REVIEW

Vesicoureteric reflux and urinary tract infection in children

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An association between vesicoureteric reflux (VUR) and renal damage was found in 1960. In 1973, the term reflux nephropathy (RN) was first used to describe the renal damage caused by VUR. Follow up studies show that about 10%–20% of children with RN develop hypertension or end stage renal disease. It is now evident that there is a sex difference in the development of RN. In most males with RN, the kidneys are congenitally abnormal. In females it is an acquired condition, the most severe damage being sustained by recurrent urinary tract infections (UTIs). The purpose of current UTI guidelines is to identify VUR or any other abnormality of the urinary tract. Since the advent of routine antenatal ultrasonography, there is no longer a need to identify an abnormality of the urinary tract after the first reported UTI. Routine investigations are not required. Recurrent UTIs and a family history of VUR need further evaluation. There is also an urgent need to establish the long term value of prophylactic antibiotics in children with VUR.

In 1973, Bailey coined the term reflux nephropathy (RN) to describe the coarse renal scarring that results from urinary tract infection (UTI) and vesicoureteric reflux (VUR). It has replaced the previous term of chronic atrophic pyelonephritis.¹ Many children with VUR also have abnormal bowel and bladder function, termed dysfunctional elimination syndromes.^{2–3}

In the wake of subsequent knowledge about the causation of RN, national guidelines for the investigation and treatment of UTIs were devised.^{4–6} Those guidelines were designed to be used in children with fever and other signs of upper tract (pyelonephritic) involvement. Because of the difficulty in characterising the site of infection in an infant (<1 year), the guidelines are also used for any symptomatic infant with a UTI. Protocols differ slightly, however the principle underpinning them is similar. Their aim is twofold; to determine if renal tract anatomy is normal and to establish if VUR is present. The guidelines, which are not evidence based, have large resource implications. Recently, a systematic review concluded that there was no evidence to support the clinical effectiveness of routine investigation in a child with a confirmed UTI.⁷

BACKGROUND

The role of the vesicoureteric valve in the maintenance of unidirectional urine flow dates

back to the time of Galen in the first century AD.⁸ VUR assumed little importance in paediatric urology until 1952, when Hutch described the causal relation between reflux and pyelonephritis in paraplegics.⁹ In 1960, Hodson and Edwards showed renal scarring in patients, some of whom had no previous history of UTI. They attributed the scarring to the direct urodynamic pressure (water hammer) effect of VUR.¹⁰ In subsequent experiments in pigs (similar renal morphology) it was shown that intrarenal reflux occurred in precisely those areas with scarring. Scarring occurred in the absence of infection, but was more rapid when infection was present.¹¹ It is noteworthy that in those experiments a urethral ring was used to create a high pressure system.

In 1978, Ransley and Risdon using a similar model showed that both VUR and infection were essential prerequisites for the development of renal scars in a normal pressure system.¹² They also noted that only when the intravesical pressure was sufficiently high to cause bladder decompensation and upper tract dilatation did VUR with sterile urine cause renal scarring. In the normal pressure system VUR and infection caused scarring in one to two weeks.¹³ When the urethra was obstructed causing a high pressure system, scarring was more rapid and extensive.

Ransley and Risdon showed that the morphology of papillae and the shape of their duct orifices determined susceptibility to intrarenal reflux¹⁴ (see fig 1). The slit-like orifices of non-refluxing (conical) papillae act as valves occluding duct orifices, when renal pelvic pressure increases. Both in the pig and the human refluxing (compound) papillae with open duct orifices are located mainly at the poles.^{14–15} About 30% of humans have only non-refluxing papillae; it has been assumed that VUR would not cause RN in kidneys with non-refluxing papillae.¹⁵ The pioneering work of Ransley and Risdon has dominated thinking about the investigation and treatment of UTIs. It was believed that both VUR and infection were essential prerequisites for the development of RN.

EPIDEMIOLOGY

In the first seven years, 1.7% of boys and 7.8% of girls have a UTI. Most occur in the first year with a male predominance in the first six months.¹⁶ In uncircumcised boys there is a 10-fold increased incidence.¹⁷ VUR is estimated to occur in 1%–2% of children, the incidence being less in black

Abbreviations: AP, anterior posterior; DMSA, ^{99m}Tc-dimercaptosuccinic acid; ESRD, end stage renal disease; MCUG, micturating cystourethrography; RN, reflux nephropathy; UTI, urinary tract infection; VUR, vesicoureteric reflux

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Figure 1 Morphology of renal papillae. Compound papillae are found at the poles. Open ducts on the concave surface facilitate intrarenal reflux when the pressure wave of reflux reaches them. The ducts that open on the sides of the conical papillae are closed by the pressure wave.

children.^{18–19} There is a predisposition of those with VUR to develop UTIs. Consequently, screening all children at the time of the first recorded UTI has shown that about a third have VUR.²⁰ It is more common in females with the exception of infancy, when most studies show not only a male preponderance, but a more severe VUR.^{21–22} Primary VUR is usually familial. It is inherited as a Mendelian dominant with partial expression, the gene frequency being 1 in 600.²³ Initially detection of RN at the time of investigation of the first UTI led to the widely held belief that the age of vulnerability was the first five years.²⁴ It has since been shown that scars can develop throughout childhood until puberty.^{25–29}

The cause of VUR is a developmental anomaly resulting in an inadequate length of the intravesical submucosal ureter.³⁰ A substantial number of children also have dysfunctional voiding, which may initiate or perpetuate VUR.^{2–3–31} VUR is often intermittent and varies in degree; being influenced by the state of hydration.³² In 1981, an international grading system consisting of five grades was established.³³ Dilating reflux (grades 3–5) has been shown to be significantly associated with RN.^{34–35} VUR has a natural tendency to resolve as the intravesical part of the ureter lengthens with growth. By age 10 about 75% of VUR has resolved.^{36–37} Rate of resolution is faster in males and slowest in those with the highest grades.^{21–37} Studies in the literature are conflicting when the rate of resolution between unilateral and bilateral VUR is compared.^{37–38}

The association of VUR with nephropathy is paradoxical. While most children with renal lesions do not have VUR, numerous studies show a close relation between VUR and nephropathy. The higher the grade, the greater the risk of damage and loss of renal function.^{27–29–39–41} Prognosis is worst when RN is bilateral.^{29–39} Unilateral RN is compensated for by hypertrophy of the contralateral normal kidney.²⁹ The importance of VUR therefore seems to be its association with a worse outcome. Pyelonephritic damage leading to renal failure in the absence of VUR has not been reported.

RADIOLOGICAL EVIDENCE

In the early studies of RN, urography was used to show RN and parenchymal scarring was graded.³³ In the 1980s ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy became widely used to show renal lesions because of its increased sensitivity.⁴² Pyelonephritic inflammatory changes are immediately apparent, scarring later occurring at the site of those changes.³⁵ By contrast, urography may take from six months to two years for a scar to appear fully developed.⁴³

It has now been well established that most children with DMSA scintigraphic evidence of pyelonephritis do not have reflux.^{35–44} These renal changes resolve over a period of six

months.^{45–42} In 25%–50% renal lesions persist, a rate significantly higher than the 6%–15% of pyelonephritic scarring found by urography.^{44–46–47} The long term significance of the increased incidence of persisting DMSA scintigraphic lesions is not known. It is noteworthy that persistence of lesions (scars) is independent of the presence of VUR.⁴⁴

Ultrasonography is the initial investigation in Britain and the USA; DMSA is used in Sweden. Studies have shown that with appropriate antenatal screening there is now no need for routine ultrasonography.^{40–48} Although ultrasonography is poor at detecting VUR, in practice this seems to be of little significance.^{49–50} In a well coordinated antenatal screening programme over a five year period the incidence of missed dilating VUR was <1%.⁵¹

Under current guidelines, the youngest children (<1 in UK, <2 in USA and Sweden) are submitted to micturating cystourethrography (MCUG) to determine if there is VUR. The procedure, which is technically difficult, is not standardised and requires the cooperation of the child. Children and their parents find the experience very distressing.^{32–52} Other drawbacks are radiation exposure and risk of iatrogenic UTI.⁵³ Although this is the best technique for confirming VUR, it is not reliable because reflux is often intermittent.^{32–54} Contrast enhanced ultrasound techniques, which are accurate and free from radiation will probably increase as an alternative to MCUG.⁵⁵ These techniques are however expensive and time consuming.

It has recently been proposed that DMSA scintigraphy should now be the first line investigation for UTI, because MCUG is a poor screening test for renal damage.^{56–57} Only those with renal lesions would then have MCUG. The advantage would be that the number of MCUGs could be reduced by half with a small chance of missing a child at risk of RN.⁵⁷ These proposals recognise that severe VUR is a significant cause of end stage renal disease (ESRD) and hypertension. However, an important drawback remains the fact that most renal lesions occur without VUR and persistence of lesions is independent of VUR.^{35–44}

SEX AND REFLUX NEPHROPATHY

It has become apparent that there are two distinct groups of children with RN. The first group consists of males who frequently present antenatally or in infancy.^{58–60} They often have bilateral severe (grade 5) VUR. Their kidneys are small with a smooth outline. Renal function is diminished and kidney histology shows hypoplasia and/or dysplasia.^{61–63} The association of severe VUR with abnormal kidneys suggests an embryologic abnormality. It is speculated that a mismatch between a laterally positioned ureteral bud and the nephritic blastema early in gestation results in kidney dysplasia and an incompetent ureterovesical junction.⁶⁴

Another hypothesis to explain this constellation of abnormalities has been a transient fetal urethral obstruction.⁶⁵ Anatomical investigation of the musculature of the internal sphincter does not support a developmental abnormality.⁶⁶ The most probable explanation is an abnormal voiding pattern, which creates the effect of an obstruction. This has been well demonstrated in these children.^{67–69} For an unknown reason, perhaps genetic, in these males dysfunctional voiding may be the precursor to VUR and RN.

The second group of children with RN are mainly female.⁴¹ They are usually older and their VUR less severe. Their renal scarring is typically segmental and may become diffuse with recurrent scarring. Their reflux lasts longer during which time they are predisposed to recurrent UTIs.^{21–41} The risk of recurrent UTIs is further exacerbated by their frequent association with constipation and dysfunctional voiding.³ In comparison with males, more have normal kidneys when first investigated rendering their prospects for prevention

Figure 2 Scheme for the investigation of febrile urinary tract infection and familial VUR.

more favourable. In Italy the prevalence of RN is greater in males, but in Australia in young people (<35 years) there is no sex difference.^{70 71}

CONSEQUENCES OF REFLUX NEPHROPATHY

Hypertension is the most common consequence of RN, developing in at least 10% with onset frequently beyond childhood. Data from ESRD programmes in developed countries have shown that 5%–12% of patients have RN as the cause for their ESRD.⁷² There are, however, considerable unexplained differences between countries. In most of the ESRD programmes the statistics have been confounded by not distinguishing pyelonephritic scarring from congenitally abnormal kidneys, both categorised as RN. It is probable that many males with ESRD have congenitally abnormal kidneys as most do not have a history of UTI.⁷³ Recognising the difficulty in obtaining registry incidence of pyelonephritic scarring in the USA, a study was undertaken to evaluate the incidence of ESRD caused by pyelonephritic RN at a large institution.⁷⁴ The authors concluded that pyelonephritis accounted for <1% of ESRD.⁷⁴ In Sweden (population 8.9 million) between 1986 and 1994 there was no case of ESRD attributable to pyelonephritis.⁷⁵ The latest ESRD data from 12 registries in Europe (population 80.3 million) has distinguished pyelonephritis from congenitally abnormal kidneys. The incidence per million for pyelonephritis and congenitally abnormal kidneys was 1.9 and 1.0 respectively.⁷⁶ There were more males in both categories.

Other than ESRD registries, follow up studies have been used to obtain information about the long term consequences of RN.^{26 27 29 77–79} There are studies where children with RN have been followed up into adulthood. Like many ESRD registries interpretation of the outcome is difficult because there is no distinction between congenitally abnormal kidneys and pyelonephritic induced RN. It needs to be

emphasised that making such a distinction radiologically or histologically is often impossible.^{8 72 80} The poor prognosis attributable to RN in the past may to some extent have been the effect of congenitally abnormal kidneys. Long follow up studies (both sexes) show that about 20% of patients with reflux nephropathy develop hypertension or ESRD.^{27 77 78} In the longest follow up study (41 years) Smellie concluded that the complications of RN could have been predicted in childhood.²⁷ A follow up study (median follow up 15 years), of women with less extensive scarring on urography, showed an improved outcome as compared with earlier studies, which included both sexes.^{26 79} Renal function was well preserved with 6% having hypertension.^{26 79}

ANTENATAL SCREENING

Fetal screening by ultrasound is now a routine practice in the developed world. The most common renal abnormality detected is pyelectasis, which may be recognised from the beginning of the second trimester.⁸¹ Pyelectasis is defined by measurement of the renal pelvis anterior posterior (AP) diameter, which increases with gestation. It is a dynamic measurement, probably influenced by urine volume. Repeated measurements within a two hour period show considerable variation.⁸² Studies in which second trimester pyelectasis was defined as an AP diameter greater than 4 mm or 5 mm have reported an incidence varying between 0.6% and 4.5%.^{21 83 84} In Brussels, when these criteria were used to screen a series of 5643 fetuses, 213 (1.5%) had significant uropathy of which six (2.5%) required surgical procedures.⁸³ Using a third trimester AP diameter of >7.5 mm the sensitivity and specificity for the detection of a significant uropathy is 97.9% and 40.6% respectively.⁸⁵ In countries with routine antenatal screening virtually all significant uropathies should be apparent at birth.

TREATMENT OF URINE INFECTIONS AND REFLUX

The early work of Smellie had a profound influence on the management of UTIs with VUR.²⁴ The mainstay of her treatment was antibiotic prophylaxis until VUR resolved together with frequent voiding and avoidance of constipation.²⁴ Because Smellie's conservative management of VUR was not generally accepted, particularly by surgeons, validation was required. Randomised controlled studies were undertaken comparing medical management with VUR surgery. Although surgery effectively eliminated VUR, the outcome in terms of renal function and scarring was similar for all grades of reflux even when bilateral.^{36 38 39 86}

It is now recognised that attention to voiding patterns and bowel habits is an essential part of the management of VUR.^{2 3 87} The term dysfunctional elimination syndromes was first used by Koff to describe abnormal bladder or bowel function in children with VUR.² As many as half the children with VUR have dysfunctional elimination syndromes.³ In the past, these children frequently had surgery because medical treatment was deemed to have failed. Recently, it has become accepted that there is unlikely to be any benefit from surgery in the presence of dysfunctional elimination syndromes.^{2 3}

Smellie's management and treatment of UTI and VUR, which was started in the 1960s, has been firmly entrenched in the mind of a generation of doctors.^{24 27} Indeed, so much so that despite widespread prophylactic antibiotic use, the value of prophylactic antibiotics for VUR has never been studied in a randomised controlled trial. It is only recently that the value of these methods has been questioned. An analysis of the Australia and New Zealand Transplant Registry has not shown any benefit over the past 30 years.⁸⁸ Furthermore, a meta-analysis of randomised controlled trials has failed to show any benefit from current practice.⁸⁹

In conclusion, guidelines are made with a consideration of risk/benefit ratio. The risk of a child developing hypertension/renal failure from a first UTI is negligible, while current routine investigations are not clinically effective. UTIs are common with large resource implications. Investigation could not be justified by a cost-benefit analysis. Where there has been appropriate antenatal evaluation, it would be better to advise against routine investigations after a first recorded febrile UTI. Should there be a family history of VUR or recurrent UTIs then further evaluation is required. Figure 2 shows a scheme for evaluation of children with UTIs and familial VUR. The underlying premise of such a scheme is that antibiotic prophylaxis is effective in preventing or limiting RN. In those children with VUR, MCUGs should be repeated at two to three yearly intervals.⁹⁰ Antibiotics should be continued until VUR resolves or puberty is reached.

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