Vesicoureteric reflux and renal scars in asymptomatic siblings of children with reflux

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Abstract

The purpose of the study was to determine the incidence of vesicoureteric reflux (VUR), renal scars and hypertension in asymptomatic siblings of children with VUR. The study comprised 105 siblings of patients with VUR. Their age ranged from 4 months to 6·3 years. All had a direct radionuclide voiding cystography (DRVC) performed, and VUR was detected in 47 of 105 (45%). High grade VUR in the first year of life had an incidence of 50% compared with a 9% incidence in siblings older than 2 years, while only one of the 27 siblings with a low VUR grade was younger than 1 year. In 43 of 47 siblings with VUR, a technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) scan was performed and renal scars were found in 10, which presents 23% of siblings with VUR who were scanned and 10% of all siblings studied. One child had hypertension. Identifying VUR among asymptomatic siblings could possibly prevent renal damage and its consequences. Thus, the predictive value of positive family history alone in identifying VUR was 45% while 23% of siblings had renal scars. This incidence justifies the routine investigation of asymptomatic siblings, by using DRVC at an early stage.

Vesicoureteric reflux (VUR) is the most common abnormality detected in children with urinary tract infection (UTI). According to different authors, it is present in 22% to 52% of the children studied.[1–5] On the other hand, the incidence has been estimated to be 1% to 2% in the general population.[6] The rationale of detecting VUR is that by close follow up and/or either surgical or conservative treatment, the risk of renal damage (scarring) and its consequences due to the VUR itself, or to the VUR with associated UTI may be minimised.

The incidence of VUR among siblings (even asymptomatic) of children with known VUR is as high as 45%.[7–11] However, it was not until direct radionuclide voiding cystography (DRVC) with its low radiation exposure was routinely used that VUR detection in siblings became a more widely accepted procedure. Because VUR is normally detected after the UTI, little is known about the natural history of sterile VUR in children and there has not been sufficient data regarding their renal status (scars, hypertension) to recommend screening for VUR routinely. It is known from experimental studies in animals that high pressure reflux can produce renal damage.[12–13]

The purpose of this study was to determine the incidence of VUR in asymptomatic siblings under the age of 6 of patients with VUR and to determine the incidence of renal scars and hypertension in asymptomatic siblings with proved VUR. The results might justify a recommendation to look for VUR in young siblings.

Patients and methods

One hundred and five siblings of patients with known VUR were admitted to the study from July 1987 to June 1991 inclusive. In 90 families one sibling was evaluated. Two siblings were studied in six families and three in one family. There were 56 (53%) boys and 49 (47%) girls. The age of the siblings ranged from 4 months to 6·3 years (mean age 3·3 years). Fourteen (13%) children were younger than 1 year, 24 (23%) were between 1 and 2 years, while 67 (64%) were older than 2 years. They all had a negative history of UTI and, at the time of admission, they were all free of symptoms.

All children had a DRVC performed and VUR was found in 47 (only a 4 month old boy had a *x* ray voiding cystogram instead of DRVC). Of 47 children with VUR, 43 also had technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy done (in four patients with VUR grade 1 parental permission for DMSA scintigraphy could not be obtained).

The results were reviewed by two independent observers. In cases where there was disagreement, a consensus was reached.

For statistical analyses the χ^2, Student's *t* test, Jonckheere-Terpstra test, and linear by linear association test (StatXact software by Cytel Software Company) were used.

TECHNIQUE OF DIRECT VOIDING RADIONUCLIDE CYSTOGRAPHY

Children were catheterised under aseptic conditions. ^{99m}Tc as sodium pertechnetate was added to sterile isotonic saline in concentrations of 40–80 MBq/l. The bladder was slowly filled with the radiotracer solution under hydrostatic pressure (40–60 cm H_2O). When bladder capacity was reached, or when the child showed the urge to void, the catheter was removed, and the voiding usually began within a short period of time. Since 1990 a cyclic DRVC (filling the bladder and having the infant void around the catheter two or three times) has been used instead of conventional DRVC to increase the accuracy of the procedure. A computerised gamma camera (General Electric Maxi Camera 300, computer Digital PDP 11/34) was used to

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allow simultaneous visualisation of the radio-
tracer and to record data at a rate of 1 frame/5
seconds. Data were reviewed with image en-
hancement by decreasing the upper threshold to
20–30% of maximal radioactivity in the bladder.

All children received co-trimoxazole (Bactrim)
6 mg/kg divided into two doses for three days to
prevent UTI after catheterisation.

VUR was classified as unilateral or bilateral.
According to its extent it was graded as: VUR 1,
radiotracer reaching the ureter only; VUR 2,
radiotracer reaching the pelvis; and VUR 3,
radiotracer reaching the pelvis, which seemed
dilated.

TECHNIQUE OF ^{99m}Tc-DMSA SCINTIGRAPHY

DMSA scintigraphy was performed two hours
after the injection of ^{99m}Tc-DMSA. The dose
was adjusted for the child's height and weight.
One posterior and two posterior oblique images
containing 300 000 counts each were obtained
with a gamma camera (Siemens Basicam ZLC
Digitrac 75) and a low energy all purpose
collimator, using an appropriate zoom. The
relative contribution of each kidney to the
global renal function was calculated using a
computer image in posterior projection. DMSA
scans were considered to be abnormal if there
were focal or generalised scars, or if unilateral
function was less than 45% of total glomerular
filtration.

Results

Comparing index children and siblings, no
significant difference was found in terms of sex
ratio (p=0·4), nor was such a difference found
between the sex of index children and VUR
grade of siblings (p=0·4). There was no signifi-
cant association between VUR grades of index
children and VUR grades of siblings when
compared as a whole group (p=0·5). However,
in siblings under 1 year of age, the Jonckheere-
Terpstra test and linear by linear association test
showed significant (p=0·04) positive relation-
ship between VUR grades of index children and
VUR grades of siblings, implying that index
children with higher grade VUR also had
siblings with higher grade VUR. We found that
where index children had VUR grade 2 or 3, six
of eight siblings under 1 year of age, also had
VUR grade 2 or 3.

VUR was detected in 47 (45%) of 105
siblings. It was bilateral in 25 and unilateral in
22 of the patients, thus making 72 refluxing
units. The grades of VUR were distributed as
follows: 42 (58%) were grade 1, 24 (33%) were
grade 2, and six (8%) VUR were grade 3. There
was no significant difference between groups of
siblings without VUR and those with VUR
grade 1, 2, or 3 in terms of sex ratio (p=0·7),
but a significant difference (p=0·0001) was
found in terms of age (table). The mean age of
the children with VUR grade 2 and 3 was 24
months, compared with the mean age of 49
months in those children with grade 1 VUR,
and 39 months in children without VUR. High
grade VUR (grade 2 and 3) had an incidence of
50% (7/14) in the first year of age, compared

Distribution of VUR grades 1 to 3 according to age of 47
children with VUR among 105 asymptomatic siblings (in
cases of bilateral VUR of different grades, the higher grade
was considered). Figures are cases and percentage within
each age group

Age (months)	VUR grade			
	0	1	2/3	Total
0–12	6 (43)	1 (7)	7 (50)	14 (100)
13–24	12 (50)	5 (21)	7 (29)	24 (100)
25–76	40 (60)	21 (31)	6 (9)	67 (100)
Total	58 (55)	27 (26)	20 (19)	105 (100)

with a 9% (6/67) incidence in siblings older than
2 years. On the other hand, only one of the 27
siblings with VUR grade 1 was younger than 1
year.

In 43 of 47 siblings with proved VUR, ^{99m}Tc-
DMSA was performed and focal defects sug-
gestive of renal scarring were found in 10 cases,
which presents 23% of siblings with VUR who
were scanned and 10% of all siblings in the
study. However, in all cases unilateral renal
function was more than 44% of total glomerular
filtration. Comparing siblings with VUR and
renal scars and those with VUR without scars,
no significant difference between the two groups
was found in terms of age (p=0·2) and grade of
VUR (p=0·6). Significant difference (p=0·02)
was noted in terms of sex ratio. Nine siblings
with scars were girls and only one was a boy.

In one 9 month old male sibling, in addition
to the right VUR, grade 2, a left side kidney
agenesis was also discovered. Raised blood
pressure was found in one 32 month old boy
with bilateral VUR, grade 2, and scars in the
upper left pole.

Discussion

The study indicated that the incidence of VUR
in general, and of VUR grades 2 and 3 in
particular, was much higher in siblings younger
than 1 year, than in older siblings, which
correlates with the well known fact that VUR
tends to disappear with age.

The rationale of detecting VUR in siblings
lies in the fact that children with VUR are more
prone to pyelonephritis and to develop renal
scars than do children without VUR. Besides, it
is of considerable interest that most reflux
associated renal scars are already present when
the patient is first investigated. This suggests
that the development of irreversible renal scar-
ring within one week after the introduction of
Escherichia coli into the bladder of refluxing
piglets, as shown by Ransley and Risdon,[14] may
also be true in humans. It also indicates the
need for more prompt diagnosis and vigorous
treatment of the first UTI, as already suggested
by many authors.[15-17] It has been widely
accepted that renal scarring tends to develop
mainly in infants and young children, and that
new scars or progression of previous scars rarely
occur after the age of 5 years. Recently there is
growing evidence that this may not be so, and
that the severity of VUR, the frequency of UTI
and abnormal bladder function are the main
contributing factors.[18] It might be hoped that

close follow up and/or either surgical or conservative treatment might reduce the risk of renal scarring in asymptomatic siblings found on the basis of family history to have VUR as most of them will not yet have suffered a symptomatic UTI. However promising, this presumption has not yet been proved.

DRVC is a highly sensitive method and exposes the patient to much less radiation than the x ray voiding cystography.[11][19] We believe that the benefit of DRVC in detecting VUR in asymptomatic siblings outweighs the invasiveness of the procedure. We also believe that if screening is to be recommended, DRVC should be the procedure of the first choice. It is the VUR we are looking for, and ultrasound, intravenous urography, or DMSA scintigraphy could only identify children, to whom damage— at least to a certain extent—has already been done. Ten per cent of siblings in this study were found to have renal scars. They do not seem to be of any clinical significance yet, except in one of the 10 children with renal scarring, who has already been shown to have hypertension. Before a more conclusive decision is reached regarding the rationale of screening asymptomatic siblings of patients with VUR, a long term follow up should be done to watch the progress of scars and the development of hypertension in this group and compare it with the findings in children found to have VUR after bacteriologically proved UTI.

It is not clear up to what age the asymptomatic siblings of index children with VUR should be investigated. Van den Abbeele *et al* recommend 10 years as the limit, beyond which siblings should be screened with DRVC, while with older siblings ultrasonography of the kidneys should be done.[10] Noe and Jerkins studied 287 siblings of 221 index patients with VUR and found a 32% incidence of reflux in siblings. However, siblings younger than 18 months had a much higher incidence of reflux than did the older siblings. They recommend a screening voiding cystogram, preferably with radionuclide, for siblings younger than 5 years of age.[20] Their data correlate with ours, where the highest incidence of high grade VUR was seen in children under 2 years of age. On the other hand, a certain number of refluxes of grade 1 (which in our study were discovered mostly in the older children), would have probably been of higher grade if the siblings had been investigated at an earlier age. Aggarwal and Verrier Jones report 33 asymptomatic children with a family history of reflux nephropathy or VUR in first degree relatives.[21] Fifteen (45%) showed some abnormality of the renal tract on ultrasound or micturating cystourethrography, or both, and 12 of them were under 2 years of age.

Based upon present data we believe that the age limit of siblings to whom the DRVC should be done could be lower than 10 years of age as recommended by Van den Abbeele *et al*,[10] but

not lower than 2 years. Currently it is our practice to screen with DRVC all preschool siblings of the index child, while older siblings have renal ultrasonography. In addition, parents of a child with VUR are instructed that a newborn sibling should be screened as soon as possible. This procedure is also likely to be justified for children of parents with reflux nephropathy.

In conclusion, identifying children with VUR among asymptomatic siblings could possibly prevent renal damage and its consequences. The predictive value of positive family history alone in identifying VUR in our study was 45%, and 23% of siblings with VUR were found to have renal scars. This appears high enough to justify the routine investigation of asymptomatic siblings of children with VUR, by using DRVC at an early age.

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