Evaluation of cyclosporin-induced gingival overgrowth in the pediatric transplant patient

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Abstract

The prevalence of gingival overgrowth secondary to the administration of cyclosporin (CS) is currently reported between 8 and 70%, depending upon the source. Information concerning pediatric patients is limited. To determine the prevalence of the condition in a population of children, 26 pediatric liver or kidney transplant recipients were evaluated for the presence of overgrowth related to CS administration. Twenty-two (84.6%) exhibited gingival overgrowth. Chi-square analysis revealed no relationship between the occurrence or severity of overgrowth and transplant type, gender, age at transplant, length of time on CS, concurrent medications, or any local oral factor examined ($P < 0.05$). A statistically significant association ($P = 0.03$) was found between increased oral debris and the occurrence of gingival overgrowth; however, this was not thought to be a causative relationship. Nifedipine, a known cause of gingival overgrowth, was taken by half of the patients, but was not found to statistically influence the occurrence or severity of gingival overgrowth. Cyclosporin blood levels were evaluated over time and found to be variable, not only between patients but also for individuals. No relationship was evident between the blood level and the presence or severity of overgrowth. (Pediatr Dent 16:36–40, 1994)

Literature review

Cyclosporin (CS) is a potent immunosuppressive agent discovered in 1972 that has greatly reduced the morbidity and mortality associated with organ transplantations and improved the five-year success rate for solid organ transplants from 50 to 96%. This drug has side effects such as gingival overgrowth, frequently seen in transplant patients. CS-induced gingival overgrowth occurs in between 8 and 70% of the transplant patients, depending on the literature source.[1–5] Investigators acknowledge a higher occurrence in children; however, none has estimated a percentage.[3,6]

Peak blood and plasma concentrations of CS are achieved approximately 3–4 hr after drug administration,[2] but an accurate blood level is difficult to achieve and maintain due to variable absorption and elimination. As a result, serum levels of CS are monitored frequently by whole blood high pressure liquid chromatography (HPLC).[1]

Prednisone interacts with CS to vary the amount of each drug available in the body. In combination with CS, the metabolic clearance of prednisone is decreased, thus permitting low doses of the steroid to be effective.[7] Investigators have agreed that prednisone does not contribute to gingival overgrowth or periodontal disease, and instead, may result in decreased manifestation of the two.[1]

Hypertension occurs secondary to CS and prednisone administration because of their vasoconstrictive actions; therefore, an antihypertensive regimen must be given. Nifedipine, alone or in combination with other medications, is commonly used for this purpose. Although cases of nifedipine-induced gingival overgrowth in man have been reported,[8,9] no well-controlled histological or epidemiologic studies have been done.

Results from animal and human studies on CS-induced gingival overgrowth generally have agreed and have shown: 1) no correlation between either blood levels or oral dosage of the drug and occurrence or severity of gingival overgrowth;[3,4,6,10] 2) oral hygiene instituted after CS administration had begun was only effective in reducing inflammation, not overgrowth;[5,6,11–13] 3) gingival changes occur most rapidly during the first 2–6 months, approaching a plateau at about 12 months.[12]

Research has examined the effect of CS on gingival overgrowth; however, transplant patients are not treated with CS alone. Lundergan[12] reported that when nifedipine and CS are combined, the incidence of gingival overgrowth increased. In a study of 95 patients, 51% developed overgrowth when taking both drugs, while 8% were affected when taking only CS.

Many questions remain unanswered regarding the mechanism and pathogenesis of CS-induced gingival overgrowth as well as what determines which patients develop gingival overgrowth and which do not.[3,6,13] This study was undertaken to determine what percentage of children develop CS-induced gingival overgrowth and to what degree; and what relationship exists between the degree of CS-induced overgrowth and gender, type of transplant, length of time on CS therapy, polypharmacy, serum levels, and other local and systemic factors.

Methods and materials

Subjects examined in this study were all patients of record of Children's Medical Center of Dallas who had received either a kidney or liver transplant at the institution. Any patient who had received a transplant, was in stable condition, and who had been on CS therapy for a minimum of 12 months was a candidate for inclusion. Fixed or removable oral appliances were the only grounds for exclusion. Patients meeting these criteria were asked to participate and a written parental consent was obtained following explanation of the study.

A thorough medical history was taken from the parent on a standard form and supplemented by an extensive interview. The patient and parent were questioned regarding local factors that were being examined as possible complicators of gingival overgrowth: oral habits and obligatory mouth breathing. Following this interview, a thorough clinical exam of the oral cavity was done by the principal investigator (SA) who interviewed and examined all patients in the study and was unaware of patients' CS dose at time of examination.

Prior to examining the first patient, the principal investigator met with a periodontist to establish classifications of overgrowth and to standardize the examination process. The severity of gingival overgrowth was assessed by means of the semiquantitative index developed by Aas[14] and modified by McGaw et al.[15] Absence of overgrowth was defined as gingiva with a feather-edged margin; mild gingival overgrowth produced a blunted gingival margin; moderate gingival overgrowth covered less than one-third of the crown length; and severe gingival overgrowth was marked, covering more than one-third of the crown length. Only teeth with fully erupted crowns with opposing occlusion were used in defining the degree of overgrowth.

Gingival inflammation was examined using the Silness and Löe Gingival Index[16] and oral debris and calculus were quantified using the Simplified Oral Hygiene Index.[17] When the gingiva covered two-thirds or more of the clinical crown, no score for either oral debris or calculus was attempted.

A modified dmfs index was used to determine the caries incidence in the population. Because many patients were in the mixed dentition phase, an average dmfs was determined by dividing the number of decayed, missing, or filled surfaces by the number of teeth present to arrive at a measurement comparable among patients. No radiographs were utilized for this index.

The hospital chart was reviewed to determine the duration of CS therapy and variation of blood levels over time. Additionally, information concerning other medications taken concurrently and the patient's history of allergy were noted. The presence or absence of cardiac murmurs or asthma was noted since these were the most common nontransplant conditions seen in this population.

Data were compared item by item and chi-square analysis of the individual factors done to determine any effect on the occurrence or severity of gingival overgrowth. Chi-square analysis of this data was done in two ways: first, all four gingival overgrowth scores (none, mild, moderate, severe) were analyzed with each variable, then, analysis was repeated comparing the occurrence or lack of occurrence of overgrowth and the variable.

Results

Of 26 patients ages 1 year 6 months to 17 years 1 month (mean: 8 years 8 months), 16 (62%) were between 4 and 9 years of age. Nineteen had received a transplanted liver and seven a kidney. There were 13 males and 13 females. Age at transplant ranged from 5 months to 14 years 4 months, with the average age being 5 years 3 months. Time on CS therapy ranged from 12 months to 7 years 1 month, with the average being 3 years 6 months (Table 1).

Twenty-two of 26 patients (84.6%) demonstrated gingival overgrowth. Of those, nine (40.9%) demonstrated mild, 11 (50%) demonstrated moderate and two (9.1%) demonstrated severe overgrowth.

Chi-square analysis revealed no statistically significant relationship between either occurrence or severity of gingival overgrowth and transplant type, gender, age at transplant, or length of time on CS therapy. Chi-square analysis of the local oral factors of mouth breathing, oral habits (fingernail biting, finger sucking, and lip pulling) and gingival inflammation revealed no statistical significance. Chi-square analysis did reveal a statistically significant relationship ($P = 0.030$) between oral debris and the occurrence of overgrowth, and one that approached a statistical significance between oral debris and the severity of gingival overgrowth ($P = 0.065$). Distribution of occurrence of the above factors appears in Table 1.

Additional factors thought to influence the occurrence or severity of overgrowth were examined, but infrequent occurrence precluded statistical analysis. Distribution of occurrence appears in Table 1.

Each patient's recorded blood levels of CS with the date of measurements expressed in number of days post-transplant were graphed. Due to variability in available data, no comparisons between levels were possible. There appeared to be no correlation between the individual's CS levels and the presence or severity of overgrowth. Although no statistical analysis could be done, examination of the graphs suggests that a high CS blood level is not necessarily associated with overgrowth, nor does a low CS level necessarily indicate lack of overgrowth.

Medications most frequently taken concurrently with CS were individually evaluated with regard to their relationship to gingival overgrowth. Distribution of occurrence appears in Table 2.

Table 1. Occurrence of overgrowth with population variables

Variable	*Patients (N)*	*Overgrowth*			
		None	*Mild*	*Moderate*	*Severe*
Age at exam					
Less than 18 months	1	0	1	0	0
19 months – 3 years	1	0	0	1	0
4–9 years	16	2	6	8	0
10–15 years	6	2	2	1	1
16–18 years	2	0	0	1	1
Transplant type					
Kidney	7	1	1	4	1
Liver	19	3	8	7	1
Gender					
Female	13	3	4	6	0
Male	13	1	5	5	2
Age at transplant					
Less than 18 months	6	0	3	3	0
18 months – 3 years	8	1	3	4	0
3–9 years	6	2	2	2	0
9–13 years	6	1	1	2	2
Length of time on CS					
0–12 months	2	0	2	0	0
13–36 months	9	1	1	5	2
37–82 months	15	3	6	6	0
Obligatory mouth breathing	2	0	1	0	1
Oral habits	11	0	4	6	1
Generalized gingival index score					
0	3	1	1	1	0
1	16	1	7	8	0
2	7	2	1	2	2
3	0	0	0	0	0
Oral debris score*					
0	2	0	1	1	0
1	14	0	7	7	0
2	9	4	1	2	2
3	1	0	0	1	0
Calculus	4	2	1	1	0
Dental restorations	6	2	1	1	2
dmfs index					
None	13	1	7	5	0
Mild (<0.2)	9	2	1	5	1
Moderate (>0.2)	4	1	1	1	1
Cardiac murmur	2	0	2	0	0
History of asthma	2	0	1	1	0
Allergy	7	2	3	2	0

Chi-square evaluation reveals no statistically significant relationship between any systemic clinical factor and occurrence of gingival overgrowth at $P < 0.05$ except for *.

* Chi-square evaluation results in statistical significance of $P = 0.03$ for occurrence of gingival overgrowth.

Discussion

One of the major components of this study was comparing the degree of gingival overgrowth among patients taking CS. Gingival overgrowth is difficult to describe in a manner that can be compared, since it is a three-dimensional change of gingival volume, composed of changes in both height and width. Due to the limitations of one-dimensional probing depths in describing overgrowth, and the lack of cooperation for impressions by many children who have undergone multiple medical procedures, the visual Index of Gingival Overgrowth[15] was found to be the most acceptable technique for comparing overgrowth in this population.

Examination of 26 children receiving cyclosporin for greater than one year in association with other medications post-transplant revealed that 22 (84.6%) developed gingival overgrowth. This is far greater than the 25% reported by Hassell and Hefti[1] from well-controlled studies of adults. The question of why children have an increased incidence of overgrowth with CS administration has yet to be answered. Hassell[18] and Jones[19] reported evidence that decreased collagenase production may explain why persons with an increased rate of tissue turnover have an increased incidence of gingival overgrowth as seen in this study. If the theory of excess collagen buildup is valid, one might expect age or time since transplant to affect the severity or onset

of overgrowth; however, in the present study, no difference in occurrence or severity was seen in the 26 patients when divided by age bracket, by gender, or by time on CS.

When this study was designed, the purpose was to examine multiple clinical factors to see if any could be found to affect occurrence or severity of gingival overgrowth. An unexpected finding was the small number of patients who exhibited no gingival overgrowth. Based on previous research, it was expected that more patients would be unaffected, so that the variables examined might delineate patients with and without overgrowth.

This small number of patients without gingival overgrowth (four) impacts analysis of all variables and negates the expected comparison group.

Initially we had intended to examine the patients prior to transplant and follow them for 12 months post-transplant to monitor the changes in gingival status. Since most patients did not live locally, this was not possible; therefore, we opted for a retrospective study of patients who had been on CS for at least 12 months.

Dental management of CS-induced overgrowth has been aimed at minimizing factors that increase gingival inflammation, such as poor oral hygiene, defective dental restorations, mouth breathing, habits, and intraoral appliances; however, multiple reports have shown that factors such as plaque accumulation and calculus presence do not affect occurrence or severity of overgrowth.[5, 6, 15] This study detected no defective restorations nor any contacting the gingiva, and only a few patients with oral habits, mouth breathing or calculus build-up; therefore, while these might be expected to increase overgrowth, the majority of children demonstrated it without the presence of these variables. A statistically significant correlation was seen between increased oral debris and increased occurrence of overgrowth; however, as McGaw et al.[15] concluded, this could be because oral hygiene is more difficult in the presence of gingival overgrowth, not because the debris caused overgrowth.

Examination of the patients' medical histories revealed that there was no difference between the presence or severity of overgrowth for either type of transplant (kidney or liver). Children who had associated medical conditions, cardiac murmur or asthma, were not found to be more susceptible; however, few patients had these conditions.

From the results of our study and of previous studies, none of the local irritants or general factors examined were found to have a unique role in the development or severity of CS-induced gingival overgrowth.

Examination of the blood levels of CS in this study revealed that although levels vary greatly among patients, similar trends exist. Spikes of high blood levels are seen initially until a maintenance level is achieved. Individuals may show extreme variability in blood levels as maintenance is adjusted over time. There is no apparent association between CS blood levels and the occurrence of overgrowth, as some patients with high blood levels exhibit no overgrowth while some with low levels do. Earlier studies that examined the blood level of CS only evaluated it on the day of examination for the study

Table 2. Evaluation of medications taken

Medicines	*Patients (N)*	*Overgrowth*			
		None	*Mild*	*Moderate*	*Severe*
Immunosuppressants					
Cyclosporin	26	4	9	11	2
Prednisone	26	4	9	11	2
Azathioprine	24	4	8	10	2
Antihypertensives					
Nifedipine	13	2	4	6	1
Hydralazine	15	3	4	6	2
Captopril	7	2	4	1	0
Spironolactone	8	0	4	4	0
Furosemide	15	1	4	8	2
Propranolol	8	2	3	2	1
CS, hydralazine and nifedipine	11	1	4	5	1
Antifungal/antiviral					
Nystatin	11	3	3	5	0
Acyclovir	5	3	2	0	0
Gastric hyperacidity					
Ranitidine	5	0	3	1	1
Seizure medications					
Phenobarbital	8	0	5	2	1
Dietary phosphorus	9	1	3	5	0
Sedatives/pain relief					
Acetaminophen	8	0	4	4	0
Morphine	7	1	2	4	0
Chloral hydrate	5	0	4	1	0

Chi-square evaluation reveals no statistically significant relationship between any medication taken and occurrence of gingival overgrowth at $P < 0.05$.

and found no correlation between blood levels and dose of CS and gingival overgrowth.[3,13,15] Careful longitudinal studies are required in order to evaluate adequately changes in blood levels of CS before conclusions can be made about the effect of blood levels on gingival overgrowth.

Polypharmacy has been implicated as a factor that increases the prevalence of gingival overgrowth in epileptic patients treated with dilantin.[20] This also could be a factor for patients taking medications to control rejection of a transplanted organ. When the complete pharmacological treatment of these children is considered, a dramatic picture is presented. Multiple drugs of all types are administered in addition to the antirejection regimen. It is difficult to ascertain how the interactions of the many drugs might affect the overgrowth. Analysis of medications taken revealed that none were statistically significant in affecting the occurrence or severity of the condition.

Furthermore, the results of our study show that of the four children who did not develop gingival overgrowth, two were taking nifedipine, a known cause of overgrowth. When the patients who did develop overgrowth were examined, a similar result is seen: half were taking nifedipine and half were not. This was surprising since it has been reported that concurrent administration of nifedipine increases the incidence of gingival overgrowth in a population of patients taking CS.[21] Specifically, it was expected that all patients taking both medications would demonstrate overgrowth. Instead, our study shows that nifedipine had no effect on incidence of gingival overgrowth in this population.

This study does not account for all of the medications that the child must take because the hospital chart records only the transplant team's actions. The patients are mainstreamed to their community where their physicians are empowered to alter all medications except those for immunosuppression (cyclosporin, prednisone, and Imuran™—Burroughs Wellcome, Research Triangle Park, NC). Since these children are prone to infections and have changing needs for additional medications to control conditions such as hypertension and gastric hyperacidity, medications are altered or changed as needed.

Conclusions

1. Twenty-two of 26 pediatric patients (84.6%) who were taking CS post-transplant demonstrated gingival overgrowth.
2. There is no apparent association between the occurrence of overgrowth and blood levels of CS in this sample of children.
3. There is a statistically significant association ($P = 0.03$) between increased oral debris and increased presence of gingival overgrowth; however, no causative relationship is implied.
4. There is no significant association between any other variable and gingival overgrowth ($P < 0.05$).
5. Among the medications taken concurrently with CS, none was associated with an increased incidence of gingival overgrowth. Nifedipine, a known inducer of gingival overgrowth, did not produce an increased occurrence.

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