Epidemiology of chronic kidney disease in children in Serbia

Amira Peco-Antič1,2, Radovan Bogdanović1,3, Dušan Paripović2, Aleksandra Paripović3, Nikola Kocev1, Emilija Golubović4,5 and Biljana Milošević6,7; on behalf of the Serbian Pediatric Registry of Chronic Kidney Disease (SPRECKID)

1Faculty of Medicine, University of Belgrade, Belgrade, Serbia, 2Department of Nephrology, University Children’s Hospital, Belgrade, Serbia, 3Department of Nephrology, Institute of Mother and Child Health care, Belgrade, Serbia, 4Faculty of Medicine, University of Nis, Nis, Serbia, 5Department of Nephrology, Clinic of Children’s Internal Disease, Clinical Center of Nis, Nis, Serbia, 6Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia and 7Department of Nephrology, Institute of Children and Youth Health care, Novi Sad, Serbia

Correspondence and offprint requests to: Amira Peco-Antić; E-mail: amira@udk.bg.ac.rs

Abstract

Background. The epidemiological information from well-defined populations regarding childhood chronic kidney disease (CKD), particularly those concerning non-terminal stages, are scanty. The epidemiology of CKD in children is often based on renal replacement therapy (RRT) data, which means that a considerable number of children in earlier stages of CKD are missed as they will reach end-stage renal disease (ESRD) in adulthood. Here, we report the basic epidemiological data on childhood CKD in Serbia, gathered over the 10-year period of activity of the Serbian Pediatric Registry of Chronic Kidney Disease.

Methods. Since 2000–09, data on incidence, prevalence, aetiology, treatment modalities and outcome of children aged 0–18 years, with CKD Stages 2–4 and CKD Stage 5, were collected by reporting index cases from paediatric centres.

Results. Three hundred and thirty-six children were registered (211 boys, 125 girls, male/female ratio 1.7). The median age at registration was 9.0 years [interquartile range (IQR) 3–13]. Median follow-up was 4.0 years (IQR, 1–9). The median glomerular filtration rate (GFR) at the time of the registration was 39.6 mL/min/1.73m² (IQR, 13.8–65.4). Median annual incidence of CKD 2–5 stages was 14.3 per million age-related population (p.m.a.r.p.), while those of CKD 2–4 or CKD 5 were 9.1 and 5.7 p.m.a.r.p., respectively. The median prevalence of CKD 2–5 was 96.1 p.m.a.r.p., 52.8 p.m.a.r.p. in CKD 2–4 and 62.2 p.m.a.r.p. in CKD 5. The main causes of CKD were congenital anomalies of kidney and urinary tract and hereditary nephropathies. Kidney survival was the worst in children with glomerular diseases and in those with advanced CKD. Haemodialysis was the most common first modality of RRT. Mortality rate was 4.5%, mainly due to cardiovascular and infectious complications.

Conclusions. Epidemiology of paediatric CKD in Serbia is similar to that reported from developed European countries. The knowledge of the epidemiology of earlier stages of CKD is essential for both institution of renoprotective therapy and planning of RRT, a fact of paramount importance in countries with limited resources.

Keywords: end-stage renal disease; epidemiology; non-terminal renal failure; renal replacement therapy

Introduction

The epidemiological reports on non-terminal stages of paediatric chronic kidney disease (CKD) from well-defined populations are rare [1–5]. The existing epidemiological data on
CKD in children mainly focus on renal replacement therapy (RRT) [6–11], which represent only part of the population suffering from CKD during childhood, as a considerable number of children with renal impairment will reach end-stage renal disease (ESRD) in adulthood. Knowledge of the epidemiology of earlier stages of CKD is crucial for early detection, primary prevention and for the assessment of the impact of renoprotective therapy. Furthermore, a population-based paediatric CKD registry is necessary for planning of RRT, which is highly dependent upon economy and availability of health care resources. This aspect is very important for developing countries with limited financial capacities, such as Serbia. Therefore, in 2000, the Serbian Pediatric Nephrology Working Group established the Serbian Pediatric Registry of Chronic Kidney Disease (SPRECKID). Here, we report the basic epidemiological data resulting from the first 10 years of SPRECKID activity.

Materials and methods

The index cases were defined using the following criteria: (i) decreased glomerular filtration rate (GFR) for at least 3 months <90 mL/min/1.73m² for children ≥2 years and for younger ones, serum creatinine persistently above mean + 2D [12]; (ii) age <19 years at the time of registration and (iii) written informed consent for data collection, reporting and storage.

All the Serbian centres potentially involved in caring of children and adolescents with CKD were invited to report index cases. The Unit of Pediatric Nephrology of University Children’s Hospital in Belgrade acted as the national coordinating centre that developed the study standards, processed the data and coordinated with regional principal investigators. The data collection was structured into the SPRECKID core data set including date of birth, gender, cause of renal disease, referral region, body height and body weight, serum creatinine, date of RRT initiation, treatment modality, changes of therapy, death and its cause, and transfer of registry.

The children were reported on a prospective basis, but retrospective check-up was also performed. New cases were reported using a standardized registration form containing a predefined list of diagnoses classified into five groups: congenital anomalies of the kidney and urinary tract (C AKUT), hereditary renal disorders, glomerular diseases, miscellaneous causes and CKD of unknown origin. Updating of the data was done every year.

The incidence was calculated as new cases per year, while point prevalence rate included all living patients followed in registry on 31 December of the current year. Both incidence and prevalence were expressed per million age-related populations (p.m.a.r.p.). The estimated number of paediatric population ‘at risk’ (number of children between the age of 0–19 years) for the morbidity analysis was derived from the 2002 state census according to which, total population (not including Kosovo) was 7.498 million, while population <19 years of age was 1.67 million [11].

The staging of CKD registered population was done according to CKD classification described by the Clinical Practice Guidelines of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI guidelines) [13]. Thus, registered population were categorized as those that comprise CKD Stages 2–5; Stages from 2 to 4 were designated as non-terminal chronic renal failure (CRF), while CKD Stage 5 (ESRD) was defined as either GFR <15 mL/min/1.73m² or a need for the initiation of kidney replacement therapy by dialysis or transplantation. For children <2 years of age, the percentage of loss of kidney function in each stage of the KDOQI guidelines was extrapolated taking into account the reference values of GFR in children <2 years [13]. The assessment of GFR was performed according to the Schwartz’s formula [14]. Creatinine was measured by the Jaffe method in all centres.

Descriptive and analytical statistics were done by SPSS 19.0 software. Data were described as frequencies and percentages for categorical variables or as medians and interquartile ranges (IQRs) for continuous variables. The IQR is the difference between the third and first quartiles. Because it uses the middle 50% of the data, the IQR is not affected by extreme values. Comparisons between parametric variables were done by the t-test, while the proportions were compared with χ² test. A P-value <0.05 was considered to be statistically significant. Patients and kidney survival were analysed using Kaplan–Meier life table method. Risk for progression to ESRD was assessed using multiple Cox proportional hazards regression.

Results

From January 2000 to December 2009, 336 children were registered (211 boys, 125 girls, male/female ratio 1.7). The median age at registration was 9.0 years (IQR 3–13). Median age at the time of the diagnosis of CKD was 5.2 years (IQR, 0.9–11), while the age distribution was as follows: <1 year 25.3%, 1–5 years 25.9%, 6–10 years 22.9%, 11–15 years 21.1% and 4.8% were >15 years. Male gender predominated in all categories for all ages. Females were older than males at the time of the diagnosis of CKD (7.1 ± 4.9 versus 5.8 ± 5.5; P < 0.05), while the age difference at the time of registration (8.9 ± 5.0 versus 8.1 ± 5.9) was not statistically significant. Median follow-up of the patients in registry was 4.0 years (IQR, 1–9); 16.5% of the patients were followed in registry for 10 years.

The majority of the patients were from Serbia (90.2%), 4.5% were from Bosnia and Herzegovina, 4.2% were from Montenegro and 1.2% was from Republic of Macedonia.

Renal function and classification of CKD

The median GFR at the time of the registration was 39.6 mL/min/1.73m² (IQR, range 13.8–65.4). At the entry into the study, 104 (31.0%) patients were in CKD Stage 2, 90 (26.8%) in CKD Stage 3, 45 (13.4%) in CKD Stage 4 and 97 (28.9%) were in CKD Stage 5. Thus, overall number of CKD 2–4 patients at registration was 2.4 times those with CKD 5 patients. The distribution of the patients according to CKD stage during the whole study period is presented in Table 1.

Incidence and prevalence

The median annual incidence of CKD Stages 2–5 for the 10-year period was 14.3 p.m.a.r.p. (IQR, 10.9–20.4). It was higher during the second (2005–09) than during the first

<table>
<thead>
<tr>
<th>Table 1. Distribution of the patients’ prevalence according to the CKD stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD stage, number of the patients (%)</td>
</tr>
<tr>
<td>2000</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>CKD 2</td>
</tr>
<tr>
<td>CKD 3</td>
</tr>
<tr>
<td>CKD 4</td>
</tr>
<tr>
<td>CKD 5</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
A critical period of age for rapid progression of CRF was during puberty, leading to almost 75% of the patients to the ESRD at 18 years (Figure 1a). Kidney survival was the worst in children with glomerular diseases and in those with advanced CKD stage (Figure 1b and c). Prognostic value of age at the time of diagnosis of CRF, CKD stage and primary disease in progression to ESRD was found by Cox multiple (Figure 2).

Discussion

CKD is now recognized as a growing health problem due to the rapidly increasing trend of its prevalence [15–20]. There is not enough reliable data on the epidemiology of the earlier stages of CKD. According to the report of the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of adult patients with early stages of CKD (CKD 1–4; 10.8%) is ~50 times greater than the prevalence of the terminal stage (CKD 5; 0.2%) [19]. There is no comparable data for children. Our results showed that prevalence of CKD Stages 2–4 is 2.4 times greater than the prevalence of CKD Stage 5. The actual proportion could be higher than the value we found as CKD is often asymptomatic in its early stages and therefore is under-diagnosed and under-reported. Furthermore, it is certain that our data underestimated the true morbidity from CRF in adolescents, as some of these patients might be cared and followed up by adult nephrologists. On the other hand, the prevalence rate for ESRD patients in this study may be partially overestimated related to the addition of data from patients aged 20–24 years to the prevalent group due to their longer follow-up in paediatric centres and delayed transfer to the adults centres. Turkish and Belgian authors reported even lower CKD 2–4/CKD 5 patients’ ratio (2.06 and 1.71, respectively) [4, 5]. Nevertheless,
the comparison of epidemiology of CRF in children is rather difficult due to the methodological differences in case definitions. With median annual incidence of 14.3 p.m.a.r.p. and point prevalence of 96.1 p.m.a.r.p., our data are comparable to those reported from other European countries, such as France [21], Italy [1], Belgium [5] and Turkey [4] (Table 3).

Unlike CRF (non-terminal CKD), ESRD is better defined and recognized. According to data from the literature, paediatric ESRD constitute only a few per cent of the total ESRD patient population [7, 19, 20]. In Serbia, adjusted incidence and prevalence rates of ESRD in adults in 2008 were 179.9 and 599.06 per million of total population (p.m.t.p.), respectively [23], while in the same period, corresponding numbers for children were 2.03 and 9.7 p.m.t.p., respectively. Thus, paediatric ESRD constituted 1.6% of the total ESRD patients in Serbia. Compared to the data from other paediatric studies [5–11, 22], with ESRD incidence of median 5.7 p.m.a.r.p. (IQR, 4.2–9.4), Serbia belongs to the same category as the Netherlands (5.8 p.m.a.r.p.) [10], Belgium (6.2 p.m.a.r.p.) [5] and France (7.5 p.m.a.r.p.) [22]. The highest incidence rates of ESRD for children were reported from the USA, New Zealand and Austria, at 14.8, 13.6 and 12.4 per million populations, respectively [6], while the lowest (4 p.m.a.r.p.) was found in Japan [11]. Median prevalence of CKD 5 of 62.2

Fig. 1. (a) Estimated kidney survival in patients with CKD by age. (b) Kidney survival according to primary disease. (c) Kidney survival according to CKD stage.
p.m.a.r.p. (IQR, 49.0–71.5) in our study is comparable to data from the majority of European countries as reported by the Annual Data Report from the United States Renal Data System for the 0–19 age group in 2003 [6], but higher than the overall point prevalence (33.6 p.m.a.r.p.) for age groups 0–14 in 2007, as recently reported by the European Registry for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association [7].

The predominance of male patients (m/f = 1.7) in our study is in accordance with data from other paediatric CRF registries worldwide [1–5, 20, 21, 22, 24–28]. This age distribution may be explained by the influence of the main causes of CKD in children, such as CAKUT and hereditary renal disorders, which are more prevalent in boys than in girls (Table 2). These disorders were recognized earlier than glomerular ones whose frequency increased with increasing age and CKD stage, reaching the second rank of ESRD causes (Table 2). Similar findings were also reported by other authors from developed parts of the world [20]. In our study, only 1.8% of the patients’ primary renal disease remained unknown. While paediatric registries have reduced the number of children with ‘no diagnosis’ from 39% in 1976 [29] to fewer than 5% in the recent years [1], the adult registries still report corresponding rates of 20–27% that may be attributed to under-diagnosed CAKUT in adults [30].

RRT for children with ESRD in Serbia has been carried out in one specialized paediatric centre (at University Children’s Hospital in Belgrade) since 1980; RRT consisted of chronic HD in the beginning, but, from 1986, encompassed kidney transplantation and chronic peritoneal dialysis [31]. In general, HD was the first modality of RRT in the majority of patients. Although HD is still the favoured mode of dialysis in incident ESRD patients, transplantation has been the most common form of RRT in prevalent patients since 2005. Cadaveric kidney transplantation in children in Serbia started only in 2004, and the majority of kidney transplantations are still carried out from live related donors. The rate of pre-emptive transplantation has been low (11.7%) but the median waiting time was <2 years (15.1 months).

Like other authors [1], we found that progression of CRF is increased during puberty. It seems dependent on baseline GFR or aetiology as the faster progression was documented in CKD 4 than in CKD 2–3 patients as well as in those with glomerulopathies than in those with CAKUT.

The mortality rate of 4.5% in our patients was similar to that reported by other authors [5]: 26.7% of patients died in pre-terminal renal failure due to primary disease or severe coexisting morbidities, whereas remaining patients died while on HD due to cardiovascular and infectious complications. Data from literature show that cardiovascular and infectious complications are the main cause of increased mortality in ESRD paediatric patients, which is still 30–150 times higher than among children without ESRD [32–34].

Limitations of this study are related to potential under- and incomplete reporting. Registry data was submitted on a voluntary basis so potential for under-reporting exists. Furthermore, information was collected mainly from paediatric centres, and therefore, information on individuals aged

### Table 3. Epidemiology of CRF in Serbia compared with other countries

<table>
<thead>
<tr>
<th>Country (reference)</th>
<th>Period</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Gender M/F</th>
<th>Definition of CRF</th>
<th>Incidence (p.m.a.r.p.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Prevalence (p.m.a.r.p.)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Primary renal disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France [21]</td>
<td>1975–90</td>
<td>127</td>
<td>0–16</td>
<td>1.35</td>
<td>sCr &gt;175 μmol/L</td>
<td>10.5</td>
<td>29.0</td>
<td>53.5</td>
</tr>
<tr>
<td>Sweden [22]</td>
<td>1986–94</td>
<td>118</td>
<td>0.5–16</td>
<td>1.6</td>
<td>CCR &lt;30 mL/min/1.73m²</td>
<td>7.7</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Italy [1]</td>
<td>1990–2000</td>
<td>1197</td>
<td>0–20</td>
<td>2.03</td>
<td>CCR &lt;75 mL/min/1.73m²</td>
<td>12.1</td>
<td>74.7</td>
<td>57.6</td>
</tr>
<tr>
<td>Belgium [5]</td>
<td>2001–05</td>
<td>143</td>
<td>0–20</td>
<td>1.3</td>
<td>CCR &lt;60 mL/min/1.73m²</td>
<td>11.9</td>
<td>59</td>
<td>19</td>
</tr>
<tr>
<td>Turkey [4]</td>
<td>2005</td>
<td>282</td>
<td>0–19</td>
<td>1.3</td>
<td>CCR &lt;75 mL/min/1.73m²</td>
<td>10.9</td>
<td>57.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Spain [5]</td>
<td>2007–08</td>
<td>605</td>
<td>0–18</td>
<td>1.9</td>
<td>CCR &lt;90 mL/min/1.73m²</td>
<td>8.66</td>
<td>71.06</td>
<td>59</td>
</tr>
<tr>
<td>Serbia</td>
<td>2000–09</td>
<td>336</td>
<td>0–19</td>
<td>1.7</td>
<td>CCR &lt;90 mL/min/1.73m²</td>
<td>14.3 (10.9–20.4)</td>
<td>96.1 (77.0–109.9)</td>
<td>58</td>
</tr>
</tbody>
</table>

<sup>a</sup>sCr, serum creatinine; CCR, creatinine clearance; CRF, pre-terminal chronic renal failure; HN, hereditary nephropathy; GN, glomerulopathies.

<sup>b</sup>Mean or median (as reported) cases per million age-related population.

<sup>c</sup>Point prevalence for the end of the investigation.
15–17 years could be incomplete. Despite these limitations, this research database resulted in a rich and useful data source on non-terminal CKD in children in Serbia, which are still lacking.

Conclusion

SPRECKID provided valuable information concerning the epidemiology of mild to severe CKD in children in Serbia during the period 2000–09. Incidence, prevalence and aetiology of paediatric CKD in Serbia are similar to those reported from developed European countries. In contrast to RRT from these countries, HD was a preferred mode of RRT for children in Serbia, while pre-emptive transplantation and chronic peritoneal dialysis are still underused. Mortality rate was in acceptable range (4.5%), mainly due to cardiovascular and infectious complications.

Acknowledgements. The study was supported by the Ministry of Science and Environmental Protection, Government of Serbia, 175079. We thank Jelena Bubalo, Mirjana Kostić, Maja Kovačević, Divna Krušić, Gordana Miloševski-Lomić, Predrag Miljković, Bilsana Multić, Marko Petrović, Jovana Putnik, Snežana Radasavljević, Brankica Spasojević, Nataša Stajić, Vesna Stojanović, Milesa Đapić for their help in making SPRECKID.

A.P.-A. took part in conception, design, analysis and interpretation of data, drafting of the article, provided intellectual content and gave final approval of the enclosed version to be published. R.B. took part in conception, design, analysis and interpretation of data, reviewing of the article, provided intellectual content and gave final approval of the enclosed version to be published. D.P. took part in analysis and interpretation of data, reviewing of the article, provided intellectual content and gave final approval of the enclosed version to be published. A.P. took part in analysis and interpretation of data, reviewing of the article, provided intellectual content and gave final approval of the enclosed version to be published. N.K. took part in analysis and interpretation of data, reviewing of the article, provided intellectual content and gave final approval of the enclosed version to be published. B.M. took part in analysis and interpretation of data, revising of the article, provided intellectual content and gave final approval of the enclosed version to be published.

Conflict of interest statement. None declared.

References


*Received for publication: 19.4.11; Accepted in revised form: 19.8.11*