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Original Article

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Recurrence of severe steroid dependency in cyclosporin A-treated childhood idiopathic nephrotic syndrome

Markus J. Kemper[1,2], Eberhard Kuwertz-Broeking[3], Monika Bulla[3], Dirk E. Mueller-Wiefel[2] and Thomas J. Neuhaus[1]

Pediatric Nephrology, [1]University Children's Hospital, Zurich, Switzerland, [2]University Children's Hospital, Hamburg and [3]University Children's Hospital, Münster, Germany

Abstract

Background. In patients with steroid-dependent nephrotic syndrome (SDNS), long-term remission (LTR) can usually be achieved with cyclosporin A (CSA), after alternative treatment with cytotoxic drugs or levamisole has failed. Nevertheless, severe SDNS recurs in some patients despite CSA maintenance therapy. Few data are available on the clinical course and treatment strategies in these patients.

Methods. We carried out a retrospective chart analysis of 46 patients with SDNS treated with CSA, after failure of cyctotoxic treatment with cyclophosphamide (CPO). Median age at primary manifestation was 3.0 years (range 0.8–6.9) and median current age is 20.4 years (range 8.6–29.1). Patients were recruited from three centres caring for a total of 186 patients with steroid-sensitive nephrotic syndrome.

Results. In 14 of the 46 patients (30%; 10 male), severe SDNS recurred again despite CSA maintenance therapy. Seven patients relapsed beyond the age of 18 years. Nine of 14 patients received a further course of cytotoxic treatment as first intervention: six were treated with chlorambucil (CLA) and three with CPO. Four of the CLA-treated patients remained in LTR in contrast to none after CPO. Five patients received levamisole after CSA: only one went into LTR, while in one other CSA could be discontinued although further relapses occurred. One further patient was switched to CLA after levamisole, finally inducing LTR. Overall, six patients required two or more drugs, and in four of these CSA maintenance ultimately had to be restarted.

Conclusion. We conclude that SDNS can recur in patients despite CSA maintenance therapy. Treatment strategies for this subgroup of patients are complex and should be standardized to optimize long-term outcome. A subgroup of patients with childhood SDNS continues to relapse into adulthood.

Keywords: childhood; cyclosporin A; long-term remission; maintenance therapy; steroid-dependent nephrotic syndrome

Introduction

The idiopathic nephrotic syndrome of childhood is characterized by steroid responsiveness in 80–90% of cases (steroid-sensitive nephrotic syndrome; SSNS) [1]. Initial treatment with prednisone (60 mg/m^2) leads to long-term remission in a variable proportion of patients, but up to 40–60% develop a relapsing course [2–4]. In particular, the development of steroid-dependent nephrotic syndrome (SDNS; i.e. relapses during steroid treatment or shortly after discontinuation) is a major problem in up to half of these patients.

In SDNS, cyclophosphamide is frequently used as first alternative to steroids, although recent studies revealed conflicting results concerning the long-term remission rate [5–7]. Also, the success of levamisole, a further alternative treatment option in SDNS, is not predictable [8,9]. After failure of these adjunct treatments, cyclosporin A (CSA) is indicated and used frequently as a next step of intensified therapy [10–12]. With this regimen, steroid dependency can often be controlled effectively, but CSA dependency develops and long-term treatment is necessary.

A subgroup of patients treated with CSA develop occasional relapses, often controlled by additional low-dose alternate-day steroids [10]. In some patients, however, a complicated course develops characterized by recurrence of severe SDNS despite maintenance

Correspondence and offprint requests to: Markus J. Kemper, MD, Pediatric Nephrology, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland. Email: kemper@uke.uni-hamburg.de

immunosuppression with CSA. There are very few published data on this issue, with only one study addressing this problem [13]. In this study of 52 CSA-treated patients, CSA had to be discontinued in 16 patients for various reasons, including eight patients in whom SDNS had recurred. In order to acknowledge this potential problem and clinical challenge, we retrospectively analysed our experience with 14 patients from three large paediatric centres, in whom SDNS recurred despite CSA maintenance treatment.

Subjects and methods

At the time of analysis, 186 patients with the idiopathic nephrotic syndrome of childhood according to criteria of the International Study of Kidney Diseases in Children [4] were followed in the participating institutions. Chart review was performed for all patients.

All patients were steroid responsive at initial presentation and were treated according to the standards of the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) [2,3]. Forty-six of the 186 patients (25%) ultimately received CSA; 12 of 54 at centre 1 (Zurich), 17 of 90 at cenre 2 (Hamburg) and 17 of 42 at centre 3 (Münster). Primary manifestation of SSNS in these patients had occurred at a median of 3.0 years (range 0.8–6.9), with a median age of 20.4 (range 8.6–29.1) years at the time of data analysis (Table 1). All patients had received cytotoxic treatment with cyclophosphamide before CSA. Ten of these were treated according to the current protocol of the APN with 2 mg/kg for 12 weeks, and two patients had received an 8 week course plus a 4 week course. Renal biopsy prior to administration of cyclophosphamide revealed minimal change nephrotic syndrome (MCNS) in all patients. Renal biopsies were not routinely performed during the course of CSA treatment. Patients in whom CSA was discontinued for reasons other than SDNS (nephrotoxicity $n=2$, thrombocytopenia $n=1$) were not included in the analysis.

Treatment of relapses of SSNS was according to the APN, i.e. administration of prednisone 60 mg/m^2/day until urinary remission had been achieved for 3 days, followed by alternate-day prednisone in a dosage of 40 mg/m^2 for 4 weeks [2]. All patients relapsing on CSA responded to this standard treatment.

Steroid dependency in patients relapsing on CSA was defined according to the APN standard definition as at least two relapses during alternate-day (40 mg/m^2) treatment with prednisone or within 14 days after stopping this treatment [5]. Long-term remission was defined according to the same APN studies as remission of treatment lasting >2 years [5].

CSA was administered at a dose of 5 mg/kg/day aiming at trough levels of 80–120 µg/l. Three patients received classical CSA only. Nine patients were started on classical CSA but were changed to CSA neoral after its introduction in 1995, and two were treated only with CSA neoral. If frequent relapses occurred on CSA, trough levels of 150 µg/l were aimed at in centre 2 and of 200–250 µg/l in centre 3. Chlorambucil was given at a dose of 0.15 mg/kg (cumulative dose 12.6 mg/kg) and cyclophosphamide at a dose of 2 mg/kg for 12 weeks, respectively. Discontinuation of CSA and steroids was achieved within the 12 weeks of the second cytotoxic course ($n=6$) or within 4 weeks thereafter ($n=3$).

Levamisole was given in a dose of 2.5 mg/kg/48 h as previously described [9]. Tapering of CSA was started after 2 months, if no relapses occurred.

Results

In 14 of the 46 patients (30%) treated with CSA, SDNS recurred (five patients at centre 1, six patients at centre 2 and three patients at centre 3). All 14 patients had developed at least two relapses during high-dose alternate-day steroids (>40 mg/m^2/48 h), leading to steroid toxicity with obesity, cushingoid facies and/or striae or behavioural disturbances. At the time SDNS recurred, patients had been treated with CSA for a median of 5.1 years (range 1.2–11.5; Table 1).

The treatment strategies in these 14 patients are summarized in Table 1 (individual course) and Figure 1 (according to treatment schedule). A repeated course of cytotoxic treatment with concurrent discontinuation of CSA was the most commonly used strategy in nine patients. Six patients were treated with chlorambucil, and four of these went into treatment-free long-term remission for >2 years. One of these patients, however, developed severe SDNS again, after being in long-term remission for 6 years. She is currently in remission on mycophenolate mofetil monotherapy. Three further patients received cyclophosphamide; however, no patient went into long-term remission; one patient remained without relapse for 15 months but developed infrequent relapses afterwards (four in 2 years), which are currently controlled by intermittent steroid therapy. The other two patients became steroid dependent within 6 months after discontinuation of cyclophosphamide.

Five patients received levamisole. Only one patient, however, remained in long-term remission on levamisole monotherapy after cessation of CSA; this patient had been treatment refractory before and had already received two courses of cyclophosphamide. In a further patient, CSA could be discontinued; however, relapses (five in 2 years) persisted requiring intermittent steroid treatment. One patient received chlorambucil after levamisole and after occasional relapses (three in 6 years) requiring low-dose alternate-day steroids. This medication was discontinued successfully 12 months ago. In the other two patients, SDNS persisted and CSA could not be stopped.

Four of the 14 patients after failure of the above interventions were restarted on CSA maintenance: two of them occasionally had steroid-sensitive relapses (up to four per year) but none required (low-dose) maintenance steroids; in one patient, CSA ultimately was discontinued successfully and she has been in remission off treatment for the last 12 months.

So far, seven of the 14 patients have been experiencing relapses beyond 18 years of age. At present, four of these are still under paediatric care.

Table 1. Patient characteristics

Patient no./ sex	Age at presentation (years)	Sequence before CSA	Duration of NS at CSA start (years)	Duration of CSA at recurrence of SDNS (years)	Sequence after CSA	Current age (years)	Current status
1 M	2.1	Pred/CPO	0.9	2.0	CHLOR	13.6	Long-term remission 9 years
2 F	2.2	Pred/LEVA/CPO	3.0	1.2	CHLOR	13.6	First relapse after 6 years, steroid dependency, remission on MMF
3 M	0.8	Pred/CPO	1.4	3.8	CHLOR	8.6	Remission 5 years
4 F	3.4	Pred/CPO	1.8	10.0	CHLOR	19.6	Remission 4.2 years
5 F	3.1	Pred/LEVA/CPO	2.1	5.1	CHLOR/LEVA	14.3	Frequent relapses, maintenance steroids
6 M	1.6	Pred/CPO/LEVA	8.9	5.1	CHLOR/CSA	19.0	Remission on CSA
7 M	3.0	Pred/CPO	5.9	7.1	LEVA/CHLOR	23.3	Three relapses in 6 years, steroids tapered
8 M	3.1	Pred/CPO/CPO	9.8	5.7	LEVA	26.5	Long-term remission 9 years
9 M	1.7	Pred/CPO	12.2	11.5	LEVA	29.1	Five relapses in 2 years
10 M	4.1	Pred/CPO	3.2	7.7	LEV/CPO	17.8	One relapse after 15 months
11 M	6.9	Pred/CPO	2.1	8.3	LEV/CSA	21.2	Further steroid-sensitive relapses on CSA (2/year)
12 F	4.6	Pred/CPO/CPO	5.3	4.7	LEV/FK/CHLOR/CSA	21.9	Remission on CSA, patient d/c CSA: no relapses for 2 years
13 M	2.2	Pred/LEVA/CPO	12.9	4.6	CPO	22.6	Steroid dependency
14 M	3.1	Pred/CPO	7.6	2.7	CPO/CSA/LEV/MMF+ CSA/CHLOR/CSA	22.4	Further relapses on CSA (4/year)
Median (range)	3.0 (0.8–6.9)		4.3 (0.9–12.9)	5.1 (1.2–11.5)		20.4 (8.6–29.1)	

CSA = cyclosporin A; CPO = cyclophosphamide; CHLOR = chlorambucil; LEVA = levamisole; MMF = mycophenolate mofetil; Pred = prednisolone.

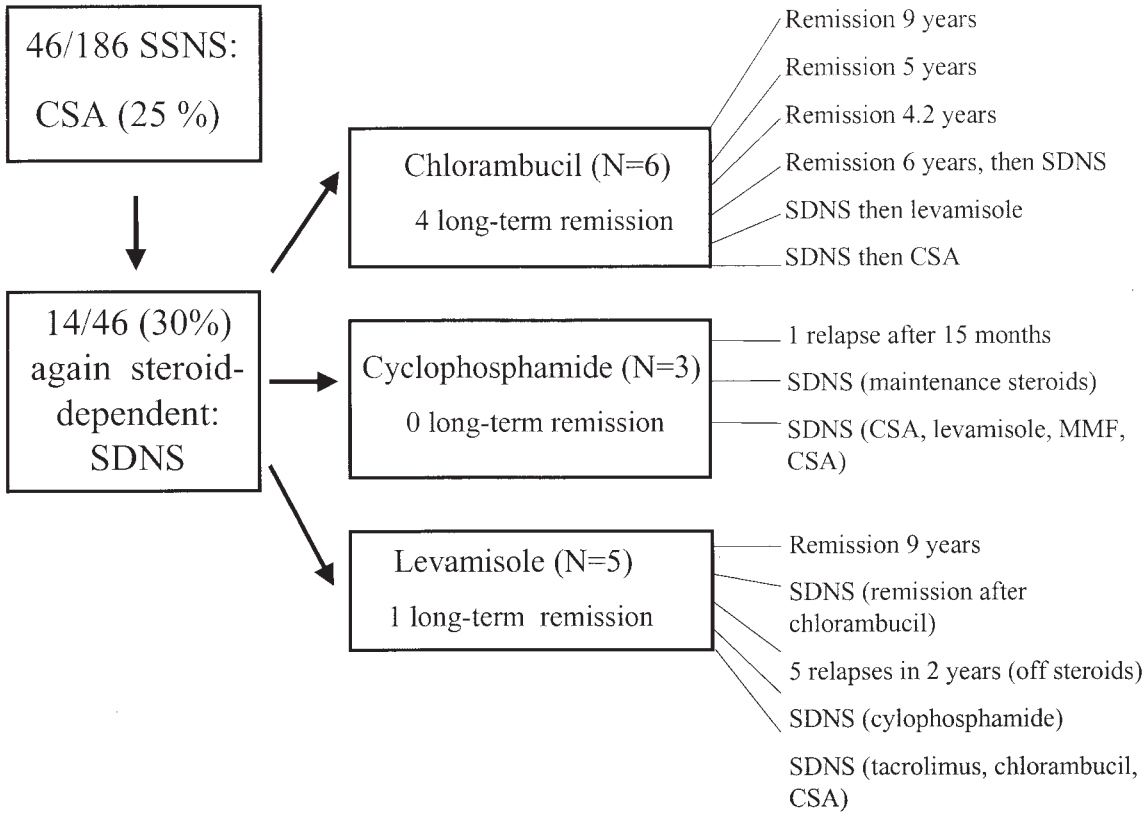

Fig. 1. Therapy of patients with recurring SDNS according to treatment schedule.

Discussion

SSNS previously was regarded as a disease of childhood, with most patients reaching remission around puberty [14]. We here provide further evidence that a significant number of patients experience a treatment-refractory course despite an extended array of immunosuppressive drugs and continue to relapse into adulthood. The recurrence of severe SDNS despite CSA maintenance therapy represents a special challenge.

There is limited information on this phenomenon and, so far, only two studies from one centre [10,13] have addressed the issue of relapses during CSA treatment for SSNS, while one other study mainly described patients with FSGS [15]. Hulton [10] reported on 40 CSA-treated patients, and relapses occurred in 40 and 56% in the first and second year, respectively, requiring additional low-dose maintenance steroids in 40% of patients. In this study, however, some patients had an interrupted course which might have affected relapse rate. Short-term CSA (i.e. <1–2 years) currently is no longer recommended in general, as most patients are cyclosporin dependent. In another series [13] from the same institution, 16 of 53 patients were reported in whom CSA had to be discontinued: eight of these had developed a relapsing course with SDNS again and five were even secondary steroid and CSA resistant. A recent update from this centre, however, documents a slightly improved prognosis for children with SSNS treated with CSA although an additional four patients ultimately needing chlorambucil are reported [16]. The definitions of SDNS between the studies differs, however; by using the definitions of the APN, our patients did in fact have a severe course relapsing on high-dose alternate-day steroids. By including in the analysis all patients from the centres treated with CSA, we tried to minimize a selection bias. This is supported further by the absolute current number of patients with SSNS, indicating that less problematic patients are also followed in the institutions.

Concerning treatment options, in our retrospective experience, a second course of cytotoxic treatment was the most commonly used strategy in recurring SDNS. Despite concerns relating to the cumulative side effects, especially regarding gonadal toxicity and malignancy [14,17], steroid toxicity in the patients with recurring SDNS was severe, and repeated cytotoxic treatment was regarded as justified in these patients, especially as alternatives were not available. While cyclophosphamide is preferred for the first course of cytotoxic treatment, we opted for chlorambucil in six of our patients encouraged by previous personal experience. Fifteen patients had received chlorambucil after CSA treatment failure, inducing a stable remission for a median of 6 months in 11 of these, although two patients had a further relapse [13]. Our data, although less optimistic but with longer follow-up, underline that chlorambucil may be preferable to cyclophosphamide

in patients with SDNS on CSA maintenance. Four compared with no patients had a long-term remission of >2 years. Despite this, even after a long remission of up to 6 years, some patients may develop relapses again, calling for long-term follow-up of patients with complicated SSNS. This is especially important as the side effects of this regimen may be more severe compared with cyclophosphamide.

Levamisole is a further option, but from previous experience and our current data the benefit in the described subgroup with a refractory course is limited. Individual patients, however, may benefit, as did one patient in our series, and also, in patients having already received two courses of cytotoxic drugs, there may be no alternative. Also discontinuation of CSA and reversal of SDNS may be possible, even if occasional relapses occur. The roles of other drugs (e.g. mycophenolate mofetil or vincristine) are unclear at present. Some patients may even remit finally after discontinuation of immunosuppressive treatment, as did one patient in our cohort.

Although conclusions from retrospective studies always have to be drawn cautiously, the role of CSA in the treatment of SSNS may be limited. Other alternatives should be tried first [18,19], as long-term treatment with CSA and even CSA dependency have to be anticipated. Treatment with high dose CSA (aiming at trough levels beyond 200–250 μg/l) as suggested for steroid-resistant nephrotic syndrome could be an alternative for patients with recurring SDNS on CSA. In centre 2, SDNS was not influenced by increasing trough levels to 150 μg/l, and neither was the course altered in centre 3 with even higher trough levels. Kinetic studies (e.g. C-2 levels) might be preferable to find the optimal dosing regime for CSA in SSNS and SDNS to minimize toxicity [12] and optimize response. So far, there is no consensus on which CSA dose or trough levels should be aimed at in SSNS.

One further aspect is the long duration of SSNS in some patients, although our results are more optimistic than the recent study of Grimbert *et al.* [20]. In our series, seven patients (i.e. 4% of the total population with SSNS) compared with 102 patients born between 1970 and 1975 (i.e. 42%) of patients in that study had documented relapses in adulthood. Together with young age at presentation (defined at <6 years at onset), the use of immunosuppressive drugs and especially CSA in 43% were significant predictors of a complicated course, underlining the importance of our results. In fact, very young age, as in our series (median 3 years), may be an even more relevant prognostic marker than age <6 as suggested by Grimbert, because the majority of patients will have presented before that. However, it should be noted that evaluation of prognostic factors should be performed prospectively and this was beyond the scope of our study; importantly, genetic and immunological factors need to be included, such as, for example, the HLA system. Nevertheless, the documentation of relapses as well as continued intensive treatment of a subgroup of SSNS patients into adulthood (exemplified by the present age range of our patients) indicates that long-term follow-up is mandatory and transfer of these patients into adult nephrology care is necessary.

In summary, a significant proportion of children with SSNS develop a complicated course that is insufficiently controlled by CSA maintenance. Treatment of these patients is a challenge and there is a need for more prospective and controlled data, or at least standardized consensus recommendations [18,19]. If a repeated course of cytotoxic treatment is considered, we currently would recommend chlorambucil instead of cyclophosphamide until further less toxic alternatives become available. It is now emerging that despite an intensified array of immunological drugs, some patients with childhood SSNS fare less well than previously thought and need treatment and follow-up into adulthood [21].

Conflict of interest statement. None declared.

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