ORIGINAL ARTICLE

Independent risk factors for chronic cyclosporine induced nephropathy in children with nephrotic syndrome

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Background: Cyclosporine A (CsA) has been widely used in children with steroid dependent and steroid resistant nephrotic syndrome (NS) because of its efficacy in relieving these patients from systemic side effects of steroids. However, its long term use is controversial, since chronic CsA induced nephropathy (CsAN) may develop in a considerable number of patients.

Aims and Methods: In order to clarify the risk factors for the development of CsAN, the clinical characteristics of children with steroid dependent or steroid resistant NS taking CsA (target blood trough levels 50–150 ng/ml) for more than six months, managed at a single centre, were retrospectively analysed.

Results: Thirteen of 30 children (24 boys and 6 girls) taking CsA (mean duration 43 months, range 6–144) had CsAN defined as the presence of CsA associated arteriopathy with or without striped tubulointerstitial lesions. The multivariate analysis revealed that CsA treatment for more than 36 months and an age younger than 5 years at the start of CsA treatment were independent risk factors for the development of CsAN. The univariate analysis also showed that patients with CsAN had more frequent relapses during CsA treatment than those without CsAN.

Conclusion: An alternative treatment should be seriously considered after a 36 month administration of CsA in order to prevent CsAN. Data also suggest that CsA treatment in children younger than 5 years should be avoided if possible.

Cyclosporine A (CsA), a cyclic peptide extracted from the fungus *Tolypocladium inflatum*, is an immunosuppressive agent, which was first introduced for the prevention of post-transplant rejection.

Since then, the application of CsA has been extended to the treatment of children with nephrotic syndrome (NS) for the past 15 years.^{1–6} This has relieved children with steroid dependent and steroid resistant NS from steroid toxicity, such as growth retardation, cataracts, and osteoporosis. However, there is controversy concerning its long term treatment because of its potential toxicity for chronic CsA induced nephropathy (CsAN). At present, there is scarce information regarding the risk factors responsible for the development of CsAN in children with NS.

Therefore, we analysed the clinical and histological information in 30 children with NS treated with CsA at a single centre in order to identify the risk factors for the development of CsAN.

SUBJECTS AND METHODS

Patients

Thirty patients (24 boys and 6 girls) with NS (steroid dependent or steroid resistant) treated by long term CsA for more than 6 months (mean 43 months, range 6–144) at Saitama Children's Medical Centre were enrolled. Their age ranged from 3 to 19 years. Renal biopsy was performed in all patients between February 2003 and March 2005. Morphologic findings in 22 of these patients have been reported previously.⁷ All patients were initially diagnosed at our centre during 1989 to 2004 as having idiopathic NS. The definitions and criteria for NS, remission, relapse, steroid dependency, and steroid resistance were those of the International Study of Kidney Disease in Children.^{8,9}

Estimated glomerular filtration rate (GFR) was calculated by the method of Schwartz.¹⁰

The median age at diagnosis of NS was 4.0 years (range 1.3–14.8) and CsA treatment was started at a median age of 6.2 years (range 1.5–15.3). Renal biopsies before CsA treatment were performed in 19 of 30 patients: histological diagnoses were minimal change disease (MCD) in 14, focal segmental glomerulosclerosis (FSGS) in four, and diffuse mesangial proliferation in one. None of them showed arteriolar and tubulointerstitial lesions suggesting CsAN.

All patients and their parents gave their informed consent.

Therapeutic protocol

CsA (Sandimmun or Neoral, oral formulation, Novartis Pharma Co., Tokyo, Japan) was commenced at a daily dose of 2.5–5 mg/kg given in two divided doses.

In 25 patients with steroid dependent NS, CsA was introduced when they achieved remission by steroid therapy, while in five patients with steroid resistant NS it was started when they were diagnosed as having steroid resistant NS. CsA was effective in inducing complete remission in four patients and incomplete in one patient with steroid resistant NS.

Blood CsA trough level and serum creatinine were measured monthly by monoclonal antibody fluorescence polarisation immunoassay and the creatinase method, respectively. The dose of CsA was adjusted to reach the trough level of 50–100 (steroid dependent NS) or 100–150 (steroid resistant NS) ng/ml according to the previous result.

Abbreviations: CsA, cyclosporine A; CsAN, CsA induced nephropathy; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; MCD, minimal change disease; NS, nephrotic syndrome

Figure 1 Characteristic CsA associated arteriolopathy in a patient with steroid dependent NS receiving CsA for 24 months (periodic acid-methenamine $\times 900$). A ring-like nodular hyaline deposit on the outer wall of the afferent arteriole was observed (arrow).

When the patients developed relapse despite CsA treatment, only prednisolone was used to achieve remission: it was tapered off within 6–12 months once remission was obtained.

Histological evaluation

Renal biopsy was performed in all 30 patients after CsA treatment in order to investigate the presence of CsAN. Renal specimens were examined by light microscopy (staining: periodic acid-Schiff, periodic acid-methenamine, and acid-fuchsin-orange G trichrome), immunofluorescence microscopy, and electron microscopy. The specimens were evaluated by a single pathologist (HM) blinded to the patients' clinical profile.

CsAN was assessed by the presence of typical CsA associated arteriolopathy, with or without characteristic striped tubulointerstitial lesions. CsA associated arteriolopathy and striped tubulointerstitial lesions were defined by the presence of ring like nodular hyaline deposits in the outer wall of the afferent arteriole (fig 1) and tubular atrophy (grade 1, $<7\%$; grade 2, $7-30\%$; grade 3, $>30\%$) with accompanying interstitial fibrosis (fig 2).¹¹

Figure 2 Characteristic striped tubular atrophy and interstitial fibrosis and glomerulosclerosis accompanied by CsA associated arteriolopathy in a patient with steroid dependent NS receiving CsA for 90 months (haematoxylin-eosin $\times 100$).

Statistical analysis

In order to clarify the risk factors for the development of CsAN, we compared the variables between patients with CsAN (CsAN positive) or without CsAN (CsAN negative) as shown in table 1.

Non-normal data, such as age of children at diagnosis or treatment, duration of treatment, and number of relapses were summarised by medians and ranges; the Mann-Whitney U test was used to compare the two groups, i.e. CsAN positive and CsAN negative. Normally distributed data, such as mean CsA trough levels and doses, GFR, and systolic blood pressure were summarised by mean (SD) and were analysed using Student's *t* test. Fisher's exact test was used to evaluate the association between categorical variables. Logistic regression was used to identify an independent risk factor for the development of CsAN. Age at initiation and duration of CsA were employed as independent variables. An interaction between age at initiation and duration of CsA was also tested. Age at diagnosis of NS and initiation of CsA were significantly correlated (Spearman's correlation coefficient by rank test; $r_s = 0.67$, $p = 0.0003$), so age at the diagnosis of NS was not employed as a independent variable in order to avoid the effect of multicollinearity. The age and duration variables used as predictors were dichotomised as (<5 v ≥ 5 years) and (<36 v ≥ 36 months), respectively. Analyses were performed using SAS, version 8.02 (SAS Institute, Cary, NC, USA); the level of statistical significance was set at $p < 0.05$.

RESULTS

Histological findings

Renal histological findings after CsA treatment revealed MCD in 24 and FSGS in six. All 11 patients in whom pre-CsA renal biopsy was not performed had a diagnosis of MCD by post-CsA biopsy. Thirteen (43%) of 30 patients were found to have evidence of CsAN: five had typical CsA associated arteriolopathy without striped tubulointerstitial lesions, while eight had both CsA associated arteriolopathy and striped tubulointerstitial lesions. Table 2 summarises the histological and clinical characteristics of all 13 patients with CsAN.

Characteristics of patients with CsAN

Multivariate analysis revealed that duration of CsA treatment for more than 36 months (odds ratio = 11.3, 95% CI 1.37 to 93.1, $p = 0.02$) and age younger than 5 years at the start of CsA treatment (odds ratio = 9.91, 95% CI 1.38 to 71.2, $p = 0.02$) were independent risk factors of CsAN. No interaction between age at initiation and duration of CsA was observed, though this cannot be ruled out due to the small sample size. The longer the duration of CsA, the higher was the incidence of CsAN (see fig 3). In addition, the younger the age at initiation of CsA, the higher was the incidence of CsAN (see fig 4).

Univariate analysis also showed that patients with CsAN had more frequent relapses during CsA treatment than those without CsAN.

DISCUSSION

Although steroids are still the first line drugs to treat children with NS, a considerable number of children become seriously debilitated by their long term use. In such cases, alkylating agents including cyclophosphamide or chlorambucil have been replaced to alleviate steroid toxicity. However, the risk of developing malignancy and gonadal toxicity in adolescent children and the poor responsiveness in patients with steroid dependent NS or steroid resistant NS to these agents have limited their use.¹²⁻¹⁵

In an attempt to improve the management of these patients, CsA was first used in 1985 in children with NS. Since then, numerous reports have shown that CsA is

Table 1 Clinical and laboratory characteristics of CsAN positive and CsAN negative patients

Clinical and laboratory characteristics	CsAN positive n = 13	CsAN negative n = 17	p value
Initial responsiveness SRNS/SDNS	2/11	3/14	0.6
Histological findings FSGS/others	4/9	2/15	0.2
	Median (range)	Median (range)	
Age at diagnosis of NS (years)	2.4 (1.3–7.2)	5.7 (1.8–14.8)	0.007
Age at initiation of CsA (years)	4.1 (1.5–12.3)	8.8 (3.4–15.3)	0.02
Number of relapse (/year/patient)	1.0 (0.5–3.6)	0.5 (0–6)	0.01
Duration of CsA (months)	42 (18–144)	24 (6–89)	0.004
	Mean (SD)	Mean (SD)	
Mean CsA trough level (ng/ml)	82.8 (17.5)	74.3 (25.5)	0.3
Mean CsA dose (mg/kg/day)	5.0 (2.1)	4.4 (1.1)	0.3
GFR before CsA (ml/min/1.73 m ²)	118.8 (16.2)	124.7 (15.0)	0.4
GFR after CsA (ml/min/1.73 m ²)	117.2 (23.9)	130.2 (16.6)	0.09
Systolic blood pressure before CsA (mmHg)	108.3 (11.3)	108.1 (13.1)	0.9
Systolic blood pressure after CsA (mmHg)	115.7 (10.5)	110.8 (9.7)	0.2

SDNS, steroid dependent nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome.

effective in children with steroid dependent NS and steroid resistant NS to relieve steroid toxicity and to achieve remission, respectively.^{1–6} In clinical practice, long term use of CsA is inevitable to maintain remission in many cases despite the serious concern about the development of CsAN because most children relapse when CsA is withdrawn or the dosage is tapered.¹⁶

In this study, we have tried to clarify the risk factors or predictors of development of CsAN in children with NS taking long term CsA. We performed renal biopsy in all patients after CsA treatment as it has been postulated that renal function is not a reliable indicator and that histological examination is the only way to confirm CsAN.^{6, 11–17, 18}

Iijima *et al*¹⁹ analysed clinical characteristics based on the renal histology in 37 children with MCD taking long term CsA (mean 30.3 (SD) 2.2 months, target blood trough level 100 ng/ml). They found that the duration of CsA for more than 24 months and the persistent heavy proteinuria for more than 30 days during CsA were significant risk factors for the development of CsA induced tubulointerstitial lesions.

Our retrospective study disclosed by multivariate analysis that long term CsA treatment for more than 36 months was an independent risk factor for CsAN in children with NS. This result agrees with previous reports^{6, 20–23} which showed that patients taking CsA treatment for more than 36 months tend to have considerably more tubulointerstitial lesions

(75–78.9%) compared to those taking CsA for less than 36 months (7.1–16.7%).

Recently, Ulinski *et al* reported that a switch from CsA to mycophenolate mofetil seemed to be safer for children with steroid dependent NS and steroid resistant NS in terms of side effects as well as disease control, at least in the short term.²⁴ On the other hand, we have successful experience with high dose mizoribine (mean 10.1 mg/kg/day) for children with steroid dependent who are also CsA dependent.²⁵ This therapy reduced CsA exposure and relapse rates.

Furthermore, the multivariate analysis also revealed that an age younger than 5 years at the start of CsA treatment was another independent risk factor for CsAN. Inoue *et al* similarly reported that young age at the start of CsA treatment might be a risk factor for CsAN over the two years of study in 13 children with steroid dependent NS, although it did not reach statistical significance due to the small number of patients.¹⁸ The reason why younger children are more prone to develop CsAN is currently unknown. Conventional trough levels (C0) monitoring, commonly performed in young children, could lead to a larger dose of CsA than minimum requirement, because C0 might be lower than that estimated from corresponding AUC (area under the concentration-time curve) since younger children clear CsA more rapidly than older children or adults.²⁶ Therefore, converting from C0 monitoring to a single measurement of

Figure 3 Relation between the incidence of CsAN and duration of CsA treatment (the number of patients with CsAN/the number of patients during each interval). **Figure 4** Relation between the incidence of CsAN and age at the start of CsA treatment (number of patients with CsAN/number of patients during each interval).

Table 2 Histological and clinical characteristics of all 13 patients with CsAN

No.	Steroid responsiveness	Histological findings (pre/post-CsA)	Grade of tubular atrophy	Obsolescent glomeruli/total glomeruli	Age at the start of CsA (y)	Duration of CsA (mth)	Mean CsA trough levels (ng/ml)	Relapse (/year)
1	D	MCD/MCD	1	0/22	3.2	27	96.8	3.6
2	D	MCD/MCD	1	0/37	4.3	18	77.6	1.9
3	D	-/MCD	1	0/16	6.2	24	68.3	1
4	D	-/MCD	1	0/23	1.5	23	62.5	1
5	D	MCD/MCD	1	0/26	3.9	31	75.5	1.2
6	D	MCD/MCD	2	0/8	11.5	42	88.5	0.9
7	R→D	FSGS/FSGS	2	6/19	3.9	86	57.7	0.6
8	D	MCD/MCD	2	2/34	4.1	144	97.2	0.6
9	D	MCD/MCD	2	0/9	3.4	98	94.2	2.3
10	D	FSGS/FSGS	2	3/17	4.7	133	70.2	0.8
11	D	-/MCD	2	1/17	12.3	86	85.8	0.7
12	D	MCD/FSGS	3	6/15	11.1	90	79.6	0.5
13	R	FSGS/FSGS	3	9/12	2.3	37	122.7	—*

*This patient had been in incomplete remission for the duration of CsA treatment.

D, steroid dependent; R, steroid resistant; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis.

blood concentration two hours after CsA administration (C2) may reduce the incidence of CsAN, as C2 monitoring has been reported to be a more accurate predictor of drug exposure than C0²⁷ and results in a reduction of CsA dose.²⁸

Alternatively, genetic screening for mutations of podocin could be useful in order to reduce the possibility of unnecessary administration of steroids or CsA; as it has recently been postulated that children with SRNS and homozygous or compound heterozygous mutations in the gene encoding podocin do not respond to standard steroid or CsA treatment but have a reduced risk for recurrence in a renal transplant, early renal transplantation might be an alternative strategy in such patients.²⁹

In conclusion, alternative treatment involving cessation, tapering, or replacement should be seriously considered before 36 months of administration of CsA and the use of CsA in children younger than 5 years should be avoided if possible. Further studies in different populations are needed to confirm these conclusions because our findings are from a single centre and some of the numbers in this study are small.

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What is already known on this topic

- Risk factors for CsAN in patients with nephrotic syndrome are: dosage greater than 5.5 mg/kg/day, presence of renal insufficiency, percentage of glomeruli with lesions of FSGS, duration of CsA for more than 24 months, and persistent heavy proteinuria for more than 30 days during CsA

What this study adds

- Long term CsA administration for more than 36 months and an age younger than 5 years at the start of CsA treatment are independent risk factors for CsAN in children with nephrotic syndrome

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IMAGES IN PAEDIATRICS.....

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Rash associated with Heaf test

An 8 year old boy of Somalian origin presented to general paediatric outpatients with weight loss, abdominal pain, and general malaise. His initial investigations showed an erythrocyte sedimentation rate of 78 mm/h and a C reactive protein of 100 mg/l.

While under investigation he presented acutely with right sided abdominal pain and vomiting. He had a laparotomy which showed a perforated terminal ileum requiring a right hemicolectomy with ileo transverse anastomosis.

Histology of the caecum showed diffuse ulceration with transmural fissuring associated with granulomatous inflammation, and central necrosis consistent with tuberculosis. Ziehl Nelsen staining revealed acid fast bacilli. Postoperatively, a Heaf test was placed which was strongly positive. He did not have a scar and the family were unsure if he had had a BCG. HIV serology was negative.

Four days after the Heaf test he developed discrete, papulovesicular lesions on his trunk, back, and buttocks which were not itchy and non-tender (fig 1). These continued to enlarge (fig 2).

He was commenced on quadruple antituberculosis therapy.¹ In view of the skin lesions oral steroids was added for two weeks and then weaned.

Papulonecrotic tuberculid is thought to be a hypersensitivity reaction to the mycobacterium.² It is usually associated with a strongly positive tuberculin test and underlying systemic tuberculosis. The inability to culture *M tuberculosis* or to demonstrate it microscopically from lesional biopsy specimens, together with reports of tuberculid-like eruptions after BCG vaccination, supports this concept.³

Figure 1 Parental consent was obtained for publication of this figure.

Figure 2 Parental consent was obtained for publication of this figure.

The lesions will regress when the patient receives antituberculosis therapy.

Competing interests: none

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