RENAL FAILURE
2025, VOL. 47, NO. 1, 2474743
https://doi.org/10.1080/0886022X.2025.2474743

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CLINICAL STUDY

Factors associated with chronic calcineurin inhibitor nephrotoxicity in children with minimal-change disease

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ABSTRACT

Background: Calcineurin inhibitors (CNIs), such as cyclosporine (CsA) and tacrolimus (TAC), are commonly used to treat children with complicated minimal change nephrotic syndrome. However, chronic nephrotoxicity associated with CNIs poses a significant safety concern. This study aimed to identify the risk factors that contribute to chronic nephrotoxicity in these patients.

Material and methods: Clinical and pathological data of MCD children treated with CsA or TAC in our center between 1 January 2003 and 31 December 2022, were retrospectively reviewed. Kidney biopsies were performed on 80 patients who received CNI treatment for more than 6 months.

Results: Chronic CNI nephrotoxicity (striped interstitial fibrosis with tubular atrophy) was observed in 15% (12/80) of patients. Higher CNI culminating amounts were shown in patients who developed nephrotoxicity regardless of CsA or TAC treatment. Risk factors for chronic CNI nephrotoxicity included persistent nephrotic-range proteinuria for more than 30 days during CNI treatment, increased urinary NAG level, and CNI resistance. Multivariate analysis revealed that increased urinary NAG level and CNI resistance were the independent risk factors for chronic CNI nephrotoxicity in children with MCD.

Conclusion: MCD children who developed CNI resistance were susceptible to chronic CNI nephrotoxicity. Urinary NAG might be a valuable biomarker for CNI nephrotoxicity prediction in MCD children.

ARTICLE HISTORY
Received 18 January 2025
Revised 22 February 2025
Accepted 26 February 2025

KEYWORDS
Calcineurin inhibitors; minimal-change disease; children; nephrotoxicity

Introduction

Minimal change disease (MCD) is one of the most common causes of idiopathic nephrotic syndrome (NS) in children [1]. While glucocorticoids induce remission effectively in MCD children, those with frequently relapsing NS (FRNS), steroid-dependent NS (SDNS) or steroid-resistant NS (SRNS) require second-line immunosuppressive and glucocorticoid-sparing agents [2,3].

Calcineurin inhibitors (CNIs) such as cyclosporine (CsA) and tacrolimus (TAC) are commonly used in children with complicated minimal change nephrotic syndrome [2,3]. CNIs exert their effects through both immune and non-immune mechanisms: they inhibit T-cell proliferation by blocking the key signaling protein phosphatase calcineurin [4,5] and stabilize the actin cytoskeleton of podocytes [6,7]. CNIs are indicated as second-line therapy for children with FRNS or SDNS who develop serious glucocorticoid-related adverse effects, and as the initial second-line treatment for children with SRNS [3]. However, long-term treatment with CNIs may cause severe adverse effects of irreversible and progressive tubulo-interstitial injury and glomerulosclerosis [8–10]. This chronic nephrotoxicity becomes a major drawback in prescribing CNIs for the second-line therapy of NS in children [10–12]. The incidence of CNI nephrotoxicity in children with NS ranges from 6% to 58% after 2 to 10 years of CNI treatment [12–15]. While data regarding chronic CNI nephrotoxicity in children with MCD is limited.

In this study, we conducted a retrospective analysis of the clinicopathological features, treatment effectiveness, and incidence of CNI nephrotoxicity in children with MCD to identify the risk factors for chronic CNI nephrotoxicity in these children.

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Material and methods

Patients

Clinical and renal pathologic characteristics of 80 patients (aged 0.5-14 years old), diagnosed with NS and subsequently treated with CNI (CsA or TAC) for more than 6 months between 1 January 2003 and 31 December 2022 were retrospectively reviewed. Children with NS who received long-term therapy with CNI underwent systematic biopsies. In this study, we retrospectively analyzed MCD to assess the nephrotoxicity of CNI. Patients with secondary NS, IgA nephropathy, kidney transplantation, severe hypertension, focal and segmental glomerular sclerosis (FSGS), severe diabetes or inadequate biopsy material (<10 glomeruli) were excluded. The study received full approval by the Medical Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [No. 2020-368].

Study design and definitions

In this study, the diagnostic criteria of NS, FRNS, SDNS, and SRNS were adopted from the kidney disease: improving global outcomes (KDIGO) clinical practice guideline for glomerulonephritis [16]. CNI sensitivity was defined as no relapse or less than 2 relapses within 6 months in FRNS, steroids reduced to the dosages below the initial dependent dosages or successful steroid cessation in SDNS, and complete or partial remission within 6 months in SRNS. CNI resistance was defined as persistent complicated NS during CNI treatment or resistance to CNI developed after 6 months of therapy.

CsA or TAC (based on patients and/or their family members preferences) was prescribed for children diagnosed with idiopathic NS, initial dose of 3-7 and 0.05–0.15 mg/(kg • d) was given in two divided doses daily, respectively. Blood samples were collected before the morning dose to measure the baseline levels (C0 levels). The doses of CNIs were adjusted according to treatment response without exceeding the recommended upper limits of CsA- or TAC-trough level, which was 50–150ug/L and 4–10ug/L, respectively [17]. Blood CsA- or TAC-trough level was monitored monthly. Steroids were gradually tapered off once complete remission was achieved for both SRNS and FR/SD NS. CNI dosages were gradually tapered off after 6 months of treatment and maintained for at least 24 months unless severe adverse events or CNI resistance developed. If the measured concentration during treatment does not reach the recommended levels, we will introduce ketoconazole or Wuzhi Tablet to achieve a higher drug level (within the recommended range) [18,19]. Those who were CNI sensitive but relapsed after discontinuation might restart CNI treatment. For individuals who experience persistent complicated NS during CNI treatment or develop resistance to CNI after six months of therapy, we will discontinue CNI treatment and conduct a reassessment. Those patients may have switched to alternative treatments, such as mycophenolate mofetil (MMF). Additionally, the study only evaluates the outcomes at the end of CNI treatment.

Kidney biopsy

Kidney biopsies were reviewed by two pathologists who were blinded to treatments. All patients underwent serial section renal biopsy and were examined with electron microscopy to exclude Focal Segmental Glomerulosclerosis (FSGS). Histologic lesions of chronic CNI nephrotoxicity were characterized by striped interstitial fibrosis accompanying by tubular atrophy in the kidney cortical labyrinth [10,20].

Statistical analysis

Statistical analysis was performed with IBM SPSS 26.0 software. Quantitative data were summarized using mean ± standard deviation, median, range and interquartile range (IQR). Qualitative data were expressed as proportion and percentage. Standard distributed data were analyzed by Student's t test. Fisher's exact test was performed to evaluate the association between categorical variables. Non-normal data were analyzed by the chi-square and the Mann-Whitney U test. Logistic regression was used to identify the independent risk factors for the development of chronic CNI nephrotoxicity. p-value < 0.05 was considered significant in all analyses.

Results

A total of 80 children diagnosed with MCD were analyzed in this study, including 43 FRNS, 9 SDNS and 28 SRNS (14 primary SRNS and 14 secondary SRNS), with a median age at NS onset 2.9 (range 0.8–11.0) years old (Figure 1). The median age at CNI initiation was 5.2 (range 1.3–12.7) years old with a median course of NS 9 (range 1–107) months before CNI initiation. Patients were on CNI treatments for a median duration of 27 (range 6–77) months. Of 80 patients, 29 had received CsA monotherapy, 34 had received TAC monotherapy and 17 had received CsA at first and changed to TAC subsequently. The median doses of CsA and TAC over the

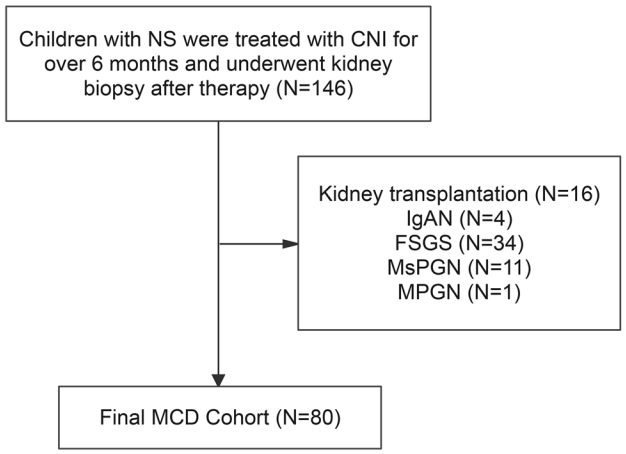

Figure 1. Participant recruitment and exclusion flowchart. NS, nephrotic syndrome; CNI: calcineurin inhibitors; MCD: minimal-change disease; IgAN: IgA nephropathy; FSGS: focal and segmental glomerular sclerosis; MsPGN: mesangial proliferative glomerulonephritis; MPGN: membranoproliferative glomerulonephritis.

study period were 4.0 (1.2–8.0) mg/(kg•d) and 0.08 (0.03–0.13) mg/(kg • d), yielding the mean trough levels of 83 (40–198) ug/L and 5.4 (3.2–8.7) ug/L, respectively. All FR/SD NS patients were sensitive to initial CNI treatments. Complete remission was achieved in 92.9% of primary SRNS and 85.7% of secondary SRNS patients. At the time of kidney biopsy, 72.5% of patients remained CNI sensitive, while 27.5% of them developed CNI resistance.

Acute kidney injury occurred in 3 (3.8%) patients during CNI treatments. Hypertension was mild to moderate and controllable in 4 patients. Hyperuricemia occurred in 51 (63.8%) patients. 2 (2.5%) patients had hyperkalemia accompanied with increased serum creatinine levels but returned to the normal range after CNIs were tapered off. In this study, the occurrence of the above-mentioned CNI-related complications did not differ between patients with or without CNI nephrotoxicity (data are not shown). Furthermore, the duration of CNI treatment did not correlate with hyperuricemia ($p = 0.076$) or hypertension ($p = 0.433$).

Chronic CNI nephrotoxicity was observed in 12 (15.0%) biopsies. Among them, only 1 patient had moderate nephrotoxicity with 25–50% striped interstitial fibrosis and arteriolar hyalinosis, while the nephrotoxicity in the other 11 patients was mild (lesions limited to 25% samples). Detailed characteristics according to the presence of CNI nephrotoxicity are shown in Table 1 and Figure 2. Duration of persistent nephrotic-range proteinuria, CNI resistance and duration of CNI treatment were significantly different between patients with and without CNI nephrotoxicity. Of the 80 patients, 4 (5.0%) received ACE inhibitors (ACEi) during CNI treatment. ACEi use was found in 2 out of 12 (16.7%) patients with chronic nephrotoxicity and 2 out of 68 (2.9%) without it, with no significant difference between the groups ($p = 0.105$).

To investigate the relationship between CNI exposures and nephrotoxicity, we compared the trough levels and cumulative drug amounts in both CsA and TAC groups. While the median drug trough levels did not differ significantly between patients with and without nephrotoxicity, higher cumulative drugs amounts were observed in patients with nephrotoxicity in both CsA and TAC groups (Tables 2 and 3).

Logistic regression was performed to identify the independent risk factors for developing CNI nephrotoxicity (Table 4). Duration of persistent nephrotic-range proteinuria, CNI resistance and duration of CNI treatment remained to be

Table 1. Characteristics of 80 MCD patients with or without chronic CNI nephrotoxicity.

Characteristics	With nephrotoxicity	Without nephrotoxicity	*p*-value
Male (*n* [%])	8 (66.7)	54 (79.4)	0.452
Age at diagnosis of NS (years; median [range])	4.2 (0.8, 8.0)	2.8 (1.0,11.0)	0.438
Steroid-resistant NS (n [%])	6 (50.0)	22 (32.4)	0.326
Months of NS before CNIs (median [range])	18 (1, 90)	9 (1, 107)	0.470
Rise in Scr during CNI treatment (n [%])	1 (8.3)	5 (7.6)	1.000
Number of relapse (per year; median [Q1, Q3])	1.4 (1.0, 3.0)	1.2 (0.5, 2.0)	0.190
Duration of persistent nephrotic-range proteinuria during CNI treatment (days; median [Q1, Q3])	31 (22, 38)	27 (6, 71)	0.001
Laboratory tests at biopsy			
24-hour urinary protein (mg/kg; median [Q1, Q3])	129 (81, 230)	84 (35, 159)	0.054
Urinary-NAG (U/L; median [Q1, Q3])	32.6 (27.8, 56.0)	13.2(9.3, 26.9)	0.002
Urinary β2M (mg/L; median [Q1, Q3])	0.21 (0.20, 0.23)	0.20 (0.16, 0.26)	0.811
eGFR (ml/min per 1.73m^2; mean ± SD)	142 ± 43	157 ± 39	0.283
Uric acid (umol/L; mean ± SD)	442 ± 151	436 ± 133	0.915
CNI resistance (*n* [%])	9 (75.0)	13 (19.1)	<0.001
Total time on CNI before biopsy (months; median [range])	36 (20, 77)	27 (6, 71)	0.043
Ketokonazole or Wuzhi Tablet (*n* [%])	9 (75.0)	46 (67.6)	0.744

MCD: minimal change disease; CNI: calcineurin inhibitor; NAG: N-acetyl-beta-D-glucosaminidase; β2M, β2-microglobulin; eGFR: estimated glomerular filtration rate.

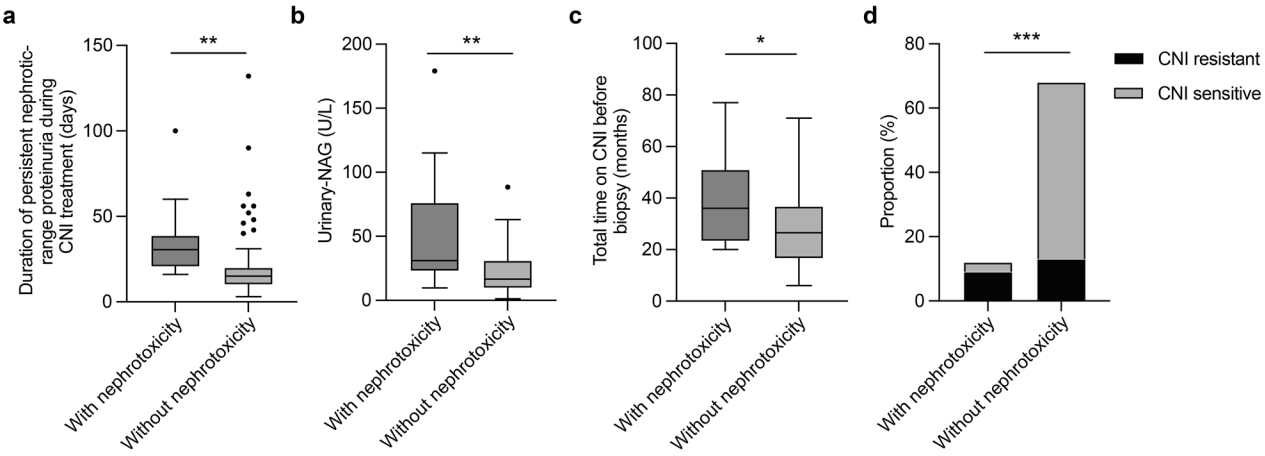

Figure 2. Comparison of clinical and laboratory parameters between MCD children with and without chronic CNI nephrotoxicity. (a) Duration of persistent nephrotic-range proteinuria during CNI treatment, (b)Urinary-NAG, (c)Total time on CNI before biopsy, and (d) Proportion of CNI resistance. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. CNI: calcineurin inhibitor; NAG: N-acetyl-beta-D-glucosaminidase.

significant variables in univariate analysis. Multivariate analysis revealed that CNI resistance was the independent risk factor of CNI nephrotoxicity.

Discussion

Chronic nephrotoxicity remains to be the major safety concern of CNI immunosuppressive regimens, especially in children [10,21]. In this study, chronic nephrotoxicity developed in 12 (15.0%) of the 80 MCD children receiving CNI treatments. Previous study of 13 children with steroid-dependent MCD reported that 54% of them developed chronic nephrotoxicity after 2 years of CsA treatment [13], whereas only 1 (6%) patient had CNI-induced histological lesions after a median course of treatment 30 (range 26–43) months in another observational study [14]. Recently, Wael Abukwaik et al. reported that 3 children (12.5%) with FR/SDNS showed evidence of chronic nephrotoxicity after treating with CNIs for a median 66.5 (range 12–153) months [15]. Overall, the incidence of CNI nephrotoxicity varies from 6 to 58% after 2 to 10 years of CNI treatments [12–15]. These inconsistent results may be due to the differences in CNI treatment, types of NS and the definitions of chronic nephrotoxicity.

Iijima K et al. reported use of CsA for >24 months and presence of heavy proteinuria for >30 days during CsA therapy were the risk factors for tubulointerstitial lesions in childhood MCD [22], which is consistent with our study. CsA treatment duration was reported to be correlated with CsA nephrotoxicity [11,22], while several retrospective results showed that nephrotoxicity was infrequent in those who had received low maintenance levels of CNI treatments for a range of 2-11 years [14,23,24]. Hence, a large, controlled prospective cohort is required to clarify the relationship between CNI treatment duration and nephrotoxicity.

In this study, it is noteworthy that patients with nephrotoxicity had higher cumulative CNI amounts than those without nephrotoxicity, suggesting that CNI drug accumulation might be associated with chronic nephrotoxicity. Meyrier et al. reported that a dosage greater than 5.5 mg/kg per day was a risk factor for CsA nephrotoxicity [25]. Thereafter the recommended dose for CsA is reduced in patients with PNS [2]. Optimal starting doses and initial target levels of CsA and TAC have been recommended [3]. Co-administration of ketoconazole with CsA in children with PNS has desirable impacts on both treatment responses and costs [18]. Wuzhi tablet, the extract of Schisandra sphenanthera, is a traditional herb that can also be co-administrated with CNI to maintain its therapeutic level without influencing the immunosuppressive effect [19]. Moreover, Kengne-Wafo et al. reported that high second-hour (C2) level of CsA (>600ug/L) was associated with an increased risk for CNI nephrotoxicity [12] suggesting that C2 monitoring would be a more accurate predictor of drug exposure than the trough level [26]. Unfortunately, C2 levels were not measured in our study, further studies are needed to investigate the role of C2 level for predicting CNI nephrotoxicity.

Our data revealed that MCD children who had urinary NAG levels twice higher than the normal value were at increased risk of nephrotoxicity. NAG is an enzyme present in kidney proximal tubular cells and excreted as an indicator of renal tubular dysfunction [27]. The presence of abnormal Scr and elevated blood UA levels following CNI treatment suggest chronic nephrotoxicity [15]. However, the comparable serum UA levels between patients with and without CsAN limits its usefulness as a biological marker [12]. Moreover, urinary NAG is easy to be detected and it is significantly increased in patients with chronic CNI nephrotoxicity, making it a potential marker to predict CNI nephrotoxicity.

Table 2. 29 MCD with or without chronic cyclosporine (CsA) nephrotoxicity.

	With nephrotoxicity	Without nephrotoxicity	*p*-value
CsA trough level (ug/L, median [min, max])	100 (82, 198)	82 (40, 130)	0.142
Cumulative amount of CsA	3600 (1811, 3960)	1451 (499, 3115)	0.037

Table 3. 34 MCD with or without chronic tacrolimus (TAC) nephrotoxicity.

	With nephrotoxicity	Without nephrotoxicity	*p*-value
TAC trough level (ug/L, median [min, max])	6.6 (4.0, 7.3)	5.0 (3.2, 8.7)	0.318
Cumulative amount of TAC	212 (154, 508)	134 (48,248)	0.008

Table 4. Logistic regression analysis of risk factors for CNI nephrotoxicity.

	Univariate analysis			Multivariate analysis		
Parameter	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Duration of CNI treatment (months)						
>24	2.368	0.589–9.524	0.225	1.424	0.267–7.604	0.679
6–24 (reference)	1.000			1.00		
Urinary-NAG (U/L)						
>24	9.783	1.977–48.412	0.005	7.645	1.341–43.569	0.022
0–24 (reference)	1.000					
Duration of persistent nephrotic-range proteinuria during CNI treatment (days)						
>30	5.182	1.408–19.066	0.013	3.652	0.706–18.885	0.122
0–30 (reference)	1.000					
CNI resistance	12.692	3.008–53.553	0.001	7.691	1.575–37.560	0.012

CNI: calcineurin inhibitor; OR: odds ratio; CI: confidence interval.

Our data showed that CNI resistance was another independent risk factor of developing nephrotoxicity in MCD children. Gradual decline in sensitivity and development of secondary resistance of CsA over long-term treatment was proposed previously [28,29]. Of note, treatment modification with other steroid-sparing agents and genetic testing are recommended in SRNS adults who are resistant to CNIs [30]. Moreover, CNIs should be discontinued in those who fail to achieve at least a partial response within 6 months [3]. Our study proposes that MCD children receiving CNI treatments should also be monitored carefully, and if resistance occurs, reevaluation for therapeutic decision-making is of great importance to prevent unfavored toxicity. Further prospective studies are necessary to validate this finding to optimize the exploitation of CNIs in children with MCD in clinics.

This study has several limitations. First, its retrospective design and inclusion of patients from a single center who underwent kidney biopsy after prolonged CNI treatment may introduce selection bias, limiting the generalizability of our findings to the broader population of children with MCD, particularly those who did not require biopsy. Additionally, we did not assess C2 levels, which may provide a more accurate measure of drug exposure and nephrotoxicity risk than trough levels. Further research is necessary to validate urinary NAG as a biomarker for CNI nephrotoxicity in future cohorts.

In conclusion, children with MCD who developed resistance to CNI were found to be vulnerable to chronic nephrotoxicity from these drugs. Urinary NAG may be a valuable biomarker for predicting CNI nephrotoxicity in MCD children. Based on our findings, we recommend discontinuing CNI treatment in children who experience persistent complicated NS during CNI therapy or who develop resistance to CNI after 6 months of treatment.

Acknowledgments

The authors are grateful to all the children who participated in this study. The authors would like to thank Xiaohong Zheng for her assistance in recording the medical cases.

Ethical approval and consent participants

The study was in compliance with the Helsinki Declaration and approved by the Medical Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [No. 2020-368].

Authors' contributions

All authors contributed to the study conception and design. XJ, YM and SY designed the study. Material preparation, data collection and analysis were performed by BJ, ZL, LC, ZY, AL. The first draft of the manuscript was written by BJ, CC and YP. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by grants from the National Key Research and Development Program of China Nos. 2022YFC2705100 and 2022YFC2705101.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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