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Editorial comment

Vesico-ureteric reflux: a medical perspective on management

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Primary vesico-ureteric reflux (VUR) is a relatively common abnormality of the urinary tract which is associated with an increased risk of urinary tract infection (UTI) [1] and renal scarring [2]. It is one of the commonest congenital anomalies recognised in humans and is a normal finding in dogs and rabbits. The prevalence in young children has been estimated to be as high as 1%–2% of the population. Evidence that it is not present in the majority of normal people was summarised by Goldraich and Barratt [3]. VUR is a silent condition and does not normally give rise to symptoms directly, so that the true prevalence can only be estimated indirectly from relatively small study populations. The situation is further complicated by the observation that VUR tends to improve or disappear with increasing age in children on long-term low-dose prophylaxis [4] and in girls with untreated asymptomatic bacteriuria [5].

There is no simple non-invasive test for VUR and ethical considerations limit opportunities to evaluate the role of VUR in healthy asymptomatic children. Severe VUR may on occasions give rise to mild or moderate dilatation of the renal pelvis or lower ureter visible on ultrasound, however many cases of severe VUR are not detectable using ultrasound. Reliable detection is only possible with invasive tests such as micturating cystogram using radio-opaque contrast medium or isotopes instilled into the bladder by catheter, or by indirect isotope cystography using 99m technetium diethylene triamine pentaacetic acid or 99m technetium mercapto-acetyl-triglycine, as outlined by Greenfield in his review.

There is a considerable body of evidence linking VUR with both congenital renal anomalies [6] and renal damage following UTI [7]. Renal scarring is thought to be an acquired condition, referred to as reflux nephropathy (RN), and much evidence points to the development of RN following UTI at an early age in children who have VUR [8]. There is also evidence in some studies that older children have more renal damage than younger children and that RN is associated with recurrent infection, more severe grades of VUR and delays in treatment [9, 10]. These observations lead to the conclusion that better management of UTI and VUR in infants and very young children might also reduce or prevent the acquisition of renal scarring. However, a causal relationship has not been proven [11].

Greenfield's comprehensive review of VUR and RN emphasises the difficulties inherent in a programme of long-term prophylactic antibiotic therapy. He refers to the compounding factors produced by differing cultures and healthcare systems. It is interesting to note that non-compliance with medical treatment was independent of many of these factors. The difficulties in medical management must be balanced against the difficulties and complications of surgery. O'Donnell [12] estimated the success rate for reimplantation of the ureter at 90% and 80% for grades IV and V, with obstruction occurring in 5% of cases. Obstruction is almost invariably associated with the development of new scars. Unfortunately the group that might benefit most from surgical correction of VUR are children under 2 years with severe VUR, but this is also the group with the highest failure rate and the greatest risk of complications.

Because of the tendency for VUR to improve with increasing age, it is difficult to establish the efficacy of treatments designed to hasten the resolution of VUR. Surgical correction of VUR is a well-established technique for the elimination of VUR, however as VUR does not usually give rise to any symptoms, success is more appropriately assessed in terms of a reduction of acquired renal damage or prevention of reinfection. These issues were addressed in two important studies, the Birmingham Study and the International Reflux Study. In both these studies children were randomly allocated to medical treatment with long-term low-dose prophylaxis or surgical treatment by reimplantation of the ureter. Neither study showed significant superiority of either form of treatment, either for the rate of reinfection or for the progression of renal damage [13, 14].

Although the association of VUR and RN is well established, there is no clear evidence that surgery to the lower end of the ureter will protect the kidney.

The development of renal scarring and impaired renal function due to RN is insidious and sporadic. Studies such as the International Reflux Study, which showed no significant difference in mean values over a relatively short period of time, may overlook serious deterioration in a minority of cases. In the International Study, although there was no significant difference in outcome between medically and surgically treated patients, there was a subgroup of patients that did slightly better with surgical treatment [14].

Although prophylaxis with long-term low-dose trimethoprim or nitrofurantoin has been shown to reduce the rate of reinfection [15], there is no prospective, controlled study to confirm that this form of treatment is more effective than early detection and treatment of intercurrent infection in preventing the development of RN in children presenting following an infection. Similarly there are no data on the optimum management of children who have VUR detected as a result of genetic advice or antenatal ultrasound screening, who have never been exposed to bacteriuria. There are no data to demonstrate how long therapy should be continued, or whether it is safe to discontinue prophylaxis in children with persisting VUR over a certain age. The presence of VUR in the absence of infection [16] and in the presence of chronic asymptomatic bacteriuria [17] has been shown to be benign when assessed by intravenous urography and glomerular filtration rate [18]. It is possible that prompt diagnosis and treatment of every UTI in infancy and early childhood would be more effective in preventing RN than either prophylaxis or surgery.

In most developed countries enormous efforts are made to ensure that every child is thoroughly investigated for the presence of VUR and RN following the first diagnosed UTI, because of the perceived importance of recognising and treating VUR. However, the causative role of VUR in the pathogenesis of VUR is just one of many host factors predisposing to UTI and scarring [19]. As bacterial virulence factors and other host susceptibility factors undoubtedly play an essential role in determining the predisposition to infection, development of symptoms and the extent of damage, it may be inappropriate to place so much importance on the detection and treatment of a single host factor.

In 1994, a study in Wales showed that many doctors involved in the primary care of sick infants and children were unaware of the symptoms associated with UTI in early childhood. Many were unable to collect urine from these children and urine samples were only collected in the minority of children under 2 years with a fever (Audit of the diagnosis and management of UTI in children under 2 years in Wales, unpublished data). It is likely that similar problems exist elsewhere in the UK and in other countries, particularly where sick children are seen by doctors with little training in paediatrics.

Our understanding of the natural history and management of VUR and RN developed as a result of several long-term follow-up studies starting in the 1950s. Information was derived from intravenous urography and micturating cystography. Prophylactic antibiotics were rarely used to prevent infection following micturating cystography. Studies on renal growth were hampered by a lack of suitable control data, particularly for adolescents, and by acute changes in kidney size resulting from the development and resolution of acute pyelonephritis. Classical renal scars took months or years to develop to a size that could be readily detected at intravenous urography and interpretation of the renal outline on intravenous urography in infants is extremely difficult. In the last decade renal scars have been detected by 99m Tc dimercaptosuccinic acid scanning. It is clear that the lesions detected in this way are not entirely synonymous with the lesions detected by intravenous urography [20]. This observation has resulted in some new theories on the aetiology of RN and has thrown doubt on the essential role of VUR in the generation of renal scarring. It is likely that a variety of combinations of host susceptibility factors and bacterial virulence factors can be responsible for the development of renal scarring, rather than VUR alone [21]. Clearly further studies are needed to resolve these conflicting theories and to throw further light on the aetiology and optimum management of UTI, VUR and RN.

Although UTI and VUR are common conditions, RN is much less common, although potentially more serious. There is no sound evidence that it is necessary or even desirable to subject so many children to intensive radiological investigation. Potential benefits should be carefully balanced against the economic implications and psychological disadvantages of this intensive screening programme. In 1994 Winberg [22] pointed out the failure of both surgery and prophylaxis to achieve the objectives of preventing reinfection and renal damage, and recommended development of specialised teams working within the community and parental education so that each infection could be diagnosed promptly and treated appropriately. If this approach was effective, the need for extensive investigation of every child following a UTI might be reduced without putting children at risk of RN due to delays in treatment [10].

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Literature abstract

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Lupus nephritis in children: a longitudinal study of prognostic factors and therapy

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There are only a few studies in the pediatric literature that have analyzed risk factors for renal failure in childhood lupus nephritis. This study reviewed the outcome of 56 children (4 to 18 yr of age) with lupus nephritis seen at the authors' institution over a 27-yr period (1965 to 1992), in relation to risk factors and therapy. All children underwent percutaneous renal biopsy before the institution of therapy. From 1965 to 1987, treatment for Class III and IV lupus nephritis consisted of high-dose pulse methylprednisolone, 500 mg daily for 10 days, followed by oral prednisone. From 1987 to 1992, IV cyclophosphamide was given monthly for 6 months and then every 3 months for a period of 3 yr for patients with Class III and Class IV disease. Of 56 children, 42% had Class IV and 21% had Class III histology at onset. The mean follow-up period was 4 yr and ranged from 0.5 to 20.3 yr. Life-table analysis showed that the cumulative proportion of patients surviving was 82.8% at 5 yr and 67.7% at 10 yr. Renal survival was 44.4% at 5 yr and 29% at 10 yr, after the initial diagnosis of lupus nephritis was made. Age at diagnosis, race, six, initial serum creatinine level, and the presence of proteinuria, hypertension, and DNA antibody titers were reviewed with respect to disease progression, as was the histological class at diagnosis. The effect of the different therapies was also examined. Univariate analysis revealed a significant association of progression to ESRD with an elevated serum creatinine level ($P = 0.021$), decreased C3 complement ($P = 0.024$), hypertension ($P = 0.053$), and histological classification of Class IV lupus nephritis ($P = 0.031$). Multivariate analysis demonstrated that progression to ESRD was independently associated with an initial Class IV histology (relative risk, 1.78; $P < 0.003$), hypertension at presentation (relative risk, 1.67; $P < 0.003$), and a low C3 complement level in conjunction with a high creatinine level (relative risk, 1.52; $P < 0.028$). Among children with lupus nephritis, those with Class IV disease, hypertension, high creatinine levels, and low C3 complement levels at the time of diagnosis are at increased risk for ESRD. Initial histological classification of lupus nephritis was the most reliable prognostic factor for disease progression. This study was unable to detect a difference in outcome for the two treatment groups.