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EDITORIAL COMMENTARY

Outcome of post-infectious renal scarring

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Abstract In this issue of *Pediatric Nephrology*, Gebäck et al. from Gothenburg, Sweden, show that after a mean follow-up after childhood urinary tract infection of 41 years, kidney function decreases from a mean of 93 ml/min/1.73m^2 to 81 ml/min/1.73m^2. This was found in women with severe bilateral renal scarring. They had experienced their UTI during childhood in the 1950s and 1960s and had been drawn from a population-based cohort of more than 1,000 children. A previous paper on this same group of women had shown a higher systolic blood pressure of 3 mmHg during the day and 5 mmHg during the night compared with a control group. This contrasted with a follow-up study published earlier by the same group on two different cohorts in which no impairment of kidney function or increase in hypertension could be found. The present follow-up time was 13 years longer than that of any previous studies. Data on the long-term outcome of children who have had one or several urine infections is very important, as the fear of long-term complications has been driving the extensive investigations to which these children have traditionally been subjected. Further population-based follow-up data can help us to outline modern guidance on imaging after UTI.

Keywords Post-infectious renal scarring · Urinary tract infection · Long-term follow-up · Kidney function · Blood pressure · Pregnancy complications

Gebäck et al. describe in this issue of *Pediatric Nephrology* the long-term follow-up of women who had experienced urinary tract infections (UTIs) as children. With this paper and a recent paper on long-term follow-up of blood pressure [1, 2], the authors extend our knowledge on the long-term effects of renal scarring in a major way. The group in Gothenburg, Sweden, have a long-standing interest in UTI and have published numerous papers on many different aspects of the disease. This started back in the 1960s with the late Professor Jan Winberg, and was later nurtured by Professor Ulf Jodal and during the recent decade by the present group. The importance of the Gothenburg studies is that they provide population-based long-term follow-up.

The 86 women in Gebäck's study were monitored at a mean age of 41 years. They were initially recruited from a study by Martinell et al. on 111 women attending a follow-up clinic for women with previous childhood UTIs [3]. These women were monitored for renal scarring, glomerular filtration rate and blood pressure at a median follow-up of 14.8 (5.9–32.2) years after their first UTI [4]. Gebäck now presents a further 20-year follow-up with a total median follow-up time of 35 years (range 23–50) [1]. This present study was performed between 2001 and 2004 and we can thus hope for further follow-up of these women who were born 50 to 60 years ago.

The Gothenburg group has also published follow-up on another cohort of children who had UTI. Wennerström et al. in 2000 reported on 57 invited subjects. They were studied for renal scarring, renal function and blood pressure with a follow-up time of 16 to 26 years [5, 6]. The strength of that study was that it presented data on nearly all subjects with non-obstructive post-infectious renal scarring from a full 10-year cohort of 1,221 consecutive children with UTI in Gothenburg. The population of Gothenburg is about 500,000 inhabitants.

Importance of the outcome of febrile UTI

Knowledge about the long-term outcome of children who have had a febrile UTI is essential. The fear of severe long-term

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complications has been the main driver for the extensive programs with radiological investigations and long-term follow-up that have been recommended all over the world during the last half-century. Accurate knowledge of what happens to the boys and girls who have experienced one or several episodes of acute pyelonephritis is thus strongly sought after.

Reliable outcome data are, however, very difficult to obtain, as they need two important prerequisites: a population-based group of children and monitoring for a very long time. Many outcome studies are based on groups of children collected in tertiary centres and are thus biased towards more severe cases. The Gothenburg group is among the very few in the world that have been able to provide this, and their data are arguably the most important for future decisions on the management guidelines for children with a UTI.

Renal scars can cause three main complications: long-term impaired kidney function, high blood pressure and complications during pregnancies when the girls grow up and want to become mothers.

The risks of developing these complications have been hotly debated in the medical literature. The different opinions in this field are the major reason why it has been difficult to reach agreements on management protocols for children with UTI. The literature on long-term outcome was recently reviewed effectively by Toffolo and coworkers [7]. I will not repeat their review here, but will quote many of their results.

Kidney function

Outcome data regarding kidney function were in Toffolo's review very variable, with a range of impaired kidney function between 0 % and 56 %, reflecting the great heterogeneity of the studies [7]. The authors found 19 studies on 3,148 children who could be evaluated. Follow-up time varied between 0.5 and 41 years. Eight studies were prospective and only two population-based. Of the 1,029 children in the prospective studies chronic kidney disease (CKD) was present in 55; 43 of those already showed CKD at the start of follow-up. The authors summarise that only 0.4 % of the children with normal glomerular filtration rate (GFR) at onset presented with decreased renal function at follow-up.

The two monitored cohorts from Sweden show the longest published prospective follow-up. In the Martinell cohort, at the first follow-up after median 15 years, the author found a significantly lower GFR (86 ml/min/m^2) in the group of 19 women with severe renal scarring compared with a GFR of 92 ml/min/m^2 in the women without scars. The corresponding serum creatinine values were 92 and 86 μmol/L. No significant difference was found for those with mild or moderate scarring. In this study, scarring was defined by intravenous urography; thus only more pronounced scars were found than with dimercaptosuccinic acid (DMSA) scintigraphy, which is now the most frequently used technique.

In this issue of *Pediatric Nephrology* Gebäck et al., in their prolonged follow-up of this group, find that the kidney function had deteriorated since the previous follow-up [1]. The GFR in women with bilateral renal scarring had gone down from 93 ml/min/m^2 to 81 ml/min/m^2 (P=0.01), while it had remained stable in those without any scars. One woman was in CKD stage 3 and 14 in CKD stage 2. They had unfortunately not been able to record proteinuria.

In the cohort of men and women with a median of 22 years of follow-up reported by Wennerström et al. there were no subjects with a significantly impaired kidney function, not even in the group with bilateral renal scarring [5]. However, this latter small group of subjects, 7 patients drawn from the 1,221 of the original 10-year cohort, did show a non-significant reduction of renal function from a GFR of 94 ml/min/m^2 to GFR 84 ml/min/m^2 (P=0.14) and compared with those with unilateral scarring their kidney function was significantly lower (P=0.007). The median albumin creatinine ratio was 1.6 mg/mmol and 0.6 mg/mmol in the two groups.

Blood pressure

The long-term outcome for blood pressure was also found to be very heterogeneous in the 17 published studies reviewed by Toffolo et al. [7]. The quality of the studies was again very variable, with only five reporting blood pressure at recruitment. At the end of follow-up the prevalence of hypertension varied between 1.2 % and 35 %.

In the Martinell cohort the author found at the first follow-up after a median of 15 years an incidence of hypertension of 5.5 % (3 out of 54 women) [4]. In Gebäck's further follow-up after 35 years an incidence of hypertension of 38 % (22 of 58) was found in the women with scars. The control group without scars showed hypertension in 14 % (4 out of 28) of the women and this was significantly lower compared with the group with kidney scars. Ambulatory blood pressure measurements also showed significantly higher systolic blood pressure in the group with scars. The difference was about 3 mmHg during the day and 5 mm Hg during the night [2]. In contrast, Wennerström, in a cohort followed for 16 to 26 years, found no difference in 24-h blood pressure between the patients with and those without renal scars [5].

Pregnancy outcome

In Toffolo's review the data on pregnancy outcomes were also very divergent [7]. Five series presented data from 282 pregnancies in 159 women. Thirty-five different events, including hypertension, proteinuria and pre-eclampsia, occurred in 12 %

of the pregnancies. Martinell monitored 65 pregnancies in 41 women and did not find any increased risk of serious complications, neither for the mothers nor for the children [3].

Summary

We have learned a lot from the important follow-up studies carried out by the Gothenburg group. They found remarkably few long-term problems related to renal scarring. A follow-up to a median age of 41 years (range 35–51 years) was needed to start to find significant increases in blood pressure and somewhat impaired kidney function in 15 women. These women were drawn from a large population-based cohort of more than 1,000 children with a UTI.

There is a difference between the results from the two different cohorts from Gothenburg. A worse outcome is seen in the Martinell cohort compared with the Wennerström cohort. One difference is that the women in the Martinell studies were born between 1950 and 1968, while the patients in Wennerström's study were diagnosed between 1970 and 1979 [5]. The major interest in UTIs in Gothenburg started during the 1960s and one can assume that the management of these children improved greatly at that time. Another difference between the cohorts is that the Martinell group of children were followed for 13 years longer than the Wennerström cohort. It is, however, very important to remember that these very good long-term results are seen in a country with a strong tradition of early and accurate diagnosis of febrile UTI in children. The situation may be different in other parts of the world and long-term data from other populations are very much needed.

In my opinion, the Gothenburg data support the modern guidelines, which place less emphasis on imaging in children with uncomplicated UTIs and instead focus on the very thorough and effective diagnosis and treatment of acute pyelonephritis during the first years of life. In many countries this is unfortunately still difficult to achieve.

Conflict of interest The author declares no conflict of interest.

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