Etiology and prognosis of chronic kidney disease in children: Roma ethnicity and other risk factors

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Chapter 3

End-stage renal disease in Slovak children: epidemiology from a European perspective

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Abstract

The aim of this study was to examine the occurrence of end-stage renal disease (ESRD) in Slovak children, to compare it with earlier Slovak data and with data from other European countries, and to explore etiology. Over the years 2003-2009, data on the incidence and prevalence of all cases of ESRD in children from all four Slovak tertiary pediatric centers were collected. The data were compared with two earlier Slovak studies and with European data from the European Society of Paediatric Nephrology. The median annual incidence rate of ESRD in Slovak children under 15 years of age was 6.6 per million age-related population (pmarp). The prevalence rate on 31st December 2009 was 24.1 pmarp. Compared with the last study (18.6 pmarp), the differences were not statistically significant. The comparison with neighboring countries and with the European average shows no significant difference in incidence, while prevalence is significantly lower compared to neighboring Austria and some other (mostly western) European countries as well as the European average. In conclusion, during the past decade, the incidence and prevalence rates of ESRD in Slovak children have remained stable. Compared to the European average, the prevalence in Slovak children is significantly lower.

Keywords: end-stage renal disease, incidence, prevalence, etiology, renal replacement therapy

Introduction

The pediatric population suffering from end-stage renal disease (ESRD) in Europe is growing. Children with formerly lethal diseases nowadays survive until adulthood and beyond (Reiss et al. 1996). The reported number of children on renal replacement therapy (RRT) has almost tripled during a relatively short period of 15 years (Mehls et al. 1996, van der Heijden et al. 2004, van Stralen et al. 2010).

Nevertheless, reliable epidemiological information on ESRD and RRT in European children is not easy to obtain. One source of information is the annual reports of the European Renal Association – European Dialysis Transplantation Association (ERA-EDTA), but these reports are somewhat limited since data are often lacking, especially from Central and Eastern European countries. This is probably a consequence of the absence of official national or regional registries in most of these countries, including Slovakia (Warady and Chadha 2007). In 2007, the European Society of Paediatric Nephrology (ESPN) began collecting data on pediatric renal replacement therapy (RRT) patients exclusively on the basis of national or large regional registries in an attempt to solve the problem of insufficient information.

In Slovakia, only two pediatric epidemiologic studies on this topic have been published so far. The first such study was by Zvara et al. in the years 1975-1977 and included children under the age of 15 years with chronic kidney disease (CKD) (Zvara et al. 1978). As a result of unavailability of dialysis and transplantation, the prevalence of RRT at that time was only 1.5 per million age-related population (pmarp) under 15 years of age (0.4 per million total population-pmtp). The next study on Slovak children was done in the year 2002 by Podracka et al., but this study was done on CKD children in a different age category (under 18 years of age) revealing a prevalence rate of 29.3 pmarp for this age group (7.4 children pmtp) (Podracka and Kovacs 2004).

Up to now, a national register with the potential of monitoring health care of pediatric end-stage renal disease patients has not been established in Slovakia. Therefore, the main aims of the present study are:

1. To evaluate the actual incidence and prevalence rates of ESRD and RRT in Slovak children;
2. To compare the results regarding 2003-2009 with those from earlier epidemiological surveys carried out in Slovakia;
3. To compare the incidence and prevalence rates of ESRD and RRT in Slovak children with those of children from other European countries;
4. To compare the etiology, i.e. primary renal diseases and treatment modes, with earlier studies on Slovak children and on children from other European countries.

Materials and methods

Patients

According to a new ERA-EDTA policy, this epidemiologic study evaluated data from all four tertiary centers for pediatric nephrology in Slovakia (Bratislava, Košice, Banská Bystrica and Martin) treating all pediatric RRT patients (Briggs 2000). The total sample consisted of 83 patients below the age of 19 years (32 girls, 51 boys) treated for ESRD in Slovakia in the period 1 January 2003 - 31 December 2009. Population data were obtained from the Statistical Office of the Slovak Republic.

Procedure and measures

Data were collected using questionnaires sent to the heads of all four pediatric dialysis and transplantation centers in Slovakia. For each patient age, gender and clinical variables were retrieved. Clinical variables were derived from the medical files by one of the authors (GK) regarding the primary renal disease, the date and mode of the first RRT (peritoneal dialysis (PD), hemodialysis (HD) or preemptive transplantation), and changes in treatment including date and type of each transplantation (preemptive or non-preemptive, from a living or deceased donor). The primary renal diseases were recorded as diagnosed by all four centers in Slovakia and divided into the categories according to ERA-EDTA (ERA-EDTA Registry 2008).

For comparison of incidence and prevalence rates of RRT with other European countries on the basis of ESPN datasets, the upper age limit was set at 14 years. Patients were divided into 5-year categories (0-4, 5-9, 10-14). For complete analysis of the Slovak situation, we added an extra category of 15-18-year-old children, as these patients are considered pediatric (under 19 years old) in Slovakia and other countries.

Incidence and prevalence rates were calculated as pmarp and pmtp in the different age categories (0-4, 5-9, 10-14, 15-18). Prevalence rates were expressed as the number of ESRD patients alive and on RRT on 31 December of each year. Data on RRT from other European countries were derived from ESPN/ERA-EDTA annual reports (ESPN/ERA-EDTA Registry 2009, ESPN/ERA-EDTA Registry 2010).

Statistical analyses

Descriptive data regarding incidence and prevalence rates of RRT from 2003 to 2009 were presented. Poisson regression was used to find significant differences between the last study from 2002 and actual data from 2009. Differences between Slovakia and neighboring countries were compared over the years 2007-2008 using test of proportions. The differences were considered statistically significant at a p level of 0.05. SAS 9.2 was used for the statistical analyses.

Results

Between 1 January 2003 and 31 December 2009, 52 new patients reached ESRD before the age of 19 and initiated RRT in Slovakia. The median age of the patients at the start of RRT was 12 years, and the range was 0-18 years. The male/female ratio of the patients was 1.58.

Age distribution and incidence and prevalence rates

The largest portion of the patients (n=20) was aged 10 to 14 years when they initiated RRT; 18 patients were 15 to 18 years old; and six were younger than age of 5 years at the time of RRT initiation (Table 3.1). The median annual incidence rate of RRT (during the study period 2003-2009) was 6.6 pmarp under age 15 years (1.5 pmtp). The current prevalence rate of RRT in Slovak children under 15 years old (measured on 31 December 2009) was found to be 24.1 pmarp (3.7 pmtp). Table 3.1 shows the incidence and prevalence rates in detail during the whole study period. The average mortality of patients under the age of 15 years on RRT during the whole period was 1.3%.

Comparison with earlier Slovak epidemiological surveys

In the first Slovak study, done in 1977 by Zvara et al., only the prevalence rate under the age of 15 years was explicitly described (1.5 pmarp, 0.4 pmtp) (Zvara et al. 1978). The study performed in 2002 presented data regarding children under the age of 18 years (Podracka and Kovacs 2004). To allow for a direct comparison, we recalculated the rates for children under the age of 15 years. The incidence rate was then 4.1 pmarp under 15 years (0.7 pmtp), and the prevalence rate 18.6 pmarp under 15 years (3.2 pmtp). A slightly positive trend both for incidence and prevalence is currently present, although the differences between 2002 and 2009 are not statistically significant.

Slovakia compared to other European countries

The comparison of incidence and prevalence of RRT among Slovak children with children from other European countries using data published by ESPN in 2009-2010 for the years 2007-2008 is presented in Table 3.2. The comparison with Slovakia's neighboring countries and with the European average shows no significant difference in incidence. The Slovak prevalence does not differ than that of most of its neighbors, but it is significantly lower compared with neighboring Austria. The same holds true in the comparison of Slovak prevalence with some other (mostly western) European countries as well as the European average.

Table 3.1 Incidence and prevalence rates of RRT in Slovak children according to age and gender over the years 2003-2009

	Total	Gender		Age groups			
	0-18	Girls	Boys	0-4	5-9	10-14	15-18
	n [pmarp]	n [pmarp]	n [pmarp]	n [pmarp]	n [pmarp]	n [pmarp]	n [pmarp]
Incidence							
2002	n.a.	n.a.	n.a.	0 [0.0]	1 [3.2]	3 [7.7]	n.a.
2003	6 [4.6]	2 [3.2]	4 [6.1]	0 [0.0]	1 [3.3]	2 [5.2]	3 [8.9]
2004	9 [7.2]	4 [6.6]	5 [8.2]	2 [7.7]	1 [3.4]	4 [10.9]	2 [6.1]
2005	8 [6.6]	2 [3.7]	6 [9.6]	2 [7.7]	1 [3.5]	5 [14.3]	0 [0.0]
2006	6 [5.1]	5 [9.3]	1 [1.6]	0 [0.0]	2 [7.8]	2 [6.0]	2 [6.3]
2007	9 [8.3]	4 [7.6]	5 [9.0]	1 [3.8]	0 [0.0]	3 [9.5]	5 [16.2]
2008	4 [3.8]	3 [5.8]	1 [1.8]	1 [3.7]	1 [3.8]	1 [3.3]	1 [3.3]
2009	10 [8.9]	1 [1.8]	9 [15.7]	0 [0.0]	2 [7.7]	3 [10.3]	5 [17.3]
Median 2003-2009	8 [6.6]	3 [5.8]	5 [8.2]	1 [3.7]	1 [3.5]	3 [9.5]	2 [6.3]
Prevalence							
2002	n.a.	n.a.	n.a.	1 [3.8]	6 [19.1]	11 [28.4]	n.a.
2003	35 [27.3]	13 [20.7]	22 [35.1]	1 [3.8]	3 [10.0]	9 [23.6]	22 [64.9]
2004	41 [32.8]	14 [23.0]	27 [44.3]	1 [3.9]	6 [20.6]	9 [24.5]	25 [75.9]
2005	43 [35.3]	14 [23.6]	29 [48.8]	2 [7.7]	6 [21.1]	12 [34.3]	23 [71.4]
2006	42 [35.4]	18 [31.1]	24 [41.4]	1 [3.8]	8 [29.1]	14 [42.1]	19 [59.9]
2007	44 [37.9]	18 [31.8]	26 [46.0]	2 [7.5]	6 [22.5]	15 [47.3]	21 [68.0]
2008	39 [34.3]	20 [36.0]	19 [34.2]	3 [11.0]	5 [19.1]	12 [39.8]	19 [62.9]
2009	40 [35.7]	18 [32.9]	22 [40.3]	2 [7.1]	4 [15.4]	14 [48.1]	20 [69.1]
Median 2003-2009	41 [35.3]	18 [31.1]	24 [41.4]	2 [7.1]	6 [20.6]	12 [39.8]	21 [68.0]

n.a. not available

Table 3.2 Incidence and prevalence rates of RRT in European children under 15 years from 2007-2008 with Slovak data derived from Table 3.1

	Incidence rates					Prevalence rates				
	2007	2008	Average (2007-2008)	Contrast vs. Slovakia	Sig.	2007	2008	Average (2007-2008)	Contrast vs. Slovakia	Sig.
Slovakia	4.6 (4.7)	3.6 (3.6)	4.1 (4.2)	1	-	26.7 (27.0)	26.1 (23.9)	26.4 (25.5)	1	-
Neighboring countries										
Austria	7.7	4.4	6.1	1.49	n.s.	40.1	39.5	39.8	1.51	0.02
Czech republic	6.1	3.4	4.8	1.17	n.s.	22.3	21.0	21.7	0.82	n.s.
Hungary	2.3	2.0	2.2	0.54	n.s.	28.3	20.7	24.5	0.93	n.s.
Poland	6.9	6.6	6.8	1.66	n.s.	34.4	34.8	34.6	1.31	n.s.
Slavic countries										
Belarus	n.a.	5.6	n.c.	n.c.	n.c.	n.a.	18.3	n.c.	n.c.	n.c.
Croatia	2.9	8.8	5.9	1.44	n.s.	27.7	29.4	28.6	1.08	n.s.
FYR of Macedonia	7.9	0.0	4.0	0.98	n.s.	18.3	16.0	17.2	0.65	n.s.
Montenegro	0.0	24.5	12.3	3.00	n.s.	8.1	32.7	20.4	0.77	n.s.
Serbia	4.4	11.5	8.0	1.95	n.s.	24.5	33.7	29.1	1.10	n.s.
Russia	7.8	3.4	5.6	1.37	n.s.	16.1	9.8	13.0	0.49	<0.0001
Slovenia	7.1	14.2	10.7	2.61	n.s.	21.3	35.4	28.4	1.08	n.s.
Ukraine	n.a.	1.7	n.c.	n.c.	n.c.	n.a.	2.3	n.c.	n.c.	n.c.
Remaining European countries										

Belgium	n.a.	3.3	n.c.	n.c.	n.c.	n.a.	57.2	n.c.	n.c.	n.c.
Denmark	4.9	6.8	5.9	1.44	n.s.	37.0	40.1	38.6	1.46	0.04
Estonia	0.0	5.0	2.5	0.61	n.s.	10.0	15.0	12.5	0.47	n.s.
Finland	12.3	3.4	7.9	1.93	n.s.	92.4	79.5	86.0	3.26	<0.0001
France	6.5	5.4	6.0	1.46	n.s.	34.2	30.4	32.3	1.22	n.s.
Greece	8.1	7.5	7.8	1.90	n.s.	28.8	30.5	29.7	1.13	n.s.
Iceland	15.2	0.0	7.6	1.85	n.s.	30.5	30.2	30.4	1.15	n.s.
Italy	4.2	4.3	4.3	1.05	n.s.	29.7	31.6	30.7	1.16	n.s.
Latvia	3.2	0.0	1.6	0.39	n.s.	3.2	3.2	3.2	0.12	0.003
Lithuania	5.7	2.0	3.9	0.95	n.s.	32.2	33.3	32.8	1.24	n.s.
Norway	3.3	6.6	5.0	1.22	n.s.	45.2	42.9	44.1	1.67	0.006
Portugal	9.8	8.0	8.9	2.17	n.s.	39.2	42.4	40.8	1.55	0.01
Spain	n.a.	7.4	n.c.	n.c.	n.c.	n.a.	39.5	n.c.	n.c.	n.c.
Sweden	7.1	6.5	6.8	1.66	n.s.	48.5	44.1	46.3	1.75	0.001
Switzerland	n.a.	5.1	n.c.	n.c.	n.c.	n.a.	44.1	n.c.	n.c.	n.c.
The Netherlands	7.5	5.1	6.3	1.54	n.s.	44.4	45.7	45.1	1.71	0.0009
United Kingdom	7.7	7.6	7.7	1.88	n.s.	51.6	51.5	51.6	1.95	<0.0001
Average (ESPN)	6.5	5.2	5.9	1.44	n.s.	33.6	28.6	31.1	1.19	0.01

Source: ESPN and ERA-EDTA datasets 2007, 2008; our recalculations in brackets
n.a. - not available, n.c. - not calculated, Sig. - significance, Slovakia - reference category

Etiology

The distribution of primary diseases leading to ESRD in Slovak children between 1 January 2003 and 31 December 2009 is shown in Table 3.3. Congenital anomalies of the kidneys and urinary tract (CAKUT) with kidney (hypo)dysplasia comprised the major cause. Cystic diseases were the next in importance. The predominance of congenital and hereditary disorders as a leading cause of ESRD compared with acquired nephropathies was evident.

The distribution of primary diseases could not be compared directly with previous studies because the etiology in those studies was only described in regard to all CKD patients but not regarding those in ESRD separately. Regarding all CKD patients, the reported distribution of primary diseases was: CAKUT 52.4%, hereditary disorders 14.3%, glomerular diseases 28.6%, interstitial nephritides 4.8% in 1977; CAKUT 37.5%, hereditary disorders 26.5%, glomerular diseases 11.5%, interstitial nephritides 18.5% in 2002.

Table 3.3 Etiology of ESRD in new patients (cohort 2003-2009)

Etiology	Total	Gender	
	0-18	Girls	Boys
	n (%)	n (%)	n (%)
1. CAKUT	18 (34.6)	5 (23.9)	13 (42.0)
Renal hypo-/dysplasia	8 (15.3)	1 (4.8)	7 (22.7)
Vesico-ureteric reflux	3 (5.8)	2 (9.5)	1 (3.2)
Obstructive uropathy	7 (13.4)	2 (9.5)	5 (16.1)
Urethral valve	0 (0.0)	0 (0.0)	0 (0.0)
Obstruction without valve	6 (11.5)	1 (4.8)	5 (16.1)
Neurogenic bladder	1 (1.9)	1 (4.8)	0 (0.0)
2. Cystic disease	10 (19.2)	3 (14.4)	7 (22.7)
Polycystic kidney disease	4 (7.7)	1 (4.8)	3 (9.7)
Juvenile nephronophtisis	4 (7.7)	2 (9.5)	2 (6.5)
3. Hereditary nephropathy	5 (9.6)	3 (14.4)	2 (6.5)
Alport syndrome	2 (3.8)	2 (9.5)	0 (0.0)
4. Glomerulonephritis	8 (15.4)	5 (23.9)	3 (9.7)
FSGS	5 (9.6)	3 (14.3)	2 (6.5)
5. HUS	1 (1.9)	1 (4.8)	0 (0.0)
6. Vasculitis	2 (3.8)	0 (0.0)	2 (6.4)
7. Miscellaneous	6 (11.5)	3 (14.4)	3 (9.7)
8. Unknown	2 (3.8)	1 (4.8)	1 (3.2)
Total	52 (100.0)	21 (100.0)	31 (100.0)

ESRD: end-stage renal disease, CAKUT: congenital anomalies of kidneys and urinary tract, HUS: hemolytic-uremic syndrome, FSGS: focal segmental glomerulosclerosis

Treatment mode

During the study period, 27 patients (51.9%) (younger than 19 years old) started RRT on PD and 24 patients (46.2%) started their RRT on HD. Only one patient (1.9%) was transplanted preemptively. Out of all the first transplantations 22.0% were from living-related donors. In previous Slovak surveys initial treatment modalities were not described (Zvara et al. 1978, Podracka and Kovacs 2004). Compared to published data on the overall proportion of preemptive transplantations in Europe (15.1%), the proportion of preemptive transplantations in Slovak children is significantly lower. Regarding the prevalent treatment modalities measured on 31 December 2008 the proportion of HD patients (n=8; 20.5%) does not significantly differ from the ERA-EDTA data (n=180; 13.1%), and the proportion of PD patients (n=12; 30.8% vs n=100; 7.3%) is significantly higher and of transplanted patients (n=19; 48.7% vs n=1097; 79.7%) significantly lower compared to the ERA-EDTA 2010 annual report.

Discussion

This study presents an overview of the epidemiology and etiology of ESRD and RRT in Slovak children, focusing on changes observed in the period 2003-2009 compared to historical data and data on the European perspective. The median annual incidence rate of RRT in Slovak children under age 15 years in this period was 6.6 pmarp. These rates were somewhat higher than that in the preceding study on Slovak children in 2002 (Zvara et al. 1978), but without statistical significance. Data on the incidence of RRT regarding the first Slovak study from 1978 are not available, but it seems likely that the number of patients initiating RRT was lower as a consequence of the unavailability of dialysis and transplantation in the past. Compared with neighboring countries and with the European average, no significant differences in incidence rates were found. Explanations for these similarities are the similar demographic structure but also the seemingly comparable availability of dialysis. An increase in the incidence rates of RRT can thus be expected, as the European RRT incidence is currently rising (van der Heijden 2004, Warady and Chadha 2007, ESPN/ERA-EDTA Registry 2010).

On the basis of the available prevalence data (1.5 pmarp in 1977, 18.6 pmarp in 2002, 24.1 pmarp in 2009), it could be assumed that the initially steep rise of RRT prevalence rates stabilized a couple of years after introducing dialysis and transplantation into the treatment regime of Slovak children. Later variations could easily be due to fluctuation by chance (18.6 pmarp in 2002, 27.0 pmarp in 2007, 24.1 pmarp in 2009). Regarding neighboring countries, prevalence rates were significantly higher in the neighboring Austria but not in other neighboring countries. Moreover, the average European prevalence rate was higher. The higher

prevalence in Austria and in some other mostly western European countries may be due to the combination of improved medical care for patients in earlier stages of CKD in combination with earlier treatment of ESRD, especially in younger ages where a low weight can also play a significant role for establishing dialysis (van der Heijden 2004, Warady and Chadha 2007).

The predominance of congenital and hereditary reasons as the main causes of ESRD in children has similarly been found in a study on neighboring Poland (Zurowska et al. 2006) and in many other previous studies on Europe (Ardissino et al. 2003, British Association for Paediatric Nephrology 2005, Lewis et al. 2010) and other parts of the world (U.S.Renal Data System 2005, North American Pediatric Renal Trials and Collaborative Studies 2007). A study of the British Association of Paediatric Nephrology published in December 2009, the most recent European study, reported a higher proportion of CAKUT (50.0%) and congenital nephrosis (9.3%) (Lewis et al. 2005). A Dutch study on the period 1987-2001 reported a relatively very high proportion of urethral valves (14.3%) as the reason for ESRD, which contrasts with the Slovak results, in which there was zero contribution of urethral valves among RRT patients. Environmental, ethnic and other differences might explain the different occurrence of primary renal diseases in Europe compared to our findings (Warady and Chadha 2007).

Strengths and limitations

An important strength of our study is that we obtained data on the entire country using a rigorous data collection. A limitation is the relatively small number of children, which limits the potential for subgroup analyses.

Conclusion

A slightly positive trend both for incidence and prevalence rates of pediatric RRT patients has been present in Slovakia during the past decade, although no significant difference compared to the last study (2002) was found. The comparison with the neighboring countries and with the European average shows no significant differences in incidence. The prevalence does not significantly differ from that of most of its neighbors but is significantly lower compared with neighboring Austria and some other (mostly western) European countries as well as the European average.

A central national registry for children on RRT should be established, not only to facilitate epidemiological analyses and longitudinal studies but also as a first step toward monitoring and improving the quality of health care and quality of life of Slovak children.

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The authors declare that they have no conflict of interest.

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