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ORIGINAL ARTICLE

Response to cyclosporine in steroid-resistant nephrotic syndrome: discontinuation is possible

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Abstract
Background Steroid-resistant nephrotic syndrome (SRNS) is still regarded as a serious disease although treatment with cyclosporine (CSA) has improved outcome. However, the duration of treatment in responders is unclear, and treatment of patients with genetic causes is a matter of debate.
Methods Thirty-six patients with SRNS were studied retrospectively. Median age at presentation was 3.2 (range, 0.06–15.0) and median follow-up 15.5 years (range, 1.8–27.7), respectively; 23 (64 %) had focal segmental glomerulosclerosis (FSGS) on biopsy. In 33/36 patients (92 %), genetic testing was performed for at least three most common genes known to be mutated in SRNS.
Results Nineteen patients (53 %), especially those with minimal change nephrotic syndrome (MCNS) at initial biopsy ($p<0.002$), entered complete remission with CSA monotherapy, including one patient with compound heterozygous *NPHS1* and dominant *ACTN4* mutation, respectively. Ten patients entered partial remission (28 %, all FSGS), including two with *NPHS2* mutations. Seven patients (six FSGS, one MCNS) did not respond to treatment. In 15 of 19 responders to CSA, treatment was stopped after a median of 3.1 years (range, 0.5–14) and no further relapses occurred in 11/15 (73 %) patients with median follow-up of 9.7 years.
Conclusions CSA monotherapy is effective in SRNS. Discontinuation of CSA is possible in many patients with complete remission.

Keywords Steroid-resistant nephrotic syndrome · Cyclosporine · FSGS · Minimal change disease · Genotype

Introduction

Idiopathic nephrotic syndrome (INS) is the most frequent form of nephrotic syndrome in childhood, including two main histologic subtypes: minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Studies of the International Study of Kidney Disease in Children (ISKDC) have indicated that a response to steroids can be expected in the majority of patients with MCNS [1]. Thus, nowadays renal biopsy to identify patients with FSGS or other lesions is performed when a 4-week course of oral prednisolone has failed to induce remission.

The treatment of steroid-resistant nephrotic syndrome is still controversial, as indicated by a survey among pediatric nephrologists from the U.S. [2]. However, in recent years the value of calcineurin inhibitors has been documented and is recommended by Kidney Disease Improving Global Outcomes (KDIGO [3, 4]), although an initial study found no benefit [5]. Cyclosporine (CSA) especially has been used in SRNS and FSGS alone, or in combination with prednisolone or after induction treatment with methylprednisolone [6], including a placebo-controlled study by Liebermann et al. [7]. Also, a French Society study indicated a good response in 40 % of patients [8]. Recently, children with both MCNS as

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well as FSGS achieved excellent remission rates of 82.1 and 85.7 %, respectively, with CSA [9]. Tacrolimus has also been used successfully in the treatment of SRNS, and in some countries is the preferred choice [10, 11]; remission rate 85.7 vs. 80 % for tacrolimus and CSA, respectively, with fewer side effects in the tacrolimus group [12]; this drug, however, is not licensed for first-line use in nephrotic syndrome in Germany.

Several issues regarding calcineurin treatment in SRNS are unresolved. One relates to the duration of treatment in patients with response. In steroid-sensitive patients, treatment with CSA usually results in CSA dependency, i.e., discontinuation is not possible. Response to CSA usually occurs within months in most patients, although some patients need to be treated for longer periods [13]. No systematic data are available regarding whether CSA can be discontinued in steroid-resistant patients. In the follow-up study by Hamasaki et al., 71 % of patients were still on treatment at 5 years, including 7/22 with MCNS who frequently relapsed [14].

Another emerging issue is the impact of genetic testing on treatment in SRNS. Up to 30 % of SRNS cases may be of genetic origin [15], e.g., due to altered ultrastructure of the podocyte, such as induced by mutations in the *NPHS1* and *2* and *WT1* genes. Little systematic data is available on other treatment modalities in genetic SRNS, such as CSA. One study found an inferior response to CSA in patients with mutations, but this study included many children with infantile NS [16].

The aim of this present study was to perform a clinical analysis of all patients presenting to our department since 1991 receiving CSA treatment for SRNS. In addition to providing data on initial clinical response, we provide follow-up data in patients where treatment was discontinued according to the local practice. Lastly, we analyzed the impact of genetic testing for at least three common genes known to be mutated in SRNS in this cohort of children.

Patients and methods

A retrospective chart review was undertaken for 36 patients with SRNS. For this type of study formal consent is not required. Nephrotic syndrome was defined according to the Arbeitsgemeinschaft Pädiatrische Nephrologie (APN) and ISKDC [1, 17]. All patients were treated according the protocols of the APN, i.e., prednisone 60 mg/m^2 per day. Steroid resistance was defined according to the ISKDC as persisting proteinuria despite a 4-week course of prednisone, and this was the indication for renal biopsy. Since 2004, all patients also received three intravenous pulses of methylprednisolone after renal biopsy, however none on the patients presented here responded to this intervention. Patient baseline characteristics are presented in Table 1.

Renal biopsies were reviewed by a single pathologist. CSA was started at a dose of 150 mg/m^2/day in two doses, aiming at trough levels of 100–150 ng/ml in the first 12 months and 80–100 ng/ml thereafter. Steroids were discontinued over a time course of 2–6 months (median 3). Response was defined as:

- complete remission (CR): disappearance of proteinuria and normalization of serum albumin levels.
- partial remission (PR): proteinuria 100–1000 mg/m^2/day and increase of serum albumin levels >25 g/l or cessation of edematous status
- no response (NR): persisting nephrotic range proteinuria and serum albumin levels <25 g/l.

In patients with CR, tapering of CSA was started on an individual basis usually over a period of 12–24 months. One patient discontinued CSA deliberately on his own (non-adherence).

Genetic testing for the three most common genes known to be mutated in SRNS (*NPHS1* and *NPHS2*, *WT1*) was performed by the laboratory of Prof. F. Hildebrandt (Freiburg, Germany and Ann Arbor, MI, USA) after parental consent was given.

Exclusion criteria: six patients with syndromic FSGS were excluded (two with Schimke immuno-osseous dysplasia, two with Galloway Mowat-like syndrome, and two with Pierson syndrome): none was treated with CSA. Two patients from one family with COQ6 mutations and deafness were treated with CSA with equivocal response and will be reported elsewhere. Patients with diffuse mesangial sclerosis on renal biopsy (with and without *WT1* mutations) were excluded. Two patients with FSGS presented in CKD stage 4 so that treatment with CSA was not considered; one of these patients had a homozygous *NPHS2* mutation.

Results

Response to CSA Thirty-six children were included in the analysis, of which 23 (64 %) had FSGS and 13 (36 %) MCNS. From the total group, 19 (53 %) were classified as responder, seven (19.4 %) as non-responder, and ten (28 %) as partial responder. Figure 1 illustrates the response to treatment including follow-up data.

Complete remission Nineteen patients (53 %) had a CR under CSA. When accounting for underlying histology, 7/23 (30.4 %) of patients in the FSGS group had CR compared to 12/13 (92 %) with MCNS; thus CR was significantly more frequent in MCNS (p <0.002). Median time to CR was 2 months (range, 0.5–7.8 years) months; this includes two patients who went into PR initially and finally reached CR after 40 months and 7.8 years, respectively. The latter patient had fluctuating low CSA trough levels, initially, and was then lost to follow-up for 4 years,

Table 1 Patient details

	SRNS (36) Median (range)	FSGS (23) Median (range)	MCNS (13) Median (range)
Age at manifestation (years)	3.2 (0.06–15)	3.7 (0–15)	2.3 (0.1–4.6)
Initial serum albumin (g/l)	16 (6.5–28)	16.5 (6.5–28)	13.5 (7–27.4)
Initial proteinuria (g/m^2/d)	5.2 (1.3–78)	4.6 (1.3–78)	8.5 (3.4–18.3)
Serum albumin before CSA (g/l)	23 (9–44)	21.5 (9–40)	26 (10–44)
Proteinuria before CSA (g/m^2/day)	2.5 (0.3–55.8)	3.4 (1–55.8)	1.3 (0.3–3.8)

There were no significant differences in parameters between FSGS and MCNS ($p>0.05$)

SRNS steroid resistant nephrotic syndrome, *FSGS* focal segmental glomerular sclerosis, *MCNS* minimal change nephrotic syndrome, *CSA* cyclosporine

although continued CSA. Upon returning, she was still in PR, but with regular medication, proteinuria finally disappeared 7.8 years after initial presentation.

In four patients with CR, treatment was changed to tacrolimus due to cosmetic side effects (hypertrichosis +/− gum hyperplasia).

Partial remission Ten of 36 patients (28 %) had a PR; all patients had FSGS. Serum albumin increased from 19.7± 5.81 to 25.8±5.0 g/l after 6 months, and to 28±4.5 g/l after 12 months. Despite an initial PR with reduction of proteinuria, 5/10 patients developed CKD and entered end-stage renal disease (ESRD) after a median of 3.4 (range, 0.49–17) years. Two of ten patients experienced an increase of serum creatinine from 0.6 to 2.1 mg/dl and 0.7 to 2.5 mg/dl after 8 and 11.3 years, respectively, but did not yet enter ESRD.

No response Seven patients (19 %) had NR to CSA: six patients with FSGS and one patient with MCNS. In four patients, (all FSGS) ESRD occurred at a median of 1.5 (range, 0.5–3.9) years after initiation of CSA treatment. Although one patient had an initial PR with serum albumin of 28 g/l, she was classified as NR because she reached ESRD after 6 months. One patient was lost to follow-up; one patient with MCNS has stable GFR after 2-year follow-up following discontinuation of CSA due to non-response and parental wish. One patient entered CR after addition of mycophenolic acid; subsequently CSA was tapered and recently discontinued.

Discontinuation of cyclosporine In 15/19 (79 %; six FSGS, nine MCNS) patients with CR, CSA was stopped at a median of 3.1 years (range, 0.5–14), including one patient, who stopped treatment by himself. This includes the two patients with delayed CR to CSA (see above). Relapses occurred in four cases but responded to treatment. In the remaining 11/15 (73 %) patients, or 11/19, (58 %) of patients with CR including all patients with FSGS, no further relapses occurred despite discontinuation with a follow-up of 9.7 (0.7–21.6) years.

Genotype–phenotype correlations

In 33/36 patients (92 %), genetic testing was performed. All patients were screened for *NPHS1*, *NPHS2*, and *WT1* mutations by PCR and Sanger Sequencing. Additionally, 21 of these 36 patients were screened again for 27 monogenic causes of SRNS in a recently developed Next Generation Sequencing panel [15]. In six patients (17 %), a genetic cause of nephrotic syndrome is likely, including four patients with homozygous *NPHS2* mutations; one patient had a compound heterozygote *NPHS1* mutation and one with a dominant

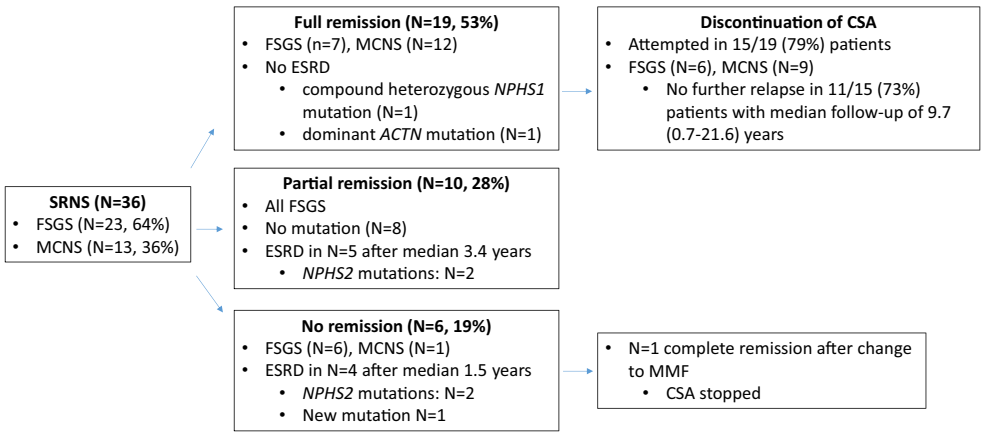

Fig. 1 Flow-chart indicating response and follow-up of patients treated with cyclosporine (CSA). *MCNS* minimal change nephrotic syndrome, *ESRD* end stage renal disease, *FSGS* focal segmental glomerular sclerosis, *MMF* mycophenolate mofetil, *SRNS* steroid resistant nephrotic syndrome

Table 2 Genotype–phenotype correlations, including patients with heterozygous mutations (*), which are not regarded as disease-causing

Patient	Genetic findings	Clinical course
1	*NPHS2*: c.413G>A, p.Arg138Gln (hom)	No response ESRD after 2.4 years
2	*NPHS2*: c.413G>A, p.Arg138Gln (hom)	No response ESRD after 2.1 years
3	*NPHS2*: c.467dupT, p.Leu156Phefs*11 (hom)	Partial remission ESRD after 5.0 years
4	*NPHS2*: c.413G>A, p.Arg138Gln (hom)	Partial remission but patient stopped treatment deliberately after 12 months. Returned in ESRD after 1.8 years
5	*NPHS1*: c.928G>A, p.Asp310Asn (het); c.2816-3T>G, splice (het)	Complete remission after 8 weeks. Currently in remission on low dose CSA treatment (CSA trough levels <25 ng/l)
6	*ACTN4*: c.2020C>T, p.Arg674Cys (het)	Complete remission after 10 weeks. Currently on CSA treatment
7 *	*NPHS2*: c.686G>A, p.Arg229Gln (het)	Complete remission CSA successfully discontinued
8 *	*NPHS2*: c.686G>A, p.Arg229Gln (het)	Complete remission CSA discontinuation planned
9 *	*NPHS1*: c.3110-2A>G, splice (het) *MYH9*: c.5143G>A, p.Gly1715Ser (het)	No response. Treatment stopped. Stable GFR on ACE-inhibitor, still nephrotic (no edema)

ESRD end stage renal disease, *CSA* cyclosporine, *GFR* glomerular filtration rate

ACTN4 mutation (Table 2). In one patient with no response and rapid development of ESRD, *NPHS1* and *NPHS2* screening was negative, but a potential new mutation was recently found (F. Hildebrandt, unpublished data). Two patients had heterozygous *NPHS2* mutations (both CR) and in one patient with NR a heterozygous *MYH9* and *NPHS1* mutation was detected; we do not consider these heterozygous mutations disease-causing, however.

Renal function Ultimately, 9/36 (25 %) patients progressed to end-stage renal disease after a median of 2.4 years (range, 0.5–18.1 years). Five were from the group with PR, four from the group with NR; four of these patients had mutations in the *NPHS2* gene and one has an unpublished mutation. The evolution of serum creatinine in patients during follow-up is shown in Fig. 2.

Discussion

Our single-center experience over 20 years not only underlines the value of calcineurin inhibition for induction of CR and PR in pediatric SRNS, including individual patients with genetic forms, but we also demonstrate that this treatment can be discontinued successfully in at least half of the patients with CR without further relapses. This is quite extraordinary since patients with steroid-sensitive NS will usually relapse after discontinuation of calcineurin inhibitors.

Treatment of SRNS is usually carried out aggressively as progression into ESRD can occur, and recurrence after renal transplantation is still problematic. The benefits of calcineurin inhibition, especially CSA in SRNS, have been documented in several adult and pediatric studies [18], indicating that is in part a treatable disease. Initially, data from the French Society

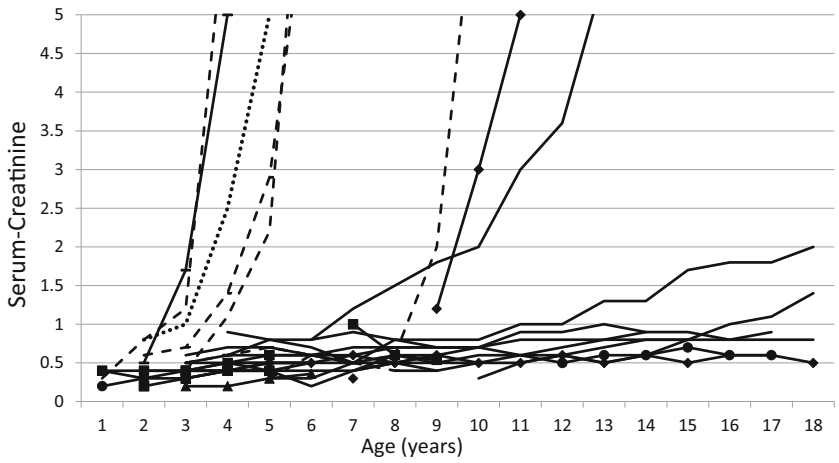

Fig. 2 Individual serum creatinine of patients over time. *Dashed lines* indicate patients with *NPHS*2 mutations and one patient with an unpublished mutation. Patient with * entered end stage renal disease (ESRD) 18.1 years after diagnosis at age 24

study indicated a good response in 40 % of patients [8]. Ingulli [19] reported a benefit of increased doses on reduction of proteinuria, however toxicity is significant, especially because of the concomitant use of steroids. Response to CSA usually occurs within months in most patients, although some patients need to be treated for longer periods. In our series, two patients actually required 40 months and 7.8 years to reach full remission despite early PR, but in both we have been able to discontinue CSA successfully. Thus, treatment in patients with PR should not be stopped too early.

The rate of CR achieved (53 %) is comparable to many published studies. Higher remission rates have been found, e.g., by Ehrich (84 %), using a protocol with methylprednisolone [18], but differences in study designs apply. For instance, in that study, the proportion of patients who underwent genetic testing was lower (56 %) and the number of patients with MCNS was not clearly stated. In another recent randomized study comparing cyclophosphamide pulses and CSA from Germany, the CR or PR rate with CSA was 60 % after 3 months [6]. A recent report on CSA use in Japanese patients with SRNS, including both MCNS as well as FSGS, achieved excellent remission rates of 82.1 and 85.7 %, respectively, although in that study the FSGS arm was relatively underpowered [14]. On the other hand, studies with much lower response rates have also been published, for example the controlled study by Gipson et al., where CR or PR was only achieved in 22 of 138 (16 %) CSA-treated patients; eight patients in this group died, underlining the fact that SRNS is a serious disorder [20].

It has been suggested that patients should receive intravenous methylprednisolone pulses if remission has not been achieved after 4 weeks of oral prednisolone [21]. Until 2004, we did not use this approach, but since then it has been practiced locally and in most German centers. Systematic studies as to whether pulse steroids improve remission rates of patients with no response to oral steroids have not yet been performed [22], but seem warranted, although in our series no patient has responded. The same applies for the concomitant use of ACE inhibitors, which are now standard treatment in patients with proteinuria.

Studies on the discontinuation of calcineurin inhibitors in SRNS are scarce [3]. In one series, CSA treatment was stopped in seven patients after conversion to mycophenolate mofetil. In another study, CSA was stopped in 22 patients and post-hoc analysis revealed sustained remission after 26 weeks [23]. In our experience, discontinuation is possible without conversion after induction of CR in at least 58 % of patients. This should be done with caution, since relapses can occur, but our limited experience is very positive in most cases and long-term follow-up is available for these patients. Again, despite these limitations, the discontinuation of CSA has never been reported for patients with SRNS before, and opens the doors for further future studies into this field. Currently, we aim to gradually reduce CSA in patients for whom remission has been maintained for 1 year, with the exception of one patient, where it was stopped rapidly after 6 months. We slowly taper CSA over at least 12 months, sometimes for longer periods, depending on the initial course, closely monitoring proteinuria. It should be noted that this policy is only founded upon uncontrolled long-term experience, and prospective studies would have to confirm this approach.

We have not done routine biopsy studies to exclude toxic CSA side effects, partly because of our positive experience with discontinuation, which also alleviates CSA toxicity. For scientific purposes, biopsies might have been helpful to confirm a cure of FSGS in this cohort of patients, but we chose to not perform them for ethical reasons. It is unresolved so far why CSA discontinuation is feasible in patients with SRNS in contrast to SSNS. Possibly, the immunopathogenesis of these disorders is distinctly different.

The treatment of genetic forms of SRNS is unclear [24]. Usually, at the onset of nephrotic syndrome, data on genetic testing are not readily available, and initiation of some form of treatment seems mandatory; usually this includes steroids and calcineurin inhibitors. This might change when results of genetic testing are available within a very short time, e.g., together with results of the kidney biopsy. However, we have seen partial remission in two patients, and even full remission in another two patients with genetic forms of SRNS, confirming data by Santin who found partial remission in 7/26 mutation carriers [25]. This may impose a dilemma. The exact mechanisms by which calcineurin inhibitors work in idiopathic and genetically determined SRNS are as of yet unknown, but may be explained via stabilization of actin cytoskeleton in the podocyte [26, 27].

Our study is clearly limited by its retrospective design and lack of a control arm. The issues of pulse steroid and concomitant ACE use have been addressed. A major problem is the definition of PR. It has been suggested that patients with PR may have improved renal survival and often will not progress to ESRD. However, a definition of PR is problematic, and various criteria have been used, from e.g., disappearance of edema and increase of serum albumin (exact value not specified) [25], to normalization of serum albumin >35 g/l [6] to a six-item score, looking at proteinuria at different stages during follow-up [20]. The criterion of normalization of serum albumin or proteinuria may be problematic, however. For example, in our series, one patient had an initial reduction of proteinuria and an increase of serum albumin, fulfilling the criteria of PR, but then had a rapid deterioration of renal function into ESRD. Five patients who fulfilled our definition of PR progressed to ESRD, so the effect of CSA can be questioned; only controlled trials can solve this issue. However, these patients progressed more slowly than non-responders (3.4 vs. 1.5 years), which might be an indicator that PR is important in individual patients. On the other hand,

two patients initially had PR, but reached CR later. Taken together, it seems that PR is a relatively soft and arbitrary end-point, although the reduction of proteinuria is usually very clinically relevant. For the future, a consensus on defining PR seems desirable, also in order to allow a comparison of studies.

In summary, calcineurin inhibition seems to be justified as a first-line treatment in SRNS. It is successful in many patients and, in our experience can be stopped successfully in individual patients with CR after treatment. Individual patients with genetic forms of SRNS may show PR or even CR, however the majority progress to ESRD rapidly. These results indicate a potential for interesting therapeutic approaches [28] in SRNS that need to be addressed in multicenter prospective studies.

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Conflict of interest The authors declare no conflict of interest

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