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ORIGINAL ARTICLE

Five-year outcome of children with idiopathic nephrotic syndrome: the NEPHROVIR population-based cohort study

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Abstract

Background The optimal therapeutic regimen for children at onset of idiopathic nephrotic syndrome (INS) is still under debate. A better knowledge of the disease's course is necessary to design more appropriate and/or personalized treatment protocols.

Methods We report the 5-year outcome of patients included from December 2007 to May 2010 in the prospective multicentric and multiethnic population-based NEPHROVIR study. Patients were treated at onset according to the French steroid protocol (3990 mg/m^2, 18 weeks). Data were collected at 5 years or last follow-up.

Results Out of the 188 children with nephrotic syndrome (121 boys, 67 girls; median age 4.1 years), 174 (93%) were steroid-sensitive. Six percent of steroid-sensitive patients required intravenous steroid pulses to get into remission. Relapse-free rate for steroid-sensitive patients was 21% (36/174) at last follow-up (median 72 months). A first relapse occurred in138 steroid sensitive patients (79%) with a median time of 8.3 months (IQ 3.4–11.3). Out of the 138 relapsers, 43 were frequent relapsers. Age at onset below 4 years was the only predictive factor of relapse, while gender, ethnicity, and delay to first remission were not. At 96 months of follow-up, 83% of frequent relapsers were still under steroids and/or immunosuppressive drugs.

Conclusions The treatment of the first flare deserves major improvements in order to reduce the prevalence of relapsers and the subsequent long-lasting exposure to steroids and immunosuppression.

Keywords Nephrotic syndrome · Children · Steroid-sensitive · Frequent relapser · Immunosuppressive drug · Methylprednisolone pulse · Nephrovir

Introduction

The optimal therapeutic regimen for managing children at onset of idiopathic nephrotic syndrome (INS) is still under debate [1, 2]. A better knowledge of the disease's course is necessary to design more appropriate treatment protocols, both for first flare and relapses. Recently, a large-scale study has reported the 2-year outcome of the ISKDC regimen in a Japanese population and displayed a low rate of frequently-relapsing nephrotic syndrome (FRNS) at 2 years of follow-up [3]. The long-term outcomes in several other series have also pointed out the

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Table 1 Clinical data and outcome of 188 children with idiopathic nephrotic syndrome

	Total	Steroid sensitive	Non-relapsers	Non-frequent relapsers	Frequent relapsers	Steroid resistant
N	188	174	36	95	43	14
Age at onset (year)	4.1 (2.8–7.0)	4.1 (2.8–6.8)	5.4 (3.7–9.7)	3.9 (3.7–6.5)	3.7 (2.7–5.4)	9.3 (3.2–11.4)
Male/female ratio	1.8	1.9	1.4	1.7	2.9	1.3
Time to first remission (day)	na	9 (7–10.5)	8 (6–10)	8 (7–10)	9 (7–12.5)	na
MP pulses, *N*	22	10	1	5	4	12
Time to first relapse (months)	na	na	na	8.4 (5.0–14.4)	3.6 (2.5–5.4)	na
Use of steroid-sparing therapy, *N* (%)	na	93(53)	1	51(56)	41(95)	14
Levamisole, *N*	na	65	0	39	26	1
Mycophenolate, *N*	na	56	1	26	29	6
Cyclophosphamide, *N*	na	7	0	3	4	1
Calcineurin inhibitors, *N*	na	23	0	7	16	14
Rituximab, *N*	na	19	0	6	13	8
Time to treatment discontinuation (months)	na	50	4.5	50	–	91
Follow-up (months)	na	72 (57–84)	55 (41–76)	73 (55–85)	76 (66–90)	84 (69–89)
Steroid and/or IS at last follow-up, *N* (%)	na	71 (41)	0	36 (38)	35 (81)	8
ESRD, *N*	na	0	0	0	0	1

Data value: median (IQ 25–75) or *N* (%) cases

MP methylprednisolone pulse, *ESRD* end-stage renal disease, *na* not applicable

long duration of the disease, with relapses still occurring at 10-year follow-up [4] or into adulthood [5–7]. Most of these studies are retrospective and reported from tertiary centers or long-term follow-up of randomized control trials with recruitment bias. In addition to those studies, three randomized controlled trials have investigated the outcome of patients after different cumulated doses of initial prednisolone from 2240 to 3885 mg/m^2 [8–10]. In France, all patients are uniformly treated with an 18-week prednisone course (total cumulated dose of 3990 mg/m^2) [11]. The aim of this study is to report the 5-year outcome of a large, prospective, and population-based cohort of patients of mixed ethnic background and to compare the results with previous studies in patients with different genetic backgrounds and cumulated dose of steroids.

Study population and methods

Patients included in a previous multicentric ($N = 39$ centers), prospective, case-control study called NEPHROVIR were included [12, 13]. This study was population-based and included all children, aged between 6 months and 15 years (i.e., less than 16 years), living in one of the eight counties of the Paris area and presenting with a first episode of INS between December 3, 2007 and May 31, 2010.

INS was defined by a proteinuria > 0.25 g/mmol (2 g/g) of urinary creatinine, hypoalbuminemia < 30 g/L (3 g/dL) (all patients had a serum albumin below 25 g/L at presentation), negative hepatitis serology, and normal C3 complement value.

All patients were treated according to the protocol of the French Society of Pediatric Nephrology [11]. They received 60 mg/m^2 (max 60 mg) of oral prednisone daily for 4 weeks, followed by, for steroid-sensitive nephrotic syndrome (SSNS), 60 mg/m^2 every other day (eod) for 8 weeks, 45 mg/m^2 eod for 2 weeks, 30 mg/m^2 eod for 2 weeks, and 15 mg/m^2 eod for 2 weeks, that is to say, a total course of 18 weeks and 3990 mg/m^2. Remission was defined by negative proteinuria < 0.02 g/mmol.

If no remission after 4 weeks of oral prednisone, patients received three intravenous pulses of methylprednisolone (MP) at a dose of 1 g/1.73 m^2. Steroid-resistant nephrotic syndrome (SRNS) was defined by no response 8 days after the last MP pulse. Relapse was defined by proteinuria > 0.25 g/mmol and hypoalbuminemia < 30 g/l or by proteinuria > 0.20 g/mmol lasting long enough to require treatment changes. Clinical course, relapses, and treatments were registered for patients at 5 years or last follow-up. FRNS was defined by two relapses within 6 months after initial treatment or four relapses in any period of 12 months [14].

Ethnicity was self-reported according to parents and grandparent's ethnic origins. Annual incidences were calculated based on official statistical data from the National Institute for Statistics and Economic Studies (INSEE), freely available on their website.

Statistical analyses were performed using PRISM software and SAS. Categorical covariates were compared

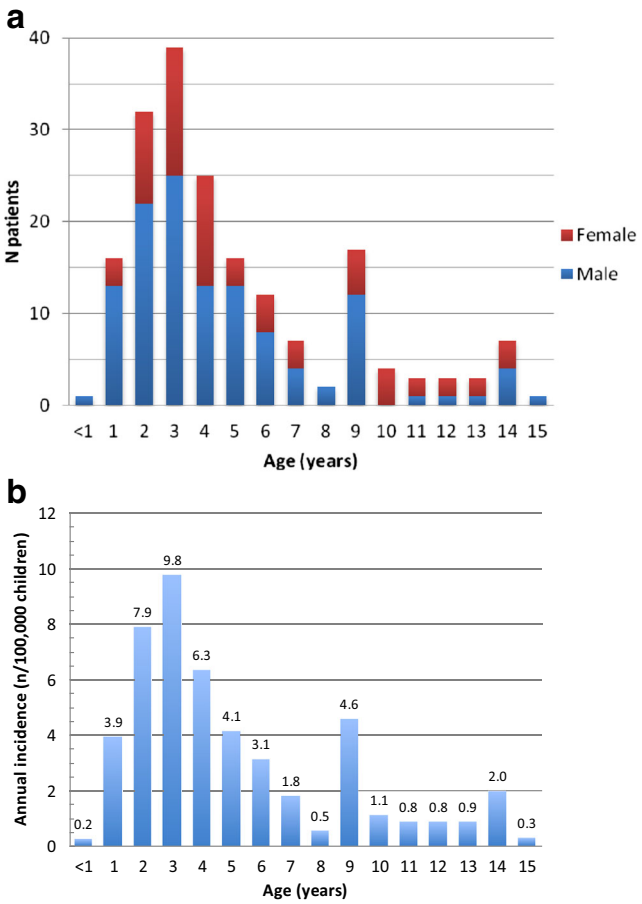

Fig. 1 Age and sex distribution of $N = 188$ patients with idiopathic nephrotic syndrome and incidence by age. **a** Age and sex distribution of patients shows two different patterns. Before the age of 10 years (89% of patients), the population displays a Gaussian distribution with a male predominance. After the age of 10 years, the male to female ratio is reversed. **b** The annual incidence of idiopathic nephrotic syndrome in the Paris area is higher between 1 and 6 years old. After the age of 10 years, the incidence is stable across ages

with Fisher exact tests. Time-course events were analyzed using the Kaplan-Meier method and the log-rank test. A Cox regression model was used to identify factors associated with the risk of relapse. A p value < 0.05 was considered as significant.

Results

Response of the first flare to steroids

During a 30-month period, between December 2007 and May 2010, 188 children living in the Paris area presented with a first manifestation of nephrotic syndrome: 121 boys and 67 girls (M/F ratio 1.8/1) (Table 1). Age and gender distribution are presented in Fig. 1a. Annual incidence was 3.35 cases/100,000 children aged less than 16 years old, and incidence by year of age is represented in Fig. 1b.

Of these 188 patients, 174 (93%) had SSNS (Fig. 2): 113 boys and 61 girls (1.9/1). After 4 weeks of oral prednisone, 164 patients (87%) were in remission. Intravenous methylprednisolone pulses were given to 22 patients who did not respond to 4 weeks of oral prednisone, according to the French protocol, allowing further remission in 10 patients (response rate 45%). Median time to first remission in all steroid-sensitive patients was 9 days (IQ 7–11), with no significant differences according to age younger or older than 4 years ($p = 0.09$), nor ethnicity ($p = 0.87$), nor outcome status ($p = 0.35$) (Fig. 3). No severe complications due to intravenous methylprednisolone were reported in those patients. Only 14 patients (7%) were steroid-resistant: 8 boys and 6 girls (1.3/1), after 4 weeks of oral prednisone and three methylprednisolone pulses.

Of note, two more patients living in Paris area during the same period of time had a nephrotic syndrome of genetic

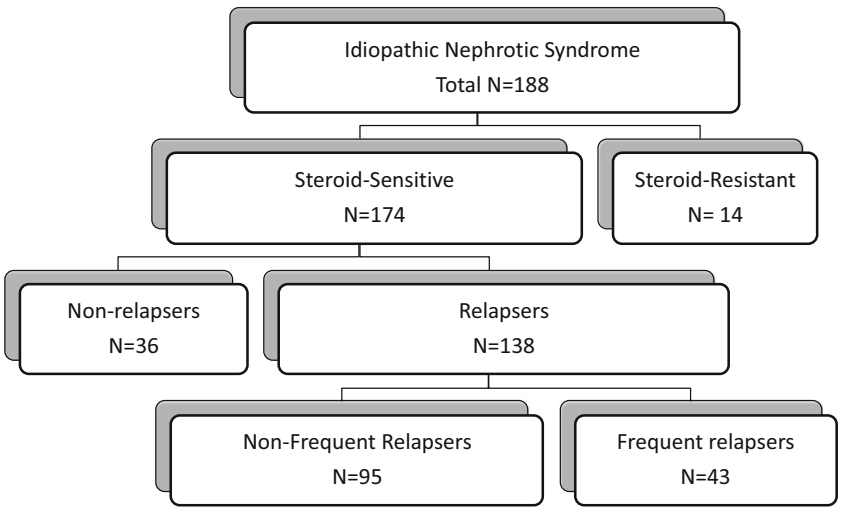

Fig. 2 Flow chart of $N = 188$ patients with idiopathic nephrotic syndrome

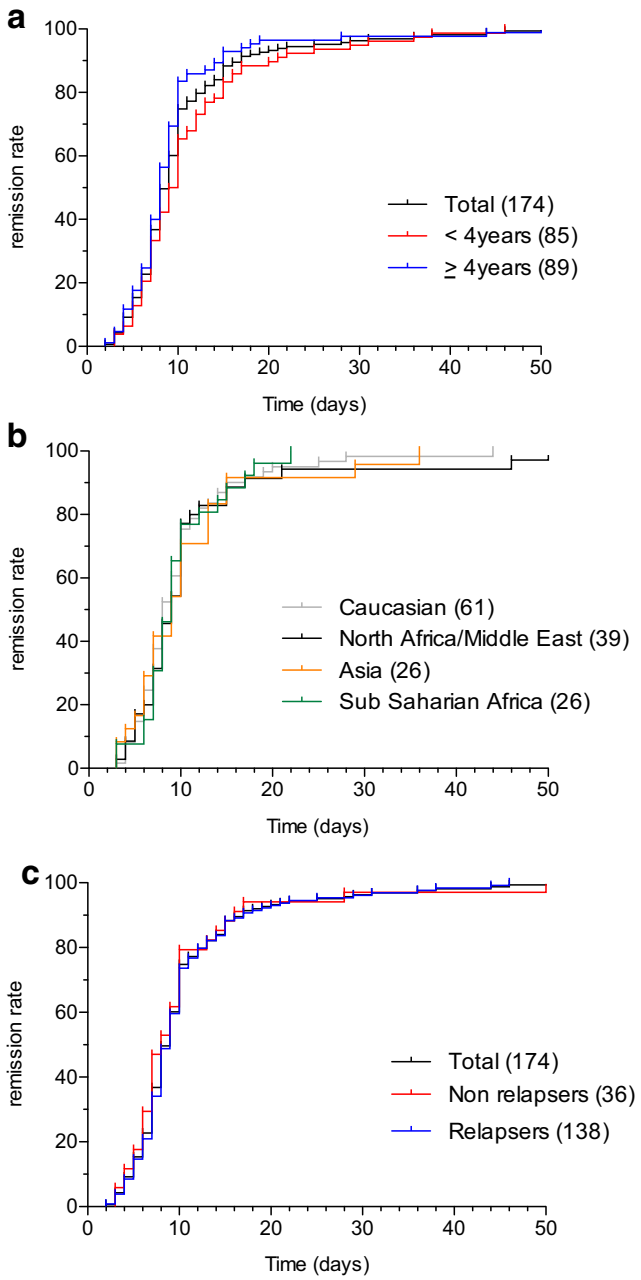

Fig. 3 Time to first remission in $N = 174$ patients with steroid-sensitive nephrotic syndrome. Kaplan-Meier analysis of time to remission by age (**a**), ethnicity (**b**), and relapsing status (**c**)

origin and were not included in this series (one with *NPHS3* mutation, one with *WT1* mutation).

Outcome of SSNS

Of the 174 patients with SSNS, 36 (21%) had no relapse (NR) with a median follow-up of 60 months (IQ 48–79). Clinical characteristics of these patients are summarized in Table 1. One-hundred and thirty-eight patients (79%) experienced one or more relapse, with a median follow-up for relapsers of 74 months (IQ 60–86). The time from disease onset to first relapse is presented in Fig. 4. The median time to first relapse was 8.3 months (IQ 3.4–11.3). First relapse occurred earlier in patients younger than 4 years old, with a median delay of 5.5 months compared to 11.5 months in patients older than 4 years (Fig. 4a; $p < 0.001$). The association between age at diagnosis and risk of relapse is presented in Fig. 4b. Conversely, no difference in time to first relapse was found according to ethnicity (Fig.4c), nor delay to first remission (Fig. 4d and Table 2). According to the course during the first year, the 138 relapsers were distributed into 43 frequent relapsers and 95 non-frequent relapsers (Fig. 2).

Treatments

Steroid-sparing drugs were given in 92/138 relapsers (66%) (Table 1). After 5 years of follow-up (median follow-up 72 months, IQ 57–84), 71/174 (41%) of SSNS patients were still receiving steroids and/or steroid-sparing therapies. Among FRNS, 81% were still under medication at last follow-up (Fig. 5a). Of note, 38% of non-frequent relapsers were still treated at last follow-up and the median duration of treatment was 50 months. Non-frequent relapsers mainly received levamisole and mycophenolate as steroid-sparing agents. Age (Fig. 5b) and ethnicity were not associated with a shorter or longer delay until treatment discontinuation in both frequent and non-frequent relapsers.

Among the 10 patients who required three steroid pulses to obtain the first remission, one patient had no further relapse and one had only one relapse. Eight patients had a complicated outcome, and all received one or more steroid-sparing drug during follow-up. At last follow-up, 7 patients were off treatments and 3 patients remained under treatment after 31, 93, and 99 months, respectively.

Outcome of SRNS

All 14 steroid-resistant patients were included in the analysis. Histology showed focal and segmental glomerular sclerosis (FSGS) in 5 cases, minimal changes (MCD) in 8, and was not determined in 1. Thirteen patients were sensitive to the association of prednisone-cyclosporine. All these 13 patients experienced one or more relapses. After a median follow-up 84 months, 4 out of 13 were still receiving one or more immunosuppressive drug, 3 were receiving only a non-specific anti-proteinuric therapy (blocker of the renin-angiotensin system), and 6 were discharged of any treatment. Immunosuppressive treatment withdrawal occurred after a median delay of 91 months. Eight SRNS patients received rituximab, of whom four remained in stable remission without any treatment after a median follow-up of 74 months. The last

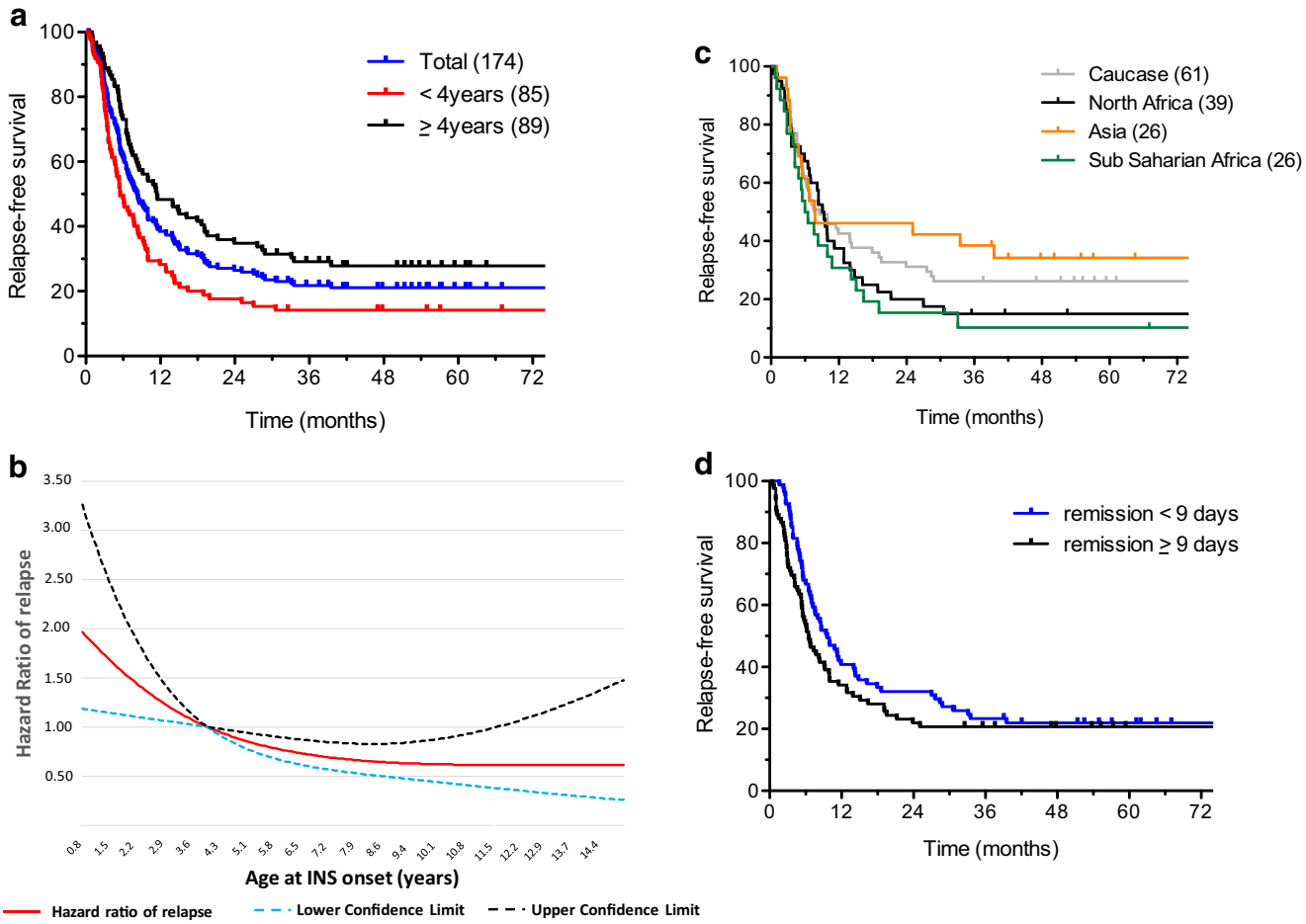

Fig. 4 Survival without relapse of $N = 174$ patients with steroid-sensitive nephrotic syndrome. **a** Kaplan-Meier analysis of relapse-free survival by age at onset. **b** Regression of the risk of relapse on age at onset of idiopathic nephrotic syndrome. **c** Kaplan-Meier analysis of relapse-free survival by age at onset by ethnicity and **d** by delay to first remission

steroid-resistant patient was also resistant to cyclosporine and developed end-stage renal disease after 8 months of treatment. She was secondarily classified as a multiresistant INS when she developed an early recurrence of massive proteinuria on renal transplant.

Discussion

This study reports the 5-year outcome of a region-wide population-based cohort of children with a first manifestation of INS occurring during a 30-month period. The exhaustiveness and the time and space homogeneity are notable and represent the strength of these data.

Age distribution per year is not commonly released in epidemiological works on childhood INS. This series displays a normal distribution of age between 1 and 9 years. A curious rebound was observed in patients aged between 9 and 10, for which no explanation is found. After 10 years of age, the annual number of cases is lower and roughly equal by year of age. One may extrapolate that it represents the beginning of the adult form of the disease with a stable incidence across ages. In addition, the gender ratio is reversed after 10 years of age with a majority of girls (1.4/1). This gender ratio has been also observed in numerous series of patients starting the disease at adult age.

Most patients experience a remission in a dramatically short delay. Interestingly, a similar curve of remission has been shown in patients from West Japan [15], suggesting that the response to prednisone or prednisolone at identical dosage is independent of the ethnic background. Consistently, we did not observe any differences between ethnicities in our series. The response rate after 4 weeks of oral prednisone (87%) is similar to those reported in other populations [3]. Interestingly, the addition of three intravenous methylprednisolone pulses leads to an additional fraction of patients who are classified as steroid-sensitive, half of them being finally non-frequent relapsers. Even if the number of patients is limited, it reduces the frequency of steroid resistance and as a consequence the related morbidity of renal biopsy and the use of calcineurin inhibitors without any additional risk. The addition of

Table 2 Cox regression model of factors associated to first relapse ($N = 174$, steroid-sensitive nephrotic syndrome)

		Univariate analysis		Multivariate analysis	
		OR	95%CI	OR	95%CI
Age at onset	≤ 4 years old	1		1	
	> 4 years old	0.55	[0.40–0.77]	0.65	[0.45–0.94]
Gender	Male	1		1	
	Female	0.84	[0.59–1.20]	0.89	[0.61–1.30]
Ethnicity	Caucasian	1		1	
	North African	1.27	[0.83–1.97]	1.08	[0.67–1.73]
	African	1.22	[0.55–2.71]	1.3	[0.77–2.20]
	Asian	0.93	[0.54–1.60]	0.87	[0.49–1.53]
	Other	1.22	[0.55–2.71]	0.87	[0.34–2.20]
	Unknown	1.5	[0.78–2.91)	1.69	[0.80–3.56]
Time to remission	≤ 9 days	1		1	
	> 9 days	0.89	[0.63–1.26]	0.91	[0.63–1.32]

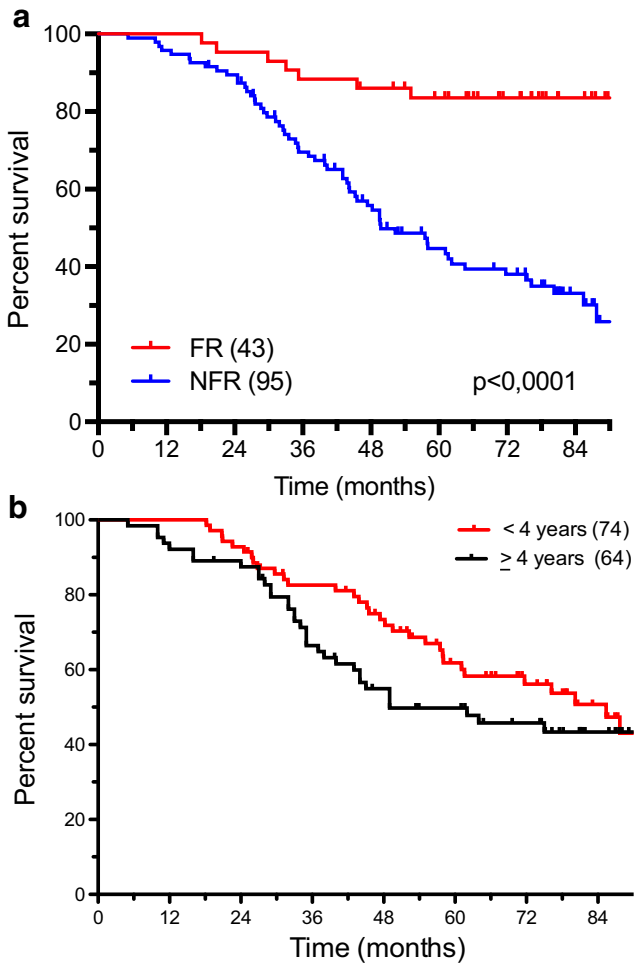

Fig. 5 Duration of treatments in steroid-sensitive nephrotic syndrome. Kaplan-Meier analysis of time to treatment discontinuation by relapsing status (**a**) and by age at onset (**b**). *FR* frequently relapsing, *NFR* non frequently relapsing

methylprednisolone pulses is a specificity of the French steroid protocol. Retrospective studies from other countries have also showed interesting response rates from 29 to 62% [16–18]. Intravenous methylprednisolone pulses are certainly an interesting option of treatment, but no randomized trial has compared the efficiency and tolerance of 4 weeks 60-mg m^2 day + 3 IV MP pulses to 6–8 weeks of oral prednisone at 60-mg·m^2·day course.

Relapse after the treatment of the first flare affects the majority of patients and more precisely those children aged less than 4 years. Indeed, in our series, the age of onset is the only parameter statistically predictive of relapse. The definition of FRNS has been first published by the ISKDC in 1974 [19] and refined in the KDIGO guidelines [20]. FRNS was defined by ≥ 2 relapses within 6 months after initial remission or ≥ 4 relapses within any 12-month period. Recent randomized controlled trials suggest that those definitions do not cover all the morbidity of the disease [10, 21]. Enlarged definitions including patients receiving additional immunosuppressive treatments due to steroid toxicity before meeting the strict definition of FRNS, as well as patients relapsing under or after completion of immunosuppressive treatments, have been proposed and used in recent randomized control trials [10, 21]. In our series, long-term follow-up data consistently showed that non-frequent relapsers may also display a long-lasting disease and a subsequent exposure to steroid toxicity.

In this prospective cohort, treatment strategies after relapse, choice of drug, and duration varied according to the physicians' choices and the local practices of both primary and secondary centers [22]. Follow-up data are the results of various treatment practices. However, a striking finding of our study is the disease severity, with a long disease duration under steroid or immunosuppressive therapy in a substantial

number of our patients, over passing the group of the frequent relapsers. In the French protocol, where the first flare is treated during 4.5 months, a substantial number of patients not responding to the FRNS definition received steroids sparing agents in the first year of the disease due to steroid toxicity. This group of patients was prominently treated with levamisole and mycophenolate.

The challenge of treating patients with newly presenting nephrotic syndrome is not only to obtain a rapid urinary remission but also to prevent further relapses and long-lasting disease, as well as reduce the burden of immunosuppressive drugs. Age and ethnicity are certainly major factors to be considered in the treatment protocols. The results of this study confirm with accurate figures the high morbidity of this disease in more than a half of patients and support the organization of a worldwide discussion to improve the treatment of first flare.

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Compliance with ethical standards

The study was reviewed and accepted by local Ethics Committee. Informed consent was obtained from all participants included in the study.

Conflict of interest The authors declare that they have no competing interests.

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