Review Article

Does Hypertension Develop After Reflux Nephropathy in Childhood? A Critical Review of the Recent English Literature

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Urinary tract infection in children is important, not only because of the acute infectious episode, but also because of underlying urologic abnormalities and consequential renal scarring which, in turn, is believed to cause long-term sequelae such as hypertension, renal insufficiency, and complications in pregnancy. It is reasonable to anticipate the development of hypertension after renal scarring, as the renin-angiotensin-aldosterone system is activated; however, evidence for this widely held concept is scanty. In a survey of the English literature from 1989–2003, nine articles reporting the prevalence of hypertension in reflux nephropathy were identified and are described in this review. From six cohort studies that followed patients for 15–29 years to adulthood, the reported risk of hypertension ranged from 5.6–27.9%; however, only one study reported a significantly greater risk in patients with renal scarring compared to a non-scarred control group. In four other studies that also included non-scarred, comparator groups, the risks were similar in patients and controls. There was a trend towards increasing blood pressure with more severe scarring. The observed variation in results was likely due to different methodologic limitations, such as referral bias, a significant percentage of defaulters, failure to correct for confounding factors, and different methods of measuring blood pressure and defining hypertension. These and related issues are critically reviewed here. [*Hong Kong J Nephrol* 2005;7(1):3–8]

Key words: childhood, hypertension, reflux nephropathy, renal scarring

兒童的泌尿道感染不僅會造成泌尿功能障礙，更可能會導致腎臟的瘢痕化、及可能隨之而起的長期後遺症如高血壓、腎功能障礙、及妊娠併發症。一般認為，基於 renin-angiotensin-aldosterone 系統的活化，高血壓是腎瘢痕化的可能結果之一；然而，至今仍缺乏足夠的數據以證實兩者的關連。在一項 1989–2003 年的英語文獻回顧中，共有九篇報導了逆流性腎病患者的高血壓現象 (詳見本文描述)。從六項為期 15–29 年的隊列研究結果可見，高血壓的風險從 5.6 至 27.9% 不等，然而僅有一項的結果顯示，腎瘢痕化患者的高血壓風險顯著高於非瘢痕化的對照組；其他四項研究則發現瘢痕化組與對照組的風險相似。此外，研究亦發現，瘢痕化愈嚴重，血壓增幅愈趨明顯。各研究的結果互不一致，相信可歸因於研究方法的限制，例如轉診的偏差、違規者的影響、干擾因素的影響、及血壓測量方法與高血壓的定義不一等。本文將對這些及相關的問題作出回顧與探討。

Introduction

Urinary tract infection (UTI) is common in childhood, affecting about 5% of febrile children under 5 years of age [1]. Vesicoureteric reflux (VUR) is frequently associated with febrile UTI and, in previous reports, was present in 12–50% of cases. Renal scarring was a common finding in children with UTI, and its prevalence increased with age, being 10% in preterm infants with VUR, 26% in children up to 8 years old, 47% in children over 8 years old, and 94% in adults [2]. The severity of renal scarring was related to the

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number of pyelonephritic episodes [3], the grades of VUR [4], and the delay in diagnosis and treatment [5,6]. Although it is now recognized that renal parenchymal damage may result from congenital dysplasia or pyelonephritic damage, it is clinically difficult to differentiate between these two causes, and previous studies have included them together. Current dogma is that renal scarring in early life will lead to later complications such as chronic renal insufficiency, hypertension, and complications during pregnancy [1].

It is logical to expect the development of hypertension secondary to reflux nephropathy because patients with such nephropathy are reported to have high plasma renin activity (PRA) [7], which would lead to increased secretion of angiotensin II and aldosterone, with subsequent sodium and fluid retention. There is also increasing evidence of local modulation of the renin-angiotensin-aldosterone system, thus causing intraglomerular hypertension, secondary glomerulosclerosis, and renal insufficiency [2].

However, despite the theoretical plausibility, the reported incidence of hypertension in patients with reflux nephropathy has been variable. A review by the American Academy of Pediatrics in 1999 mentioned that the rate of hypertension in studies of reflux nephropathy varied from 0–50%. The rate is apparently lowest in patients with low-grade VUR and those with the least renal scarring. However, the quality of the studies relating reflux nephropathy to renal failure and hypertension has been poor [1].

Evidence from the Literature

Does reflux nephropathy in children lead to hypertension in later life and, if so, what is the risk? We performed a literature search using the medical subject headings or key words: "urinary tract infection" or "pyelonephritis"; "vesicoureteral reflux" or "renal scarring" or "reflux nephropathy"; and "hypertension" or "blood pressure". The search strategy was applied to MEDLINE and EMBASE from January 1989 to November 2003. The title and abstracts of the 144 articles retrieved were studied, and nine relevant articles were identified. The reference lists from retrieved articles were also reviewed to include any missing references and references in non-indexed journals. For this review, we defined "reflux nephropathy" as renal parenchymal damage associated with primary VUR; hence, we excluded articles reporting cases with known congenital or obstructive renal malformations. The nine articles are briefly described below and are summarized in Table 1.

Jacobson et al from Stockholm, Sweden, identified 53 patients with UTI and renal scarring on intravenous pyelogram (IVP) between 1951 and 1967 [8,9]. However, only 30 patients were evaluable for the study outcome. In this retrospective cohort study, the mean age of patients at diagnosis was 2.8 years (range, 0.7–13 years), and mean age was 33 years (range, 22–41 years) at the time of study. Hence, the follow-up duration was 27 ± 6 years (mean ± standard deviation [SD]). Blood pressure (BP) was measured with mercury sphygmomanometry. Overall, seven patients had hypertension (BP > 140/90 mmHg), including three patients with bilateral scarring and end-stage renal failure, and four with unilateral scars. Diastolic and/or mean BP values for patients were higher than those for controls. However, there was no difference in BP between patients with severe versus mild scarring (Grade A/B vs C/D).

Bailey et al reported outcomes for 31 infants with gross VUR corrected by ureteric-reimplantation surgery from 1952–1970 [10]. Five infants had died before 1 year of age. Four patients were lost to follow-up, and one died as the result of a traffic accident at age 11 years. The remaining 21 patients were assessed in 1990, after a follow-up period of 16–37 years. Four patients had normal kidneys and normal renal function; one of them had hypertension. Seventeen patients had reflux nephropathy detected before the age of 3 years. Among these 17 patients, four had bilateral renal scarring, of which two had chronic renal insufficiency, with hypertension in one. The other 13 patients had unilateral renal scarring, of which one had a single kidney, end-stage renal failure and hypertension, and another two had diastolic hypertension. Thus, the overall incidence of hypertension was 23.8% (5 of 21 patients).

Wolfish et al from Canada reviewed the cases of 146 children with UTI and primary VUR: 128 patients had an IVP result available, and 45 had renal scarring [11]. The mean age at diagnosis was 5 years, and that at the time of study was 14.4 years, thus giving a mean follow-up duration of 9.6 ± 3.2 years. BP was measured by a Dinamap® 8100 device (GE Healthcare, Chalfont St. Giles, UK). The researchers found that no patients had hypertension, although BP percentiles were progressively higher from the non-scarring to the focal-scarring and diffuse-scarring groups.

In 1996, Martinell et al from Sweden reported outcomes for 111 women with recurrent UTI: 54 women had renal scarring and 69 had VUR [12]. The outcomes were compared with data for a control group of 48 patients without UTI. Patients were diagnosed (from 1956 to 1968) at a mean age of 5 years, and were studied at age 15–33 years, thus giving a mean follow-up duration of 14.8 years. Spot BP was measured using a mercury sphygmomanometer. The incidence of hypertension was 5.6% (3/54 patients) in the renal-scarring group, 3.5% (2/57) in the non-scarring group, and 2.1% (1/48) in the control group.

In the same year, Goonasekera et al reported 15-

Table 1. Summary of studies reporting hypertension in patients with reflux nephropathy (in order of duration of follow-up)

Authors (year) [Ref]	Study design	Year UTI detected	Age at follow-up assessment (yr)	Duration of follow-up (yr)	Incidence of hypertension	Remarks
Wolfish et al (1993) [11]	Retrospective cohort; 45 scar +ve, 83 scar –ve patients	1974–1991	14.4	9.6	0%	Trend towards increasing BP from normal to mild scar +ve to severe scar +ve groups
Lama et al (2003) [17]	Retrospective series; 100 scar +ve patients	NR	13.5	9.7	0%	ABPM; selected cases; BP in patients with severe scarring was greater than that in patients with mild scarring
Martinell et al (1996) [12]	Retrospective cohort; 54 scar +ve, 57 scar –ve women	1950–1968	20	14.8	5.6% (3/54 scar +ve group) vs 3.5% (2/57 scar –ve group)	
Goonasekera et al (1996) [7]	Prospective series; 100 patients (scar +ve or –ve)	1960–1978	27	15	18% (18 of 100 in initial cohort)	Excluded known cases of hypertension; five nephrectomy cases; 45 patients lost to follow-up
Wennerstrom et al (2000) [15]	Prospective cohort; 53 scar +ve, 47 scar –ve patients	1970–1979	25	22	9.4% (5/53 scar +ve group) vs 6.4% (3/47 scar –ve group)	ABPM; population-based; patients selected from cohort of 1,221; excluded 21 scar +ve cases
Jacobson et al (1989) [8]	Retrospective cohort; 30 scar +ve patients	1951–1967	33	27	13.2% (7/53)	Excluded 23 patients; hypertension prevalence may therefore have been up to 57% (30/53)
Smellie et al (1998) [13]	Prospective cohort; 85 scar +ve, 141 scar –ve patients	1955–1980	35	28.8	24.7% (21/85 scar +ve group) vs 2.1% (3/141 scar –ve group)	
Bailey et al (1992) [10]	Prospective cohort; 17 scar +ve, 4 scar –ve patients	1952–1970	NR	16–37	23.5% (4/17 scar +ve group) vs 25% (1/4 scar –ve group)	All patients had surgery; 10 died or were lost to follow-up
Patzer et al (2003) [16]	Retrospective series; 61 scar +ve patients	NR	11–12	NR or > 5	27.9% (17/61)	ABPM; excluded patients receiving antihypertensive therapy

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; NR = not reported; UTI = urinary tract infection; +ve = positive; –ve = negative.

year follow-up data for a prospectively studied cohort of 100 children from London, England, who had UTI and VUR [7]. These children were diagnosed between 1960 and 1978 when aged 2–15 years. Their BP (measured by Dinamap® device), PRA and glomerular filtration rates (GFR) were measured every 5 years. Patients with hypertension were excluded from further assessments, as were five patients who had undergone nephrectomy. At the 15-year assessment (follow-up duration, 20–31 years), 55 patients were assessed. Overall, 18 of the 100 patients had hypertension, including one boy who died from hypertensive encephalopathy. Most of the hypertensive patients (83.3%; 15/18) developed the condition at age 15–30 years. PRA increased progressively from baseline to the 10-year assessment, with no further increase at the 15-year assessment. The investigators estimated that the probability of remaining free of hypertension after 5, 10, and 15 years was 95%, 84%, and 79%, respectively.

Smellie et al also prospectively followed 226 children with UTI and VUR managed at a London clinic [13]. The patients were diagnosed between 1955 and 1980. Renal scarring (detected by IVP) was present in 85 patients (38%) and absent in 141 (62%). All patients were assessed in 1988 (after 10–35 years' follow-up) by measuring GFR, and BP using a mercury sphygmomanometer, and by performing ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy. In 1995, a further postal survey was conducted in these patients, and 161 (71%) responded, thus extending the follow-up period to 18–44 years (mean, 28.8 years). Among findings at the last follow-up visit, 21 of 85 patients (24.7%) with renal scarring, and 3 of 141 non-scarred patients (2.1%), had sustained hypertension. Of particular note, one girl with renal scarring died from intracranial bleeding due to malignant hypertension.

Three recent studies used ambulatory BP-monitoring (ABPM) in children with reflux nephropathy. Wennerstrom et al reported a population-based, prospective-cohort study in Sweden [14,15]. They followed 1,221 children with UTI, and studied 53 of 74 patients in this cohort who had renal scarring. From the patients without renal scarring, 47 matched controls were selected. Patient ages at assessment were 16–26 years, giving a median follow-up period of 22 years. BP was measured by ABPM (SpaceLabs 90207; Spacelabs Medical Inc, Issaquah, WA, USA). Patients also had their GFR, PRA, and atrial natriuretic peptide (ANP) level measured. Hypertension, which was defined as mean systolic or diastolic BP above the 95th percentiles for adult norms, was present in 9.4% (5/53) of patients with renal scarring and in 6.4% (3/47) of non-scarred patients. The researchers also found that, while PRA was similar in the two groups, ANP was significantly greater in patients with rather than those without renal scarring. The investigators suggested that ANP may have a protective effect against hypertension in such patients.

The second study using ABPM in patients with reflux nephropathy was reported by Patzer et al from Heidelberg, Germany, in 2003 [16]. Among 84 children with UTI, 61 were available for assessment using ABPM (SpaceLabs 90207) at age 5.9–18 years. All patients were followed up for a minimum of 5 years. Overall, 27.9% (17/61) of patients had hypertension, with mean BP above the 95th percentiles for age and sex. When compared with normal children, the patients had a greater elevation of mean 24-hour systolic and mean BP values, with fewer nocturnal dips than in controls. SD scores for BP correlated positively with the grade of renal scarring found on DMSA scans.

The third ABPM study was conducted by Lama et al in 2003 [17]. The authors described a retrospective case series of 100 children with primary VUR and renal scarring who had been followed up for at least 5 years at a center in Naples, Italy. The mean age at diagnosis was 3.8 years, whereas that at the time of study was 13.5 years. Hypertension was assessed by ABPM using a SpaceLabs 90207 device. No patients had hypertension, as defined by 24-hour mean BP values above the 95th percentiles for age and sex. However, patients with severe rather than mild scarring on DMSA had a significantly lower creatinine clearance, and significantly greater albuminuria, PRA, 24-hour/daytime/night-time systolic BP/diastolic BP/mean BP. The proportion of patients with a BP load of > 30% was 42% (21/50) in patients with severe renal scarring, and 16% (8/50) in those with mild scarring.

Discussion

The designs and main findings of the nine retrieved study articles are summarized in Table 1. The reported prevalence of hypertension in patients with renal scarring ranged from 5.6–27.9%. The data in Table 1 suggest that the prevalence of hypertension increased with the duration of follow-up and patient age at assessment. Of three studies in which patients were aged less than 20 years and had been followed up for less than 10 years, two reported that no patients had hypertension [11,17] and one reported a prevalence of hypertension of 27.9% by ABPM [16]. Of six studies in which patients were over 20 years old and had been followed up for 15–29 years, the reported prevalence of hypertension was 5.6–24.7% [7,8,12,13,15]. Overall, the highest rates of hypertension were noted in the studies by Smellie et al [13] and Bailey et al [10], both of which had long durations of follow-up.

Only five studies included a comparator group of patients without renal scarring [10–13,15]. Although no formal statistical analysis was reported, the risk of

hypertension was greater in scarred than non-scarred patients (24.7% vs 2.1%) in the study by Smellie et al [13], whereas in three other studies, no difference between scarred and non-scarred patients was found [10,12,15]; however, patient numbers were small. In the fifth study, no hypertension was detected in either the patient or control group [11].

It remains controversial as to whether hypertension is worse in patients with severe scarring compared to patients with mild scarring or normal kidneys. Jacobson et al reported no difference in BP between patients with severe versus mild scarring [8]. However, studies reported more recently, and which used ABPM, showed that ambulatory BP parameters were greater in groups with severe rather than mild scarring, although no patients in these studies had hypertension [11,17].

Does currently available evidence support the concept that reflux nephropathy leads to hypertension? For studies to recognize reflux nephropathy as a specific causal factor of hypertension, a genuine association between the two conditions must be demonstrated, as must true causation, as summarized in Table 2 [18]. Clearly, the retrieved studies in this review had several limitations.

Firstly, most were retrospective studies, and only three had prospectively followed cohorts [7,13,15]. Only five studies included a comparator group of patients without renal scarring [10–13,15]. All studies recruited patients in follow-up clinics and were therefore subject to referral bias, except for one population-based study in unselected patients from the general population [15].

Secondly, there was a high dropout rate in some studies. For instance, one trial identified 53 patients but studied only 30 [8]. Seven patients were found to be hypertensive and 23 had dropped out. The prevalence of hypertension could have varied from 13.2% (7/53) to 56.6% ([7+23]/53).

Thirdly, other confounding variables were generally not mentioned in the studies retrieved. Hypertension is a multifactorial condition that may be influenced by gender, body mass index and the presence or absence of a family history of hypertension or diabetes mellitus. Also, reflux nephropathy is believed to be heterogeneous, with congenital scarring (renal dysplasia) and acquired scarring (pyelonephritis) having different causes and outcomes. Such confounding variables were not corrected for in the comparison between patients with and those without scarring, because relevant data were not available in retrospective studies.

Fourthly, the retrieved reports included patients whose initial illnesses were treated at different times (i.e. varying from the 1950s to 1980s); patients studied more recently may have milder illness because of improved detection and management of UTI and VUR. Also, patients were assessed at varying ages (11–35 years) or after different durations of illness (9–29 years). As reported by Goonasekera et al, 15 of 18 hypertensive patients were diagnosed at age 15–30 years [7], thus suggesting that studies in younger patients may not have an adequate duration of follow-up.

Lastly, investigators used different techniques for BP measurement (i.e. spot BP was measured with a mercury sphygmomanometer or Dinamap® device, whereas ambulatory BP was measured with a SpaceLabs 90207 device). The definition of hypertension also showed inter-study variability, from the adult criterion of BP > 140/90 mmHg to criteria based on percentile charts for either spot or ambulatory BP. Thus, to some extent, this explains the different rates of hypertension recorded in the various trials reviewed.

Table 2. Assessing causation [18]

Demonstration of true association
- Appropriate study design with valid comparison groups
- Avoidance of recruitment, measurement, observer, or recall bias
- Exclusion of, or correction for, confounding factors
- Exclusion of chance, or showing statistically significant difference
Demonstration of true causation
- Temporal relationship
- Biologic sense
- Consistency across studies
- Dose-response relationship
- Strength of association
- Cessation effect

Conclusion

Despite the widely held belief that UTI in childhood leads to renal scarring, with subsequent hypertension later in life, there was little direct evidence from the literature supporting this hypothesis. From the few cohort studies that followed patients for an adequate duration to adulthood, the risk of hypertension ranged from 5.6% to 27.9%. There was a trend towards increasing BP with worse scarring. However, only one study reported a significantly greater risk of hypertension in patients with versus those without renal scarring, and four other studies, which also included a control group of patients without renal scarring, reported that scar-positive and scar-negative patients had similar rates of hypertension. Overall, the marked variability in results was probably due to different methodologic weaknesses in the nine studies reviewed.

References

1. Downs SM. American Academy of Pediatrics Technical Report. Urinary tract infections in febrile infants and young children. *Pediatrics* 1999;103:e54.
2. Goonasekera CDA, Dillon MJ. Hypertension in reflux nephropathy. *BJU Int* 1999;83:1–12.
3. Jodal U. The natural history of bacteriuria in childhood. *Infect Dis Clin North Am* 1987;1:713–29.
4. American Academy of Pediatrics Committee on Quality Improvement: Subcommittee on Urinary Tract Infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103:843–52.
5. Smellie JM, Ransley PG, Normand IC, Prescod N, Edwards D. Development of new renal scars: a collaborative study. *Br Med J (Clin Res Ed)* 1985;290:1957–60.
6. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. *BMJ* 1994;308:1193–6.
7. Goonasekera CD, Shah V, Wade AM, Barratt TM, Dillon MJ. 15-year follow-up of renin and blood pressure in reflux nephropathy. *Lancet* 1996;347:640–3.
8. Jacobson SH, Eklof O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow-up. *BMJ* 1989;299:703–6.
9. Jacobson SH, Eklof O, Lins LE, Wikstad I, Winberg J. Long-term prognosis of post-infectious renal scarring in relation to radiological findings in childhood — a 27-year follow-up. *Pediatr Nephrol* 1992;6:19–24.
10. Bailey RR, Lynn KL, Smith AH. Long-term follow-up of infants with gross vesicoureteral reflux. *J Urol* 1992;148:1709–11.
11. Wolfish NM, Delbrouck NF, Shanon A, Matzinger MA, Stenstrom R, McLaine P. Prevalence of hypertension in children with primary vesicoureteral reflux. *J Pediatr* 1993;123:559–63.
12. Martinell J, Lidin-Janson G, Jagenburg R, Sivertsson R, Claesson I, Jodal U. Girls prone to urinary infections followed into adulthood, indices of renal disease. *Pediatr Nephrol* 1996;10:139–42.
13. Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 10-41 years in 226 adults. *Pediatr Nephrol* 1998;12:727–36.
14. Wennerstrom M, Hansson S, Jodal U, Sixt R, Stokland E. Renal function 16 to 26 years after the first urinary tract infection in childhood. *Arch Pediatr Adolesc Med* 2000;154:339–45.
15. Wennerstrom M, Hansson S, Hedner T, Himmelmann A, Jodal U. Ambulatory blood pressure 16-26 years after the first urinary tract infection in childhood. *J Hypertens* 2000;18:485–91.
16. Patzer L, Seeman T, Luck C, Wuhl E, Janda J, Misselwitz J. Day- and night-time blood pressure elevation in children with higher grades of renal scarring. *J Pediatr* 2003;142:117–22.
17. Lama G, Tedesco MA, Graziano L, Calabrese E, Grassia C, Natale F, et al. Reflux nephropathy and hypertension: correlation with the progression of renal damage. *Pediatr Nephrol* 2003;18:241–5.
18. Raina P, Turcotte K. Assessing harm and causation. In: Moyer VA, Elliott EJ, eds. *Evidence Based Pediatrics and Child Health.* London: BMJ Publishing Group, 2000:46–55.