Research Square

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Relapsing childhood steroid sensitive nephrotic syndrome: what determines eventual remission?

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Abstract

Background

Childhood idiopathic nephrotic syndrome (INS) responds to corticosteroids (CS), but tends to relapse, often requiring steroid sparing agents (SSA). Long standing treatment free remission (LTFR) evolves in most cases, but whether this is related to puberty or disease length is unknown.

Methods

We retrospectively analyzed the computerized database of Israel's largest health maintenance organization. Children with a new INS diagnosis between 2000–2010 were divided into 2 groups according to INS presentation age. Disease length was determined based on CS or SSA use. Children with disease shorter than 1 year or those not reaching LTFR, defined as more than 3 years from last purchase, were excluded.

Results

Out of 1,669,977 eligible children, 608 were diagnosed with INS, 524 relapsed, 174 were excluded, leaving 350 for analysis: 272 (77.7%) and 78 (22.2%) presented between 2-6.9 and 7-9.9 years, respectively. There was no difference in the need for SSA, time to SSA initiation and drug purchase count between the groups. After 15.5 ± 5.1 years of follow up, time until LTFR was longer in the older group (5.4 ± 4 vs 7.1 ± 5.1 years, $p = 0.002$), without correlation between INS onset age and disease length. Many patients, especially in the older group, still relapsed beyond Tanner stage 3's 97th percentile age (age 14 years) (14.7% vs 51.3%, $p < 0.001$), irrelevant of sex.

Conclusion

In this population-based study LTFR occurred in many cases well beyond puberty, in both groups, favoring the role for disease length on LTFR, probably due to maturational immune system changes.

Introduction

Idiopathic nephrotic syndrome (INS) is the commonest form of NS during childhood. Most of the cases present between ages 2–6 years [1] and response to corticosteroids (CS) is the best predictor of disease prognosis. The clinical course of childhood steroid sensitive INS (SSNS) is frequently characterized by relapses, which is seen in more than 60% of newly diagnosed INS children. Studies on the natural history of this disease have shown that even though most INS children will eventually experience a long-standing treatment free remission (LTFR), patients can continue to relapse 10–15 years after the onset of the disease [2]. However, the cutoff age when the likelihood of continued relapses drops off

significantly is not defined in literature. The percentage of SSNS children who continue with relapses into adulthood ranges from 5% [3] to more than 40% in different studies [4,5]. The number of relapses during childhood and adolescence and requirement for second-line therapy were risk factors for continuing relapses in adulthood [6].

Whether the resolution of INS is related to puberty and sex hormone influences or to the length of the disease and why some patients continue to relapse in adulthood is still unknown [7].

Methods

We present a secondary analysis of a previously described cohort, which has been recently published [8]. Briefly, we investigated the Clalit Health Services (Israel's largest health maintenance organization, serving 51% of the Israeli population) electronic health records (EHR), which include data from its administrative, medical, laboratory, and pharmaceutical systems. This unique, continuously monitored, validated database environment provides high reliability, consistency, and accuracy of exposure and follow-up data, as previously described [9,10]. Children (age 2–10 years) with a new EHR diagnosis of NS between the years 2000–2010 who were also treated with CS within 3 months before or after the time of diagnosis were originally included and followed up until December 2023. We then looked for those who had more than 1 relapse, and from the relapsing group further patients were excluded if they had less than 1 year of follow up. LTFR was defined as a lack of purchases for more than three years from the last purchase until the end of follow up, as this minimal time interval increases the likelihood that no further relapses will happen, as recently published [11]. CS and SSA (cyclophosphamide, mycophenolate, cyclosporine, tacrolimus or rituximab) purchases were retrieved from the computerized system. Relevant data at both diagnosis time and the last follow up were recorded. The disease length was determined as the difference between last and first CS or SSA purchases. Age at LTFR was determined as an age at last CS or SSA purchase. A single NS episode was defined as CS treatment for less than 6 months without subsequent purchases, according to the common treatment protocols at first NS episode. We divided the relapsing group into 2 subgroups according to the age of NS onset: 2-6.9 and 7-9.9 years. The hypothesis in our current analysis was that if puberty was the driving factor for LTFR, then disease length should have been significantly shorter in the older group compared to the younger one.

The study was approved by the CHS Human experimentation Committee. Informed consent was waived, due to the retrospective analysis and data anonymization.

Results

Out of 1,669,977 eligible children, 608 met the inclusion criteria of both NS diagnosis and CS prescription, 524 of them relapsed. Of them 413 (78.9%) presented between 2-6.9 years, 111 (21.1%) presented between 7-9.9 years. After a mean follow up period of 15.5 ± 5.1 years, 367 (70%) of the relapsing cohort reached LTFR, without difference between the 2 groups [284 (68.8%) vs 83 (74.8%), p = 0.22]. We excluded from this cohort 17 children with a disease length of less than one year, analyzing

finally 350 children (68.8% of the relapsing cohort) who reached LTFR (Fig. 1). Of them, 272 (77.7%) presented between 2-6.9 (mean 3.9 ± 1.4) years and 78 (22.2%) presented between 7-9.9 (mean 8.4 ± 0.9) years. Males predominated in both groups, but more prominently in the younger group (70.9% vs 55.1%, p = 0.009). The number of patients who received SSA and time to SSA start were similar [59 (21.7% vs 19 (24.4%), p = 0.62; and 2 ± 1.7 vs 1.7 ± 1.4 years, p = 0.39, respectively], as well as drug purchase count (24.2 ± 20.2 vs 22.2 ± 21.7, p = 0.5). The average ages of LTFR in the 2 groups were 9.3 ± 4.4 and 15.5 ± 5.1 respectively. Disease length from NS diagnosis until LTFR was longer in the older group (5.4 ± 4 vs 7.1 ± 5.1 years, p = 0.002), but there was no correlation between the presentation age (as a linear parameter) and disease length from diagnosis until LTFR (Fig. 2). A significant number of patients, mostly in the older group, still relapsed beyond Tanner stage 3's 97th percentile age, which is 14 years in both sexes [] [40 (14.7%) vs 40 (51.3%), p < 0.001), both in males [35 (18.1%) vs 23 (53.4%), p < 0.001] as in females [5 (6.3%) vs 17 (48.5%), p < 0.001] (Table 1).

Discussion

In this population-based study we investigated INS's length and the last relapse age in the patients who achieved LTFR, comparing those with earlier (and classical, according to most publications) vs later INS presentation within the childhood age. In the original publication we raised the possibility that LTFR is influenced by puberty [3], as most of the INS patients achieved LTFR at the age of pubertal stage 2. Based on the same cohort, in the present study we have performed purchases analysis of the patients with disease length more than one year who achieved LTFR, this time using the more stringent criterion of more than 3 years without evidence of relapse, as recently suggested by Robinson et al [11]. The LTFR study group was divided into 2 sub-groups according to the presentation age. The patient group who could be defined as achieving LTFR comprised 66.8% of the originally relapsing cohort, without a difference between the 2 study age groups.

Previous studies suggested that younger age at onset is associated with a higher risk of frequent relapses, steroid dependence, and longer time to achieve LTFR [13]. In contrast to that, in our cohort there was no apparent difference in the rate of relapses between the 2 groups, as shown in the medications median purchase count, as well as in the need for SSA or time to SSA initiation. Still, in the older group, disease length was longer in comparison to the younger group.

The younger group comprised 77.7% of the whole cohort, which is consistent with numerous past publications. The predominance of younger children in the whole cohort shifts the mean age at last relapse to a younger age, as reflected in our previous publication [8]. However, evaluating separately the older group, we show a significantly older age of reaching LTFR, well beyond puberty, which challenges the original explanation on the role of this key developmental period on INS LTFR. Alternatively, INS resolution may reflect a normalization of the immune system dysregulation, particularly involving T cell and B cell subsets. LTFR may reflect a maturation and stabilization of the immune responses with age [14]. Our data suggests that a particular INS disease length is needed for the immune system to undergo such maturational changes.

The limitations of this study include its retrospective design and the need to work with anonymized data, without the ability to inquire or check specific patient data.

Conclusions

In this population-based study, tracing LTFR by immunosuppressive medications delivery, age of presentation did not influence INS disease course, but its duration was longer in those who presented later. LTFR occurred in many cases well beyond puberty, mainly in the older group, favoring the role of a disease time course on its eventual resolution, probably due to maturational immune system changes. A prospective functional immune system changes investigation is needed to confirm this theory.

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Table 1

Table 1
Comparison of NS children with LTFR (n = 350), according to the presentation age. *CS*: corticosteroids; *LTFR*: long standing treatment free remission; *SSA*: steroid sparing agents.

Age groups	**2–6** **(n = 272)**	**7–10** **(n = 78)**	**P**
Age at diagnosis, yrs	3.9 ± 1.4	8.4 ± 0.9	
Males, n (%)	193 (70.9%)	43 (55.1%)	0.009
SSA use, n (%)	59 (21.7%)	19 (24.4%)	0.62
Time to SSA start, yrs	2 ± 1.7	1.7 ± 1.4	0.39
CS or SSA purchases (mean ± SD)	24.2 ± 20.2	22.2 ± 21.7	0.5
Age of LTFR, yrs	9.3 ± 4.4	15.5 ± 5.1	
Time period to LTFR (yrs)	5.4 ± 4	7.1 ± 5.1	0.002
Still relapsing beyond Tanner-III 97th -tile age (14 yrs), n (%)	40 (14.7%)	40 (51.3%)	< 0.001
Males	35 (18.1%)	23 (53.4%)	< 0.001
Females	5 (6.3%)	17 (48.5%)	< 0.001

Figures

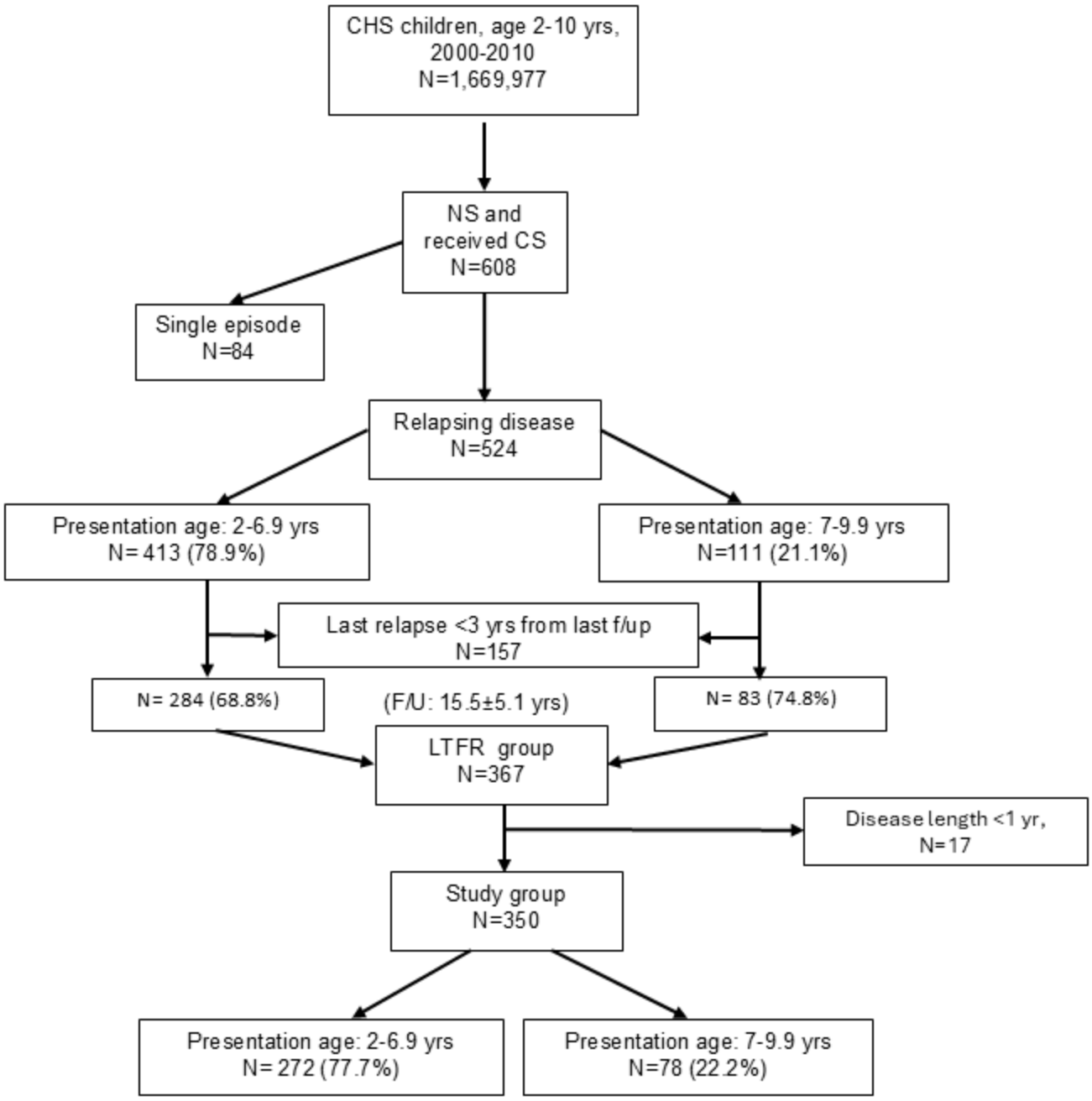


Figure 1

Study flow chart. *CHS*: Clalit Health Services. *CS*: corticosteroids; *LTFR*: long standing treatment free remission.

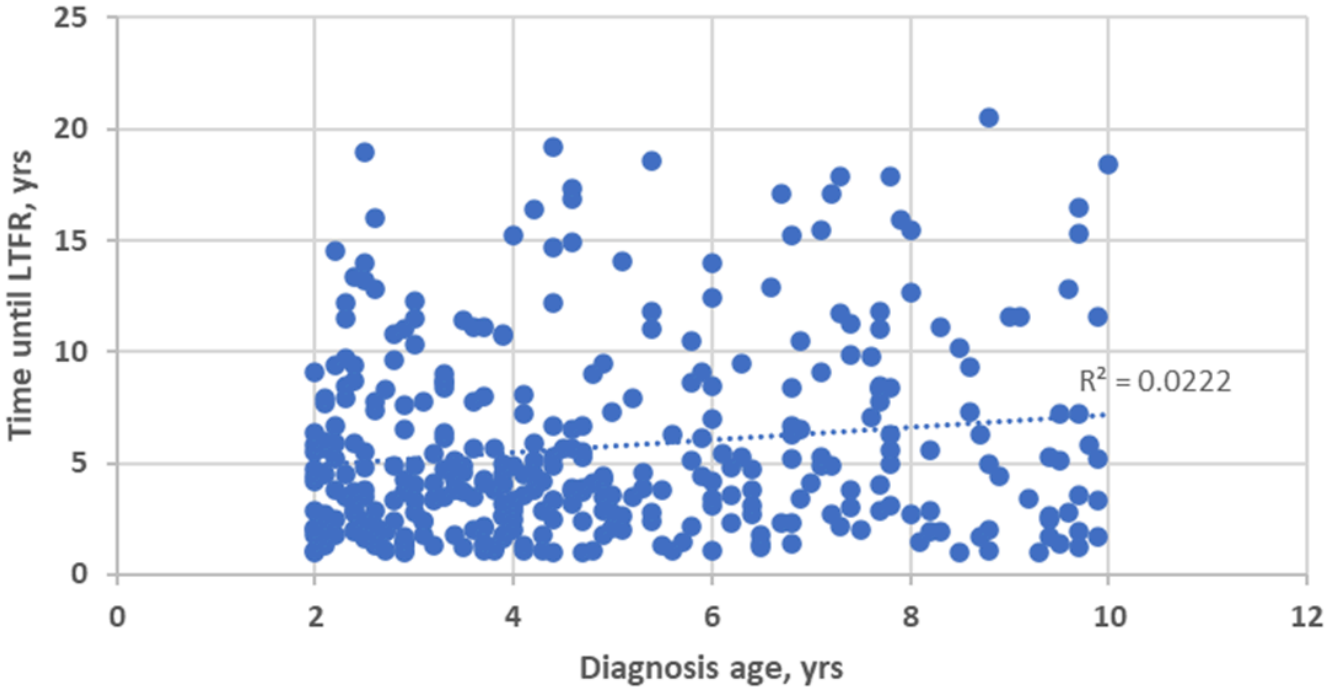


Figure 2

Correlation between the age of INS diagnosis and the time until reaching long standing treatment free remission (LTFR), studying only NS cases diagnosed between ages 2-10 years, including only those patients with more than 1 year of follow up since diagnosis and more than 3 years since the last prescription of CS or SSA (n=350).