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ORIGINAL ARTICLE

The incidence of the nephrotic syndrome in childhood in Germany

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Abstract
Background The incidence of childhood nephrotic syndrome (NS) in Germany is not well known.
Methods An ESPED-based nationwide collection of epidemiological data of children in 2005 and 2006.
Result The mean age of NS at onset was 5.5 ± 3.7 years. The gender ratio of boys to girls was 1.8:1. The average length of stay was 15.5 ± 11.2 days, with younger children remaining significantly longer in hospital. Steroid-resistance was more common in children ≥8 years ($p = 0.023$). Focal-segmental glomerulosclerosis (FSGS) was more common in children >10 years ($p = 0.029$). The ratio of males to females with FSGS was 1:1.9, thus the FSGS risk for girls at onset was 3.3-times greater. Considering the available data, the incidence of NS in Germany is 1.2/100,000 in the population <18 years, of which 1.0/100,000 are steroid-sensitive.
Conclusion Compared with international data, which primarily focused on regional and small populations, this is the largest study about the incidence of the childhood NS.

Keywords Nephrotic syndrome · Childhood · Epidemiology · Incidence · ESPED

Abbreviations

ALOS	Average length of stay
APN	Arbeitsgemeinschaft für Pädiatrische Nephrologie (Society of Paediatric nephrology)
ARF	Acute renal failure
CNS	Congenital nephrotic syndrome
DGKJ	Deutsche Gesellschaft für Kinder- und Jugendmedizin
DMS	Diffuse mesangial sclerosis
ESPED	Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland
FSGS	Focal-segmental glomerulosclerosis
HIV	Human imunnodeficiency virus
HSP	Henoch-Schönlein purpura
LRTI	Lower respiratory tract infection
MCNS	Minimal-change-glomerulonephritis
MesPGN	Mesangioproliferative glomerulonephritis
MPGN	Membranoproliferative glomerulonephritis
NS	Nephrotic syndrome
PNS	Primary nephrotic syndrome
SNS	Secondary nephrotic syndrome
SRNS	Steroid-resistant nephrotic syndrome
SSNS	Steroid-sensitive nephrotic syndrome

Corinna Elke Llamas Lopez: This present work has already been defended as a doctoral thesis.

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Introduction

Nephrotic syndrome (NS) is one of the most common chronic kidney diseases in children and is characterised by large proteinuria, hypoalbuminemia and oedema [1–3]. The primary, idiopathic form of NS, which accounts for a large portion of NS, often occurs as a result of a banal infection in infancy/early childhood. The current recommended treatment is cortisone therapy over multiple weeks [4]. The incidence of NS varies in different population groups and is currently reported to be 2–7/100,000 children [2]. To date, a precise statement about the frequency of NS in childhood in Germany has not been possible due to the lack of detailed data from a large population.

The aim of this study is to assess the incidence of NS in childhood at onset in 2005 and 2006, with the assistance of a survey unit for rare paediatric diseases in Germany (Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland, ESPED), to serve as a basis for the further planning of therapy and diagnostic studies for NS.

Material and Methods

ESPED

ESPED, a hospital-based German Paediatric Surveillance Unit examines the epidemiological data of rare paediatric diseases of patients who have been hospitalised due to the rare disease. The target group is all children in Germany, who could potentially be hospitalised in a children's hospital [5]. This organisation was built in 1992 as a research centre for paediatric epidemiology of the German Society of Paediatrics (DGKJ) and is located at Heinrich Heine University in Dusseldorf/Germany. ESPED offers research groups the opportunity to answer epidemiologic questions. A research proposal with a survey and an expose are given to a committee of epidemiologists, paediatricians, representatives of public health and lawyers which decide on the acceptance into the research program. In addition, an approval of the ethical committee has to be also obtained.

For this study, each time the ESPED received a notification of a case of NS, the notifying hospital was subsequently sent a questionnaire to complete, regarding patient data, case history, diagnosis and complications. Upon completion, the questionnaire was sent back to the study group containing the anonymised patient data.

The questionnaire was in accordance with Germany's data protection policy in hospitals and was designed in consultation with the members of the Arbeitsgemeinschaft für Pädiarische Nephrology (APN) study meeting and the survey was inaugurated as an APN-supported study. The study was approved by the ethics committee of the Faculty of Medicine, Rheinische Friedrich-Wilhelms-University, Bonn/Germany. The study has been performed in accordance with the ethical standards based on the Declaration of Helsinki in 1964. All subjects gave their informed consent to their inclusion in the study.

In addition, a telephone survey was conducted with all practising paediatricians and nephrologists (both in private practise and in hospitals) in the postcode area of 5, to detect the children with NS who were not treated as in-patients, thus not detected through the ESPED survey [6].

Patients

All in-patient treated children (0–18 years) in Germany with an initial onset of NS (hypolbuminuria <25 g/l, high proteinuria >40 mg/m^2/h, accordingly to 1 g/m^2/day and edema) from 01.01.2005 until 31.12.2006 were registered.

Statistics

Statistics were conducted using IBM SPSS version 18.0 (NY, USA). *t* tests were conducted for two independent samples, and a one-way ANOVA for more than two independent samples, p value was set at <0.05. The department of statistics (Bundesamt; Bevölkerungsstatistik for 2004 and Mikrozensus of 2005) provided the epidemiological data used to calculate the incidence of disease. All data are reported as mean ± standard deviation, unless noted otherwise.

Results

ESPED-based survey

The return rate of the questionnaire was 91%.

Incidence

In total, 444 children with an initial onset of NS in 2005 and 2006 were reported to ESPED. Of these, 347 patients were included in the statistical analysis (Table 1).

In 2004, 14,828,835 people under the age of 18 were living in German [7]. Therefore, it follows that the incidence of NS in children under 18 years was 1.2/100,000 per year in 2005 and 2006.

The telephone survey identified that a maximum of 11 out-patients (3 patients and 8 missing answers) with an initial onset of NS were not included in the ESPED survey. The population in the postcode area beginning with 5 accounts for 11.2% of the total German population, with

Table 1 ESPED received notifications of children with an initial onset of NS in 2005 and 2006, $n = 347$

	2005	2006	$\sum$
Notifications	226	218	444
Missing notifications	27	10	37
Duplicate notifications	13	5	18
Non-returned surveys	15	27	42
Evaluated surveys	171	176	347

9,243,608 inhabitants (Federal Statistics Office, as of 31.12.2006).

This resulted in a maximum of 98 children who were not registered when transferred across the whole of Germany. Based on this, the maximum incidence of NS in children <18 years in Germany is estimated to be 1.65/100,000 ($n = 347 + 27$ out-patients + 71 potential missed cases + 42 none returned questionnaires).

Age and gender

The average age of the 346 patients was 5.5 ± 3.7 years (data missing for 1 patient, $n = 347$). The median was 4.5 years (Fig. 1). Five children were less than 3 months old and had a congenital nephrotic syndrome (CNS). In 2005 104 boys (60.8%) and in 2006 118 boys (67%) developed NS.

Ethnicity

230 patients (66.3%) were of German decent and 113 (32.6%) were of other ethnic origins. The ethnic origins of 4 patients (1.2%) were unknown. With 36 patients (10.5%), children of Turkish origins comprised the largest minority (Fig. 2). The average age of onset in children of German origin was 5.7 and 5.1 years for children of non-German ancestry ($p = 0.146$).

Steroid sensitivity

282 patients (81.3%) had SSNS and 51 (14.7%) SRNS. 12 patients received no steroids (3.5%) and data were missing for 2 patients. In 2005 and 2006 the incidence of SSNS was 1/100,000 and the incidence of SRNS was 0.2/100,000 in children under 18 years in Germany.

The average age of onset for SSNS was 5.5 years (median 4.5 years) and 6.1 years (median 4.4 years) for SRNS (Figs. 3, 4). Steroid-resistance was more common in older children (≥8 years) than younger children (<8 years; $p = 0.023$) (Table 2).

Males accounted for 64.7% of patients with SSNS and 56.9% of patients with SRNS. Patients with German origins accounted for 65% of patients with SSNS in comparison to 72.5% of patients with SRNS.

The average length of stay (ALOS) for patients with SSNS was 13.3 days in comparison to 25.2 days for SRNS patients ($p < 0.001$). Patients who did not receive steroid treatment stayed significantly longer in hospital (25.8 days) than those children with SSNS ($p < 0.001$).

Histology

According to current guidelines, children with SSNS should not be biopsied. A renal biopsy was conducted on 76 patients (21.9%; $n = 347$). Of the biopsied patients, 31 had minimal change glomerulonephritis (MCNS) and 23 had focal segmental glomerulosclerosis (FSGS). Furthermore, 5 patients had diffuse mesangial sclerosis (DMS) and

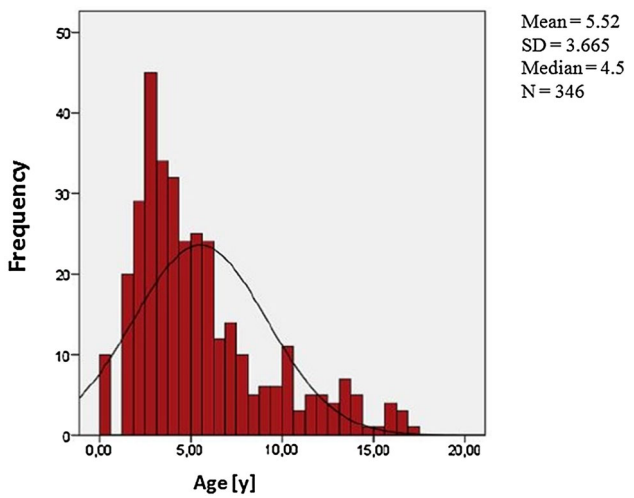

Fig. 1 Age distribution of patients with NS at initial onset in Germany for 2005 and 2006, $n = 346$

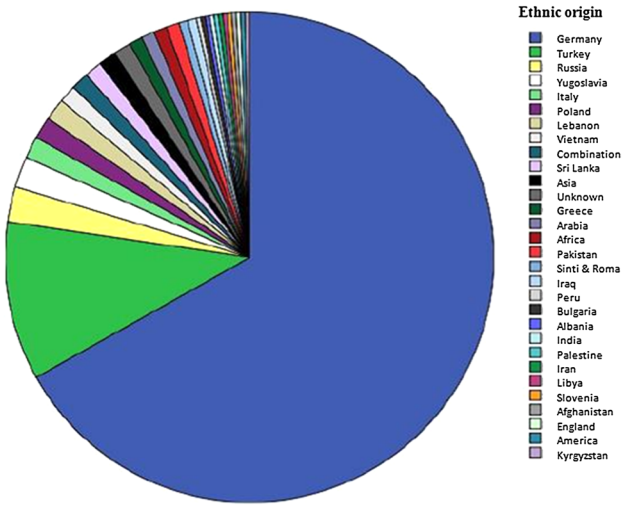

Fig. 2 Ethnic distribution of children with NS at initial onset, $n = 347$

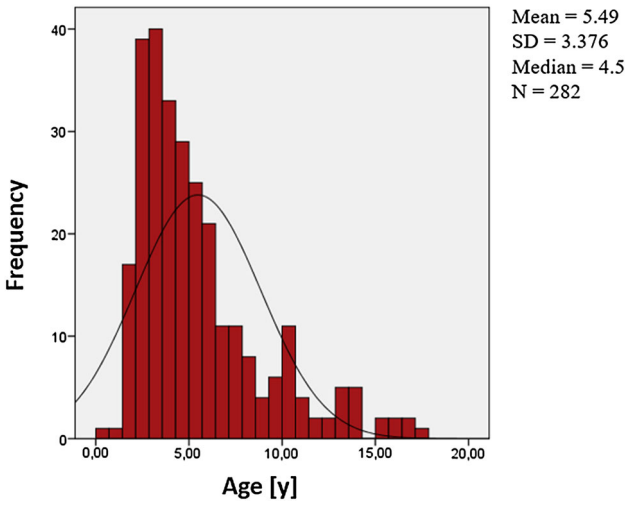

Fig. 3 Age distribution of patients with SSNS at initial onset in Germany for 2005 and 2006, $n = 282$

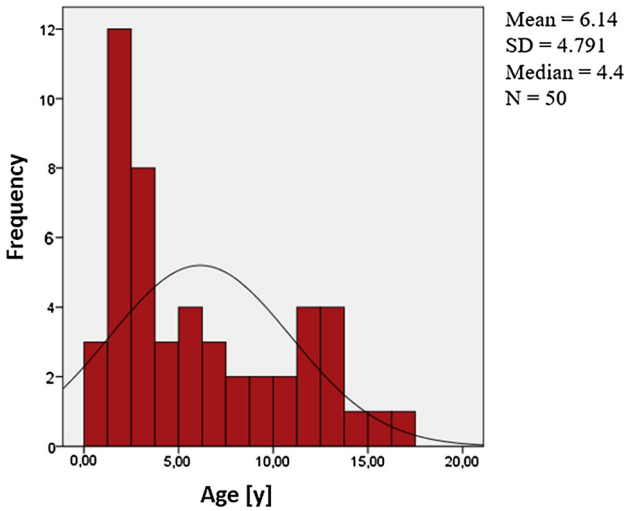

Fig. 4 Age distribution of patients with SRNS at initial onset in Germany for 2005 and 2006, $n = 50$

Table 2 Distribution of SSNS and SRNS in children <8 years and children ≥8 years of age ($p = 0.023$)

	SSNS	SRNS	∑
Children <8 years of age	232 (82.0%)	34 (68.0%)	266 (79.9%)
Children ≥8 years of age	51 (18.0%)	16 (32.0%)	67 (20.1%)

5 had Henoch-Schönlein purpura (HSP). The biopsies also revealed IgA-Nephritis in 3 patients, mesangioproliferative GN in 2 patients, with one patient having immune complex nephritis, membranoproliferative GN, membranous Glomerulonephritis (GN) Type 2 and diffuse proliferative GN. The biopsy results for 3 patients are unknown.

When the patients without biopsies but with SSNS are added, the estimated incidence of MCNS is 85.5%. Patients who underwent the biopsy (6.7 years) were significantly older than patients without the biopsy (5.2 years, $p = 0.011$). Accordingly, the incidence of MCNS is 1/100,000 and 0.1/100,000 for FSGS in children under 18 years of age in Germany.

A comparison of the average age of patients with MCNS, FSGS, diffuse mesangial sclerosis (DMS), Henoch-Schönlein purpura (HSP), and IgA nephropathy showed a significant difference ($p = 0.002$). Children with DMS were on average 1.3 years younger than those with confirmed MCNS ($p = 0.015$), FSGS ($p = 0.029$) and HSP-nephritis ($p = 0.037$). Children ≥10 years of age more commonly had a histological confirmation of FSGS than children <10 years of age ($p = 0.029$).

Of the 76 patients with a histological examination, FSGS was more common in girls ($n = 15$) than boys ($n = 8$; $p = 0.021$). In comparison to all other patients with NS, the ALOS in hospital was significantly longer for patients with FSGS (27.7 days; $p = 0.001$). Of the biopsied patients, 49 (65.3%) were steroid-resistant and 22 were steroid-sensitive (29.3%). Steroids were not administered to 4 (5.3%) patients ($p < 0.001$).

One patient with FSGS (4.3%) initially had SSNS. All other 22 patients with FSGS were steroid-resistant ab initio (95.7%).

Discussion

With an incidence of 1.2–1.65/100 000 in children under 18 years per year, the incidence of NS in Germany is relatively rare by world standards.

The return rate of our questionnaire was very high at 91%. This implies the estimated number of unreported cases of 9% ($n = 42$) registered, but without confirmation of onset. The telephone survey showed a high accuracy of detecting in-patients through the ESPED, with only a small number of missed patients (3 out-patients in postcode area 5 in 2 years).

Previous literature shows that the incidence of NS in children varies and is commonly reported between 2 and 7/100,000 children. The incidence is dependent on the country and ethnic origins of the population [1, 2, 8]. For example, in parts of Nigeria the reported incidence is 0.56/100 000 whereas in Asian children ≤16 years in Birmingham the reported incidence is 16.9/100 000 [9]. However, in comparison to the current study, these examples come from smaller areas as well as areas with relatively small populations. Furthermore, an early study examining the incidence of NS in 1949–1953 in Cleveland and Ohio used a questionnaire taking into account the causes of death to report an incidence of 2.3/100,000 in children ≤9 years in Ohio and 6.9/100,000 in Greater Cleveland/USA [10].

From 2003 to 2006 the Dutch paediatric surveillance unit analysed the incidence of primary NS in children from 0 to 18 years of age and the incidence was calculated as 1.52/100,000 children per year in the Netherlands, which is similar to previously reported incidences found across the world [11]. A similar study conducted over a 3-year time period by the New Zealand Paediatric Surveillance Unit reported an NS incidence of 1.9/100,000 in children <15 years [12]. Furthermore, the Australian paediatric surveillance unit detected an NS incidence of 1.23/100,000 in children <15 years [13]. Therefore, the range of NS incidence in these three studies is between 1.23 and 1.9/100,000 children. Another large nationwide survey in Japan (JP-SHINE study) was performed among Japanese children in the age of 6 months to 15 years with idiopathic nephrotic syndrome in the years of 2010–2012. 2099 children with idiopathic nephrotic syndrome were then followed for 4 years after diagnosis and the incidence was calculated as 6.49/100,000 children p.a. with a 1.9 male:female ratio. 32.7% of these cases were frequent relapsers and developed a steroid-dependent nephrotic syndrome. This study demonstrates a higher prevalence of nephrotic syndrome that is observed in the Japanese population in comparison to Caucasian people [14]. A large Taiwanese study analysed the epidemiology and predictors of the end-stage renal disease with idiopathic nephrotic syndrome over a period of 13 years. Thus, the average incidence was 5.66/100,000 children p.a. with an annual decrease of the incidence during the observation period [15].

This diverse range of international examples demonstrates that NS incidence varies greatly across continents and ethnic groups. Whilst the reason for the difference between different ethnic groups remains unclear, it could be attributed to genetic variations.

In the present cohort, the average age of NS onset occurred at 5.5 years. Similarly, Simpson et al. have reported an average age of onset of 5.4 years in New Zealand [16]. The average age of onset is reported as 4.6–4.9 years in Turkey [17, 18], 4.8 years in Israel [19] and 6.6 years in the USA [20]. However, children with FSGS or SRNS are on average older at onset than those with an uncomplicated SSNS (Fig. 5) [21–23]. In the current study the average age of onset for children in with SRNS was 6.1 and 5.4 years for those with SSNS. Of particular importance is the observation that children ≥8 years are more frequently steroid-resistant than younger children. It has also been reported that FSGS is more common in children ≥6 years [20]. Conversely, in the current study FSGS was more common in children ≥10 years. Furthermore, children with FSGS are on average older than those with MCNS [24–26]. The age difference between the patients with MCNS and FSGS for

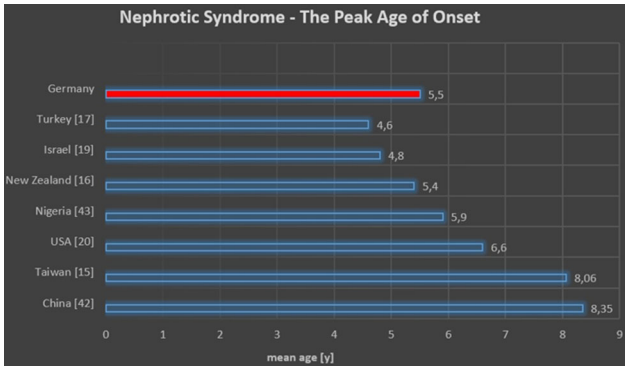

Fig. 5 Comparison of peak ages of nephrotic syndrome nationwide

Caucasians is lower than for African–Americans and children from other ethnicities [20]. Therefore, ethnic differences could also play a role in the relationship between age of onset and histological diagnosis of NS.

Moreover, a comparison of genders revealed that the percentage of girls with SRNS was greater than SSNS. The male to female ratio for patients with SRNS was 1.3:1 and 1.8:1 for SSNS. This finding corresponds with a previous study, which reported the ratio for SRNS as 1.2:1 and 1.7:1 for SSNS, in favour of males [23]. Conversely, an Indian study reported the SRNS ratio to be clearly in favour of girls (1:1.6) [27]. On the other hand, FSGS was more common in girls than in boys in this cohort [$n = 15$ (65.2%) versus $n = 8$ (34.8%)]. Mc Kinney, Nammalwar and Thomson have previously reported a similar female dominated observation for FSGS, however, this is yet to be reported in another country [23, 27, 28].

As mentioned above, ethnic origin plays an important role in the histology of NS. Histological examinations of NS have mostly verified MCNS, with previous studies showing a frequency of 72.7% in Korea [29] and 87% in Trinidad (of which 96% are steroid-sensitive), although the majority of the children in the study were of Asian origin [30]. In contrast, a Turkish based study revealed MesPGN was the most frequent histological observation, followed by MPGN, with FSGS and MCNS both being exceptions [17]. In another study with 954 patients in South Africa, 30.5% of patients had FSGS, 20.7% had MCNS and 20% had a membranous nephropathy as a result of Hepatitis-B; however, the results vary in different regions of Africa [28, 31].

Almost of all the children in our study with steroid-resistance had biopsies, of which 50% of the patients also had FSGS. Previous studies have shown varied results. For example, Fuchshuber and Kim reporting that up to 75% of children with steroid-resistance have FSGS [21, 32] whilst Nammalwar reported that 32.9% of patients with SRNS also had FSGS [33]. Further investigation is needed to determine the relationship between steroid-resistance and

FSGS. Current literature reports the portion of patients with idiopathic NS in Europe and North America to be approximately 90% [34]. Similarly, primary NS (PNS) was frequently observed at initial onset in our study at 93.9% and secondary NS was rare (5.5%). Of these, 8 patients had HSP and 5 cases had a streptococcal infection. The relationship of HSP and SNS has previously been well established [29, 35–38]. Notably, the distribution of PNS and SNS are profoundly different in Africa than in other continents; with various infections (HIV, malaria, hepatitis, tuberculosis, etc.) playing a role in this observation.

Infections and thrombosis account for a significant portion of the complications for NS patients [8]. Before the introduction of antibiotic therapy, these infections were frequently a cause of death [39]. Schwartz et al. reported a mortality rate of up to 23% in children with NS before 1959 [40]. According to the ISKDC study, 2.6% of children died as a result of NS, whereby severe infections are the main cause of death, especially for patients with SRNS [41]. The most frequent infections in this cohort were gastroenteritis (8.1%) and LRTI (6.3%).

In summary, the worldwide incidence of NS is higher than that reported in the current study for Germany. Through the determination of the NS incidence in Germany the reliability and feasibility of therapy and diagnostic studies in children can be improved.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflicts of interest exist.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the Faculty of Medicine, Rheinische Friedrich-Wilhelms-University, Bonn/Germany at which the studies were conducted (IRB Approval Number 081/05) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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