Cyclosporine-A Induced Gingival Overgrowth

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Abstract

Background. The link between the gingival overgrowth and cyclosporine pharmacokinetical variables, especially cyclosporine doses which appear to act as stimulator of the gingival proliferative changes, presents a field of interest of large number of researches. The existence of undefined association and/or interaction between the cyclosporine and periodontal variables, could be responsible for this type of gingival overgrowth. The aim of this study was to examine the correlation between the degree of gingival overgrowth, daily doses of cyclosporine A and parodontal parameters.

Methods. 120 patients with renal transplants were included in this examination. The cohort was divided into a four groups according to the daily dose of cyclosporine (100, 125, 150, 175 mg).

The degree of gingival overgrowth (GOI) was investigated, using a MacGaw index. The plaque index (PI), apical migration, total daily doses of cyclosporine and plasma concentration, was recorded for various groups and a prospective longitudinal follow - up was conducted.

Results. Statistically significant correlation was found between GOI and cyclosporine dose ($\rho = 0,3$; p < 0,01) and also with dental plaque ($\rho = 0,6$; p < 0,01), gingival inflammation ($\rho = 0,3$; p < 0,01) and lost attachment ($\rho = 0,1$; p < 0,05). The lost attachment varied significantly between groups, (p < 0,05). Gingival inflammation index (GII) also differed among groups with different dose (p < 0,01). Our findings showed differences in gingival overgrowth index between groups (p < 0,05).

Conclusions. Our results show a positive correlation between gingival overgrowth and pharmacological parameters, especially the high doses (above 175 mg) of cyclosporine and also with parodontal parameters which lead to parodontal destructions. Additionally, we underlined the effect of local factors as a cofactor in the development of this side effect.

Key words: gingival overgrowth, cyclosporine A, renal transplants recipients, dental plaque, periodontal destruction.

Introduction

The gingiva and associated soft tissues of the periodontium may be enlarged in response to various interactions between the host and the environment. Although such enlargement usually represents an inflammatory response to bacterial plaque, increased susceptibility as a result of systemic factors or conditions should always be considered during the course of patient evaluation (2).

Cyclosporine A (CyA) has been widely used for its ability to act as a safe, low - toxicity immunosuppressant with a potential application in prevention of graft rejection and management of a wide range of systemic disorders (1). This agent has a selective effect on the immune system, a feature that has led to significantly prolonged survival and improved quality of life for transplant patients. Cyclosporine exerts its effect selectively by diminishing the activity of T - helper and cytotoxic natural killer cells. It has been reported that cyclosporine exerts its inhibitory effect on

T- cells by interfering with the uptake of intracellular ionic calcium. T - suppressor cells are less affected, resulting in a net imbalance that favors suppression. The unaffected B- cell lines allow the patient to maintain an intact humoral immune response to bacterial pathogens (4).

Despite its advantages, CyA also has potentially serious side effect, such as nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, increased risk of lymphoma, and the most notable one is in terms of dental medicine is gingival overgrowth (GO) (3).

The side effect occurs in approximately 8 % to 70% of patients with an apparently wide variation in patient's susceptibility and clinical expression.

The variability of clinical expression of cyclosporine - related overgrowth implies a multifactor pathogenesis. Several factors, including age, genetic predisposition, pharmacokinetic variables, plaque - induced inflammatory and immunological changes, and activation of growth factors, are believed to be important in the onset of CyA induced GO (5). External irritants, such as dental plaque and calculus as well as orthodontic and prosthodontic appliances, seem to increase the severity of gingival overgrowth.

Plaque is known to induce many inflammatory changes in gingival tissue. It is suspected that the various cells that mediate plaque production might also modulate the fibroblast - drug interactions in GO (5).

From recent studies, CyA- induced gingival overgrowth has been suggested to represent a tissue with relatively increased amount of non - collagenous matrix and relatively decreased collagenous matrix, compared to normal gingival tissue.

Kristina Mitic, Dental Clinical Center "St. Pantelejmon", Clinic for Periodontology; Vodnjanska 17 St, 1000 Skopje, R. Macedonia; Tel.: +389 70 350 909; Fax.: +389 2 3227 080; E-mail: bijanmitic@mt.net.mk The heterogeneous clinical response appears to be related to variations in host susceptibility to the drug or its metabolites. This could be a result of differences in subpopulations of fibroblasts or a varying predisposition of the gingiva to invasion by microorganisms as a result of cyclosporine interference with the T - cell immunity (6).

The pathogenesis of these side effects remains uncertain. Some studies suggest that drug pharmacokinetic variables are important in the expression of the gingival changes (7), whilst others implicate periodontal variables, in particular patient's oral hygiene, as being an important determinant (8, 9, 10, 11). Furthermore, the effect of age, duration of drug therapy, transplant type, genetic factors on the patient's susceptibility to the drug might also influence such conditions.

The existence of undefined attitudes about the interaction between the medicament - dental plaque, would have the primate in the ethiopathogenesis of this type of gingival overgrowth. Hence, the aim of this study was to examine the correlation between the degree of gingival overgrowth, periodontal and pharmacological parameters.

Patients and methods

We examined 120 renal transplant recipients on maintenance cyclosporine therapy, at the Clinic for Paradontology, Dental Clinical Center "St. Pantelejmon" and Department of Nephrology, University Clinical Center – Skopje. All patients underwent transplantation at least 6 months previously and were treated by standard triple protocol of maintenance immunosuppression: cyclosporine A (Neoral; 6 to 8 mg/kg/day) to reach target C₂ levels (blood concentration 2 hours after administration of the drug), prednisolone (1 mg/kg/day tapered to 0.1 mg/kg/day after 4 weeks) and mycophenolate mofetil (Cellcept 1.5- 2 g/day). In addition, all patients were on maintenance dose of calcium channel blocker Diltiazem 90 mg b.i.d.

The cohort was divided in four groups according to the total cyclosporine's daily doses: first group received 100 mg, second 125 mg, third 150 mg and the forth 175 mg/day.

The age, daily doses of CyA and the duration of the prescribed dose, were recorded for all patients.

After clinical examination of patients for the presence of gingival overgrowth, further differential evaluation was performed on the basis of patient's history and x-ray results. Clinical examination and analysis of gingival status, was implemented using: plaque index (PI) of Silness & Löe (1964) to assess the oral hygiene on the lingual, labial and interproximal surfaces on the same teeth. The level of gingival inflammation was assessed using Löe - Silnes (GI) index (1964). Gingival overgrowth was evaluated using McGaw et al (14) gingival overgrowth index (GOI) for each interdentally papillae and lost attachment index (15).

Blood samples were drawn from the cubital vein, two hours after cyclosporine morning dose. Whole blood CyA levels were determined by blood polyclonal Abbott TDx fluorescence polarization immunoassay (FPIA) at the Pharmacology Institute, Medical Faculty in Skopje. Statistical analysis

The Mann -Whitney U - test was used to examine the differences between groups. The correlations between variables were determined using Spearman's rank correlation coefficient. The Kruskal - Wallis analyses of variance by

ranks were used to detect intergroup differences (A p-value <0,05 at two tailed level was assumed significant).

Results

Patients mean age at time of renal transplantation was 36.2 ± 9.5 years. The mean duration of therapy was 42.4 ± 36.2 months. Duration of therapy was not significantly correlated with the index of gingival overgrowth (ρ = 0, 03).

The mean cyclosporine concentration (ng/ml) in all four groups was presented in figure 1. As expected, a higher cyclosporine concentration was observed in the serum of patients treated with greater dose, and the highest concentration was found in the fourth group (175 mg). At figure 2 a positive correlation between serum concentration of cyclosporine and gingival overgrowth was depicted. However, the distribution of plaque index frequencies (1, 2, 3) was not significantly different among various groups of patients examined (Figure 3). Furthermore, the degree of gingival overgrowth positively correlated with the plaque index (ρ =0, 691; p<0, 01) (Figure 4).

There were significant statistical differences in the distribution of lost attachment at different groups. Further between group statistical analyses found significant differences between the first (100mg) and second group (125mg), and between second (125mg) and third group (150mg) (Figure 5).

The correlation between gingival index (GI) scores and daily doses of cyclosporine was evaluated in all four groups (Figure 6). The dose of cyclosporine positively correlated with the gingival index (ρ =0,3; p<0,01). Between group comparison showed the forth group (175mg) to significantly differ as compared to the first (100mg) and second (125mg) group; no statistically significant differences were found among the other groups.

There was a significant difference among distribution of frequency for gingival overgrowth between the examined groups (Figure 7). Furthermore, the forth group (175mg) was presented to have much higher gingival overgrowth when compared with the first (100mg) and second (125mg) group. Other significant intergroup differences were not established. In addition, the degree of gingival overgrowth was in positive correlation with the cyclosporine doses (ρ =0,3; p<0, 01).

Figure 1. Spearman's coefficient shows a positive correlation between the cyclosporine's doses and serum concentration in all examined groups (ρ =0,284; p<0,01).



Figure 2. Mean concentration of cyclosporine according to gingival overgrowth (GO).



Figure 3. Plaque index (PI) according to daily doses of cyclosporine (mg)



Figure 4. Degree of gingival overgrowth (GO) according to plaque index



Figure 5. Lost of attachment according to daily doses of cyclosporine



Figure 6. Degree of gingival index (GI) according to doses



Figure 7. The degree of gingival overgrowth (GO) according to cyclosporine's doses



Discussion

The association between CyA therapy and gingival overgrowth was first noticed in the early 1980s when the drug was undergoing initial evaluation in transplant rejection treatment.

Cyclosporine A - induced gingival overgrowth commences as a papillary enlargement that is more pronounced on the labial aspects of the gingiva than on the palatinal or lingual surfaces. The amount of overgrowth ranges from slight contour changes in the papillary tissues of the gingiva to a complete coverage of the teeth. Overgrowth is restricted to the wide of attached gingiva but can extend coronally and interfere with occlusion, mastication, and speech. All segments of the dentition can be affected, but the anterior segment appears to be a predilection site (12).

Instead of an esthetic problem, the overgrowth may result in unclean areas that are more prone to caries, development of periodontitis, and infections that could result in septicemia. In addition to being disfiguring and uncomfortable for affected individuals, moderate and severe forms of gingival overgrowth impair oral hygiene and may lead to increased accumulation of microorganisms. Oral infections can potentially impair systemic health (14, 16), and elevated oral infections stemming from gingival overgrowth could lead possibly compromise the general health of patients. This is most obvious in the case of organ transplant recipients who require continuous therapy with cyclosporine A, thereby being rendered as critically susceptible to life- threatening systemic infections, along with a concomitantly developed gingival overgrowth. The effective management of these patients clearly requires the active involvement of both dental and medical professionals to minimize the possibility of these complications (17).

In our study, independently of the applied doses, high levels of plaque index (PI) exist in all groups of patients, pointing out to the fact that there is a low level of oral hygiene in examined patients. The long-term therapeutical procedure and the seriousness of the primary medical problem linked to a continuous drug therapy in all kidney transplant recipients makes them unmotivated in the process of maintaining of oral hygiene.

Our study demonstrates a positive correlation between plaque index and gingival overgrowth (ρ =0,6; p<0,01), and also a positive correlation between gingival index and degree of gingival overgrowth (ρ =0,7; p<0,01). It has been stated that the dental plaque has a fundamental role in the pathogenesis of gingival overgrowth induced by cyclosporine (18, 19), and reported a significant correlation between plaque or gingivitis and the prevalence and severity of gingival overgrowth.

In contrast, other found no correlation between plaque or gingivitis and gingival overgrowth (20). However, it's still not quite clear about the real plaque role; does it have a primary effect or it is a consequence of pseudo- pockets with altered gingival morphology which makes the plaque control difficult.

Although, we are not quite sure is the gingival overgrowth a result of an inflammatory component, or it occurs because of the cyclosporine simulative effect to the collagen production, we would like to confirm that gingival overgrowth will affects plaque elimination considering increased gingival inflammation, gingival bleeding and loss attachment. On the other hand, untreated gingival inflammation leads to gingival overgrowth and periodontal destruction.

Periodontal destruction, measured trough the level of loss attachment, is in a positive correlation with the degree of gingival overgrowth (ρ =0,1; p<0,05).

The dosage of cyclosporine and the plasma concentration of the drug in our study show a positive correlation with gingival overgrowth ($\rho=0,3$; p<0,01). A comparable experience for the correlation with gingival overgrowth was reported by Margiotta et al (21) and Hefti et al (20). In contrast, results of other authors (22) do not support a role of dose dependency of the drug, explaining that the dose is just a trigger factor which initiate the gingival changes, but that it is developed in time restricted sensitivity of the fibroblast in correlation with their response to the medicament. However, an increase of the cyclosporine dose will certainly increase the drug serum concentration, although it is affected also from other individual characteristics. On the other hand, this increased immunosuppression might inhibit the immunity of the periodontal - tissue complex of the plaque products, which will in turn affect periodontal status.

Conclusion

Etiology of cyclosporine- induced gingival overgrowth is multicausal and associated with the local and pharmacological factors. Close cooperation between paradontologists and nephrologists is necessary to follow this undesirable effect, and should be directed towards an elimination of the oral infections which can compromises oral health, and basic human health.

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