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Vesicoureteric reflux: which treatment for which child ?

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Summary

Vesicoureteric reflux is common in children. It is mainly of significance insofar as it is frequently associated with kidney damage. Children with grade I reflux require no active treatment; spontaneous cure with growth can be confidently expected. Most cases of grade II reflux have no reflux nephropathy and go on to spontaneous cure. In those with grade III VUR, and aged less than 5 years, treatment by operation has the great advantage that 6 months after the operation, when a check cystogram has demonstrated that the reflux has been cured in more than 95 % of ureters. In children over 5 years old, with grade III VUR, it is probable that abolishing the reflux is irrelevent insofar as further kidney damage is concerned. If the passage of time shows that the child is suffering from recurrent, symptomatic upper tract infections, than operation is of the treatment of choice.

Key words: Vesico-ureteric reflux, reflux nephropathly.

Reflux Nephropathy

The clinical and pathological significance of vesico-ureteric reflux (VUR) lies mainly in its association with reflux nephropathy (RN). RN develops as a result of infection ascending from the urethra via the bladder and an incompetent ureterovesical valve to the renal pelvis; access to the renal parenchyma is via the collecting tubules. In the presence of intrarenal reflux (IRR) this access is greatly facilitated. There is both experimental [11] and clinical [14] evidence to support the view that IRR is important in the pathogenesis of RN. It is particularly noteworthy that the scars of RN occur predominantly in those parts of the kidney where compound refluxing papillae are usually found. Furthermore, it is common clinical experience that new scars are rarely seen to develop in children over the age of 5 years, the age beyond which IRR is not seen [14]. This would seem to imply that once the "at risk" refluxing papillae have been damaged by the initial infection the remainder of that kidney is at very low risk of being scarred by further infection, even in the presence of persistent VUR.

There is a notable lack of evidence to support the view that sterile VUR can damage the kidney. Certainly in the experimental model renal scarring can be produced by sterile reflux, but only at very high pressure [13]. Such sustained pressures do not occur in these children clinically. In the refluxing child with a stable bladder the kidneys are exposed to abnormally high pressure only during micturition. It is difficult to imagine how such brief, intermittent, high-pressure episodes could result in kidney damage in the short term. On the other hand, occurring as they do several times a day for 5, 10 or 15 years, it is not beyond the realms of possibility that they might eventually produce some damage.

A few children with VUR suffer from flank and loin pain comparable in severity with ureteric colic. A greater number suffer from longstanding loin discomfort, especially related to micturition. Such symptoms are abolished by successful reimplantation. Pain and discomfort are nature's way of alerting us to damage in the body. It would be imprudent to disregard such symptoms as of no significance, just because their significance is not at present understood.

The extent to which total renal function is affected in RN is closely related to the extent of renal scarring and the presence or absence of compensatory hypertrophy in the remaining unscarred areas

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of kidney. The extent of damage is infinitely variable, depending on whether one or both kidneys are affected and whether the process is focal and isolated, or generalised.

Long-term follow-up (mean 13 years) [18] has shown that in cases with unilateral RN 11.3 % will develop significant hypertension. If the disease is bilateral the incidence rises to 18.5 %.

Although the majority of children with VUR and RN who are treated thrive and grow into adulthood, and although 80 % of them will experience spontaneous cure of their VUR by that time (if not already abolished by operation), "reflux nephropathy is not a bening disorder in adults" [7]. Kincaid-Smith reports that in a ten year period, of 145 patients aged 14-65 years who presented with RN, 7 deteriorated to end-stage renal failure failure (ESRF) [7]. The most useful predictive sign of impending failure was the development of proteinuria. Once this appears, ESRF will supervene within 5-10 years. The development of proteinuria indicates the emergence of a glomerular lesion. That this glomerulopathy may develop in the contralateral non-refluxing kidney in a case of unilateral VUR is particularly worrying [1]. There is more to VUR than meets the eye! Women with impaired renal function caused by RN run a real risk in becoming pregnant. The onset of ESRF may be greatly accelerated, occurring either during pregnancy or shortly thereafter [6].

Vesicoureteric Reflux

There are varying degrees and many descriptive classifications of VUR. In the Birmingham Childrens' Hospital the following system is used:

VUR grade I Into the lower ureter
VUR grade II Filling but not distending the pelvicaliceal sestem
VUR grade III Filling and distending the pelvicaliceal system

Primary VUR is due to a congenital deformity of the vesicoureteric junction. Most commonly this defect consists of an abnormally short tunnel where the ureter traverses the detrusor muscle. With general growth of the child there is also growth of the intramural ureter so that what was initially an incompetent valve may well become an effective antireflux mechanism with the passage of time. Indeed 80 % of primary refluxing ureters in children become non-refluxing by the time they reach adulthood [15]. This spontaneous cure rate is not affected by the frequency or otherwise of recurrent urinary infections [9].

On the other hand the incidence of persistent VUR in the nonoperated group in the Birmingham series 5 years after diagnosis is 50 %. Only 20 % of ureters in children over the age of 6 years, and with bilateral grade 111 VUR at diagnosis, have stopped refluxing after 5 years' observation (Birmingham Reflux Study Group 1987) [4].

It seems reasonable to suppose that the apearance of the ureteric orifice at cystoscopy would be helpful in assessing the likelihood of resolution of VUR. If the orifice is grossly abnormal, gaping and without a tunnel, one can confidently predict that resolution will not occur within 5 years. However in the commoner, less abnormal, looking orifices cystoscopy is of less value. Even in experienced hands there is a poor correlation between the prediction of cessation of VUR and orifice assessment [2].

Bladder in VUR

Bladder instability is a common finding in association with VUR. A history of urgecy of micturition and, especially, urge incontinence in a child with VUR is almost pathognomonic of detrusor instability. Taylor et al [16] were able to demonstrate a lack of any significant correlation between bladder instambility and RN in VUR. Furthermore, it was not possible to demonstrate, over a 2 year period, that untreated instability adversely affected the spontaneous cure rate of VUR as compared with stable controls. However, Koff and Murtagh [8], in a more prolonged study (1.5-7 years with a mean of 3.9 years in those with persistent VUR), demonstrated a significant improvement in the resolution rate of VUR when the unstable bladders were treated diligently with bladder drill and anticholinergics.

Need for Treatment

In a study of RN in children in South Brazil Gc draich [5], have demonstrated that, untreated, r

disease is progressive. In their patients the diagnosis was invariably late, with the result that the majority had suffered recurrent symptomatic infections by the time of diagnosis. Analysis showed that whereas in patients under 2 years old at diagnosis the incidence of renal scarring was 28.3 %, in those aged 6 years it was 53.7 %. Once treatment with continuous low-dose prophylactic chemotherapy was instituted this progressive trend was halted.

However, another study Verrier Jones et [17] concludes that "prolonged urinary tract infection (UTI) was not associated with a reduction of glomerular filtration rate in girls after the age of 4 years and no benefit from intermittent antibiotic therapy was shown". This was a study of covert, asymptomatic infection diagnosed by bacterial colony counts without any importance being attached to the presence or absence of pyuria. And herein lies part of the problem.

Unfortunately, it has become fashionable, especially in paediatric nephrology circles. almost completely to disregard symptoms and pyuria in studies of RN. The clinical diagnosis of acute pyelonephritis is still a valid one. The signs and symptoms are very familiar to general practitioners, casualty officers, general paediatricians and surgeons- the doctors who usually see most of these children in their presenting acute illness. The diagnosis is confirmed by finding pus and organisms aplenty in the urine. To label such an illness "UTI" and equate it in any way, but in particular in terms of its pathological significance to the kidney, with so-called UTI diagnosed on the basis of totally asymptomatic bacteriuria is surely mistaken.

Recurrent attacks of acute pylelonephritis also occur. Each attack produces a febrile illness which is acutely debilitating and produces real morbidity in terms of loss of feeling of well being, quite apart from any damage it might be doing to the kidneys. Symptoms are important!

It stands to reason, and there is experimental evidence [12] to support the view, that if the appropriate antibiotic is given in the very early stages of acute parenchymal infection of the kidney permanent tissue damage can be completely aborted. This has important implications for the urgency with which it is necessary to treat every case of childhood acute pyelonephritis but, especially, the first presenting attack. Over the years it has become overwhelmingly clear that the first kidney infection is the one that results in the most damage. No sensible doctor would delay instituting effective antibiotic treatment for meningitis or osteomyelitis. Acute pyelonephritis must be thought of in the same league.

Treatment.

Essentially, there are two modes of treatment of VUR, namely operative and non-operative. It is misleading to refer to these as "operative" and "conservative"; there is nothing conservative about a mode of treatment which involves a two year old girl in taking antibiotics daily and attending the doctor regularly for maybe 3 years or more.

Non-operative treatment consists of low dose continuous prophylactic antibiotics. Equally impontant it includes medical supervision by someone who is willing and able to induce compliance with such a regime. Additionally, bladder drill and anticholinergics are useful adjuncts in patients with detrusor instability.

Treatment is continued throughout the period of risk with regular monitoring of the urine and renal function. Once the reflux can be seen to have resolved the antibiotics can be stopped. At this stage those children without evidence of RN can be discharged from medical supervision. Those with RN will need continued medical supervision, albeit, at infrequent intervals depending on the severity of the kidney involvement. Some will need supervisiyon because of the presence of impaired renal function; all will need it for annual blood pressure monitoring. Furthermore, since it has now become clear that a proportion of such patients will at some stage, even in the apparently normal kidney, develop a glomerulapathy which heralds ESRF within 5-10 years, all will need regular monitoring for the development of proteinuria.

For those in whom the reflux persists, is there a point at which the risk of development of RN abates? The general consensus appears to be that after the age of 5 years the risk of new scarring developing as the result of VUR is absolutely minimal. The relationship between persistent re-

flux and the subsequent development of glomerulopathy is a compeletly unknown quantity at present.

Operative treatment consists of an antireflux procedure of some sort. In practised hands the technical results of open operation are uniformy good, and even in dilated ureters the success rate in abolishing the reflux without producing ureteric obstruction exceeds 95 %. The less invasive subureteric Teflon injection technique of O'Donnell and Puri [10] is attended by slightly less success but shows great promise. As in the other groups, once the reflux has been abolished, and if there is no evidence of established RN, the child can be discharged from medical care. However, if there is RN, subsequent follow-up must be as in the non-operated group.

Which treatment for which child ?

Since July 1975 the Birmingham Reflux Study Group has been conducting a prospective randomised trial of operative versus non-operative treatment of severe VUR. When 96 children had completed 2 years' observation following entry to the trial the first formal assessment of the results was made and reported (Birmingham Reflux Study Group 1983). Using the following parameters there was no significant difference in the results of the two groups.

a. Height, b. Weight, c. Blood pressure, d. Incidence of breakthrouhg UTI, e. New scar formation,
f. Progression of existing scars, g. Renal growth, h. Total renal excretory function

Further follow up and assessment of 104 children (145 ureters) for 5 years since starting treatment has failed to reveal any clear difference between the two groups (Birmingham Reflux Study Group 1987). In the non-operative group, of those ureters with grade III VUR at entry, 49 % were unchanged at 5 years, while a further 20 % had only improved to grade II, still a significant degree of reflux (Table 1).

Is this background knowledge helpful in deciding how to choose the appropriate treatment for a particular child? I believe it is and that it leads to the following scheme. Children with grade I VUR require no active treatment; spontaneous cure with growth can be confidently expected.

Table 1. Changes in VUR grade after 5 years non-operative treatment.

VUR grade		Ureters
Grade III at allocation		75
Outcome grade:		
	III	37 (49 %)
	II	15 (20 %)
	I	11 (15 %)
	0	12 (16 %)

Most cases of grade II VUR have no RN and go on to spontaneous cure. While awaiting that happy outcome chemoprophylaxis is essential until the child is 5 years old. Operations rarely indicated but it may be the prudent choice in the child under 5 years of age if the parents do not comply with prescribed medical treatment. In the older child, if recurrent symptomatic pyelonephritis becomes a problem, there is little to choose from between the two forms of treatment.

In those with grade III VUR, and aged less than 5 years, treatment by operation has the great advantage that 6 months after the operation, when a check cystogram has demonstrated that the reflux has been cured in more than 95 % of ureters, antibiotic prophylaxis can be discontinued. The nagging worry that persistent marked reflux over the course of years may cause further renal damage, as yet undefined, is also alleviated. The risk of subsequent symptomatic pyelonephritis is virtually abolished.

In children over 5 years old, with grade III VUR, it is probable that abolishing the reflux is irrelevant insofar as further kidney damage is concerned. Neither will curing the reflux reduce the incidence of urinary tract infection; but, in the absence of VUR, the infection will be confined to the bladder and urethra. Thus, in this age group, symptoms assume a real importance in decision making. If the passage of time shows that the child is suffering from recurrent, symptomatic, upper tract infections then operation is the treatment of choice.

Some parents react with horror to the thought of an operation on their child. The facts need to be put to them in as balanced a fashion as possible. In particular, they need to be reausserd that non-operative treatment is nearly as good as opera-

tive. Its only disadvantages are the need for prolonged antibiotic intake and the fact that 50 % at least of the ureters will still be refluxing even after 5 years' treatment; the pathological significance of which remains entirely speculative. There is a tingy but important minority of patients with severe reflux who experience severe loin or iliac fossa pain. Others experience significant discomfort short of pain, especially at micturition. Operation is the treatment of choice in such patients.

The evidence of others [19] in adult patients confirms my own experience in children that the surgical correction of VUR in patients with chronic renal impairment, caused by RN, does nothing to delay the emergence of ESRF.

Conclusion

Vesicoureteric reflux is common in children. It is mainly of significance insofar as it is frequently associated with kidney damage. It has been estimated that the chance of any one patient with RN progressing to ESRF is 1 in 1000 (Kincaid-Smith 1984). The recent definition of a glomerulopathy developing late in apparently stable patients with RN has helped to highlight, once again, the fact that we continue to walk on shifting sands. Much is known but there is more to learn. Close collaboration between urologists and nephrologists remains the key to progress.

References

1. Bailey RR, Swainson CP, Lynn KL, Burry AF: Glomerular lesions in the "normal" kidney in patients with unilateral reflux nephropathy. Contrib Nephrol 39:126-131, 1984.
2. Bellinger NF, Duckett JW: Vesicoureteric reflux: a comparison of non-surgical and surgical management. Contrib Nephrol 39:81-93, 1984.
3. Birmingham Reflux Study Group: Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: Two years' observation in 96 children. Br Med J 287:171-174, 19836.
4. Birmingham Reflux Study Group: Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: Five years' observation. Br Med J 295:237-241, 1987.
5. Goldraich NP, Goldraich IH, Anselmi OE, Ramos OI: Reflux nephropathy: the clinical picture in South Brazilian children. Contrib Nephrol 39:52-67, 1984.
6. Kincaid-Smith P: Closing remarks. Contrib Nephrol 39:374-377, 1984.
7. Kincaid-Smith PS, Bastos MG, Becker GJ: Reflux nephropathy in the adult. Contrib Nephrol 39:94-101, 1984.
8. Koff SA, Murtagh D: The uninhibited bladder in children: effect of treatment on vesicoureteral reflux resolution. Contirb Nephrol 39:211-220, 1984.
9. Mulcahy JJ, Kelalis PP: Non-operative treatment of vesicoureteric reflux. J Urol 120:336, 1987.
10. O'Donell B, Puri P: Endoscopic correction of primary vesicoureteric reflux: results in 94 ureters. Br Med J 293:1404-1406, 1986.
11. Ransley PG, Risdon RA: Reflux and renal scarring. Br J Radiol 51 (Suppl 14):1-35, 1978.
12. Ransley PG, risdon RA: Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritis scar. Kidney Int 20:733-742, 1981.
13. Ransley PG, Risdon RA, Godley ML: High pressure sterile vesicoureteric reflux and renal scarring: an experimental study in the pig and minipig. Contrib Nephrol 39:320-343, 1984.
14. Rolleston GL, Maling TMJ, Hodson CJ: Intrarenal reflux and the scarred kidney. Arch Dis Child 49:531-539, 1974.
15. Smellie J, Edwards D, Hunter N, Normand ICS, Prescond N: Vesicoureteric reflux and renal scarring. Kidney Int. 8 (Suppl 4):S65-S72, 1975.
16. Taylor CM, Corkery JJ, White RHRW: Micturition symptoms and unstable bladder activity in girls with primary vesicoureteric reflux. Br J Urol 54:494-498, 1982.
17. Verrier Jones K, Asscher W, Verrier Jones R et al: Renal functional changes in schoolgirls with cover asymptomatic bacteriuria. Contrib Nephrol 39:152-163, 1984.
18. Wallace DMA, Rothwell DL, Williams DI: The long term follow up of surgically treated vesicoureteric reflux. Br J Urol 50:479-484, 1978.
19. Weston PMT, Stone AR, Bary PR, Leopold D, Stephenson TP: The results of reflux prevention in adults with reflux nephropathy. Br J Urol 54:677-681, 1982.