Original Article

Idiopathic nephrotic syndrome in New Zealand children, demographic, clinical features, initial management and outcome after twelve-month follow-up: Results of a three-year national surveillance study

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Aim: To describe the demographic, clinical features, steroid response, histopathology and complications of all children diagnosed with idiopathic nephrotic syndrome (INS) in New Zealand over a 3-year period.

Methods: A questionnaire seeking relevant clinical information was sent to all paediatricians who reported a new case of nephrotic syndrome to the New Zealand Paediatric Surveillance Unit. A follow-up questionnaire was sent to reporting paediatricians after the first 12 months of follow-up.

Results: The incidence was 1.9 children per 100 000 under age 15 years. There was no significant difference in INS between ethnic groups. Approximately 80.4% were steroid responsive with median time to response of 8.4 days and mean time to relapse was 15.1 ± 12.1 weeks (10.1–19.8 95% confidence interval). Follow-up at 12 months after diagnosis showed that two-thirds were either steroid dependent or frequent relapsers. Steroid resistance patients had a more variable course with some developing chronic renal failure and other remaining persistently nephrotic.

Conclusion: The incidence and outcome of children with INS are similar to overseas studies. A large variety of steroid treatment regimens were noted. Current evidenced-based guidelines to treat INS were used infrequently.

Key words: childhood; ethnicity; nephrotic syndrome; outcome.

The incidence of idiopathic nephrotic syndrome (INS) in New Zealand children is not known. Of the overseas incidence studies (the USA,1,2 the UK3,4), only one was population based.5 In the 1950s, the annual incidence of nephrotic syndrome (NS) in children aged below 16 years in the USA, derived from the Erie County Survey, was approximately 2 per 100 000 children and the cumulative prevalence was about 16 per 100 000.6 The incidence was lower in white children (1.9 per 100 000) than in non-white children (2.8 per 100 000) although the numbers of non-white children were small and the incidence was higher in lower socio-economic groups. Similar results were obtained in the Ohio Study,7 where case ascertainment was by questionnaire requesting data on hospitalised cases seen between 1944 and 1953. A retrospective study of hospital records in Birmingham, UK revealed that the annual incidence of NS was 2.6 per 100 000 children for European children, 3.4 for Afro-Caribbean children and 16.9 for Asian children from the Indian subcontinent.8 This study assumed that all children with NS were treated in the major hospitals. A study from Leicestershire, published at about the same time, found similar results4

There is no information on the epidemiology or management of INS in New Zealand children. In 1998, Simpson et al. published a biopsy series of children with INS and highlighted some of the differences between their group and overseas studies.7 A prospective study between 1 July 2001 and 1 July 2004 was undertaken to define demography, clinical features, complications and treatment in children newly diagnosed with INS in New Zealand.

The aims of the present study were to:

1 Compare the age, sex and ethnicity of children with steroid-responsive and steroid-resistant NS.
2 Describe renal histopathology seen in children with steroid-resistant NS.
3 Describe the distribution of infrequent relapsers, frequent relapsers and steroid dependence among steroid-responsive NS.

Key Points

1 The incidence of idiopathic syndrome in New Zealand is similar to that in other international studies with no ethnic predominance.
2 Complications arising from steroid-sensitive nephrotic syndrome are rare.
3 Two-third of patients are either steroid dependent or frequent relapsing.

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4 Ascertained the steroid regimens to treat the first presentation of NS.
5 Describe the frequency and type of complication-associated NS.
6 Describe the 1-year outcome of children with NS.

Methods

New Zealand paediatricians were asked to report to the New Zealand Paediatric Surveillance Unit, any child with newly diagnosed INS satisfying the case definition between 1 July 2001 and 1 July 2004. The definition for INS was any child between the ages of 3 month and 15 years presenting with oedema, hypoalbuminaemia with normal renal function and in the absence of a systemic illness causing NS. Infants with congenital NS and those with NS presenting after age 15 years were excluded. An initial questionnaire was sent to reporting paediatricians requesting demographic and clinical information. A follow-up questionnaire was sent to the patient’s primary paediatrician 12 months later requesting information on response to steroid treatment, number of relapses, vaccination status, biopsy result and complications of NS. Ethnicity of the index case was determined from the reported ethnicity of the parents on the hospital admission data. Three children had parents from two differing ethnic groups, for example, Indian mother and a Maori father. The study was approved by the Auckland Research Ethics Committee. The ethnic group Asian included peoples from all Asian countries and those from the Indian subcontinent. The 2001 Statistics New Zealand Population Census was used for population-based comparisons.

Statistical analysis

Software Graphpad Instat 3 and Graphpad Prism 4 (Graphpad Software Inc, San Diego, CA, USA) were used. Unpaired t-test and χ² test were used to analyse for statistical significance.

Definitions of steroid response and relapse

Remission – albustix showing 0 to trace protein for 3 consecutive days.
Relapse – albustix showing 3+ or more on 3 consecutive days.
Infrequent relapser – one relapse in 6 months or less than four per year.
Frequent relapser – two or more relapses per 6 months or more than 4 per year.
Steroid dependence – two consecutive relapses during reducing or alternate day steroids or within 14 days of cessation of steroids.
Steroid resistance – no response to steroids after 4–6 weeks of daily high-dose therapy.
Hypertension – as defined by the Second Task Force on Blood Pressure Control in Children.6

Over the 3-year initial reporting period, 95.8% of the questionnaires were returned to the surveillance unit. Duplicate reported cases and cases that were initially diagnosed overseas were excluded. The data set was validated with hospital discharges for NS in children under age 15 years for July 2001–July 2004 collected by the New Zealand Health Information System.

Results

Fifty-one children were reported to have INS, of whom 49 were diagnosed in New Zealand with two children diagnosed overseas and were thus excluded from further study. The annual prevalence of INS was 16.3 per 100 000 (11.1–21.5, 95% confidence interval (CI)) children under age 15 years. The incidence was 1.9 per 100 000.

The demographics and clinical features are shown in Tables 1 and 2, respectively.

Ethnicity

Figure 1 shows the ethnic composition of the group. There was no significant difference in the proportion of ethnic groups represented in the study compared with the general population of New Zealand under age 15 years (χ² P = 0.3). Steroid-resistant NS was not more common in Maori and Pacific Island ethnic groups than Caucasians (six of nine steroid patients were European).

Initial steroid treatment and subsequent response

All 49 patients were given an empirical trial of prednisone. Steroid responsiveness was observed in 80.4% of the group, with a mean time to response of 12.1 days (8.9–15.4 95% CI), median of 8.4 days, range 3–54 days. Mean and median time to relapse was 15.1 weeks (10.1–19.8 95% CI) and 15 weeks, respectively. The initial dosing prednisone was variable, ranging from 1.1 to 2 mg/kg/day with 70% of patients receiving 2 mg/kg/day and 82% receiving their therapy in a single daily dose.

Table 1 Demographic features at presentation

<table>
<thead>
<tr>
<th>Gender,† n</th>
<th>Males</th>
<th>35</th>
</tr>
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<tbody>
<tr>
<td>Females</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age, mean/median (SD)</td>
<td>6.1/4.9 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Age distribution, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1–5 years</td>
<td>26 (53)</td>
<td></td>
</tr>
<tr>
<td>6–10 years</td>
<td>14 (29)</td>
<td></td>
</tr>
<tr>
<td>&gt;11 years</td>
<td>9 (18)</td>
<td></td>
</tr>
<tr>
<td>†Comparison of age at presentation between males and females (P = 0.2, unpaired t-test).</td>
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Table 2 Clinical features at presentation, n [%]

<table>
<thead>
<tr>
<th>Clinical features at presentation, n [%]</th>
<th>35 (71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microhaematuria</td>
<td>15 (31)</td>
</tr>
<tr>
<td>Gross-haematuria</td>
<td>49 (100)</td>
</tr>
<tr>
<td>Elevated blood pressure (&gt;95th centile)</td>
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<tr>
<td>Normal renal function</td>
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†Biopsy showed minimal change disease with weak C1q immunofluorescence.
A wide variety of steroid regimens were used after the initial treatment with 25 different regimens recorded. Duration of steroid therapy following initial remission varied from 1 to 8 weeks of daily treatment. Nine were treated with 2–8 weeks of daily prednisone with reduction, 15 treated for 1–7 weeks of alternate day prednisone without reduction and 26 treated with 1–16 weeks of alternate day therapy with progressive reduction. The median duration of total steroid treatment was 12 weeks (range 2–19 weeks).

Renal biopsy

Twenty-three of 49 (46%) had biopsies performed in the first 12 months. Indications for biopsy were steroid resistance (8), frequent relapsing or steroid dependence (13) and unusual presentation (2) (gross haematuria and post bone marrow transplant). Of the eight children biopsied for steroid resistance, four had local segmental glomerulosclerosis (FSGS), two minimal change disease (MCD) and two diffuse mesangial proliferation (DMP). All patients with frequent relapsing or steroid-dependent NS had MCD.

Adjunctive therapies

Antibiotic prophylaxis and pneumococcal vaccination

Antibiotic prophylaxis was administered to 33/46 children, with oral penicillin V being prescribed in the majority. Sixty per cent of patients were administered the pneumococcal vaccine during the 12 months of follow-up.

Diuretics and albumin infusions

Twenty-six per cent (13) patients received diuretics as part of their initial therapy with most (78%) also receiving infusions of concentrated albumin for hypovolaemia or severe oedema. The reason for albumin administration was not requested in the initial questionnaire. There was no obvious difference between those who were given diuretics with or without albumin in terms of the frequency of hypertension or age at presentation.

Complications of NS

The complications of NS and prophylaxis of thromboembolism are shown in Table 3. All episodes of sepsis occurred while the patients were nephrotic. No patients were recorded as having invasive sepsis while on antibiotic prophylaxis. There was no relationship between the use of aspirin and the need for diuretic therapy or albumin infusions (four of the aspirin group had diuretics and/or albumin and four did not). One patient presented with a sinus venous thrombosis of the central cerebral sagittal vein and was subsequently diagnosed to have steroid-sensitive NS.

Status of patients at 12 months

Of the original 49 patients, 46 were available for follow-up at 12 months and their outcome is shown in Table 4. Three either were lost to follow-up or had left the country. All were alive at the 12-month follow-up questionnaire but those with steroid resistance ($n = 9$) had varying degrees of impaired health. One patient with FSGS progressed to end-stage renal failure and had commenced peritoneal dialysis, four were hypertensive because of FSGS or steroid-dependent NS. Eight patients were being treated with alternative immunological therapy (cyclosporin A, levamisole, cyclophosphamide) because of steroid resistance or...
dependence. Recent follow-up of those with FSGS showed they were developing renal insufficiency and the two patients with DMP remain persistently and severely nephrotic after failing treatment with cyclosporin.

Discussion

This is the first prospective study of childhood NS in New Zealand. New Zealand has a population of 4.1 million people, with a unique demography including a large number of migrants from the Pacific Islands and more recently an influx from China and South-East Asia. A previous study from New Zealand had suggested that glomerular diseases were over-represented in adults whose ethnic groups originated from the Pacific Islands. That study showed that Maori and Pacific Island adults had a higher incidence of NS; however, Simpson et al., in a 10-year retrospective study of renal biopsies for childhood NS, were unable to confirm this pattern for the paediatric age group. The present population-based study was also unable confirm the results of the earlier adult study. This may be due to small patient numbers in each ethnic group. The incidence of INS in New Zealand children, 1.9 per 100 000 children under age 15 years, is very similar to international published studies. Studies also indicate there is a higher incidence in low socio-economic groups and non-Caucasian ethnic groups; however, this relationship could not be investigated in this current study as in 30% of the patients, information on the occupational status of either parent was not available. Also the author acknowledges the difficulties of eliciting assignment of ethnicity. The small numbers in each ethnic group limits the statistical power to detect significant differences in the study population.

A relatively high proportion (46%) of the group had a renal biopsy. It has been standard practice in our unit to perform a biopsy in patients with frequently relapsing or steroid-dependent NS prior to commencing alternative immunosuppressive therapy such as cyclophosphamide or cyclosporin A. This biopsy protocol remains our current practice in spite of a number of studies indicating that steroid responsiveness was more accurate in predicting outcome than exact histological diagnosis. Our unit believes that a histological diagnosis assists the nephrologist in providing the most appropriate treatment and guide to prognosis. Nine of 46 patients were steroid resistant which is lower than the 66% in the earlier biopsy-based report by Simpson et al. Analysis of the renal biopsy group showed that 74% were minimal change and 17% were FSGS. The proportion of patients with MCD is comparable to that reported in the study of the International Study of Kidney Disease in Children; however, a higher incidence of FSGS (17%) is observed in the present study. This figure is identical to that observed in the renal biopsy study by Simpson et al. Earlier series in the 1960s and 1970s showed that FSGS composed of 7–10% of children with NS. More recent series show 20–60% of patients with this pathological lesion with a higher frequency in African American compared with Caucasians.

Sixty-six per cent of our steroid-responsive group had frequent relapses or steroid dependence with a mean of 5.3 relapses per year. This rate of relapse is consistent with published data. Although the median duration of total steroids was 12 weeks, many patients were given relatively short courses of prednisone. Recent reviews and meta-analyses of published controlled clinical have recommended that initial presentation of steroid-sensitive NS be treated with prolonged course of prednisone of between 3- and 7-month duration. This would result in fewer relapses without a significant increase in steroid toxicity. One review suggested that increased dose of steroids as well as prolonged duration was important in reducing the risk of relapse. Our current study provides an opportunity for the education of paediatricians in the optimal steroid treatment of NS based on current evidence-based guidelines.

Serious infection complications arising from NS were relatively uncommon, with only three episodes of invasive pneumococcal sepsis. All cases occurred at the time of diagnosis and were not preventable. A recent review by McIntyre and Craig highlighted that there were no controlled trials on the use of penicillin prophylaxis or pneumococcal vaccination in childhood NS.

One-quarter of our patients were given frusenide and 20% salt poor albumin during their initial presentation. Published evidence-based recommendations for albumin infusions remain lacking. The author's policy has been to restrict the use of albumin and diuretics to patients with significant abdominal pain secondary to intravascular volume depletion and severe genital oedema. It was unclear from the results of the survey how many of the patients receiving albumin had significant volume depletion or severe oedema as most of the patients were under the care of general paediatricians in other centres. The dangers of albumin infusions have been reported in a number of studies. Haws and Baum showed that albumin infusions caused hypertension in 46% of the treatment courses and addition hypokalaemia, and hypernatraemia was observed in 40% and 17% of treatment courses, respectively. Yoshihura et al. indicated that albumin administration might delay the response to steroid therapy and induce more frequent relapses after remissions. The present study was unable to confirm a link between albumin infusions and relapse frequency with only 10/29 relapers having had albumin compared with 19/29 who did not have albumin infusions. Although the study did not seek specific details of complications of albumin therapy, none were reported to the investigator. The author recommends 0.5–1.0 g/kg of 20% albumin solution given over 2–3 h followed by 1 mg/kg of intravenous frusenide. We have observed occasional episodes of transient hypertension that were easily managed with antihypertensive medication.

In conclusion, the present study confirms the incidence of paediatric INS is similar to that in other countries but could not confirm that non-Caucasian races had a higher incidence of NS. There was a wide variety of steroid treatment regimens indicating possible confusion to the most satisfactory regimen based on current evidence-based guidelines. Results of this study form a useful basis for developing guidelines on the management of childhood NS.

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