Pediatr Nephrol (2007) 22:785–787
DOI 10.1007/s00467-007-0483-5

EDITORIAL

Continuing medical education: introducing four papers on vesicoureteral reflux

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Published online: 3 April 2007

Keywords Vesicoureteral reflux · Reflux nephropathy · Medical education

Vesicoureteral reflux (VUR) is defined as the passage of urine from the bladder back into the ureters. VUR points to an anomaly at the ureterovesical junction whose normal architecture prevents the backflow of urine. VUR is one of the most frequent anomalies of the urinary tract, and yet, every single aspect of the condition—prevalence, diagnosis, treatment and outcome—remains controversial up to the present, despite the considerable experience of both paediatric nephrologists and urologists worldwide, the large number of publications and several well-conducted studies carried out over the past three decades.

There is clearly a lack of consensus on VUR, and this has many causes. In the first place, there is the multimodal character of the condition. Indeed, VUR can be primary or secondary, congenital or acquired, genetic and sporadic, permanent or intermittent and, according to internationally accepted definitions, mild, moderate or severe. Moreover, spontaneous resolution has been documented convincingly in most paediatric patients with VUR.

The second reason for the lack of unanimity in the approach to VUR is the lack of evidence-based data due to the paucity of well-conducted, prospective, randomised, and controlled studies on the different aspects of VUR. The largest study carried out so far was the International Reflux Study in Children (IRSC), in which eight European centres and 16 groups in the USA participated. It included many hundreds of children followed for more than 10 years [1, 2]. Yet the main question the study concentrated on was whether medical or surgical treatment is the better one. There was no difference except for less febrile urinary tract infections (UTI) after surgery. In retrospect, this excellent study had several flaws, the main one being that bladder dysfunction was not taken into account is a systematic way. A smaller-scale study was performed in Birmingham to come to the same conclusion [3]. But again, the aim of the study was rather limited.

A third factor that contributes to the confusion is the equivocal definition of reflux nephropathy (RNP). Reflux damages kidneys in two ways. The first is the congenital renal malformation associated with intrauterine gross reflux. It interferes with nephrogenesis and leads to renal cortical hypoplasia and medullary dysplasia. It is commonly diagnosed by prenatal ultrasonography. If bilateral, it causes chronic kidney disease from birth and has nothing to do with UTI. There are several animal models for this form of what I prefer to call “obstructive nephropathy”. The second form of renal damage associated with reflux is acquired segmental scarring of the renal parenchyma due to mostly recurrent, acute pyelonephritis causing renal nephron loss to originally normal kidneys. It is the consequence of VUR combined with UTI and intrarenal reflux (IRR). In the past, scarring was rather well visualised on intravenous urography, an investigation that risks falling into oblivion but nowadays mainly looked for by renal scintigraphy and in particular 99mTC dimercaptosuccinic acid (DMSA) scanning. Computerised tomography (CT) is quite a nice alternative but comprises high radiation exposure. Magnetic resonance (MR) is maybe the best modern technique to demonstrate acute pyelonephritis. Renal scarring due to

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bacterial invasion of the kidney and subsequent scarring was experimentally reproduced in the most convincing way by elegant studies in the pig by Ransley and Risdon in the 1970s, work that, unjustly, has almost been forgotten, as judged from today's literature [4].

The choice to produce a series of educational articles on VUR was, for the authors invited to contribute, quite a challenge and not an easy task. *Pediatric Nephrology* is very grateful to them. Luisa Miller and her collaborators provide a most exquisite paper on the genetics of primary VUR and associated renal dysplasia [5]. The paper brings the latest information on the genetics of the ureteral bud and defines with great precision the above-mentioned congenital form of RNP. Constantinos Stefanidis and Ekaterini Siomou were asked to critically review the different techniques of imaging for VUR and RNP [6]. They state, quite rightly, that one should be flexible and choose the techniques on an individual basis, with the main goal being to identify acquired renal scarring in patients at risk. The most controversial aspect of VUR is undoubtedly the medical management. Tej Mattoo writes a clear, honest contribution to this topic [7]. Recognising that there is little evidence-based material to rely upon, he comes to the wise recommendation "to err on the side of caution and consider VUR and UTI risk factors for renal scarring and treat each patient on individual basis". The fundamental role of antibiotic prophylaxis is clearly advocated as the main and most efficient first step in the treatment of VUR and its complications. A fourth contribution concerns the surgical treatment of VUR. Nicola Capozza and Paolo Caione present a scholarly overview of classic and more modern techniques surgeons use to correct VUR [8]. They plead for a logical, coherent approach in which endoscopic treatment takes a predominant place, given it is minimally invasive and hence child friendly. Together, these contributions provide a solid basis to a rational and prudent approach to a common but also controversial condition. Not all aspects of VUR could be covered, though, and some important issues remain somewhat underexposed. It might be worthwhile to mention a few of these aspects to close this introduction.

VUR is familial, more often than was expected and accepted in the past, and the genetics of these familial forms is incompletely understood. It is not clear what the implications are in terms of screening and therapy.

TcDMSA is the preferred technique to document acute pyelonephritis and scarring. Yet, a note of caution is appropriate. The scanning comprises a non-negligible irradiation especially in girls, false negative findings can never be excluded, the distinction between fresh and old lesions and especially between acquired scarring and congenital dysplasia is not always easy. One might expect that magnetic resonance will help us here in being both less invasive and more efficacious.

The role of physiological bladder instability, bladder-sphincter dysfunction and the lazy bladder syndrome in the genesis and the maintenance of VUR cannot be over-estimated. Surgery for VUR before appropriately treating dysfunctional voiding should be considered a medical error. The high intravesical pressure that accompanies the different forms of dysfunctional voiding is a most important risk factor for IRR. The combination of VUR, UTI and IRR leading to renal damage is the prominent lesson one can take from the animal experiments mentioned above.

Surgery still has its place to treat some difficult patients with VUR. Besides endoscopic and open surgery, there is now a tendency to introduce in this field laparoscopic techniques, sometimes even robot assisted. At least for a selected group of reflux patients, this approach could be indicated to combine the best of two worlds: the minimal invasiveness of the endoscopic correction and the efficacy of the open surgery [9].

Finally, yet importantly, patients with VUR and RNP deserve careful follow-up later in life. The long-term outcome of these patients is not yet fully documented. The findings of Jodal et al. at the 10-year follow-up of 252 patients participating in the IRSC are rather optimistic: only one patient had chronic renal failure, and three had arterial hypertension [2]. A similar study by a Finnish group, however, yields dismal findings [10]. From an initial cohort of 267 patients, 12 died in chronic renal failure and eight others were in chronic renal failure. Of the remaining patients, 147 agreed to participate in the long-term study: only one third of them had normal glomerular filtration rates (GFR), and microalbuminuria or proteinuria was present in 42 patients. The marked discrepancy between the two studies is not easy to understand, but selection bias is certainly one of the main reasons. Regardless, patients with bilateral RNP are at risk for progression towards end-stage renal failure. The main characteristics of progression are arterial hypertension and proteinuria, and they are a formal indication for a treatment in which angiotensin-converting enzyme (ACE) inhibitors take a prominent place.

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