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The current status of screening for vesicoureteral reflux

H. Norman Noe

Department of Urology, LeBonheur Children's Medical Center and University of Tennessee, Memphis, Memphis, Tennessee, USA

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Abstract. Reflux nephropathy is responsible for a significant percentage of end-stage renal disease in late childhood as well as being the most common cause of severe hypertension in childhood and adolescence. To prevent reflux nephropathy, it is imperative to discover reflux at the youngest age possible and preferably before any urinary tract infections have occurred. Since screening of the general population for reflux is not feasible, we have focused our efforts on the siblings of known refluxers and, more recently, the offspring of known refluxers. We have found high rates of reflux in both groups and have shown in the sibling population that early discovery of sibling reflux has significantly lowered the rate of renal damage compared with the index patients. It is imperative to screen these two risk populations at the youngest age possible, but we have recently made modifications in our recommendations for the older sibling and offspring. The results of these two screening studies are given as well as our current recommendations for screening for reflux in these risk groups.

Key words: Vesicoureteral reflux screening – Urinary tract infections – Sibling vesicoureteral reflux – Offspring vesicoureteral reflux

Introduction

Reflux nephropathy is responsible for a significant percentage of end-stage renal disease in late childhood and between 5% and 15% of end-stage renal disease in Caucasian adults under 50 years. It is also the most common cause of severe hypertension in late childhood and adolescence. Although it is now recognized that the renal parenchymal injury secondary to vesicoureteral reflux can occur in older children, it appears the majority occur early in life and, in most instances, before the age of 3–5 years. Some 30%–50% of patients with vesicoureteral reflux have already established renal scarring on initial evaluation, usually following a urinary tract infection. This represents the majority of renal scars which will occur in this population from the time of discovery forward. While both medical and surgical treatments are equally good at preventing further renal injury, neither is reliable in preventing hypertension or deterioration of renal function when the kidneys have been injured before vesicoureteral reflux is recognized and appropriate therapy initiated. This fact provided the frustration that led to our interest in screening a population felt to be at risk for reflux before the scarring process had been initiated [1].

Three mechanisms are considered as potential etiologies for renal scar formation. These are: (1) reflux of infected urine with interstitial inflammation and damage, (2) sterile reflux which may damage the kidney through a mechanical or immunological mechanism, and (3) recently recognized abnormal embryological development with subsequent dysplasia or dysmorphism. It is clear that in the first two causes of renal parenchymal change it is essential to discover the reflux early before damage can be initiated. In the third instance, high grades of reflux can be discovered prenatally and treated immediately following birth with prenatal or in utero intervention currently considered not to be indicated. Thus, the lesion of reflux nephropathy is an acquired disease entity that will require early detection if the sequelae are to be prevented, especially in the first two circumstances mentioned above.

It is now generally accepted that reflux does not normally occur in human beings [2]. Since screening of the general population for reflux is not feasible due to the invasive nature of the diagnostic procedure, we attempted in the 1970s to identify a group at risk for reflux and have subsequently carried that through to the present time [3]. At the time we initiated our study, the literature consisted of case reports and family studies with a few series of patients screened for reflux, but none in a prospective and uniform

Correspondence to: H. Norman Noe, 770 Estate Place, Memphis, Tennessee 38120, USA

manner [4–7]. It so happened at this particular time in our clinical practice that several members of different families exhibited the effects of reflux and infections, and there appeared to be sufficient evidence to allow for prospective screening for vesicoureteral reflux of the siblings of a child with known reflux. Thus began the screening process at our institution, trying to identify children with vesicoureteral reflux before their kidneys were damaged; screening has continued to the present time. These results will now be discussed and the current status for screening outlined.

Screening results

The brothers and sisters of patients with primary reflux were evaluated with an awake voiding cystourethrogram, regardless of age, presence of symptoms, or a history of documented urinary tract infections. We excluded specifically from the index patients those with a neurogenic bladder, posterior valves, ureteroceles, or any other congenital anomalies that would cause secondary forms of reflux. At the time the study was initiated, it was standard procedure to obtain an excretory urogram (IVP) in each case in which reflux was discovered. In the latter part of the study, an IVP was obtained only in cases of high grade reflux (grade III or greater, international classification) with renal ultrasound performed on patients with reflux of grade I–II. If there was an abnormality noted on renal ultrasound, the child was studied with an IVP. All patients discovered to have reflux were begun on antibacterial prophylaxis. Renal damage was defined as generalized or localized cortical loss or scarring on the IVP. Renal and polar length greater than 2.5 standard deviations below the mean was considered evidence of renal growth arrest or retardation. Few parents actually refused the sibling screening process; in fact, the majority were receptive, with many parents actually raising the question of screening before being asked to participate in this study.

The results of this study have been presented on several occasions and recently published [1]. Three hundred and fifty-four siblings were screened, with 119 (34%) found to have reflux. There was no statistical difference between female and male siblings, with the majority of the siblings discovered to have reflux being totally asymptomatic (Table 1). When grouped according to age, siblings less than 18 months had a significantly higher rate of reflux than did older children (Table 2). Reflux was graded as III–V in 61% of siblings and grade I–II in 39%. As expected, the higher grades of reflux were associated with the majority of instances of renal scarring, with those in the lower grades exhibiting scarring associated with urinary tract infections.

The incidence of sibling reflux could not be correlated with reflux grade, established renal damage, or sex of the index patient. Thus, it appears that the presence of reflux within an index patient would indicate an increased tendency to reflux within the siblings and would serve as a sole indication for a screening voiding cystourethrogram in the sibling population. This has been confirmed by others [8, 9].

Several points in this sibling study deserve emphasis. Foremost was the gratifying finding that there was a significantly lower percentage of renal damage of the siblings with reflux compared with the index patients. This difference was suggested in the original study and confirmed in the expanded series. It should be noted that the majority of siblings with renal damage were also asymptomatic. The question still remains as to whether such renal changes in the siblings are secondary to acquired damage from unrecognized infection, sterile reflux, or some form of dysmorphism induced in utero. The combination of sibling screening and the discovery of hydronephrosis secondary to reflux during prenatal ultrasound may, in the future, help us answer these questions. As noted in Table 3, which compares renal loss in index patients and siblings, no nephrectomies or biopsies were performed in the sibling group. Thus, histological confirmation is lacking as to whether these changes are due to infection, sterile reflux, or dysplasia. However, no evidence of dysplasia was found in any of the index patient kidneys. The evidence is that the rate of renal damage and certainly renal loss in the sibling group is much less than in the index group, and we believe this is due, at least in part, to early detection and the prevention of infection. It now also appears that patient age does play a role in establishing renal damage risks, as well as defining how aggressive screening should be in an asymptomatic child. Our data clearly show that younger children, particularly those less than 18 months of age, have a significantly higher rate of reflux. In this younger group, there was a statistical difference ($P = 0.017$) in the rate of damage in 13 of 52 index patients (25%) and in 4 of 54 siblings (7%) less than 18 months of age. This confirms that the younger growing kidney appears to be at increased risk for renal scarring, even from a single infection, and can be protected with early intervention.

Table 1. Symptoms of 119 siblings of reflux patients

Symptoms	No. of patients (%)
None	89 (75%)
Urinary tract infection	18 (15%)
Incontinence	11 (9%)
Hematuria	1 (1%)

Table 2. Reflux incidence in siblings of different age groups

Sibling age	Reflux rate
0–18 months	51/112 (46%)*
1.5–5 years	45/161 (28%)
>5 years	23/81 (28%)

* $P = 0.017$, chi-squared

Table 3. Renal loss or failure in index patients and siblings

	Index	Siblings
Nephrectomy	7	0
Dialysis	2	0
Renal failure likely	1	0

A second group of patients has now been identified as having a higher than expected rate of reflux. This group is the offspring of patients who have had known reflux. As the hereditary and familial nature of reflux became well recognized and accepted, it seemed obvious that the offspring of patients with known reflux would have an increased rate of reflux, perhaps the same as siblings. We encouraged many of our former patients to have their children screened at birth, once again after finding evidence in the literature to support this view. This literature review resulted in compiling 66 children of 29 known affected adults. The overall rate of offspring reflux was 43 of 66 patients (65%).

Our preliminary experience has been compiled and was recently published [10]. A total of 23 parents with previous radiographically demonstrated primary vesicoureteral reflux allowed us to screen 36 of their children for reflux using an awake voiding cystourethrogram. Of these 36 offspring, 24 (66%) exhibited reflux, a rate almost identical to that obtained in our literature search. Whether the parent was male or female did not appear to affect the rate of offspring reflux, and the majority of these offspring with reflux were asymptomatic. We feel that the numbers in this offspring study are too small to draw any conclusions other than there appears to be a very high rate of reflux in the offspring and, as such, they form a group worthy of screening efforts.

The genetic transmission for the trait of reflux is still a matter of debate. Initially, we as well as other authors favored a multi-factorial inheritance pattern. The rate of reflux in siblings (34%) appeared to be greater than expected from the multi-factorial form of genetic transmission, which would normally be 3%–5%. When taking the family histories in this sibling study, we noted a large number of parents who had had previous symptoms suggestive of infections or perhaps reflux, but we felt that adequate information on the certainty of parental reflux was necessary before drawing any conclusions. Screening the parents of newly discovered reflux patients is probably unjustified because of the known tendency for spontaneous cessation of reflux as an individual grows toward adulthood. Thus, it remained to examine the offspring of patients to see if we could determine the type of transmission of this disease process. The high rate of transmission from parent to child would now appear to favor an autosomal dominant mode of inheritance or at least a multi-factorial pattern with a single dominant gene with varying penetrance. Autosomal dominant inheritance was actually suggested most recently by a group of investigators using a computer program (POINTER) and segregation analysis [11]. Further studies, I believe, will help us clarify the genetic nature of transmission of reflux.

As with any screening methodology, risks and benefits as well as cost effectiveness must be addressed. Throughout our screening efforts, no complications were encountered when these children were evaluated radiographically. In the hands of competent and experienced pediatric radiologists, a voiding cystourethrogram can be obtained with little or no risk to the children being evaluated. All of the children screened for vesicoureteral reflux were seen the day of their screening procedure, and if reflux was present a urine culture was obtained and they were started immediately on prophylactic antibiotics, which may account for the lack of significant infections encountered as a result of the radiographic procedure.

The primary benefits of screening for vesicoureteral reflux appear to be in the prevention of renal scarring and renal growth alteration. As noted previously, we have significantly lowered the rate of renal scarring and growth alteration, particularly in the sibling group. It is this reduction in renal scarring, with its subsequent reduction of progression to end-stage renal disease and hypertension, that one should consider when evaluating the cost effectiveness of screening for reflux. First, it is estimated that between 1% and 2% of all children found to have vesicoureteral reflux following urinary tract infections will develop end-stage renal disease. At an annual cost of between U.S. $ 30,000 and 50,000 for dialysis or between U.S. $ 50,000 and 75,000 for renal transplantation, it can easily be seen that on the basis of renal insufficiency alone one can justify the cost of screening 100 children for vesicoureteral reflux (approximate cost U.S. $ 20,000).

Perhaps of even greater benefit than preventing end-stage renal disease will be the impact upon hypertension secondary to renal scarring. It is estimated that hypertension develops in 10%–20% of children with vesicoureteral reflux and renal scars with long-term follow-up [12]. Additionally, Malak et al. [13] reported a 34% incidence of hypertension on long-term follow-up of adults with reflux nephropathy, which is approximately twice that expected in the normal white population. The resultant reduction in hypertension, with its attendant cardiovascular, cerebrovascular, and renal implications, will more than make up for the cost of screening for reflux. There will also be considerable cost savings by identifying children with reflux before they need treatment for severe pyelonephritis, etc on an inpatient or outpatient basis. It thus appears that by simply using the most qualitative of parameters screening in these children can be justified without even having to consider the intangibles or the prevention of human suffering and morbidity.

Future considerations

At present, the only reliable way to demonstrate vesicoureteral reflux is by a voiding cystourethrogram or a nuclear cystogram. The complication rate of such a procedure has been low and the acceptance rate high in our community, due to the skills and compassion provided by our pediatric radiologists. In other communities, however, there appears to be some resistance to the use of this invasive technique, perhaps because of personal bias or less than ideal experience with these diagnostic studies. Regardless of one's experience, it is obvious that a non-invasive method to determine vesicoureteral reflux would be welcomed by everyone. This would be useful not only for initial diagnosis but potentially as a means to support the contention that resolution of reflux may have occurred spontaneously. To date, imaging studies other than standard cystography requiring catheterization have not proved useful. Indirect nuclide cystography does not provide enough diagnostic accuracy to justify its routine usage, requires venopuncture,

and is more expensive than standard cystography. Ultrasound is unreliable in detecting reflux and can only suggest its presence when parenchymal changes or dilatation of the collecting system are observed. Pitfalls of intravenous urography in attempting to diagnose reflux have been recognized for decades. Thus, alternative imaging techniques appear less accurate in the diagnosis of reflux.

Attempts to develop a truly non-invasive method for initial detection and subsequent follow-up of reflux have centered recently upon the measurement of urinary enzymes. The enzyme measured most frequently is *N*-acetyl-β-glucosaminidase (NAG) [14, 15]. NAG is a lysosomal enzyme which is distributed along the proximal tubule as well as the distal tubule and collecting duct. Increased levels of this enzyme appear in the urine when there has been tubular damage, such as might be seen with nephron damage associated with reflux. We recently carried out a prospective study measuring NAG levels in children undergoing voiding cystourethrography for the diagnosis of reflux, but could correlate increased urinary NAG levels only with the most severe and gross forms of reflux [16]. Thus, it would appear that urinary NAG levels are of little predictive value for the presence or absence of reflux. Other enzymes such as pyruvate kinase, hexokinase, and phosphofructokinase have much greater activity in the distal nephron and are currently being evaluated for the non-invasive diagnosis of reflux. It is also possible that serum levels of enzymes such as NAG might be useful in screening for vesicoureteral reflux in a risk population. Additional studies on chemical constituents of the cell membrane may indicate whether cell disruption secondary to reflux has occurred.

Current recommendations for reflux screening

From the foregoing, it can be seen that screening for vesicoureteral reflux is justified in both siblings and offspring of known refluxers. Although to be totally certain about the diagnosis of reflux a voiding cystourethrogram is necessary, some modifications to our original screening recommendations appear to be reasonable. As noted earlier, the growing kidney of the younger child appears to be more susceptible to reflux-mediated renal damage and, as such, we tend to be more aggressive in screening the younger age groups. We currently recommend a voiding cystourethrogram in all children, both male and female, under the age of 3 years. Between the age of 3 and 5 years, we recommend a voiding cystourethrogram in all female children and all male children who have had urinary tract infections or suspicious urinary symptoms. Male children who are totally without symptoms are screened with a renal ultrasound. If the ultrasound is abnormal in any way, then a voiding cystourethrogram is obtained. Likewise, all asymptomatic siblings and offspring over the age of 5 years are also screened with a renal ultrasound. The rationale for this action, as well as that in boys 3–5 years of age, is that if the renal ultrasound is normal, it can be assumed that: (1) reflux never existed or (2) if it did, it was mild and has possibly spontaneously ceased, or (3) if it is still present and the child is not having infections, they do not represent a group at increased risk for renal scarring, particularly if the patient is a male. We accept the fact that a few patients will be missed that might have vesicoureteral reflux, but this approach will allow us to get the highest statistical yield of those patients at risk with the minimum number of invasive procedures, and hopefully reduce the overall costs of the screening itself. It should be noted that we continue to completely evaluate with a voiding cystourethrogram and either ultrasound or IVP all children with urinary tract infections or suspicious urinary symptomatology, especially if they are in the risk group of siblings and offspring of known refluxers.

Thus, the evidence to date supports the use of screening for reflux in these two identified high-risk populations, and the long-term results appear to be beneficial to that group of children. We will continue to modify our screening recommendations using current techniques until hopefully a reliable non-invasive method can be devised to benefit this particular group of children.

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