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Incidence and Relapse Triggers of Childhood Idiopathic Nephrotic Syndrome between 2006 and 2016: A Population-Based Study in Fukushima, Japan

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Childhood idiopathic nephrotic syndrome (NS) is defined by proteinuria and hypoproteinemia. The incidence of childhood idiopathic NS varies with age, race, residential areas, and social conditions. In Japan, its incidence was estimated to be 6.49 cases/100,000 children. Our study aimed to investigate the incidence, characteristics, and rate of relapse of idiopathic NS in Fukushima between 2006 and 2016. Overall, 158 children aged from 6 months to 15 years old (65.8% male) developed idiopathic NS (median age at onset, 5.3 years). The peak age at onset was three years. The average annual incidence of childhood idiopathic NS was 5.16 (range, 3.47-9.26) cases/100,000 children. The highest incidence was in 2011, which was the year of the Great East Japan Earthquake and nuclear power plant accident, and reportedly caused psychological distress in the children at the time. Conversely, the five-year birth cohort showed minor difference from 2008 to 2012. The rate of incidence in males aged < 5 years was thrice greater than in females of the same age and almost the same for males and females aged 11-15 years. Of 507 total relapses in 115 NS children, common triggers of relapses were steroid discontinuation or reduction and infection. The average annual incidence of childhood NS based on the Fukushima population was lower than previously reported in Japan, and the annual incidence has changed over an 11-year period. These changes may be affected by social or environmental factors, including mental stress associated with lifestyle changes after the disaster.

Keywords: hypoproteinemia; idiopathic nephrotic syndrome; incidence; proteinuria; relapse
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Introduction

Idiopathic nephrotic syndrome (NS) in children is a childhood representative kidney disease that is defined by high proteinuria and hypoproteinemia caused by glomerular disorder, in particular, the loss or altered function of the podocytes. NS in adults often occurs secondarily associated with collagen disease, diabetes, and infection, among others, whereas the majority of childhood NS cases are idiopathic. The majority (80%-90%) of idiopathic NS cases in childhood respond well to steroid treatment. However, 60% of steroid-sensitive NS cases result in frequently relapsing NS/steroid-dependent NS. In addition, approximately 10%-20% of idiopathic NS cases are considered steroid-resistant NS. Worldwide, it has been estimated that the incidence of idiopathic NS in children is 1.15-16.9 per 100,000 children (Noone et al. 2018).

The frequency of idiopathic NS is known to vary according to age, environment, race, and residential areas. Globally, it has been reported that the incidence of childhood idiopathic NS is 1.2-3.35, 1.2-1.9, and 5.66 per 100,000 children in Europe (Andersen et al. 2010; El Bakkali et al. 2011; Dossier et al. 2016; Franke et al. 2018), Oceania (Wong 2007; Sureshkumar et al. 2014), and East Asia (Taiwan) (Chang et al. 2012), respectively. In Japan, childhood idiopathic NS has been estimated to affect 6.49 per 100,000 children (Kikunaga et al. 2017).

Over 50% of children with idiopathic NS experience a relapse, which is often associated with physical and/or mental episodes (Takahashi et al. 2007). Infections, allergies and vaccinations are known triggers of relapse (Abeyagunawardena et al. 2003; Yildiz et al. 2013; Uwaezuoke 2015; Riar et al. 2019). Psychological stress leading to the dysregulation of the immune system can also cause relapse (Takahashi et al. 2007; Bakkum et al. 2019).

However, the epidemiology of idiopathic NS over a long period remains to be investigated in Japan. In this study, we surveyed children who developed idiopathic NS between 2006 and 2016 in the Fukushima Prefecture and examined the demographics, characteristics, and features of relapse.

Materials and Methods

Study population and incidence

We have been conducting an annual survey of the incidence of kidney disease across the entire prefecture of Fukushima since 2006. The current study represents a retrospective observational study of subjects, aged between 6 months and 15 years, with nephrotic syndrome treated from January 2006 to December 2016 at secondary medical institutions (Fukushima Medical University, Ohara General Hospital, Fujita General Hospital, Japanese Red Cross Society Fukushima Hospital, Hoshi General Hospital, Jusendo Hospital, Ohta General Hospital, Iwase General Hospital, Shirakawa Kosei General Hospital, Takeda General Hospital, Soma General Hospital, and Iwaki City Medical Center) located in Fukushima. The initial visits for the same cases were registered during the same year. The pediatric population of Fukushima was included for the calculation of the incidence of idiopathic NS based on the national censuses conducted in 2005, 2010, and 2015. The survey was conducted in accordance with the Declaration of Helsinki and was approved by the ethics review board of Fukushima Medical University. Because all patient data were retrospectively reported using medical charts, informed consent was not obtained for individual participants but was obtained in the form of opt-out.

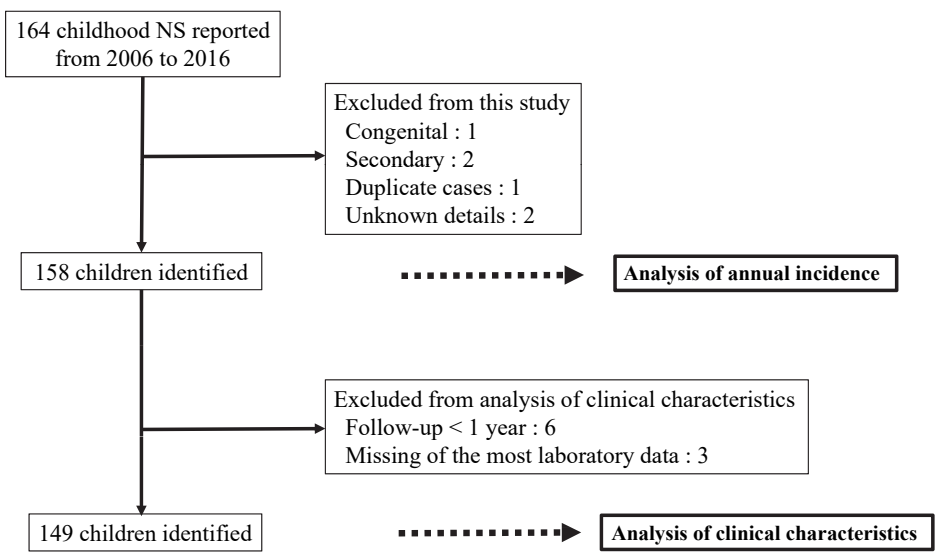

Fig. 1. Flowchart of this study participants.
Of the 158 children analyzed annual incidence, nine children were excluded due to less than 1 year of follow-up or most laboratory data missing. Finally, 149 children were analyzed for clinical characteristics.
NS, nephrotic syndrome.

Definition

Idiopathic NS is characterized by high proteinuria (creatinine ratio ≥ 2 g/g Cr or 3+ or 4+ on the dipstick) and hypoproteinemia (serum albumin ≤ 3.0 g/dL). Conditions of congenital or secondary nephrotic syndrome were excluded. Relapse was defined as proteinuria as observed by a 3+ or 4+ on the dipstick for three consecutive days. Opportunities at the initial diagnosis and triggers of relapse were based on the description of clinical recordings retrospectively, and relapses due to steroid and immunosuppressant discontinuation or reduction were defined as those that occurred within 14 days. steroid-sensitive NS was defined as complete remission within 28 days; frequently relapsing NS was defined as two or more relapses within six months of the initial steroid therapy or four or more relapses in any 12-month period. Steroid-dependent NS was defined as two consecutive relapses after weaning off steroid treatment or the cessation of steroid therapy within 14 days. Steroid-resistant NS was defined as no remission within four weeks despite steroid treatment. Late non-responders were defined as steroid resistant after steroid-sensitive NS. Initial steroid therapy was classified as either short-term therapy that lasted 2-3 months or long-term therapy that lasted over 5-6 months. When performing the statistical analysis, cases with follow-up period of < 1 year were excluded.

Renal tissues obtained by renal biopsy were histologically examined via light, immunofluorescence, and electron microscopy. Minimal change NS was defined as that when the glomerulus appears normal or when there is a considerably inconspicuous mesangial matrix expansion under light microscopy. Focal segmental glomerulosclerosis was defined as the presence of segmental sclerosing lesions in at least one glomerulus. Mesangial proliferative glomerulone-

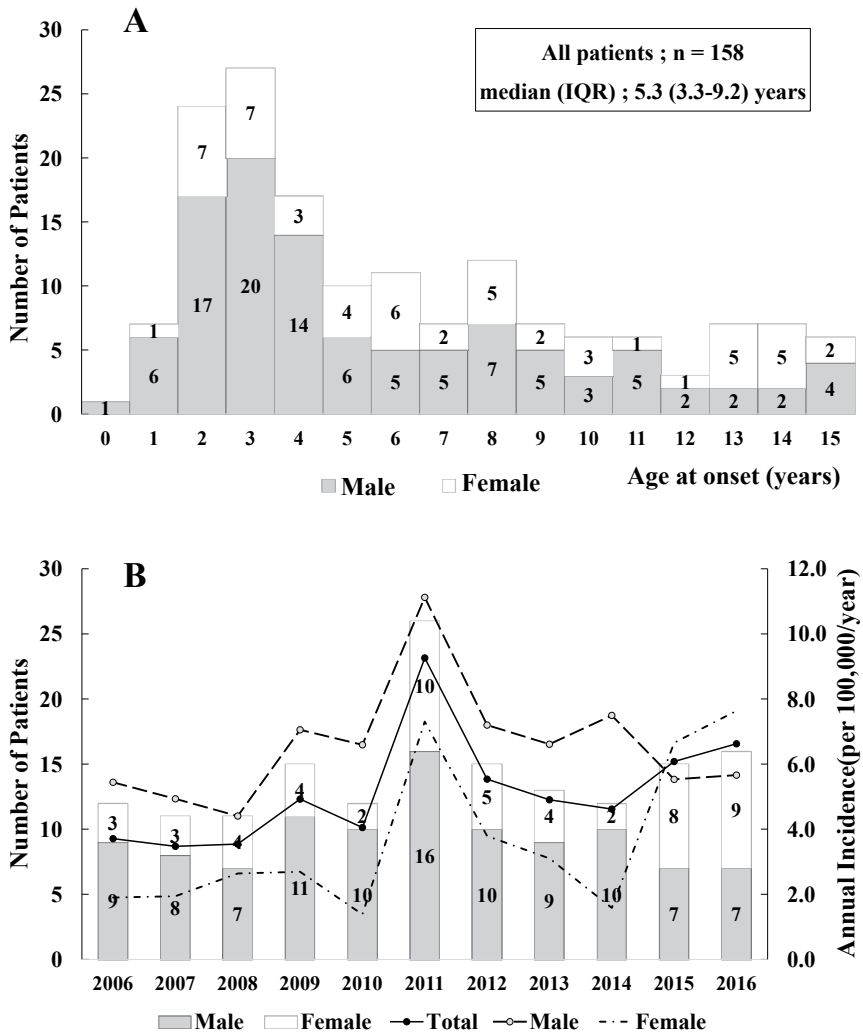

Fig. 2. Age-specific or annual incidence of idiopathic nephrotic syndrome (NS).
A. Age distribution of idiopathic NS developed from 2006 to 2016.
B. Annual distribution and incidence of idiopathic NS.
The gray bar indicates male patients (n = 104); the white bar indicates female patients (n = 54). The broken, dot-dash, and solid lines represent the annual incidence of male, female, and total patients of idiopathic NS, respectively.
IQR, interquartile range.

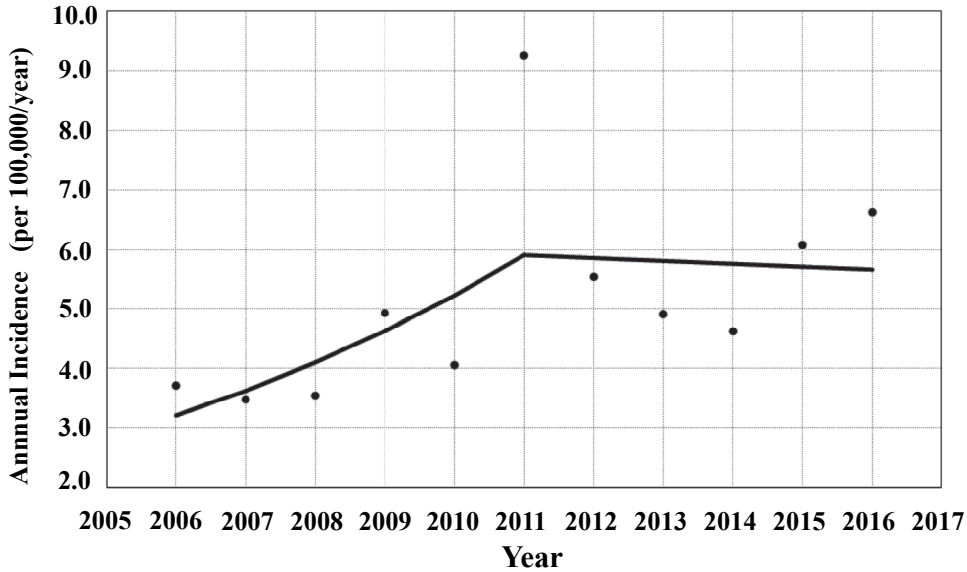

Fig. 3. Trends in childhood nephrotic syndrome (NS) in Fukushima from 2006 to 2016.
The fitted trend was calculated using joinpoint trend analysis. The line indicates the annual percent change. The incidence of idiopathic NS had a joinpoint with 2011. The annual percent change was 12.95% from 2006 to 2011 and −0.84% from 2011 to 2016.

Table 1. Five-year birth cohort of childhood nephrotic syndrome (NS) from 2008 to 2012.

Birth year	2008	2009	2010	2011	2012
5-year incident cases	11	6	8	6	6
5-year incidence (per 10,000 children)	6.71	3.75	5.08	4.20	4.48

This table shows the cumulative incidence of idiopathic NS in children aged 0-4 years born between 2008 and 2012. The highest annual incidence was in 2011; however, the five-year birth cohort showed almost no difference around 2011.

phritis was described as mesangial matrix expansion and mesangial cell proliferation, and membranoproliferative glomerulonephritis was characterized as the presence of diffuse mesangial cell proliferation attended by immune deposits along the basement membrane (Banaszak and Banaszak 2012).

Statistical analysis

The age at onset, follow-up period, sex, diagnosis opportunity, classification of steroid-responsive, histological type, initial laboratory data on treatment and relapses in the past were collected from medical records. IBM SPSS software version 26.0 was used for statistical analyses. We used the chi-squared or Fisher's exact test to compare the characteristics of the patient groups and the Mann-Whitney *U*-test to compare continuous variables. The threshold for statistical significance was $p < 0.05$.

The annual percent change (APC) of the incidence of idiopathic NS and joinpoint, wherein annual changes such as morbidity and mortality significantly increased or decreased, were estimated using joinpoint trend analysis. The model could test if the APC of each segment between joinpoints is significantly different from zero ($p < 0.05$). This analysis was performed using Joinpoint Regression Program version 4.8.0.1 (Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program, National Cancer Institute).

Results

Of 164 NS cases, six cases were excluded because of congenital or secondary nephrotic syndrome, unknown details, or duplication; 158 children developed idiopathic NS between 2006 and 2016 in Fukushima. Furthermore, nine cases were excluded from the statistical analysis of idiopathic NS characteristics because of missing of the most laboratory data or follow-up period of < 1 year. As shown in Fig. 1, statistical analysis of the annual incidence and clinical characteristics was performed using data of 158 and 149 children, respectively.

Age distribution idiopathic NS incidence

The median onset age of idiopathic NS children was 5.3 years (interquartile range, 3.3-9.2), and the peak of onset was three years. The ratio of boys to girls tended to be lower as the age of onset increased (Fig. 2A). Fig. 2B shows the number and incidence of idiopathic NS for each year. The average incidence rate over the past 11 years was 5.16 cases/100,000 children per year. The annual incidence

Table 2. Incidence of childhood idiopathic nephrotic syndrome (NS) for each age.

Age (years)	Incidence (cases/100,000 children)		
	Total	Males	Females
0	0.64	1.24	0.00
1	4.46	7.36	1.34
2	14.13	19.46	8.48
3	15.44	22.43	8.07
4	9.55	15.14	3.67
5	5.38	6.13	4.61
0-5	8.68	12.83	4.32
6	6.38	5.49	7.33
7	3.61	4.72	2.44
8	6.35	7.00	5.68
9	4.17	6.39	1.89
10	3.09	3.09	3.06
6-10	4.71	5.33	4.06
11	2.24	3.53	0.88
12	1.46	1.78	1.13
13	3.39	1.95	4.89
14	3.10	1.64	4.61
15	2.70	3.38	2.01
11-15	2.57	2.62	2.51

The rate of idiopathic NS incidence in males aged under 5 years was thrice greater than in females of the same age and almost the same for males and females aged 11-15 years.

of childhood idiopathic NS in Fukushima ranged from 3.47 to 9.26 cases/100,000 children per year. The trend in the idiopathic NS incidence in Fukushima is shown in Fig. 3. The APC in the figure represents the incidence of idiopathic NS trend assuming a certain change at the same rate as that of the previous year. The incidence of idiopathic NS had a joinpoint with 2011 (APC from 2006 to 2011, 12.95%; 95% confidence interval [CI] 1.8 to 25.4 and APC from 2011 to 2016, −0.84%; 95% CI −0.2 to 12.3). Table 1 shows the cumulative incidence of idiopathic NS in children aged 0-4 years born between 2008 and 2012. Children developing idiopathic NS by the age of four accounted for approximately 50% of all cases. Although the highest incidence was in 2011, the five-year birth cohort showed no differences in idiopathic NS incidence from 2008 to 2012.

In addition, the incidence of idiopathic NS in boys was higher than that in girls. Indeed, the incidence in boys was 6.51 (range, 4.40-11.12) cases/100,000 children, whereas that in girls was 3.55 (range, 1.38-7.63) cases/100,000 children. Table 2 shows the incidence of childhood idiopathic NS by age. The highest incidence was observed in three-year-old boys, and males overall had about three times the incidence of nephrotic syndrome than females at 0-5 years old. However, the incidence was about the same for males and females at 11-15 years old.

Characteristics of 149 cases of childhood idiopathic NS

The details of the demographic, clinical, and therapeutic features of idiopathic NS, as well as the classification of steroid responsiveness, are depicted in Table 3. Screening for idiopathic NS in children is performed at three years of age and in school-aged children in Fukushima. Cases identified as a result of the screening program represented 15% (23/149 children) of the overall cases of childhood idiopathic NS. Immunosuppressants were administered in eight cases of steroid-sensitive NS before satisfying the diagnostic criteria of frequently relapsing NS/steroid-dependent NS, which consists of an immediate single relapse after reducing steroid therapy or several overall relapses. Renal biopsy was performed in 21 children of frequently relapsing NS/steroid-dependent NS. A histological analysis of frequently relapsing NS/steroid-dependent NS showed minimal change NS, focal segmental glomerulosclerosis, and membranoproliferative glomerulonephritis in 81% (17/21), 9.5% (2/21), and 9.5% (2/21) of the cases, respectively. The annual average incidence of steroid-sensitive NS over the 11-year period was approximately six times greater than that of steroid-resistant NS (Table 3). Table 4 shows the relevant characteristics of idiopathic NS, including the initial data of steroid-sensitive NS and steroid-resistant NS. There were no significant differences observed between steroid-sensitive NS and steroid-resistant NS with the initial data.

Relapses

Of the 158 children with idiopathic NS, a total of 507 relapses occurred in the past in 115 patients (Table 5). Common triggers for relapse included steroid discontinuation or reduction (90/507 relapses; 18%) and infection (140/507 relapses; 28%). Influenza was the most obvious pathogen in nine relapse cases, and mycoplasma, respiratory syncytial virus (RSV), and varicella also caused relapse in two, two, and one patients, respectively. There were 10 relapses associated with vaccination, of which nine were due to the influenza vaccine and one to the measles-rubella (MR) vaccine. Fatigue or stress, including psychological stress such as school events, exams, and fatigue, was considered the cause of 17 cases of relapse. Eight relapses had multiple triggers (four related to an upper respiratory tract infection (URTI) and steroid reduction, one to a URTI and immunosuppressant reduction, one to a RSV infection and steroid reduction, one to an insect bite and a school event, and one to a MR vaccine and school event).

Discussion

In this study, we investigated the incidence, characteristics, and features of relapse in childhood idiopathic NS retrospectively in subjects recruited from January 2006 to December 2016 in Fukushima, which has a population of < 2 million. The annual average incidence of idiopathic NS

Table 3. Baseline characteristics of study participants and the annual incidence of idiopathic nephrotic syndrome (NS) as classified by steroid responsiveness.

Characteristics	Total (n = 149)		
	Median/n	IQR/%	Incidence(/100,000/year)
Onset age, years	5.3	3.3-9.3	
Follow-up period, years	4	2.4-6.7	
Sex (male)	98	66	
Diagnosis opportunity			
Edema	125	84	
Screening	23	15	
Digestive symptoms	9	6.0	
Classification of steroid-responsive			
Steroid-sensitive NS	129	87	4.22
Non-relapsers	40	27	1.31
Infrequent-relapsers	27	18	0.90
Frequently relapsing/Steroid-dependent NS	62	42	2.01
Steroid-resistant NS	20	13	0.66
Initial non-responder	18	12	0.59
Late non-responder	2	1.3	0.07
Biopsy	51	34	
Minimal change NS	36	26	
Focal segmental glomerulosclerosis	12	8.1	
Mesangial proliferative glomerulonephritis	2	1.3	
Membranoproliferative glomerulonephritis	2	1.3	
Initial prednisolone treatment (n = 129 excluding steroid-resistant NS)			
Short (≤ 2-3 months)	60	47	
Long (≥ 5-6 month)	69	53	
Immunosuppressants/Biologicals	77	51	
Cyclosporin	62	42	
Mizoribine	48	32	
Tacrolimus	5	3.3	
Rituximab	17	11	

Continuous variables are represented as median and IQR.
Category variables are represented as numbers and percentage.
Initial prednisolone treatment was analyzed except for 20 steroid-resistant NS patients who did not remit within 4 weeks despite steroid treatment.
IQR, interquartile range.

for the 11-year period studied was 5.16 cases/100,000 children in Fukushima, with a total of 507 relapses in the past in 115 children.

The incidence of idiopathic NS in people of Asian ancestry tends to be higher than that in people of European ancestry (Noone et al. 2018). A study including children aged 1-18 years compared the incidence of idiopathic NS based on ethnicity in Toronto and indicated that the incidence in South Asian children (15.83 cases/100,000 children) was higher than that in East/Southeast Asian children (1.81 cases/100,000 children), European children (2.60 cases/100,000 children), or other ethnicities (3.01 cases/100,000 children) (Banh et al. 2016). A subsequent study of an East Asian population in Taiwan from 1996 to 2008 indicated an average idiopathic NS incidence of 5.66 cases/100,000 children per year (Chang et al. 2012). Moreover, a large nationwide survey conducted in Japan estimated the idiopathic NS incidence to be 6.49 cases/100,000 children (Kikunaga et al. 2017). In this previous survey, it was estimated that the incidence of idiopathic NS in Tohoku, where Fukushima is located, was 5.00-5.99 cases/100,000 children. This incidence is almost consistent with our result obtained from more accurate idiopathic NS numbers and demographic changes.

The population of Fukushima Prefecture was < 2 million in 2016, which is approximately 1/60th of the Japanese population. From 2006 to 2016, the pediatric population in Fukushima decreased from approximately 320,000 to 240,000 owing to the declining birthrate in Japan. In the current study, the annual incidence of idiopathic NS in chil-

Table 4. Clinical characteristic as distinguished by steroid responsiveness.

Characteristics	steroid-sensitive NS n = 129	steroid-resistant NS n = 20	p value
	Median/n, IQR/%	Median/n, IQR/%	
Onset age, years	5.3 (3.3-9.3)	5.7 (2.6-8.5)	0.50 [a]
Follow-up period, years	3.8 (2.3-6.5)	5.3 (3.7-7.0)	0.16 [a]
Sex (male)	88 (68)	11 (55)	0.28 [b]
Trigger of diagnosis			
Edema	107 (83)	18 (90)	0.34[b]
Screening	21 (16)	2 (10)	0.37[c]
Digestive symptoms	8 (6.2)	1 (5.0)	0.65[c]
Biopsy	33 (26)	18 (90)	< 0.001[b]
Minimal change NS	26 (20)	10 (50)	0.006[b]
Focal segmental glomerulosclerosis	6 (4.6)	8 (40)	< 0.001[b]
Mesangial proliferative glomerulonephritis	2 (1.6)	0 (0)	0.75[c]
Membranoproliferative glomerulonephritis	2 (1.6)	0 (0)	0.75[c]
Immunosuppressants/Biologicals	57 (44)	19 (95)	< 0.001[b]
Cyclosporin	44 (34)	18 (90)	< 0.001[b]
Mizoribine	38 (30)	10 (50)	0.06[b]
Tacrolimus	3 (2.3)	2 (10)	0.13[c]
Rituximab	9 (7.0)	8 (40)	< 0.001[b]
Laboratory data (initial data)			
WBC (/μL)	9,000 (7,300-12,000)	9,050 (7,400-9,900)	0.74[a]
Hemoglobin (g/dL)	13.8 (13.0-14.6)	13.7 (12.9-15.0)	0.88[a]
Platelet $\times 10^4$ (/μL)	35.5 (28.6-41.7)	34.6 (30.1-37.7)	0.79[a]
Total protein (g/dL)	4.2 (3.8-4.6)	4.0 (3.8-4.3)	0.50[a]
Albumin (g/dL)	1.5 (1.1-1.8)	1.3 (1.0-1.7)	0.46[a]
BUN (mg/dL)	12.0 (9.7-17.4)	13.5 (10.7-13.9)	0.90
Creatinine (mg/dL)	0.33 (0.24-0.49)	0.38 (0.29-0.43)	0.66[a]
Estimated GFR	116 (96-134)	106 (92-119)	0.20[a]
Serum sodium (mmol/L)	138 (136-139)	138 (136-139)	0.69[a]
Serum potassium (mmol/L)	4.3 (4.1-4.6)	4.4 (4.0-4.5)	0.41[a]
Serum chloride (mmol/L)	106 (104-108)	107 (104-108)	0.71[a]
Total cholesterol (mg/dL)	412 (329-468)	363 (269-459)	0.31[a]

Continuous variables are represented as median and IQR.
Category variables are represented as numbers and percentage.
[a]Mann-Whitney *U*-test.
[b]Chi-squared test.
[c]Fisher's exact test.
NS, nephrotic syndrome; IQR, interquartile range syndrome; WBC, white blood cell; BUN, blood urea nitrogen; GFR, glomerular filtration rate.

dren aged 15 years or younger in Fukushima was determined to be between 3.47 and 9.26 cases/100,000 children, and the varying annual incidence was confirmed.

In Canada, previous reports have shown that the annual incidence of idiopathic NS increased from 1.99 cases/100,000 children to 4.71 cases/100,000 children in the Census Metropolitan Area of Toronto over a 10-year period, which was considered to be the result of changes in the ethnic ratios of the population (Banh et al. 2016). Conversely, in Taiwan, the annual idiopathic NS incidence decreased from 9.91 cases/100,000 children to 3.36 cases/100,000 children between 1996 and 2008, which was attributed to overall improvement in socioeconomic status and environmental hygiene in the country (Chang et al. 2012).

This study indicates that the annual incidence of nephrotic syndrome was the highest in 2011, which was the year of the Great East Japan Earthquake, and the resulting Fukushima nuclear power plant accident. Conversely, minor differences in idiopathic NS were observed in the five-year birth cohort in 2011. These data suggest that the increase in incidence is not cohort-specific but time-spe-

Table 5. Relapse triggers for 2006-2016 in 115 patients.

Relapse triggers	Number	%
Unknown	210	41
Infection	140	28
Upper respiratory infection	123	24
Lower respiratory infection	11	2.2
Gastroenteritis	6	1.2
Steroid reduction or discontinuation	90	18
Insect bite	23	4.5
Immunosuppressants reduction or discontinuation	9	1.8
Fatigue or stress	17	3.4
Vaccination	10	2.0
Pollen allergy	6	1.2
Biopsy	3	0.6
Treating cavity	2	0.4
Nonadherence	2	0.4
Headache	2	0.4
Kawasaki disease	1	0.2

Of the 507 relapses in 115 patients, eight relapses had multiple triggers. Four related to Upper respiratory infection (URTI) and steroid reduction, one to URTI and immunosuppressant reduction, one to respiratory syncytial virus infection and steroid reduction, one to an insect bite and school event, and one to measles-rubella vaccine, and school event.

cific, reflecting changes in the background factors around the year 2011. It has been reported that the Great East Japan Earthquake of 2011 changed lifestyles and affected children's mental distress, obesity, and hyperlipidemia in Fukushima (Yabe et al. 2014; Ono et al. 2018; Kawasaki et al. 2020). In particular, Yabe et al. (2014) reported that the mental distress of children in the evacuation area in Fukushima was twice as high compared to the norm. Furthermore, children not only in the evacuation area but also outside the evacuation area in Fukushima might have suffered from psychological and physical effects by the disaster (Ono et al. 2018). Although there are no reports related to psychological stress in the initial onset trigger of idiopathic NS, psychological stress may trigger the relapse and proteinuria in children with NS (Takahashi et al. 2007; Bakkum et al. 2019). This is likely due to a dysregulation of cortisol caused by psychological stress, leading to immune system disorders and subsequent relapse (Segerstrom and Miller 2004; Bakkum et al. 2019). Moreover, insect bites have been reported as triggers for both initial onset and relapse (Cuoghi et al. 1988; Tasic 2000; Zhou et al. 2010), suggesting that the initial onset and relapse of NS may occur via a similar mechanism. Therefore, psychological stress may also contribute to the initial onset trigger of idiopathic NS; however, further investigation in this regard is required. Nonetheless, the varying annual incidence of idiopathic NS might reflect overall social conditions, including changes in environmental sanitation due to factors such as economic growth or calamity.

Relapse in patients with NS can be triggered by infection, stress, allergy (e.g., insect bites) (Cuoghi et al. 1988), vaccinations (Alpay et al. 2002; Abeyagunawardena et al. 2003; Yildiz et al. 2013;), and Kawasaki disease (Krug et al. 2012; Maeda et al. 2018). Infections, particularly URTIs, are the most common cause of relapse, which is consistent with the results of the current study. The role of URTIs in relapse is presumed to occur via T-lymphocyte activation and cytokine release (Uwaezuoke 2015). Previous studies have shown that a short-term daily prednisolone administration during URTI can reduce the incidence of relapse triggered by URTIs (Abeyagunawardena et al. 2017). Vaccinations to prevent infectious diseases, including influenza, for patients with NS are recommended in Japan. Studies have indicated that the number of relapses was not increased in influenza-vaccinated children with NS (Klifa et al. 2019); however, there were nine cases of relapse within 14 days after the administration of the inactivated vaccine of influenza in this study. Furthermore, one case of relapse occurred nine days after the administration of the MR vaccine and after the end of steroid administration. Although the relationship between vaccination and relapse of NS herein remains unclear, physicians should provide sufficient information considering the risks and benefits of vaccination based on the patient's condition.

This survey had several limitations. First, the number of children with idiopathic NS was relatively small. Thus, the incidence of idiopathic NS may change even if a single case is missed; however, our results, which considered a period of over 11 years, are not significantly different from those of reports in East Asia, including Japan. Therefore, we believe that few cases of idiopathic NS were missed, and the average annual incidence was also mostly accurate because of our multiyear investigation. Second, because of

the study's retrospective design, it is probable that some cases of relapse were not described in the medical charts or that sufficient medical interviews were not conducted at the time of relapse. There may also be more complex triggers of relapse than those presented herein. It is difficult to determine all the triggers in cases of relapse; thus, further prospective studies are required to be reviewed.

In conclusion, the average annual incidence of idiopathic NS over the 11-year period was 5.16 cases/100,000 children, which is lower than has been previously reported in Japan. The annual incidence varied over 11 years, showing the highest incidence in 2011 (9.26 cases/100,000 children), when a major earthquake occurred. Conversely, the five-year birth cohort born between 2008 and 2012 did not show a considerable difference. The peak incidence of idiopathic NS was at three years of age, with boys showing a higher incidence than girls. However, the ratio of the number of affected boys to that of girls decreased as the age of onset increased. Between steroid-sensitive and steroid-resistant NS, with data obtained before the treatment, no significant differences were observed. The changes in the annual idiopathic NS incidence may reflect social or environmental factors, such as mental stress associated with changes in lifestyle following the aforementioned disaster.

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Author Contributions

Yohei, K., Yukihiko, K., and K.S. participated in study design. Yohei, K., K.S., and A.G. analyzed and interpreted the data. Yohei, K., Masato, H., Y.T., S.S., M.M., R.N., Y.N., Hiroko, S., M.K., Shinichi, O., H.M., S.K., K.N., N.I., Hoshiro, S., and Shinichiro, O. collected clinical and laboratory data. Yohei, K. drafted the manuscript, and R.M., H.G., A.G., and Mitsuaki, H. critically reviewed the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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