] conducted a study with 18 patients (seven males and 11 females) with nifedipine treatment and were unable to find any gender related difference. Because of the small number of cases (seven males and four females) included in this study, a definitive conclusion cannot be drawn.

Concerning the time of onset of gingival manifestations following phenytoin and nifedipine administration, the literature presents conflicting findings. Gingival manifestations following phenytoin treatment initiation were reported to occur after one [19] to ten years [20]. In our study, phenytoin-induced gingival manifestations occurred after two, eight and ten years, respectively, a finding that is consistent with the data reported in the literature. As to nifedipine-induced gingival manifestations, research showed that the onset of gingival overgrowth is usually between six to nine months after therapy initiation [7, 18, 21]. Our data showed that the onset of gingival manifestation was after five years of treatment. It is possible that the onset was actually earlier, possibly occurring several months after the initiation of the treatment, but that the patients were not aware of this onset until the gingival manifestations became generalized, significant, and caused functional disturbances.

Another risk factor for drug-induced gingival overgrowth is gingival inflammation due to bacterial plaque [1, 17, 18]. In our study, this factor played an important role in generalized gingival overgrowth in four cases in each group. The big size of the lesions (grade III according to McGaw and Lam) and the associated aesthetic and functional disturbances found in all study patients required modelling gingivectomies. The postoperative outcome was good in all patients. Medication change and an improvement of oral hygiene efforts prevented recurrences.

Conclusions

The pathogenesis of drug-induced gingival overgrowth is multifactorial. Age, gender, and duration of drug administration are not risk factors of drug-induced gingival overgrowth.

Surgical treatment and medication change are necessary when gingival overgrowth is voluminous and causes aesthetic and functional disturbances.

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