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Cosmetically disfiguring side effects of cyclosporine A in an adolescent population

Abstract

Cyclosporine A (CsA) is a potent immunosuppressive agent commonly used in nephrotic syndrome and in organ transplanted patients. However, its applications are limited, due to undesirable adverse effects. The cutaneous manifestations of the drug are well documented in the western countries and some studies indicate a higher incidence among Asian populations. However, there is paucity of data about its cutaneous side effects on Asian patients thus making it difficult to counsel patients and parents before its use. We recruited children and adolescents between 12 and 20 years attending the nephrology clinic at a tertiary care hospital in Sri Lanka who have been receiving CsA more than a year. Patients who received other medication which may aggravate gingival hyperplasia, acne or hypertrichosis were excluded from the study. The dermatological manifestations of the selected children were assessed and recorded by experienced clinicians. Our study consisted of 64 patients who satisfied the inclusion criteria. There were 41 male and 23 females with a median age of 16.6 years. All of them received CsA at a dose between 5-10 mg/kg/day at induction, which was tapered towards a dose of 3 mg/kg/day, based on clinical status as well as serum level of the drug. Among the clinical features observed, hypertrichosis was seen in 32 males (78%) and in all 23 female patients (100%); Gum hypertrophy was seen in 34 patients (53%) and acne was noted only in 8 patients. The commonest cutaneous side effect was hypertrichosis, significantly seen among female subjects, which is a serious point of distress to patients and their families. Gum hypertrophy was also observed among a significant number but could be reduced by regular dental care. These findings will be remarkably useful when counselling before commencing on CsA therapy in adolescent patients.

Keywords: cyclosporine A, gingival hyperplasia, hypertrichosis, nephrotic syndrome, renal transplantation

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Shamali Abeyagunawardena,[1] ESK DeSilva,[2] Asiri S Abeyagunawardena[3]

[1]Department of Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka

[2]Faculty of Medicine, University of Peradeniya, Sri Lanka

[3]Department of Paediatrics, Faculty of Medicine, University of Peradeniya, Sri Lanka

Correspondence: Asiri S Abeygunawardena, Professor of Paediatrics, Faculty of Medicine,University of Peradeniya, Sri Lanka, Tel 0094777843848, Email asiriabe26@gmail.com

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Abbreviations: CsA, cyclosporine A; IL, interleukin; NS, nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome; SDNS, steroid dependant nephrotic syndrome

Introduction

Cyclosporine A (CsA) is a calceneurin inhibitor widely used in post-transplant patients and in nephrotic syndrome (NS).[1] Additionally, it is used to treat auto-immune disorders such as systemic lupus erythematosus, rheumatoid arthritis, psoriasis and multiple sclerosis. Accidentally discovered while searching for novel antifungal agents, CsA was found to have immunosuppressive properties that made it an attractive immunosuppressive agent following renal and other solid organ transplantations.[2] CsA is a hydrophobic, neutral polypeptide comprised of 11 amino acids. It is produced by the fungus *Tolypocladiuminflatum gams*. CsA is variably absorbed by the gut and the peak plasma concentration is reached in 3-4 hours. The drug is mostly bound to erythrocytes (50%), lymphocytes (5%) and lipoproteins (40%). Five percent will remain free in the plasma. CsA is metabolized by the liver microsomes and excreted after 6 hours via bile in faeces. CsA selectively interferes with T cells. Particularly, it inhibits T helper cells and has no effect on T suppresser cells. It selectively inhibits macrophage activation and interleukin (IL)-1 production. It prevents IL-1 receptor production on T helper cells, inhibit IL-2 synthesis in low concentration limiting clonal amplification of cytotoxic T cells and it inhibits their ability to respond to IL-2. CsA passively diffuses through cell membrane of many cells and it is concentrated in cytoplasm and nucleus.[2]

NS is the commonest renal glomerular disorder in children and in adolescents. Steroids are the main therapeutic agents in managing paediatric NS. Those patients who do not respond to steroids (SRNS) and those who are dependent on steroids (SDNS) require alternative medications to control the disease and to reduce steroid related side effects.[3] Idiopathic NS is an immunological disorder resulting from T cell dysfunction. A disturbance to the balance between Th1 and Th2 immune mechanisms, mediated by cytokines and lymphokines, is involved in the generation of the disease and its relapse. There is accumulating evidence, from both experimental and human studies, that the highly lipophilic CsA molecule diminishes or abolishes proteinuria. CsA therapy is well established for its steroid sparing effect in steroid dependent patients and is responsible for maintaining remission in more than 75% of patients with SDNS even after cessation of steroids. Furthermore, it has been shown to be effective in inducing remission in steroid resistant NS. Moreover, the discovery of CsA had a major impact on revolutionizing the outcome of transplant medicine.[4]

CsA therapy is associated with many potential side effects that concern the physician as well as the patients. Nephrotoxicity, hepatotoxicity, hypertension, gingival hyperplasia, hypertrichosis, neurotoxicity and altered bone metabolism are some of the important side effects to monitor.[4] Gingival hyperplasia is a side effect which needs extensive dental attention. It is disfiguring and affects oral function as well. It may also cause delayed or/and ectopic eruption of teeth, impaired teeth and difficulty in maintaining good oral hygiene resulting in dental caries. Most importantly, it may affect speech and chewing. Gingival overgrowth is characterized by dense collagenous

stoma and epithelial hyperplasia.[5] Some studies have pointed at the connective tissue enlargement as the main factor of the gingival overgrowth.[6] Nevertheless, other studies have been relating epithelial hyperplasia as a frequent feature in this disease.[7] Other cutaneous side effects such as hypertrichosis, though not considered very important clinically, it can seriously affect the compliance of taking regular medications especially amongst adolescents. This could have a serious impact of graft survival in organ transplanted patients and the disease control in other immune mediated disorders. The mechanisms that cause hypertrichosis, however, have not been fully elucidated.[8]

Objectives

To identify prevalence of cosmetically disfiguring side effects in adolescents receiving long term CsA therapy in Sri Lanka.

Material and methods

This single center, cross sectional study was carried out at a tertiary care paediatric nephrology unit in Sri Lanka over a 12 month period from October 2017 to October 2018. The data of all renal patients were entered in a computerized data base from 2002, which has the ethical approval of Faculty of Medicine, University of Peradeniya. From a population of 152 patients 64 who satisfied the inclusion criteria such as age between 12-20 years, receiving CsA treatment for steroid dependent or steroid resistant NS or post kidney transplantation for more than a year. Patients who received other medications that could cause or aggravate gingival hyperplasia or other cutaneous side effects were excluded. Earlier these patients were regularly monitored for neprotoxicity, hepatotoxicity and hypertension but not for cosmetic side effects during routine clinic follow ups. After meeting the patient, it was confirmed that the patient was receiving CsA treatment and other treatments through their patient held clinical records. Informed written consent was obtained for the study when the patient was interviewed. During the interview, the duration of medication and the dosage were confirmed with the patient held clinical records. Patients who fulfilled the entry criteria were examined for CsA related cutaneous side effects. Gingival hyperplasia was assessed using Pernu's modification of Angelopoulos' and Goaz's index as follows.[9]

Grade 0- (S- 0: normal gingiva)

Grade 1-(S-1: thickened marginal gingiva that covers one third of the crown)

Grade 2-(S-2: increased marginal gingiva that covers half of the crown)

Grade 3-(S-3: a significant increase of the marginal gingiva which covers more than half of the tooth crown and the surrounding retaining gum)

Ethical clearance for the study was obtained from the local ethical review committee. All data were collected in Microsoft excel sheets and analysed by statistical t test, using IBM SPSS software version 24.

Results

Clinical data of 64 patients, children between 12.4 to 19.9 years who fulfilled the inclusion criteria were analyzed (median age=16.6 years). Of them, 41 (64%) were male and 23 (36%) were female. Table 1 illustrates the basic patient characteristics in this group. Gingival hyperplasia was present in 34 (53%) of these children. Table 2 represents the frequencies for children with each grade of gingival hyperplasia. The mean daily dose of CsA in this cohort was 3.86 mg/kg, and the mean duration was 4.25 years. The maximum duration of CsA therapy was 11.75 years whereas the minimum duration was 1.05 years. There was no significant relationship between the dosage of CsA and the grade of gingival hyperplasia (p>0.10). However, there was a significant correlation between the duration of CsA administration and the grade of gingival hyperplasia in the same patient cohort (p=0.015). Figure 1 illustrates this relationship between the duration of CsA administration and the corresponding grades of gingival hyperplasia. Age or sex did not make an impact on the presence or severity of gingival hyperplasia. In contrast, the dosage of CsA had a significant effect in causing hypertrichosis, (P=0.02) while there was no significant correlation with the duration of administration (p>0.05).

Table 1 Basic patient characteristics

Characteristics	Value
Number of patients	64
Median age (years)	16.6
Gender: Male	41 (64%)
Female	36 (36%)
Mean weight (kg)	45.79
Disease condition necessitating CsA therapy:	
SDNS	
SRNS	37 (58%)
Renal transplantation	22 (34%)
	05 (08%)

Table 2 Frequencies and percentages of children displaying gingival hyperplasia grades

Gingival hyperplasia grade	Frequency	Percentage (%)
0	5	14.7
1	18	52.9
2	9	26.4
3	2	6

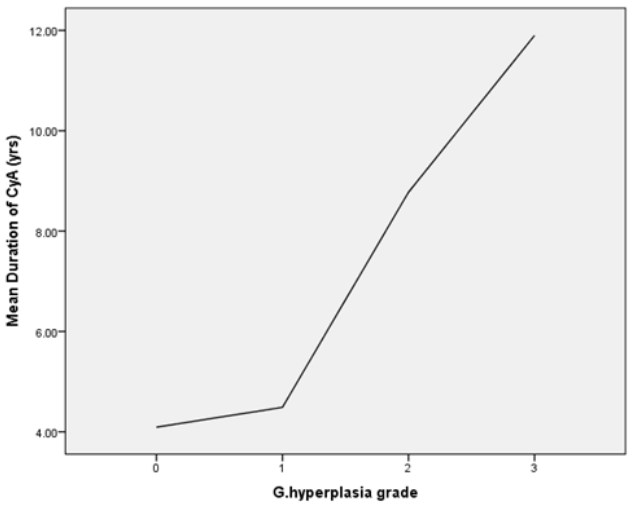

Figure 1 Positive linear relationship between the mean duration of CsA administration and the grade of gingival hyperplasia.

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Discussion

CsA remains a valuable therapeutic agent in the management of both post organ transplantation and immune mediated disorders. Cosmetically disfiguring side effects such as hypertrichosis, and gum hyperplasia are often quite distressing for patients especially during the adolescent period which could lead to poor compliance with grave consequences. It is therefore important that the physician discusses these potential side effects with the patient and with the family as well, in order to improve the acceptability of these undesirable side effects. It is well documented that drugs such as phenytoin sodium, nifedipine and prednisolone are capable of causing cutaneous side effects similar to CsA.[5] As such most of the renal transplanted patients and patients with hypertension were excluded from the study. Hypertrichosis, though not considered as a clinically important side-effect, in adolescent patients, it can become a limiting factor. The results of this study confirmed that hypertrichosis is more dose dependent than the duration of the therapy. As such when hypertrichosis becomes a concern a reduction of the dosage can be considered. This study indicates that CsA therapy causes gingival hyperplasia in a significant proportion of Sri Lankan children. Thirty four out of 64 patients (53%) whom we studied, had evidence of gingival hyperplasia. The published literature on the subject show a wide range in the prevalence of gingival hyperplasia with CsA therapy and our study results (53%) lie in its upper limit. Most of these studies had been done in European countries where the dental hygiene is likely to be better.

Most of the children (52.9%) showed mild (stage 1) gingival hyperplasia while only 2 (6%) showed severe (stage 3) gingival hyperplasia. It is interesting to note that there was no gingival hyperplasia up to 2 years of exposure to CsA treatment. Almost all the participants who had stage 1 gingival hyperplasia had 3-4 years of exposure, and stage 2 gingival hyperplasia was seen in children who were exposed for more than 4 years. The two patients with stage 3 gingival hyperplasia had exposures 7.75 years and 11.9 years respectively. Hence, this study indicates that the degree of gingival hyperplasia is directly proportional to the duration of CsA therapy. These findings will be very useful for the clinicians to time the screening for gingival hyperplasia. A follow up study can be arranged subsequently, according to the stage of gingival hyperplasia. It will also prevent unnecessary referrals to the dental hospitals thereby strengthening the patient-oriented care and lessening the economic burden to the national health care system.

Our results did not find a statistically significant relationship between CsA dose and the degree of gingival hyperplasia. Wright, G. et al., described that adolescents were most affected by gingival hyperplasia attributing it to the effects of growth hormone on fibroblasts or due to the added capability of mitotic and secretory effects of young fibroblasts.[6] Puberty could have some effect on gingival hyperplasia as hormone changes during that period may have positive effects on growth. However this study did not attempt to correlate the effect of puberty on gingival hyperplasia as most of the patients were in the pubertal age. We reckon that dental plaque formation could occur as a result of poor brushing or may be associated with gingivitis due to immunosuppressive effect of CsA. It is known that the dental plaque itself is a risk factor for gingival hyperplasia.[11] It must be noted that proper brushing of teeth and inter-dental cleaning can be considered as mechanical aids with the treatment. Several animal models have shown that plaque controlling chemicals such as chlorhexidine demonstrate positive effects in controlling gingival hyperplasia.[11,12]

Conclusion

The results of our study confirm a significant occurrence of hypertrichosis and gingival hyperplasia in adolescent age group with CsA therapy and the importance of monitoring their development during the course of the therapy. In patients following renal transplantation or with NS, tacrolimus can be substituted for CsA, since both are calceneurin inhibitors with a similar action. Tacrolimus causes fewer cutaneous abnormalities and does not trigger gingival hyperplasia thereby making it more acceptable for pubertal patients.[13]

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Conflicts of interests

Authors declare that there are no conflicts of interests.

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