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

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Chapter 8

Discussion

This study focused on the epidemiology in children with kidney diseases and added to the existing knowledge about its determinants, in particular Roma ethnicity, and its outcomes. Our findings concerned the occurrence of end-stage renal disease (ESRD) in children in Slovakia and added to the understanding of its determinants and outcomes. This chapter summarizes and discusses the main findings of our study, examines its strength and limitations and finally indicates implications for practice as well as possibilities for further research.

8.1 Main findings

Research question 1 (Chapter 3):

What are the actual incidence and prevalence rates of ESRD and renal replacement therapy(RRT) in Slovak children; what are the differences in the results regarding 2003–2009 compared with those from earlier epidemiological surveys carried out in Slovakia; what are the incidence and prevalence rates of ESRD and RRT in Slovak children compared with those of children from other European countries; what is the etiology, i.e., primary renal diseases and treatment modes, compared with earlier studies on Slovak children and with children from other European countries.

We examined the occurrence of ESRD in Slovak children over the years 2003–2009 and compared it with earlier Slovak data and with data from other European countries and explored its etiology. We found 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 31 December 2009 was 24.1 pmarp. The study showed that during the past decade, the incidence and prevalence rates of ESRD in Slovak children remained stable. Compared with the last study on Slovak children (18.6 pmarp), the differences were not statistically significant, but they were significantly higher compared to the first Slovak study published in 1978. The comparison with neighboring countries and with the European average showed no significant difference in incidence, while prevalence was significantly lower compared to neighboring Austria and some other (mostly western) European countries as well as the European average.

Research question 2 (Chapter 4):

What is the difference in occurrence of ESRD between Roma and non-Roma and what is the relative risk (RR) of Roma for ESRD by age groups?

We found that the risk for ESRD is significantly higher for Roma than for non-Roma. The RR of ESRD for Roma was 1.34, compared to the majority population. After age standardization, the RR for Roma was 2.85. A genetic propensity of Roma to renal failure may partially explain the higher risk. Moreover, a poorer control of risk factors for ESRD in Slovak Roma contributes to the increased risk.

Research question 3 (Chapter 5):

What is the share of Roma and non-Roma in a tertiary nephrology clinic for children compared with that in the general population, and secondly what is the share of Roma and non-Roma regarding early signs of primary renal diseases (PRD) and specific PRD?

We found that the share of Roma among patients was small regarding early signs like proteinuria but big regarding PRD with gross clinically apparent symptoms (e.g. Alport syndrome and systemic lupus erythematosus). In other words we found that the overall share of Roma children among patients with kidney problems is lower than their estimated share in the population of the same age, in particular for early signs, but not for major diseases.

Research question 4 (Chapter 6):

What is the occurrence of renal injury as defined by presence of severely increased albuminuria, hypertension and/or decrease of glomerular filtration rate (GFR) <60ml/min/1.73m^2 in solitary functioning kidney (SFK) children?

We found that a substantial proportion of children with SFK develop renal injury during childhood, especially those with CAKUT in the SFK. Therefore, close follow-up of albuminuria, blood pressure and eGFR are warranted to identify chronic kidney disease in its early stages.

Research question 5 (Chapter 7):

What is the prevalence of left ventricular hypertrophy (LVH) in ESRD children before and after transplantation and what clinical variables are associated with its changes?

Our study showed that LVH persists after successful kidney transplantation. However, on the individual level LVH changes considerably after successful transplantation, but this may concern both an improvement and a worsening. An explanation for this individual variability may be that the control of risk factors for LVH after transplantation varies.

8.2 Discussion of the main findings

Epidemiology of CKD/ESRD in children from a European perspective

We found an increase in the prevalence of ESRD in Slovakia during the past decades, whereas regarding the incidence we could not assess a trend because the first study on the epidemiology of CKD in Slovak children only described its prevalence (Zvara et al. 1978). In the years covered by the first study (1975 to 1977) most cases of ESRD died (undiagnosed) and no records are available to compare the incidence with the current one. A real increase of the incidence of the last stage of CKD (i.e. ESRD) may have occurred due to a better survival of earlier stages of CKD in case of formerly lethal diseases e.g. autosomal recessive polycystic kidney disease or congenital nephrotic syndrome. The increase in prevalence is probably partially due to an increase in incidence. However, in addition a better survival is likely to be a major determinant. The increased availability of dialysis and kidney transplantation for children at an increasingly younger age and improved care (e.g. better skilled specialized personal, better equipment and elimination of existing communication barriers) has added to this.

Explanations of the relatively lower prevalence of ESRD compared with that of western countries are probably similar. A lower prevalence may theoretically be due to either relatively few new cases, i.e. a low incidence, or to relatively many cases that die early, i.e. a high lethality. As we found the current incidence to be rather similar to that of neighboring countries, the only remaining explanation for this lower prevalence is a higher lethality of ESRD in patients in Slovakia. Despite the improvement in survival of dialyzed and transplanted children in Slovakia it still seems to be lagging behind the western countries, i.e. those western countries are improving quicker or keep their previous advantage. This may be interpreted as that in Slovakia care for this type of problems still needs investments to improve quality. As such, it may relate to the relatively low share of the gross domestic product (GDP) spent on healthcare. In Slovakia 8.1% of the GDP is spent on healthcare in contrast to an average 9.3% for all OECD countries, and moreover the Slovak GDP per inhabitant is much lower than the OECD mean (Organisation for Economic Co-operation and Developement 2014). In addition, differences in organization of care and training of personal may contribute to these differences.

Findings on CKD and Roma

We found that the proportion of Roma among children with CKD stages 1-4 is lower compared with that of the majority population, which is in sharp contrast with our finding of a very high proportion of Roma among children with ESRD (CKD stage 5) (Kolvek et al. 2012; Kolvek and Podracka 2012). The proportion of Roma was also relatively much larger in case of

some diseases, but this concerned mostly rare diseases. Associated with this, the relative risk (RR) for prevalent ESRD was several times higher for Roma (2.85 after age standardization) and the population's attributable risk for ESRD due to Roma having ESRD was estimated as 37.4 %, i.e. 37.4 % of all cases of ESRD in Slovak children was due to the excess risk in Roma what causes a significant additional burden of disease.

Our findings fit with recent findings showing that relatively deprived ethnic minority groups including Roma have a higher risk for ESRD. In 2014, a study on adult (Slovak) Roma was published which supported our findings of Roma being a risky population for kidney diseases (Rosenberger et al. 2014). Similarly Hungarian authors found that Roma ethnicity is independently associated with an increased mortality risk and worse graft outcome in kidney transplant recipients (Molnar et al. 2012). To the best of our knowledge these studies represent the only evidence published on Roma with kidney problems. However, higher rates of occurrence of CKD/ESRD have been shown in relatively deprived ethnic minorities for many parts of the world. Australian Aborigines and African Americans can serve as good examples (McDonald et al. 2010; U.S. Renal Data System 2009). CKD patients of Afro-American ancestry were shown to show-up late in the course of their CKD (Ifudu et al. 1999). Published evidence also shows that Indo-Asian immigrants in the United Kingdom (UK) have approximately 3–5 times higher incidence rates of ESRD compared to the majority population in the UK (Lightstone 2003). The Roma ethnic group is believed to have come to Europe from the Indian subcontinent (Zeman et al. 2003). This higher risk in native inhabitants of India thus fully fits with our findings.

The increased risk for ESRD in Roma may be due to a number of factors. First, their risk for CKD and ESRD in general seems to be higher due to specific factors, such as socio-economic circumstances, hygiene, health behaviors, and genetic constitution. E.g. a higher occurrence of infections in developing countries was shown to lead to a higher occurrence of glomerulonephritides (Hurtado and Johnson 2005). Regarding health behaviors, e.g. smoking during pregnancy and inappropriate nutrition of pregnant women have been documented to happen relatively more frequently in Roma (Bobak et al. 2005; Rambouskova et al. 2009; Balazs et al. 2013). These have a clear relation to low birth weight infants when compared to the Slovak standards (Rimarova et al. 2004), and consequently the number of nephrons, the building units of the kidney, is lower (Brenner and Chertow 1994). Moreover, a different genetic constitution may explain a part of increased risk for CKD/ESRD in some populations including Roma. This may occur via a higher incidence of specific PRDs, as well as a quicker progression of the disease into ESRD (Patzer and McClellan 2012). This also relates to the increased prevalence of diabetic nephropathy in ESRD Roma as we found in our study on adults. The

differences in genetic constitution might explain the higher incidence of diabetes mellitus in Roma and/or possibly poorer control of the disease leading to more frequent premature organ damage compared to that in the majority population. In case of pediatric patients with ESRD a higher consanguinity in Roma may add too as most of the PRDs in children are congenital or hereditary in nature (often with recessive inheritance) (Thomas et al. 1987; Ferak et al. 1987; Martinez-Frias and Bermejo 1992; Gabrikova et al. 2013).

In addition to that, entry to care seems to be relatively late in the Roma ethnic group. Several studies were published on Roma that showed them to have a lack of means, problems with transportation and to be discriminated (Erasmus MC-University Medical Centre Rotterdam Rotterdam 2007; Kolarcik et al. 2012; Babinska et al. 2013; Jarcuska et al. 2013; Sudzinova et al. 2013). Though none of the studies so far conducted focused on Roma kidney diseases, determinants of poor access to care may be expected to be pretty similar as for other diseases. The same holds for another issue regarding access, i.e. the attitude of Roma towards their own health and the health of their children. Studies comparing Roma with non-Roma have shown that Roma perceive the relationship between lifestyle and health much less as being strictly causal; issues of health and disease are interpreted rather fatalistically (Vivian and Dundes 2004; Petek et al. 2006; Van Cleemput et al. 2007). Evidence on the degree to which this affects the way Roma care for their children is completely lacking. A third and possibly crucial reason why Roma children show up only after obvious clinical symptoms have developed is a poor understanding of the disease by their parents, leading them not to respond to early signs (Koupilova et al. 2001).

One would assume that the Roma-effect would logically lead to a relatively higher occurrence of ESRD in Slovakia overall compared to Western Europe. Surprisingly the opposite is true, at least regarding children in Slovakia for whom we found that the occurrence of ESRD was relatively lower than elsewhere. In the category of 0-14 years olds the standardized RR for ESRD in Roma was found to be 1.82. An explanation for this discrepancy may be that to a certain extent the high occurrence of ESRD in other deprived minorities which are relatively overrepresented in Western Europe may compensate for the high occurrence of ESRD in Slovak Roma. However, data on minority children in these other countries are scarce (Harambat et al. 2012), so this requires further confirmation.

Solitary functioning kidney patients as a potential risk group for CKD/ESRD

We found that a substantial proportion of children with solitary functioning kidney (SFK) developed renal injury during childhood, especially those with structural anomalies in the SFK. Our findings are in line with those of a recent Dutch study on a large sample of children

(Westland et al. 2013), whereas findings of other studies vary from hardly any injury to frequent injury (Robitaille et al. 1985; Argueso et al. 1992a, Argueso et al. 1992b; Seeman et al. 2006; Sanna-Cherchi et al. 2009; Abou Jaoude et al. 2010). It is interesting that adult living-kidney donors who have a SFK are frequently shown to have a stable renal function over more than 25 years after nephrectomy (Hakim et al. 1984; Najarian et al. 1992; Goldfarb et al. 2001), while in children with SFK this is much less clear, with controversies regarding renal function. The selection of apparently healthy adult donors may be the explanation for this phenomenon (Chevalier 2009), while in case of children, variations in the shares of patients with structural anomalies in SFK among studies might explain the heterogenic findings. With this regard longitudinal follow-up studies like the Westland's and ours, which followed albuminuria prospectively, might be able to identify poorly faring children in early stages of disease already. In addition, this heterogeneity could also be due to differences in care, but in case of SFK there is a general lack of treatment options and it is unclear which patients would benefit from potential treatment anyhow.

Cardiovascular outcomes in ESRD children

We found that left ventricular hypertrophy (LVH) persists even after successful kidney transplantation. This may be interpreted as a limited reversibility of LVH. However, at individual level the variability in LVH was rather large, suggesting that modification is feasible but varies per person. The differences might be explained by differences in the control of hypertension, anemia and other risk factors. Previous studies found various predictors of the development of LVH (Johnstone et al. 1996; Matteucci et al. 1999; Mitsnefes et al. 2001; Kitzmueller et al. 2004; Bullington et al. 2006; Becker-Cohen et al. 2008). These factors could then offer an explanation for the variability at the individual level that we found. Rigorous management of post-transplant hypertension and anemia may have positive impact on cardiovascular morbidity and mortality in recipients of KTx in childhood and adolescence.

8.3 Strengths and limitations

A major strength of our study is that we employed several samples that were mostly included in full, i.e. without non-response. Even in case of studies with a limited number of patients, for on SFK and LVH, these covered all children in a full area of eastern Slovakia. The influence of ethnicity on CKD/ESRD was studied in a sample covering several years regarding a country with a large Roma minority which may limit the likelihood of only including specific subsamples of Roma. Although we did not have a full national coverage on ethnicity, we could estimate the share of the population covered by our study very accurately, both

regarding size and age-distribution (Vano 2002; Statistical Office of Slovak Republic 2011).

Data for all our studies were retrieved from medical records, which means that our findings may have been affected by incomplete or incorrect recording. We have no estimate of the degree to which this may have occurred, but in general underregistration seems to be more likely than overregistration, implying some underestimation of prevalences in our study. Regarding the occurrence of ESRD a limitation might be that the number of ESRD patients was assessed based on the number of RRT patients. However, current treatment guidelines and the good availability of treatment facilities make it rather unlikely that this would have led to missing many patients. If so, this will probably most affect the Roma group, implying that the already high rate of ESRD in Roma children is actually even higher. Bias may also have occurred in the study on SFK children. This cohort included relatively many children who were referred because they showed symptoms. Therefore, our findings may overestimate the negative consequences of SFK due to an overrepresentation of poorly faring children.

8.4 Implications for practice and policy, and for research

Our findings have several implications for practice and policy, and for research.

Implications for practice and policy

We found that the prevalence of ESRD was much higher among Roma while Roma were underrepresented in earlier stages of CKD. This suggests that access of Roma to care should be improved. This access may be improved via interventions at both the side of the patients and its setting, and at the side of the professional and the health care system (Belak 2013; Bosakova 2013). Specifically interventions should focus on segregated Roma settlements, as these are the Roma living settings with the poorest living conditions and the poorest educational status of the residents. Regarding the patient, health literacy should be improved, which may improve both adherence to preventive care and to treatment (Sørensen et al. 2012). Professionals should be aware of the unique health beliefs of Roma (Thomas 1985; Sutherland 1986; Roman 2013; Roman 2014). Understanding cultural differences together with decreased communication barriers may lead to an increased faith of Roma into the "Gadje" medical system (Sutherland 2002). Occasionally discrimination towards Roma from the side of professionals may be the cause of problematic access, and specific attention should therefore be paid to this issue in graduate and postgraduate training of the professionals involved in this case.

The other modifiable factors responsible for the higher risk of ESRD in Roma may be poor hygiene and nutrition. Increased hygiene in the settlements might have a significant impact on the overall epidemiology of CKD as the hygiene hypothesis seems to be the culprit behind the decreased occurrence of glomerulonephritides in the western world compared to the developing countries (Hurtado and Johnson 2005). Some ethnic minorities including Roma were shown to have lower birth weights (as a consequence of smoking and inappropriate nutrition during pregnancy) (Rimarova et al. 2004; Bobak et al. 2005; Rambouskova et al. 2009; Balazs et al. 2013) what was shown to have a direct impact on the kidney survival due to less nephrons (Brenner and Chertow 1994). Campaigns against smoking and interventions to improve the socio-economic circumstances of Roma might indirectly lead to heavier infants with lower occurrence of CKD (Belak 2013). Furthermore stimulation of their employment might improve their socio-economic circumstances (Bosakova 2013).

We found that having just one (functioning) kidney (SFK) puts a child at risk for CKD as a substantial proportion of children with SFK developed renal injury during childhood. Clinicians should be aware of the unfavorable prognosis of certain subgroups of individuals having SFK from childhood. All SFK patients should be referred to specialized care for follow-up and potential identification of risks for unfavorable prognosis (e.g. structural anomaly in SFK) in that particular individual. Moreover, the difference with the excellent prognosis of healthy adult kidney donors should be emphasized to professionals, implying that SFK children need much more attention in care. The excellent prognosis of adult donors is probably the result of a positive selection (i.e. individuals with risks are not allowed to become donors as a rationale behind transplantation is to treat a diseased individual and at the same time to avoid as much as possible producing another one at risk for RRT). Regarding children with SFK the prognosis is potentially in particular unfavorable in a subgroup of patients with structural anomalies. However, evidence on this is still scarce, and other factors might have an important role as well. Regular check-ups are warranted monitoring albuminuria, blood pressure and glomerular filtration rate to detect consequences early when well aimed intervention may have some impact on the prognosis.

We found that even with successful transplantation, as a treatment of choice for ESRD, the increased cardiovascular risk persists. LVH, a surrogate marker of cardiovascular risk, was shown to be common even after successful transplantation. This is an important message for clinicians: successful kidney transplantation is not a full solution, at least not in terms of cardiovascular risk even though risks are clearly lower in transplanted individuals (U.S. Renal Data System 2011). The reversibility of already present LVH seems to be rather problematic. An effort should

be put on the meticulous management of hypertension and anemia and other factors like overweight that where clearly shown to have a relation with LVH in adults. The registry of ESRD patients that has been recently established in Slovakia could be a helpful tool for monitoring and consequently improving the quality of health care and quality of life of these children.

Implications for research

Our findings show that further research is needed into the excess risk of Roma for CKD/ESRD in order to target interventions aiming at improvement more accurately. Specifically, studies identifying the pathways leading to the excess risk are needed (Reijneveld 2010). With this regard epidemiological research should cover also earlier stages of CKD. Furthermore, research should focus on the differences between the marginalized Roma populations living in the settlements versus Roma populations that are more integrated into the majority population as significant differences might be expected. How Roma care for their children and how they understand what they are told by clinicians and in preventive message might offer new routes for improvement. Another issue potentially leading to a considerable benefit might be the research of ethnic differences in polymorphisms of the genes which are thought to be associated with the progression of CKD (O'Seaghdha and Fox 2011).

With regard to the patients with SFK the scientific community is in anticipation of the possibility to measure the number of nephrons *in vivo.* This might be promising as low nephron endowment has been shown to put individuals at risk for CKD progression. This phenomenon, however, has not sufficiently been studied in SFK children (Schreuder and Nauta 2007).

Close longitudinal follow-up of cardiovascular system of ESRD patients should continue to better identify the risk factors for the development of LVH to target at. More strict control of these factors might lead to improvement of echocardiographic parameters and potentially decrease the overall mortality. Whether this indeed is the case deserves further study.

8.5 Conclusion

This thesis dealt with epidemiology in children with kidney diseases. We described the occurrence of ESRD in children in Slovakia. Our findings added to the understanding of its determinants and outcomes. We showed that a) during the past decade, the incidence and prevalence rates of ESRD in Slovak children have remained stable and compared to the European average, the prevalence in Slovak children is significantly lower; b) Roma

ethnicity is associated with a significantly higher risk for ESRD; c) the proportion of Roma in a tertiary nephrology clinic for children is overall significantly lower compared to what might be expected based on their proportion in general population; d) a substantial proportion of children with SFK develop renal injury during childhood, especially those with CAKUT in the SFK; and finally that e) the prevalence of LVH, a crucial risk factor for cardiovascular morbidity and mortality in ESRD children persists even after successful transplantation. This thesis shows that substantial health gains can be reached by improved prevention of and care for renal disorders in children.

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Summary

This study focuses on the epidemiology of chronic kidney diseases (CKD) in children and tries to add to the existing knowledge about its determinants, in particular Roma ethnicity, and its prognosis. We studied a) the epidemiology of end-stage renal disease (ESRD) in Slovak children over time and in comparison with European data (Chapters 3); b) the influence of Roma ethnicity on the epidemiology of CKD/ESRD (Chapter 4-5); and c) other potential risk factors for the development of CKD (Chapter 6) and an unfavorable prognosis of CKD (Chapter 7).

Chapter 1 introduced the main topics of the study. Furthermore, the basic model on epidemiology, risk factors and outcomes was desribed and the five research questions were formulated that have been answered in this thesis.

Chapter 2 provided information about the samples, data sources, measures and statistical analyses used in the Chapters 3-7.

Chapter 3 described the trend in occurrence of ESRD over the past decades in Slovakia and put these a European perspective. Findings showed that during the past decade the incidence and prevalence rates of ESRD in Slovak children remained stable. The comparison with neighboring countries and with the European average showed no significant differences in incidence, while the prevalence in Slovakia was significantly lower than the European average.

Chapter 4 explored Roma ethnicity as a risk factor for ESRD. ESRD in children and adults was found to be significantly more prevalent in Roma than in non-Roma in all age groups. The relative risk (RR) for prevalent ESRD for Roma was 1.34 compared to the majority population. After age standardization, the RR for Roma was 2.85. This higher risk may be a consequence of a genetic propensity of Roma to renal failure and of a poorer control of other risk factors for ESRD in (Slovak) Roma, in particular those related to socioeconomic adversity.

Chapter 5 studied ethnic differences in the epidemiology of earlier stages of CKD. Overall, Roma were found to be relatively underrepresented in the earlier stages of CKD as opposed to their overrepresentation among patients with stage 5 CKD (i.e. ESRD). In case of specific relatively rare nephropathies Roma were overrepresented.

Chapter 6 focused on children with a single functioning kidney (SFK) and assessed the occurrence of renal injury in these patients. A substantial proportion of patients with SFK was found to develop renal injury during childhood, especially the patients with a structural anomaly in their SFK.

Chapter 7 explored the epidemiology of cardiovascular consequences of ESRD, particularly left ventricular hypertrophy (LVH), before and after kidney transplantation. It showed that LVH persists even after a successful kidney transplantation, but that significant changes on the individual level occurred. This might be explained by varying control of risk factors, the most significant of which is hypertension.

Chapter 8 summarised the outcomes of the thesis, discussed them, argued their strengths and weaknesses, highlighted their implications for practice, and offered new possibilities for further research. Generally, we found that the occurrence of ESRD in children has not changed significantly over the past decade in Slovakia. Furthermore we found that Roma ethnicity is associated with a poorer development and progression of CKD. Furthermore, a substantial proportion of patients with SFK were found to develop renal injury during childhood. Finally we found that LVH persists even after successful kidney transplantation.

Future research should be focused on the excess risk of Roma for CKD/ESRD, particularly in the marginalized Roma settlements, in order to come to better targeted interventions aiming at improvement. Specifically studies identifying the pathways leading to the excess risk in Roma, to the deterioration of SFK, and to the persistence of LVH after kidney transplantation are needed. This study showed that substantial health gains can be reached by improved prevention of and care for renal disorders in children.

Samenvatting

Deze studie richt zich op de epidemiologie van chronische nierziekten (CKD) bij kinderen en probeert bij te dragen aan de bestaande kennis over de determinanten ervan, in het bijzonder Roma etniciteit, en de prognose van CKD. We bestudeerden a) de epidemiologie van nierziekten in het laatste stadium (end-stage renal disease, ESRD) bij Slowaakse kinderen over de tijd en in vergelijking met de Europese gegevens (hoofdstuk 3); b) de invloed van Roma afkomst op de epidemiologie van CKD/ESRD (hoofdstuk 4-5); en c) andere potentiële risicofactoren voor de ontwikkeling van CKD (hoofdstuk 6) en een ongunstige prognose van CKD (hoofdstuk 7).

In Hoofdstuk 1 worden de belangrijkste onderwerpen van de studie ingeleid. Bovendien wordt een basismodel met betrekking tot epidemiologie, risicofactoren en uitkomsten beschreven en worden de vijf onderzoeksvragen geformuleerd die in dit proefschrift worden beantwoord.

Hoofdstuk 2 geeft informatie over de steekproeven, gegevensbronnen, meetinstrumenten en statistische analyses die worden gebruikt in de hoofdstukken 3-7.

Hoofdstuk 3 beschrijft de trend in het voorkomen van ESRD in de afgelopen decennia in Slowakije en zet deze in een Europees perspectief. Uit onze bevindingen bleek dat in de afgelopen tien jaar de incidentie en prevalentie van ESRD in Slowaakse kinderen stabiel is gebleven. De vergelijking met de buurlanden en met het Europese gemiddelde toonde geen significante verschillen in incidentie aan, terwijl de prevalentie in Slowakije significant lager was dan het Europese gemiddelde.

Hoofdstuk 4 gaat in op de Roma etniciteit als een risicofactor voor ESRD. ESRD bij kinderen en volwassenen bleek in alle leeftijdsgroepen significant vaker voor te komen bij Roma dan bij niet-Roma. Het relatieve risico (RR) voor de prevalente ESRD voor Roma was 1,34 in vergelijking met de meerderheid van de bevolking. Na de standaardisatie voor leeftijd was de RR voor Roma 2,85. Dit verhoogde risico kan een gevolg zijn van een genetische aanleg van Roma tot nierfalen en van een slechtere controle van andere risicofactoren voor ESRD bij (Slowaakse) Roma, in het bijzonder factoren die samenhangen met een lage sociaal-economische status.

In Hoofdstuk 5 werden de etnische verschillen in de epidemiologie van de vroegere stadia van CKD bestudeerd. Roma bleken relatief ondervertegenwoordigd in de vroegere stadia van CKD maar oververtegenwoordigd in de groep patiënten met CKD stadium 5

(ESRD). Wat betreft bepaalde relatief zeldzame nierziekten waren Roma oververtegenwoordigd.

Hoofdstuk 6 richtte zich op kinderen met een enkele functionerende nier (solitary functioning kidney, SFK) en het optreden van nierschade bij deze patiënten. Een aanzienlijk deel van de patiënten met SFK bleek nierschade al tijdens de kindertijd te ontwikkelen, vooral de patiënten met een structurele anomalie in hun SFK.

In Hoofdstuk 7 werd de epidemiologie van cardiovasculaire gevolgen van ESRD onderzocht, vooral linker ventriculaire hypertrofie (LVH), voor en na niertransplantatie. Het bleek dat LVH in het algemeen zelfs na een succesvolle niertransplantatie blijft bestaan, maar dat op individueel niveau de variatie aanzienlijk was. Dit kan verklaard worden door een verschil in controle van risicofactoren, waaronder hypertensie.

In Hoofdstuk 8 worden de resultaten van het proefschrift samengevat, en besproken. Er werd op ingegaan op de sterke en zwakke punten van het onderzoek, en op de implicaties ervan voor de praktijk, alsmede nieuwe mogelijkheden voor verder onderzoek. Over het algemeen vonden we dat het optreden van ESRD bij kinderen niet significant is veranderd in de afgelopen tien jaar in Slowakije. Verder vonden we dat de Roma etniciteit wordt geassocieerd met een slechtere ontwikkeling en progressie van CKD. Bovendien werd een aanzienlijk deel van de patiënten met SFK gevonden dat nierschade ontwikkelt tijdens de kindertijd. Tenslotte vonden we dat LVH blijft bestaan, zelfs na een succesvolle niertransplantatie.

Toekomstig onderzoek moet zich richten op het verhoogde risico van Roma op CKD/ESRD, met name in de gemarginaliseerde Roma-nederzettingen, om te komen tot beter omschreven interventies ter verbetering. In het bijzonder is onderzoek nodig dat zich richt op het identificeren van de paden die leiden naar het verhoogde risico bij Roma, naar de verslechtering van de SFK, en naar het voortbestaan van LVH na een niertransplantatie. Deze studie laat zien dat een aanzienlijke gezondheidswinst kan worden bereikt door een betere preventie van en zorg voor nieraandoeningen bij kinderen.

Zhrnutie

Práca opisuje epidemiológiu chronickej obličkovej choroby (CKD) v detskom veku, prináša nové poznatky o determinantoch ochorenia a zameriava sa na špecifiká CKD v rómskom etniku. Konkrétne sa zameriava a) na epidemiológiu terminálneho štádia chronickej obličkovej choroby (ESRD) slovenských detí a vývoj epidemiologickej situácie na Slovensku v kontexte s okolitými krajinami Európy (kapitola 3); b) na faktor rómskeho etnika vo vzťahu k epidemiológii CKD/ESRD (kapitoly 4-5); a c) na potenciálne riziko rozvoja CKD (kapitola 6) a na analýzu nepriaznivej prognózy CKD (kapitola 7).

Kapitola 1 predstavuje hlavné témy štúdie obsiahnuté v piatich výskumných otázkach a zároveň formuluje základný model vyjadrujúci vzťah epidemiológie, rizikových faktorov a dôsledkov CKD/ESRD.

Kapitola 2 uvádza informácie o klinickom súbore, dátových zdrojoch a štatistických analýzach použitých v kapitolách 3-7.

V kapitole 3 sa opisuje trend výskytu ESRD na Slovensku v uplynulých desaťročiach a hodnotí demografický vývoj aj z európskeho pohľadu. Ukázalo sa, že za posledných desať rokov nedošlo na Slovensku k signifikantným zmenám incidencie a prevalencie ESRD v detskej populácii. V porovnaní so susednými krajinami a s európskym priemerom sme nepreukázali žiadne významné rozdiely v incidencii, zatiaľ čo prevalencia bola na Slovensku výrazne nižšia než európsky priemer.

Kapitola 4 pojednáva o rómskom pôvode ako riziku pre rozvoj ESRD. Výskyt ESRD bol významne častejší v populácii Rómov všetkých vekových skupín vrátane dospelých. Relatívne riziko (RR) výskytu ESRD v populácii Rómov bolo 1,34 (v porovnaní s väčšinovou populáciou). Po vekovej štandardizácii bolo toto RR dokonca 2,85. Zvýšené riziko pre ESRD (slovenských) Rómov môže byť dôsledkom ich genetickej náchylnosti k zlyhaniu obličiek ako aj dôsledkom horšieho manažmentu ďalších rizikových faktorov pre ESRD, najmä v súvislosti so sociálno-ekonomickou situáciou.

Kapitola 5 študovala etnické rozdiely epidemiológie včasnejších štádií CKD (1.-4. štádium). Preukázali sme, že Rómovia sú relatívne málo zastúpení medzi pacientami s CKD 1.-4. štádia, čo je v kontraste s ich nepomerne vysokým zastúpením v skupine detí s terminálnym zlyhaním (CKD 5. štádia t.j. ESRD). V prípade niektorých pomerne vzácnych nefropatií boli Rómovia zastúpení častejšie aj medzi pacientami CKD 1.-4. štádia.

V kapitole 6 sú sumarizované výsledky prospektívneho sledovania detí s jednou funkčnou obličkou (SFK) so zreteľom na riziko renálneho

poškodenia. Zistili sme, že v značnej časti pacientov so SFK sú prítomné známky poškodenia obličiek už v detskom veku, a to najmä u detí s anomáliami štruktúry SFK.

V kapitole 7 sme preskúmali výskyt kardiovaskulárnych dôsledkov CKD/ESRD, najmä prítomnosť hypertrofie ľavej komory (LVH) pred a po transplantácii obličky. Ukázalo sa, že LVH môže pretrvávať aj po úspešnej transplantácii obličky, a že LVH podlieha intraindividuálnym variáciám, čo sa sčasti dá vysvetliť nedostatočnou mierou kontroly rizikových faktorov, predovšetkým hypertenzie.

V kapitole 8 diskutujeme o celkových výsledkoch práce, vyzdvihujeme silné stránky a kriticky analyzujeme stránky slabé, zdôrazňujeme dôsledky pre klinickú prax a ponúkame nové možnosti ďalšieho výskumu. Súhrnne možno konštatovať, že výskyt ESRD u detí sa v priebehu uplynulého desaťročia na Slovensku výrazne nezmenil, pričom rómsky pôvod je spojený s horším vývojom a progresiou CKD. Klinicky dôležitým zistením je výskyt známok incipientného poškodenia obličiek u značnej časti detí so SFK a pretrvávanie LVH aj po úspešnej transplantácii obličky.

Budúci výskum by sa mal zamerať na analýzu príčin zvýšeného rizika CKD/ESRD v populácii Rómov, a to predovšetkým u jedincov z marginalizovaných rómskych osád. Objasnenie mechanizmov potencujúcich riziko rýchlejšej progresie chronických nefropatií u Rómov môže viesť k cielenejším intervenciám. Osobitú pozornosť si zaslúži problematika SFK a pretrvávanie kardiovaskulárneho bremena u detí s transplantovanou obličkou. Táto práca okrem iného dokumentuje, že významný benefit pre zdravie populácie možno dosiahnuť lepšou prevenciou a starostlivosťou o ochorenia obličiek u detí.

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This book is dedicated to Monika

About the author

Gabriel Kolvek was born on the 1 January 1981 in Kosice, Slovakia. He completed his master's degree in general medicine in June 2005 at the Faculty of Medicine of Pavol Jozef Safarik University in Kosice. In 2007 he began specialising in Paediatrics, and in the following year he started his PhD studies at the University of Groningen, the Netherlands. During this time he participated in a research project focusing on chronic diseases, and while taking part in this project he acquired skills in the methodology of data collection, data analysis, data dissemination and publishing. As an assistant professor he was also involved in teaching at the Medical Faculty of Pavol Jozef Safarik University. In 2012 he was awarded a certificate for the best foreign publication in Paediatrics by the Slovak Paediatric Society for the article presented in Chapter 3 of this thesis. The year 2013 was even more successful, as he was awarded a certificate for the best foreign publication in Paediatrics and for the best publication by an author under 35 years of age in Nephrology from the Slovak Society of Nephrology, both for the article herein presented in Chapter 4. His hobbies are skiing and reading, and he is a dedicated fan of the Slovak national ice hockey team.

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