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Journal of Pediatrics and Child Health Issues

Open Access Research Article

Evolution of The Idiopathic Nephrotic Syndrome In Children

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Article Info

Received: January 20, 2021
Accepted: February 03, 2021
Published: February 08, 2021

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Citation: Margarita Halty, Marina Caggiani, Valeria Cocchi, Alejandro Noria, Gustavo Giachetto "Evolution of The Idiopathic Nephrotic Syndrome In Children''. J Pediatrics and Child Health Issues, 2(1); DOI: http;//doi.org/03.2021/1.1005.

Summary

Introduction: The idiopathic nephrotic syndrome (INS) is the most common glomerulopathy in pediatrics. The purpose of this study was to estimate the INS incidence in pediatric public health patients and to describe the response to treatment, the evolutionary characteristics and complications.

Methods. A descriptive study was carried out of a historical cohort of patients under 15 years of age with the onset of INS assisted at the Nephrological Clinic of the Pereira Rossell Children's Hospital between 01/01/2009 - 12/31/2013, monitored until 12/31/ 2015, users of the Public Health Service Provider (ASSE). The annual incidence of INS in ASSE users was estimated according to data obtained from the National Data System Report (SINADI) of the Ministry of Public Health. We recorded age, sex, height, body mass index (BMI), response to initial treatment and evolution in those patients with ≥12 months follow-up.

Results. We included 42 patients with a male / female ratio of 2.2/1; the INS annual incidence in the ASSE population was 3.05/100,000 children under 15 years of age. 34 patients were steroid-sensitive (SS) and 8 steroid-resistant (SR). The mean age at onset was 5 years, for SS and 2 years 10 months for SR patients. The evolution was analyzed in the 33 patients with a follow-up of ≥12 months, with a mean of 4 years ± 1 year 9 months. In these children, the frequency of SS was 78.7% (n = 26) and of SR 21.3% (n = 7). Within the SS patients, 10 (38.6%) were steroid-dependent/frequent relapsers (SD), 8 had sporadic relapses and 8 did not relapse. Among the SD patients, 5 received Cyclophosphamide; only one patient suspended Prednisone after 3 months, the dose was lowered in 2 patients and the other 2 did not respond, one of them achieved sustained remission with Cyclosporine. Of the 7 SR patients, 4 had initial remission with Cyclosporine, 1 partial remission and 2 were resistant; 3 received Mycophenolate Mofetil, 2 did not respond, and 1 had partial remission. The biopsy in all the SR patients showed focal and segmental hyalinosis. The genetic study for NPHS2 and WT1 carried out on 4 patients was negative.

At the end of follow-up, all SS patients had achieved remission and all drugs had been withdrawn from 16 of 26 patients. Among the SR patients, 2 were in remission with Cyclosporine, 4 maintained nephrotic proteinuria (one of them with a drop in glomerular filtration rate of 60ml/min per 1.73 m2), and another was on chronic dialysis. Serious infectious complications occurred in 5 SR and 2 SS patients. One SD and one SR patient developed chronic hypertension. In SD and SR patients, a significant difference was observed in the BMI and height Z scores between the beginning and the end of follow-up.

Conclusion: The calculated incidence of INS included only patients treated by the Public Health Service Provider in Uruguay; it does not reflect nationwide incidence and it is comparable to that of other studies. The evolution of SS and SR patients

was also similar to those described. The growth of children exposed to long-term corticosteroid treatment was affected. For best results, these patients should be offered customized treatment according to current recommendations.

Keywords: Idiopathic Nephrotic Syndrome Incidence; Evolution; Complications

Introduction

Nephrotic syndrome (NS) is defined by the presence of proteinuria greater than 50mg/kg/day, proteinuria/urine creatinine ratio> 2 g/g, hypoalbuminemia lower than 2.5g/dl, and variable edema. The most common glomerular disease in children is Idiopathic Nephrotic Syndrome (INS), defined by NS and nonspecific histological changes, such as Minimal Change disease (MCD), Focal Segmental Glomerulosclerosis (FSGS) and Diffuse Mesangial Proliferation (DMP)1,2. Podocyte injury determines massive proteinuria [3,4].

The prevalence is 16/100,000 children under 16 years of age with an incidence of 1-3.3 per 100,000 per year, varying according to geographical region, ethnicity and age5-9.

The highest frequency occurs between 1 and 6 years of age, with a clear male predominance with a ratio of 2.4/110. The International Study of Kidney Disease in Children (ISKDC) described that around 80% occur in ≤ 6 years, with a male/female ratio of 2/1 at that age [7,11,12].

According to the response to treatment with corticosteroids (CC), patients are classified as steroid sensitive (SS) and steroid resistant (SR). MCD predominates (87%) among the 3 histological variants, there is overlapping between these histopathological changes and it is suggested that in some cases there may be a continuum of the disease3,7.

The ISKDC has shown that the response to corticosteroids is highly predictive of histology, since 94% of children with MCD achieve remission at 4 weeks of prednisone treatment, others at longer periods. MCD practically became synonymous with SS2. SR patients can also have MCD in 25% of cases,12 but the response to corticosteroids is the highest implication factor for the patient's prognosis, rather than histology13. In 80-90% of the cases, the INS patients are SS; up to 80% of these patients have relapses after the first episode, half go on to have frequent relapses or steroid-dependence (SD)1 and may relapse at a non-negligible percentage beyond pediatric age [13-15].

In 10–30% of SR patients, mutations in podocyte-associated genes can be detected, the most common are NPHS2, WT1, and NPSHS1 in 42, 16, and 13% of genetic cases, respectively. An undefined circulating factor of immune origin is assumed in the remaining ones [11].

The likelihood of identifying a causative mutation is inversely related to age at disease onset and is increased with either a positive family history or the presence of extrarenal manifestations. The identification of genetic factors will be important when defining the treatment11.

This study used data of the Registry of Children with INS from the Pereira Rossell Hospital (CHPR), at the Nephrology Clinic. The CHPR is the Uruguayan Reference Children's Hospital, it reports to the Uruguayan Public Health Services Administration (ASSE) and assists the population of children under 15 years of age users of the public health care service.

Using a historical cohort of patients under 15 years old, the objective of this study was to estimate the incidence of INS in ASSE users, diagnosed between 2009 and 2013 and controlled at the CHPR Nephrology Clinic. The other purpose was to describe the response to treatment, evolution and complications.

We carried out the analysis based on the new IPNA 2020 Clinical Practice Recommendations11.

Patients and Methods

A descriptive, retrospective study was carried out on a cohort of children under 15 years of age with a diagnosis of INS between 01/01/2009 and 12/31/2013. The patients were identified from the onset of their diagnosis and their Medical Record Numbers were recorded on a list. The data were subsequently included in files prepared and completed based on the clinical records of the CHPR's Nephrology Clinic. We recorded age, sex, anthropometric data, corticosteroid treatment and response for all patients.

We analyzed patients who remained in follow-up for a period equal to or greater than 12 months, and assessed their evolution from diagnosis to 12/31/2015. The following data were extracted from the medical records: treatment received, response, complications and growth.

The inclusion criterion involved having INS, defined as INS affecting children older than one year of age, with proteinuria greater than 50 mg/kg/day or a proteinuria/urine creatinine ratio greater than 2 g/g, hypoproteinemia lower than 5.5 g/l with hypoalbuminemia lower than 2.5 g/l and variable edema; the INS should not be secondary to an identifiable cause[1].

We excluded patients who were under control at the Clinic prior to that date and those with a nephrotic syndrome secondary to another underlying disease. We also excluded from the cohort to which the evolution was analyzed those patients who had been controlled at the Clinic for a period shorter than one year.

According to the glucocorticoid response, we defined SS and SR patients based on ISKDC[1], KDIGO[12] and IPNA Guidelines[11].

SS patients were those whose proteinuria disappeared after a complete corticosteroid series of 2 mg/kg/day for 4-6 weeks. SR patients were those who failed to go into remission after this period. Remission was defined as a decrease in the proteinuria/urine creatinine ratio to <0.2 g/g and partial remission to a value between 0.2 and 2. Relapse was defined as the reappearance of nephrotic proteinuria with a ratio> 2 g/g.

SD patients were those who had two or more consecutive relapses during the decrease in the prednisone dose, or within 15 days of its suspension. Those who had more than 3 relapses in a 12-month period, or more than 2 relapses in 6 months were considered frequent relapsers (FR); those with less frequent relapses were considered sporadic relapsers (SporadicR)[1,12]. In this study, CD and FR were considered together, given the difficulty in differentiating them clinically, and they were prescribed a similar treatment. Children without relapses were considered non-relapsers (NR).

For the case of patients with follow-up for at least 12 months, we analyzed: frequency of relapses, use and response to other immunosuppressive drugs, body mass index (BMI) and height at the beginning and at the end of follow-up, appearance of complications, fall in glomerular filtration rate, hypertension

(AH) and death. AH was defined as blood pressure figures of ≥ 95th percentile for the age, sex and height percentile of patients under 13 years of age and for those aged 13 and over, we considered figures of ≥130/80[16].

Quantitative variables were described using summary and deviation measures and qualitative variables using frequencies. The denominator for calculating the incidence was obtained from the National Information System (SINADI), which provided us with data on the number of children under 15 years yearly assisted by ASSE, between 2009 and 2013. We compared the onset age for SS and SR patients, the BMI and height Z scores at the beginning and end of the follow-up period using the Student's T test. P <0.05 was considered significant. The patients' data was made anonymous by a different team from the researchers, in order to protect their confidentiality, as set by the 18331 Law on Personal Data and Habeas Protection. The study was approved by the CHPR's Institutional Review Board.

Results.

42 children were included, male/female ratio 2.2/1, the mean age at the time of diagnosis was 4 years 7 months ± 2 years 6 months. We found an annual incidence of 3.05/100,000 children under 15 years of age assisted at ASSE between 2009 and 2013. Table 1 shows some characteristics of the total population and Table 2 shows the characteristics of those patients with ≥ 12 months follow-up.

34 children (80.9%) were SS, 8 were SR; in the first group we included a 4-year-old boy who presented a spontaneous remission.

SS patients received Prednisone 2 mg/kg/day for 4-6 weeks; They subsequently changed to an alternate dose with a gradual decrease in CC. Patients without remission were classified as SR. A kidney biopsy was performed in all the SR patients, and a genetic study was performed in 4 of them. Prednisone was progressively decreased.

The mean age of the SR patients' onset was 2 years and 10 months ± 1 year 6 months and of the CS' was 5 years ± 2 years 5 months (p <0.05).

A follow-up of 12 months or greater was carried out in 33 children, we lost track of 9 patients because they moved to a private health care facility, or due to other reasons unknown to us. The mean follow-up time was 4 years ± 1 year 9 months. In this group, 26 were SS (78.7%) and 7 were SR.

In the group of 26 SS children, 8 (30.7%) were NR; Prednisone was completely withdrawn from this group after a mean treatment time of 5.4 months. SporadicR were 8 (30.7%); Prednisone was suspended to this group during the patients' first relapse after an average period of 5.6 months; the average number of relapses was 0.8 relapses/year and they were treated with full dose Prednisone, up to 3 days - one week after remission, after which they switched to an alternate dose with subsequent progressive decline. The average time on Prednisone after relapses was 3.5 months. There were 10 SD patients (38.5%). Treatment of relapses was the same as for SporadicR, but Prednisone could not be discontinued without reappearance of proteinuria. Five patients received treatment with Cyclophosphamide (CP), the rest were maintained only with corticosteroids at the minimum suppressive dose for proteinuria. CP was administered to those children who required a higher dose than 1 mg/kg/day of Prednisone. An intravenous monthly dose of 500mg/m^2 for 6 months was indicated. Prednisone was discontinued in 2 children 3 months after the CP treatment ended, Prednisone was prescribed again to one of them 7 months later due to relapse. For the case of 2 other children, we could gradually decrease the treatment even though we were not able to suspend Prednisone, and another child had an immediate relapse, therefore the Prednisone dose could not be reduced. The patient who relapsed 7 months after CP received Cyclosporine (CsA) at a dose of 4mg/kg/day, with trough levels between 70-100 ng/ml, and he achieved a sustained remission and Prednisone could be reduced to 0.2 mg/kg every other day.

All SR children underwent a kidney biopsy. In all cases, the glomerular lesion found was the EHFS variety No Other Specification (NOS). We carried out the genetic study for the Wilms tumor gene mutation WT1 and podocin NPH2 in 4 SR patients; they all had negative results.

The trough level for the 7 SR patients who received CsA was between 65-120 ng/ml; it was adjusted to the therapeutic range and response. Complete remission was achieved in 4 patients, one patient had a partial remission, and the remaining 2 did not remit. One of the CsA sensitive patients developed a secondary resistance to CsA when the dose was lowered and we tried to replace it with Mycophenolate Mofetil (MMF). The treatment time using CsA ranged from 3 years 6 months-5 years 9 months for CsA sensitive patients and it was 2 years 7 months for the patient who was in partial remission. CsA was withdrawn at 8 months and at 12 months respectively for the two patients that had not shown response to CsA. We tried to replace CsA by MMF in 3 of the 4 patients sensitive to CsA, one of them had a partial and transient response, the other 2 did not respond, so CsA was administered again. They received MMF for 6 months before withdrawing it. The indicated MMF dose was 1200mg/m2/day v/o in 2 doses. Plasma dosing could not be performed since it is not available in Uruguay. One of the 2 CsA-resistant patients received 2 doses of Rituximab and showed no response. The intravenous dose administered was 375mg/m^2, 2 doses, one week apart. The patient had had a severe allergic reaction during the second intravenous infusion, despite the pre-medication, so it was withdrawn.

Table 3 shows the treatments received by each group of patients and the response obtained.

Table 4 shows the situation at the end of the follow-up period: SS patients were all in remission, one of them in partial remission; treatment was withdrawn in 16 patients. Of the 10 SD patients, 6 were on prednisone treatment, between 0.01-0.6 mg/kg every other day; one was receiving 1 mg/kg Prednisone every other day due to a recent relapse, another one CsA and Prednisone 0.2 mg/kg every other day and 2 were untreated. Of the 5 SD patients who received CP, at the end of follow-up, only 2 were not receiving CC, the remaining 3 received Prednisone 0.3-0.6 mg/kg every other day. Only 2 of the SporadicR patients received Prednisone, one 0,4, and the other one, 0,6 mg/kg. None of the NR received treatment. In the SR group, 2 were in complete remission under treatment with CsA, one of them on Prednisone 0.1 mg/kg every other day; 4 had nephrotic proteinuria, one of

them had a drop in the glomerular filtration rate to 60ml/min/1.73m^2 and another evolved to end stage kidney disease and was on dialysis treatment. A second renal biopsy was performed on one of the patients treated with CsA after 5 years, no nephrotoxicity lesions were found.

SD and SR patients received Enalapril as an antiproteinuric and nephroprotective.

We analyzed BMI and height of 29 patients; data for 4 patients were lost as the records were not complete. As shown in Table 5, the variation in the BMI Z score at the beginning and at the end of follow-up was significant in the SD and SR patients, but not in the NR or SporadicR. The height Z-score evolution at the beginning and at the end of the follow-up had a significant drop in the SD and SR patients.

Serious infectious complications predominated in the group of SR children, 3 were hospitalized for repeated episodes of peritonitis, 2 for recurrent pneumonia with sepsis. Only 2 SS patients were hospitalized due to infections: cellulitis and pneumonia.

Chronic hypertension was diagnosed in 2 patients (one SD and the other SR).

No deaths were recorded among the cases with follow-up.

Total Number of Patients	42
Male/Female Ratio	2,2/1
Mean Age at Diagnosis	4 years 7 months ± 2 years 6 months
From Montevideo	11
SS/SR Ratio	34/8
Mean Age at Onset p<0,05 SS SR	 5 years ± 2 years 7 months 2 years 10 months ± 1 years 6 months

Table 1- Patients' Characteristics (N 42).

Characteristics	Steriod-Sensitive n=26	Steroid-Resistant n=7
Sex M/F	17/ 9	5/ 2
Mean Follow-Up time	3 years 7 months ± 1 year 8 months	5 years 7 months ± 1 year 2 months
Montevideo/Rest of the country	8/ 18	2/ 5
Renal Biopsy	0	7

Table 2- Characteristics of patients with ≥12 months' follow-up, as per their response to Corticosteroids. N=33

	Steroid-Sensitive n=26			Steroid-Resistant n=7
	NR n=8	SporadicR n=8	SD n=10	
Corticosteroids	7/8	8/8	10/10	7/7
Response to Cyclophosphamide	NI	NI	5/10: 2/5 CR without CC	NI
Response to Cyclosporine	NI	NI	1/10 CR	7/7: 4/7 CR (1 SecR) 1/7 PR 2/7 NR
Response to Mycophenolate Mofetil	NI	NI	NI	3/7 2 NR 1 PR
Response to Rituximab	NI	NI	NI	1/7 NR

Table 3- Response to treatment of patients with ≥ 12 months' follow-up

NR: Non-Relapsers; SporadicR: Sporadic Relapsers; SD: Steroid-Dependent; CR: Complete Remission; PR: Partial Remission; NR: No Remission; CC: Corticosteroids; SecR: Secondary Resistance; NI Not Indicated.

Total Population N=33		Complete/Partial Remission	Nephrotic-range Proteinuria	ESKD	Median Follow-Up Time
Steroid-Sensitive n=26	NR n=8	8 / 0	0	0	3 years ± 1 year 8 months
	SporadicR n=8	8 / 0	0	0	4 years 3 months ± 1 year 10 months
	SD n=10	9 / 1	0	0	3 years 10 months ± 2 years
Steroid-Resistant n=7		2 / 0	4*	1	5 years 7 months ± 1 year 2 months

Table 4- Patients' situation at the end of the follow-up period. N=33

NR: Non-Relapsers; SporadicR: Sporadic Relapsers; SD: Steroid- Dependent.

ESKD: End Stage Kidney Disease

*One of these patients had mild chronic kidney failure with a creatinine clearance of 60ml/min/1.73m^2.

n=29	Initial BMI (score Z)	Final BMI (score Z)	P
All Patients n=29	0.41±1.02	0.95±1.02	p<0.0001
SR n=6	0.47±1.50	1.52±0.83	p<0.0001
SD n=10	0.47±1.14	1.24±0.56	p=0.0022
SporadicR n=7	0.25±0.55	0.32±0.78	p=0.456
NR n=6	0.39±1.03	0.62±1,62	p=0.382

Initial Height (score Z)	Final Height (score Z)	P
0.48±1.06	0.43±0.73	p=0.48
0.46±1.56	-0.31±0.99	p=0.020
0.61±0.90	0.10±0.90	p<0.0001
0.32±1.11	-0.14±1.13	P=0.47
0.45±1.07	0.45±0.77	p=0.98

Table 5- BMI and Height Evolution according to their response to Corticosteroids.

Discussion

The CHPR Nephrology Clinic, a clinic of the Public Reference Children's Hospital, assisted an average of 8.4 new patients per year during the period described above. Assuming that all the ASSE INS cases were referred to this specialized clinic, the incidence of 3.05/100,000 children under 15 years of age is similar to that described in the literature[5-9]. This data refers only to the population of children assisted at ASSE.

This is the second study of public sector patients with INS published in our country[17].

Males showed the highest frequency as reported in the literature[10,14,17,18] and this may vary according to age[19]; equally in adolescents and in adults [20]. Sureshkumar[21] found a predominance of females among SR patients, which does not match our findings, but could be due to our lower number of patients.

The mean age of presentation, preschool age, matches the age described, 3 years of age[19], or between 2 and 5 years of age [3,14,17].

A striking finding in this study is that the onset of the disease took place at a significantly younger age in SR patients than the one described in the literature[6]. In the ISKCD study, 80% of children with MCD (characteristically SS lesion) were ≤6 years of age, while only 50% of children with FSGS were included in this age group[7,18].

Approximately 80% of all children were SS, and the remainder were SR due to FSGS. International publications point to an increase in patients with INS due to FSGS, generally with a poorer response to CC[22], and a relative decrease in those with MCD-[24].

The frequency found of SR and SD was similar to that described[20,25,26]. Children who were steroid-sensitive and did not have relapses in the six months after onset have a lower risk of relapsing later in life[25]. Sureshkumar found that males who show a short time between onset and the first relapse predict frequent relapses or steroid-dependence during the evolution [21].

We did not find late relapses, possibly due to the short follow-up time. 20-40% of SS patients may have relapses after 18 years of age, which shows the need for long-term follow-up[13-15,27]. The need to use other immunosuppressive drugs, such as CP and CsA, as well as the higher frequency of relapses in childhood predict active disease in adulthood[14,26]. Disease activity may persist longer in patients with an onset taking place before 6 years of age, with relapses in adult life[10].

CP was administered to 5/10 SD patients, with an unfavorable response in relation to the possibility of discontinuing Prednisone. CP was a first-line drug for treating SD patients. The frequency of remission with CC withdrawal is high, 67% at 2 years, mainly for the case of children dependent on doses lower than 1.4 mg/kg/day of Prednisone[28]. The response to CP declines over time and up to 50% have relapsed at 5 years of follow-up[7].

MMF is another CC-sparing drug, although in this study it was not used in the SD group, as presently indicated. It has direct action on the mesangium and pedicels and antiproliferative of B and T lymphocytes[29]. The advantage of this drug is that although it is less effective than CsA, it is not nephrotoxic and the response improves when adequate serum levels of mycophenolic acid are reached [30-32].

CsA led to good responses in the SD patients, as described; treatment duration is debated due to its nephrotoxicity and to the dependence it generates[31,33]. For some authors, CsA should be avoided in SD patients, since these patients also have a greater tendency to relapse in adulthood[26].

Rituximab was not administered to these patients; it is another therapeutic alternative for SD patients, although the optimal dose and duration in children is still unknown. Although studies show an acceptable safety profile, it can have potentially serious adverse effects[34-37].

In SR patients, we performed a renal biopsy as recommended[7,11,12], finding FSGS in all of them, the Not Otherwise Specified variant, the most frequent[38-40]. All SR patients received CsA, according to current guidelines[1,11], and complete or partial remission was achieved initially in 5/7. The remission rate using this drug associated with converting enzyme inhibitors varies in the different studies, from 20% to 80% after two years of treatment[11,33,41]. The optimal duration of treatment is unknown and large-scale randomized studies are required to have stronger evidence to be able to support therapeutic decisions in SR patients[42]. Given the fact that the SR NS is a rare disease, the published studies are small, which makes it difficult to make recommendations with a good level of evidence[1].

We did not find nephrotoxic lesions in the patient who received prolonged treatment with CsA. Some guidelines propose performing kidney biopsy in patients who have received calcineurin inhibitors for two years or more, to assess possible toxicity[1,2,11,31,39].

MMF was indicated as an alternative to lower and withdraw CsA in 3 SR patients; no response was obtained in 2 patients and we could only obtain a partial and transitory effect in the remaining patient. Currently, it is recommended to make an attempt to convert to MMF, to reduce nephrotoxicity, by dosing its plasma levels, which we still are not able to do in our country[11]. Gipson et al. found no significant difference between the use of CsA and MMF associated with high doses of dexamethasone in SR with FSGS. For some authors, the complete or partial remission rate with MMF in SR was approximately 60%[43,44]. The available studies show less induction of remission with MMF than with CsA, so the latter continues to be the first option for SR patients[1,11].

In this study, one of the SR patients in remission received Prednisone 0.1 mg/kg/day associated with CsA. It is currently not recommended to continue with low doses of CC in SR patients, a maximum time of 6 months should be considered for withdrawal, except for those patients who become SS and SD[11].

Rituximab was administered in a single SR patient without response; the poor response has been described, although in some cases, remission could be achieved by reintroducing CsA or MMF[34].

The genetic study did not yield positive results, some of the responsible genes were researched, but it could be the case of an unsought or not yet described mutation[4]. Presently, there are more than 50 genes that are expressed in podocytes and are related to SS SR patients[4]. Mutations in genes that modify podocyte structure and function can be found in up to 30% of SR patients, which causes behavior generally multi-resistant to immunosuppressive drugs[45-49]. Few cases can have total or partial

remission with calcineurin inhibitors: 3% and 11% respectively, in both cases transient. The possibility of finding a mutation in SR patients is inversely proportional to age[50]. The possibility of a genetic diagnosis in SR cases can contribute to more rational therapeutic decisions[4,11].

Regarding patients' evolution, one patient had spontaneous remission; presently, we do not see this evolution since the treatment is usually started early. In the pre-corticosteroid era, remission was between 5% and 15% of cases, after months or years of illness. Mortality prior to the use of corticosteroids and antibiotics was 40%, mainly due to infectious and embolic complications[19,51,52].

The evolution of SS patients was satisfactory, as described. There was no record of poor adherence to treatment, a common situation in adolescents, which favors relapses[2,53]. Although the long-term evolution of SS patients is favorable, this chronic disease and the adverse effects of medications can have long-term consequences on the quality of life of children and their families[2,53].

Infectious complications were more frequent and severe in SR patients, probably because poor control of the disease perpetuates the immunodeficiency situation that characterizes INS[51].

In this study, 2 SR patients showed a fall in glomerular filtration, one of them entered a renal function replacement plan. The prognosis regarding the preservation of renal function is excellent in SS NS[13,18], with less than 5% evolving to a fall in glomerular filtration[3]. In contrast, 50% of SR patients can evolve to CKD with a fall in the glomerular filtration rate or reach extreme CKD at 5 years of age. The prognosis improves with the favorable response to CsA with partial or total remission of proteinuria[38,39]. SR NS, and FSGS specifically, is the most common cause of CKD of glomerular origin in children[38]. The response to calcineurin inhibitors is a favorable prognostic indicator, while the detection of hereditary podocytopathy is unfavorable regarding the long-term evolution of SR patients. Children with resistance to multiple drugs have longer kidney survival than those with genetic disease[55].

We could assess growth in 29/33 patients; As it was a retrospective study, there was loss of data due to incomplete recording practices. The SD and SR groups of children showed a significant impact on height and BMI. For the case of SD patients, the accumulated load of CC determined an impact on both. The CC deleterious action on growth depends on the dose and duration of therapy, with weight gain and redistribution of body fat[56].

On the other hand, persistent proteinuria determines hormone depletion, generating hypothyroidism due to loss of transporter proteins and plasma decrease in IgF1 and IgF2 transporters[57,58].

In 44% of adult relapses, we found CC adverse effects, mainly obesity and osteoporosis, besides short height and cardiovascular alterations[7]. Important behavioral alterations have also been described in SS patients with INS[59,60], though not analyzed in this study.

Current clinical guidelines propose strategies for the use of CC-sparing drugs, minimizing their use and promoting their early withdrawal[1,11,61].

Some questions remain to be answered: who develops INS and what is its cause? This answer would help us understand the factors linked to individual differences in response to medications, as well as the triggers for relapse[3]. The different responses in each patient can be explained by etiological heterogeneity. The evaluation and treatment of INS confront us with a challenge in each case[4].

The weaknesses of this study include the fact that it was a retrospective analysis, the low number of patients and the short follow-up time of chronic pathology. The study does not reflect the INS nationwide incidence in Uruguay.

Conclusions

This is the study of a historical cohort of children with INS from ASSE assisted at the Uruguayan Children's Reference Hospital for 5 years; the estimated incidence is comparable to that of other published studies. A study that includes all the Health Provider Organizations in Uruguay could provide knowledge of the incidence in the entire population under 15 years of age at the national level. The results represent a contribution to the knowledge of this pathology's evolutionary profile in patient users of the public health services. Most of the cases were SS with better evolution and fewer complications, as in other studies.

SR patients were younger than SS patients, had more severe complications and a higher frequency of kidney function impairment, which means a challenge for the health team.

The growth of children exposed to high doses of corticosteroids was affected. There is a need for customized management following the present recommendations to achieve better results with fewer adverse effects.

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