Factors affecting cyclosporine-induced gingival overgrowth in pediatric renal transplant recipients

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Abstract

The purpose of this research was to study the occurrence of gingival overgrowth (GO) in children after kidney transplantation and to investigate the relationship of GO to medical and dental parameters. Forty-nine kidney transplant patients taking the immunosuppressive drug cyclosporine A (CsA) were evaluated for plaque (PI), calculus (CI), gingival inflammation (GI), probing depth (PD), width of keratinized gingiva (GW), and gingival overgrowth (GO). Blood trough levels and oral dosages of CsA were obtained from medical charts on the day of examination. Most (77.5%) subjects exhibited GO, suggesting that GO is a frequent problem in children and adolescents ingesting CsA. GI, PD, and GW were found to be statistically significantly greater in subjects with GO than in those without GO. CsA dose/day was not significantly different between subjects with GO and those without GO. CsA dose/kg body weight and blood trough levels of CsA were significantly higher in subjects without GO, but the average length of time subjects without GO had been ingesting CsA was only 1.3 months, compared with an average 3.5 years for subjects with GO. The results indicate that in young subjects, duration of CsA ingestion may be the most critical factor related to eventual GO development. (Pediatr Dent 18:450–55, 1996)

The primary use of the immunosuppressant drug cyclosporine A (CsA) is to prevent graft rejection after organ transplantation and secondarily to treat autoimmune disorders.[1] CsA usually is administered orally or intravenously, and is absorbed through the gastrointestinal tract with great individual variability, with the peak blood concentration reached after 3 to 4 hr. CsA is metabolized by liver enzymes of the cytochrome P450 system, forming at least 18 metabolites.[2] Therapeutic CsA doses of 10–20 mg/kg per day are required to maintain blood drug concentrations of 100–400 ng/ml.[1] A relationship has been reported between blood CsA levels > 200 ng/ml and various side effects.[2]

The first dental documentation of CsA-induced gingival overgrowth (GO) was published in 1983 by Wysocki et al.[3] and Rateitschak-Plüss et al.[4] Genetic, hormonal, idiopathic, iatrogenic, and inflammatory cofactors have been linked to CsA-induced GO.[5,6] Recently, it was reported that adults with blood CsA trough levels > 400 ng/ml were at significantly greater risk of developing GO than subjects exhibiting lower levels.[7] Fifty-nine percent of the subjects with high CsA levels showed GO, compared with 17% of subjects with lower CsA levels. Gingival changes associated with CsA have been documented in a great number of adult case reports.[5,6] In contrast, little information has been published on the prevalence and time course of CsA-induced GO in children and adolescents. Five publications have reported a 13–85% occurrence of GO in young patients on CsA therapy.[8–12]

This study examined the hypothesis that the immunosuppressant drug CsA, as used in pediatric renal transplant patients, contributes to the clinical manifestation of GO. The specific aims were to: 1) document the presence of GO in children with kidney transplants via clinical examination, 2) associate documented GO with blood trough levels of CsA, 3) document the gingival health status of subjects exhibiting GO, compared with subjects without GO, and 4) detect relationships between medication and GO.

Methods and materials

Subjects/data collection

Dental examinations were performed between June 1992 and August 1993 as part of the subjects' regular follow-up appointments after cadaveric or living-related donor kidney transplantation. Forty-nine subjects aged 5.9–18.6 years participated in this cross-sectional investigation, with appropriate informed consent of parent or legal guardian. The sample of 20 females and 29 males included 37 Caucasians, 11 African Americans, and one Asian. Nineteen subjects had received a cadaveric kidney, and 30 had a haplotype transplant donated by a living relative. The subjects had not received prior treatment for GO and were not part of any experimental treatment regimen. Some subjects had

received routine dental care, (e.g., fillings, sealants) from their family dentists. All subjects were allowed equal opportunity to access private dental care; therefore, utilization frequency for dental services was not regarded as an inclusive/exclusive criterion. However, subjects were questioned about the nature and extent of their individual dental treatment and were referred for therapy as necessary.

The dental protocol included brief questions regarding medical conditions and current medications and the clinical dental examination outlined below. Data from each subject's medical record were gathered regarding medication dosage and blood CsA trough levels at the time of the dental examination. Dental data were collected by two examiners (KK and MM) who were previously calibrated against each other. The calibration of the examiners was performed on all indices applied in this study, using volunteer subjects, until satisfactory agreement was obtained.

Subjects were accepted into the study based on:

1) history of kidney transplantation, and
2) current CsA immunosuppressive therapy.

All subjects were patients of Shands Hospital at the University of Florida Department of Pediatric Nephrology and were not advised of impending examination until they presented for periodic medical examination as part of routine transplant follow-up.

CsA levels

Blood samples were obtained via antecubital venipuncture by registered nurses as part of the subjects' periodic medical examination prior to the morning ingestion of CsA. Drug concentrations measured in such blood samples are also referred to as trough levels. Routine monitoring of CsA in whole blood was performed using a selective assay (Abbott Labs, North Chicago, IL) that specifically measured the parent drug and not its metabolites.

Clinical examinations

The following teeth were examined in each patient: 1) primary teeth, and 2) permanent teeth—first molar to central incisor in all quadrants.

Plaque (PI) and calculus (CI). The presence or absence of supragingival plaque and calculus was scored using dichotomous criteria at the distofacial, midfacial, and mesiofacial site of each tooth (Hassell et al. 1984)[13]:

Plaque:
- No plaque present
- Plaque present

Calculus:
- No calculus present
- Calculus present

The average score per subject was calculated based on the number of sites exhibiting plaque or calculus and the total number of sites examined per subject. The score reflected the extent of plaque or calculus in the subject.

Gingival index (GI). The presence and severity of gingival inflammation was assessed according to the criteria established by Löe.[14]

1. Normal: healthy gingiva
2. Mild inflammation: slight change in color, slight edema; no bleeding on probing
3. Moderate inflammation: redness, edema, and glazing; bleeding on probing
4. Severe inflammation: marked redness and edema; ulceration; tendency to bleed spontaneously.

The average score per subject was calculated based on the sum of GI scores for sites exhibiting gingivitis and the total number of sites investigated in the subject.

Gingival width (GW). GW was measured to the closest mm, at each midfacial tooth surface from the gingival margin to the mucogingival junction, using a Michigan probe with Williams markings (Hu-Friedy, Chicago, IL). The average GW per subject was calculated based on the GW sum per subject and the number of sites examined.

Probing depth (PD). PD was measured to the closest mm using a Michigan probe with Williams markings at three sites (mesiofacial, midfacial, and distofacial) per tooth. The average PD per subject was determined based on the PD sum per subject and the number of sites examined.

Gingival overgrowth. GO was scored dichotomously, as either present or absent. For each tooth, a score of 1 was given, if GO was present at the clinical examination, and if GO was absent the score was 0. The average GO score per subject was calculated based on the number of sites exhibiting GO and the total number of sites evaluated.

Statistical evaluations

Means $\pm$ standard deviations (SD) were calculated for all variables. Initial computations included data representing the total sample. During further analyses, subjects with GO were assigned to group 1 while those without GO were assigned to group 2. Differences between the groups were analyzed using Student's *t*-test. The nonparametric Mann-Whitney U-test was applied if the assumptions of equal variances, as tested using the Levene test and normal distribution, were rejected. The relative risk of GO and 95% confidence intervals were computed for several variables. Because relative incidence rates were not known, relative risk was estimated using odds ratios. The subject was the basic unit for all statistical analyses.

Results

Table 1 shows general medical and dental characteristics for the 49-subject sample. Average age was 12.5 years, representing a range from 5.9 to 18.6 years. In general, subjects' height and weight were within the normal limits for their age group. Blood pressure was slightly elevated, especially when the young age of the sample was considered. Overall, subject oral hygiene was fair. The mean plaque score of 0.77 demonstrates plaque found on 77% of the subjects' teeth, on average. No subject was completely plaque-free, and 13 subjects

TABLE 1. GENERAL MEDICAL AND DENTAL CHARACTERISTICS OF THE STUDY POPULATION

Variable	*Mean ± SD, N = 49*	*Range*
Age (years)	12.5 ± 3.4	5.9–18.6
Height (cm)	140 ± 18	107–1180
Weight (kg)	45 ± 20	17–110
Systolic BP (mmHg)	124 ± 13	98–160
Diastolic BP (mmHg)	75 ± 9	50–90
Plaque	0.77 ± 0.26	0.11–1.00
Calculus	0.03 ± 0.06	0.00–0.27
Gingival index	1.03 ± 0.21	0.29–1.50
Probing depth (mm)	2.6 ± 0.5	1.6–4.1
Gingival width (mm)	3.8 ± 0.8	2.4–5.6

TABLE 2. TREATMENT-RELATED VARIABLES OF THE STUDY POPULATION

Variable•	*N*	*Mean ± SD*	*Median*	*Range*
CsA Dose/day (mg)	49	352 ± 119	300	140–650
CsA Dose/weight (mg/kg)	49	9.0 ± 4.0	7.7	2.7–17.6
Parent CsA level (ng/ml)†‡	47	178 ± 79	183	25–403
Time on CsA therapy (months)	49	33 ± 35	20	1–71
Nifedipine Dose/day (mg)§	30	52 ± 30	45	10–120

• As recorded on the day of examination. † Trough blood levels of parent drug.
‡ Two subjects had CsA levels >500 ng/ml and were excluded. § 19 subjects did not receive nifedipine therapy.

had plaque present on every tooth surface. In contrast to plaque, little calculus was observed. Seventy-three percent of subjects were free of calcified deposits. Pseudopockets, defined as coronal displacement of the gingival margin without concomitant apical migration of the junctional epithelium, have been considered indicators of GO. Nine subjects exhibited average PDs of greater than 3 mm, implying the presence of pseudopockets.

Table 2 provides information pertinent to the subjects' CsA regimens. The prescribed average daily oral dose of CsA at the time of examination was 352 mg; the weight-adjusted dose was 9.0 mg/kg. The trough level of parent CsA was 178 ng/ml. Mean length of time subjects were placed on CsA medication was 33 months, with a range from 1 month to a maximum 171 months (median 20 months). Thirty subjects had been given nifedipine to treat CsA-related hypertension. The average daily nifedipine dose at examination was 52 mg.

Table 3 compares group 1, 38 subjects with clinical signs of GO, with group 2, 11 subjects exhibiting no GO. Average ages of group 1 and group 2 were 13.1 ± 3.2 years and 11.0 ± 3.9 years, respectively ($P = 0.136$). Differences in overall plaque and calculus scores between group 1 and group 2 were not statistically significant. Group 1 was found to exhibit statistically significantly less calculus in the mandible than was group 2 ($P = 0.019$). Gingival inflammation was significantly greater in group 1 than in group 2 ($P = 0.022$). A similar result was obtained for the maxilla, whereas a comparison of the data obtained from mandibles demonstrated no significant difference in GI between the groups. Average PD of subjects exhibiting GO was significantly greater than subjects free of GO ($P < 0.001$). Compared with group 2, group 1 also showed greater PD in the mandible ($P = 0.003$) as well as in the maxilla ($P = 0.001$). Similarly, the difference in GW between group 1 and group 2 was statistically significant. Comparing mandibles and maxillae separately, group 1 exhibited statistically significantly more GW than did group 2 ($P = 0.043$ and $P = 0.040$, respectively).

Table 3 shows further that the nonadjusted daily CsA dose was not statistically different for the two groups. However, after adjusting CsA dose for body weight, CsA dose was smaller for group 1 than for group 2. This difference approached statistical significance ($P = 0.053$). Similarly, smaller CsA trough levels were found in blood samples drawn from group 1 ($P = 0.009$). Finally, subjects from group 1 had been on CsA therapy for a longer period of time than subjects from group 2 ($P < 0.001$).

TABLE 3. STATISTICAL COMPARISON BETWEEN SUBJECTS EXHIBITING PRESENCE OF GINGIVAL OVERGROWTH

Variable	*Group 1, N = 38*	*Group 2, N = 11*	*P*
Plaque index	0.8 ± 0.2	0.7 ± 0.3	0.335†
Mandible	0.7 ± 0.3	0.6 ± 0.4	0.378†
Maxilla	0.9 ± 0.2	0.8 ± 0.3	0.472†
Calculus index	0.02 ± 0.05	0.05 ± 0.08	0.274†
Mandible	0.01 ± 0.02	0.07 ± 0.14	0.019†
Maxilla	0.03 ± 0.10	0.03 ± 0.04	0.639†
Gingival index	1.1 ± 0.2	0.9 ± 0.3	0.022†
Mandible	1.0 ± 0.2	0.9 ± 0.3	0.086
Maxilla	1.1 ± 0.2	0.9 ± 0.4	0.028†
Probing depth (mm)	2.8 ± 0.5	2.2 ± 0.4	< 0.001
Mandible	2.6 ± 0.5	2.1 ± 0.4	0.001
Maxilla	2.9 ± 0.6	2.2 ± 0.4	0.001
Gingival width (mm)	4.0 ± 0.8	3.3 ± 0.6	0.004
Mandible	3.6 ± 0.9	3.0 ± 0.5	0.042†
Maxilla	4.3 ± 0.9	3.6 ± 0.7	0.014
Gingival overgrowth	0.6 ± 0.3	not found	NA
Mandible	0.6 ± 0.3	not found	NA
Maxilla	0.6 ± 0.3	not found	NA
Age (years)	13.1 ± 3.2	11.0 ± 3.9	0.136
CsA dose/day (mg)•	353 ± 116	350 ± 132	0.944
CsA dose/kg (mg/kg)•	8.4 ± 4.1	10.8 ± 3.0	0.053
Trough parent CsA (ng/ml)•	156 ± 61‡	241 ± 94‡	0.001†
Time on CsA therapy (months)	41.8 ± 34.9	1.3 ± 0.8	< 0.001†

• As recorded on the day of examination. † Mann-Whitney's test. ‡ One subject with CsA level >500ng/ml was excluded from calculation.

TABLE 4. RELATIVE RISK OF GO ESTIMATED FOR VARIOUS VARIABLES

Variable	*Group 1† N = 38*	*Group 2 N = 11*	*Estimated Relative Risk**
Dental aids			
Toothbrush	33	9	1.5 (0.2–8.9)
Toothbrush & floss	5	2	
Mouth breather			
No	13	2	0.4 (0.1–2.3)
Yes	25	9	
Nifedipine			
No	13	6	2.3 (0.6–9.0)
Yes	25	5	
Race			
Black	6	5	0.2 (0.05–0.98)
Other	32	6	
Gender			
Female	16	4	1.3 (0.3–5.1)
Male	22	7	

* Estimated relative risk of GO and (95% confidence interval).
† Group 1 includes subjects exhibiting overgrowth and group 2 subjects without gingival overgrowth.

Although oral hygiene was fair, all subjects verbalized use of home care measures to maintain oral hygiene. Forty-two of the subjects (86%) used a toothbrush as their only oral hygiene tool (Table 4). The remaining seven subjects reported using both toothbrush and floss. Subjects using only a toothbrush exhibited 1.5 times higher relative risk for developing GO than subjects using toothbrush and floss. Note, the 95% confidence interval includes the value of 1. It is therefore not possible to reject the null hypothesis. There was no statistically significant difference in PI or GI between subjects using only toothbrushes as compared to subjects using both toothbrush and floss ($P = 0.774$ and 0.099, respectively). Thirty-four subjects recorded mouth breathing habits, while the remaining 15 subjects stated they either were not mouth breathers or they were unaware of it. The estimated relative risk of GO for mouth breathers was not statistically significantly different from nose breathers. The estimated relative risk of GO was slightly but statistically significantly smaller in African Americans than in other races (95% confidence interval, 0.05–0.98), but there was no difference in relative risk between genders.

Subjects included in this study were taking CsA as part of an immunosuppressive therapeutic regimen. Other data collected during dental examinations included prescription medications that subjects were concurrently ingesting in addition to CsA. These medications included nifedipine (average daily dose 52 mg), azathioprine (average daily dose 60 mg), and prednisone (average daily dose 14 mg). In group 2, five subjects received nifedipine at an average daily dose of 48 mg, and 10 subjects received on average 58 mg azathioprine. Table 4 shows that subjects on nifedipine therapy were exposed to a 2.3-fold greater relative risk of having GO. However, the 95% confidence interval included the value of 1, so the null hypothesis could not be rejected. All subjects in group 2 had been taking an average daily dose of 35 mg of prednisone. Twenty-five subjects in group 1 were taking nifedipine at 53 mg on average, and 37 subjects of the same group were taking azathioprine at 61 mg on average. All subjects in group 1 received prednisone at 7 mg on average. Comparisons between group 1 and group 2 using average per subject doses showed statistically nonsignificant differences for azathioprine or nifedipine. However, prednisone dosage was much smaller in group 1 than in group 2. The difference was statistically significant at the < 0.001 probability level.

Discussion

Reports have shown that the prevalence of CsA-induced GO varies from 25%[15] to 70%.[16] This study found that 77.5% of pediatric and adolescent samples exhibited GO at the time of examination. All subjects who had been taking CsA medication longer than 3 months expressed clinically visible GO. Specifically, these findings contrast with a recent report by Allman et al.[12] Additionally, GO in this study of young people was more common than the reported prevalence of CsA-induced GO in adults, supporting a recent hypothesis that drug-induced GO may be age dependent.[7] A similar finding was also reported by Daley et al.[16], who investigated CsA-induced GO in patients with type I diabetes.

Papillary and marginal gingival enlargement yielding firm, nodular, or granular, edematous tissues has been documented with the use of the antiepileptic drugs phenytoin, sodium valproate, and primidone; the calcium channel blockers nifedipine, verapamil, diltiazem, and nitrendipine; and the immunosuppressant CsA.[6] Other side effects of CsA include nephrotoxicity, hypertrichosis, and hypertension.[1] In this study, the calcium channel blocker nifedipine was used to control hypertension. Calcium channel blockers selectively antagonize Ca^{2+} movements in the cardiovascular system, where they may inhibit calcium ion entry through "slow channels" across cardiac and vascular smooth muscle membranes, leaving serum calcium concentrations unchanged. Nifedipine is a potent peripheral vasodilator that causes a reflex increase in heart rate in response to its vasodilating action. The resulting vasodilation reduces total peripheral vascular resistance, lowering blood pressure. It has been well documented that nifedipine can contribute to GO.[6, 17, 18]

Slavin and Taylor[19] reported that renal transplant patients taking both CsA and nifedipine had more severe GO than those taking CsA alone. Thomason et al.[20] examined the plaque index, papillary bleeding index, and probing depths of anterior teeth of adult patients.

Their findings showed an increase in the severity of GO when both nifedipine and CsA were taken simultaneously, possibly suggesting no change in the number of patients responding to overgrowth stimulus but increasing the magnitude of the response of combined therapy in those who respond. However, the extent of GO was not related to CsA dosage, and the results of our study corroborate the observations by Thomason et al.[20] Another study[21] found no association between CsA-induced GO and dose or duration of CsA in five liver transplant patients. Results of our study strongly suggest that duration of CsA ingestion may be a critical factor for GO development in pediatric renal transplant patients.

An additional concern when treating pediatric renal transplant recipients is the effect of long-term steroid therapy on growth. CsA therapy with concurrent corticosteroid administration facilitates immunosuppression and consequent graft retention.[22] Reasonable steps to minimize the dose of steroids in cyclosporine regimens is a well-accepted practice.

Good oral hygiene has been reported to be less likely to lead to GO associated with CsA therapy.[8] Oral hygiene levels may have been reduced in these chronically ill children partially due to parents' preoccupation with more urgent aspects of care. The results of this study did not show a relationship between level of oral hygiene and presence of GO. The severity of GO was not considered at the time of dental examination.

As mentioned previously, seven subjects reported using floss in addition to a toothbrush. An estimate of the relative risk of GO did not account for the differences between the two subsamples (toothbrushing alone or toothbrushing and flossing), as indicated by a large 95% confidence interval that included the value 1. Nevertheless, an intensive course in plaque control and the removal of local irritants has been shown to improve the gingival condition associated with CsA-medicated renal transplant patients,[4] but such measures do not necessarily prevent gingival overgrowth from developing. A site-by-site relationship between presence of plaque and GO was not noted in this study population. The relationship between GO and PD, and between GO and GW was clear. As the number of sites with GO increased, PD and GW also increased. Deep gingival pockets probably affected the subjects' ability to adequately perform oral hygiene.

Blood samples collected via anticubital venipuncture were analyzed for parent CsA and the results recorded in the subject's hospital chart. Individual readings used in subject data analysis accurately described blood trough levels on the date of the actual dental examination. These measurements reflected cumulative CsA doses, which were dependent upon individually prescribed regimens, metabolic differences, medical status, etc. However, all blood was routinely obtained for monitoring of CsA trough levels before the subjects' morning dosage, thereby ensuring the most accurate and consistent blood CsA levels. Absorption of CsA is variable and incomplete from the gastrointestinal tract. Bioavailability is approximately 30% but may increase with increasing dosage and duration of treatment. Oral consumption yields peak plasma/blood concentrations in about 3.5 hr at 1 ng/ml per mg of dose in the plasma and 1.4–2.7 ng/ml per mg of dose in the blood. CsA is metabolized in the liver and excreted in the bile and urine. In kidney transplantation it is suggested that trough whole blood CsA levels be 160–240 ng/ml during the first month after transplantation, 100–160 ng/ml during months two and three, and 60–120 ng/ml thereafter.[23] Trough levels of CsA in this present sample exceeded these recommendations for most subjects (Table 3). Just 38.3% of the sample had CsA concentrations smaller than 150 ng/ml. Two cases measuring 819 ng/ml and 841 ng/ml CsA were excluded from calculations. It is likely their morning medication intake immediately preceded blood sampling.

Periodontal parameters selected for this study were those examined in other clinical epidemiological studies of GO.[13] The correct decision about whether a patient exhibited CsA-induced GO or volume increase due to inflammation (gingivitis) was a priority from the study's inception. Clinically, it was relatively easy to differentiate between the two. Gingival surface texture (bumpy, resembling an orange peel versus smooth) and tissue color (lighter pink and fibrotic appearing versus bright red) were characteristics used to identify whether the subject actually had clinical GO or gingivitis. These observations contrast with determining clinical GO based on measurements of sulcus depth where the diagnosis of GO was recorded positive when the probing depth was equal to or exceeded 4 mm without exhibiting loss of periodontal attachment (i.e., pseudopockets).[10]

The type of dentition (primary, mixed, permanent) may have had some effect on the results, though statistical analysis did not support this hypothesis. One subject had a complete primary dentition, 22 demonstrated mixed or transitional dentitions, and 26 had complete permanent dentitions. Seow[8] documented that CsA therapy was associated significantly with gingival enlargement of the primary dentition. Oral hygiene tends to be more difficult during the stage of mixed dentition and may have contributed to increased plaque and gingivitis. Currently, it is thought that GO severity is related to the presence of gingival inflammation and can be at least partially controlled with good oral hygiene and plaque removal.[24]

Subjects in group 2, on average, had received kidney transplants more recently than subjects of group 1. Therefore, group 2 had been placed on CsA immunosuppressive therapy subsequent to group 1. As expected[23], subjects of group 2 were ingesting greater daily doses of CsA than were those in group 1, resulting in significantly higher trough blood parent CsA.

Therefore, group 2 might be expected to show the greatest amount of GO, because they exhibited both higher dosages and greater blood CsA levels than group 1. Results did not support this. Instead, they indicated that occurrence of GO was associated with neither increased clinical findings (PI, CI, GI) nor increased blood levels of CsA. Increasing the length of time CsA was therapeutically ingested appeared to be the single most critical factor for eliciting whether or not the pediatric/adolescent kidney transplantation population developed GO.

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