

SEVERE VESICoureTERAL REFLUX AND CHRONIC RENAL FAILURE: A CONDITION PECULIAR TO MALE GENDER? DATA FROM THE ITALKID PROJECT

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Primary vesicoureteral reflux (VUR), one of the principal causes of chronic renal failure (CRF), occurs as a result of two distinct and sex-related mechanisms: congenital renal hypoplasia, which is prevalent in males, and acquired renal scarring in females.

We used data from the Italkid Project, a prospective population-based CRF registry of patients undergoing conservative treatment, to evaluate the gender distribution and severity of primary VUR, the age at diagnosis, and the diagnostic and therapeutic methods adopted in children with CRF. The prevalence of males (77.5%), the severity of VUR (grade IV-V), and the early age at diagnosis (18% prenatally) seem to suggest that congenital renal damage is the major cause of pediatric CRF. (*J Pediatr* 2004;144:677-81)

Primary vesicoureteral reflux (VUR) is a common genetically determined condition¹ that is associated with varying degrees of renal damage and represents one of the main causes of chronic renal failure (CRF) in children.²⁻⁴ The damage can be explained by two mechanisms, which lead to instrumentally indistinguishable and often co-existing renal lesions whose prevalence differs between sex. The first is congenital renal hypodysplasia, which has very often been found in male newborns with severe VUR diagnosed on the basis of fetal ultrasound abnormalities.⁵⁻¹¹ The second is acquired segmental scarring as a result of urinary tract infections (UTIs),^{12,13} which has been mainly documented in female children affected by mild/moderate reflux and recurrent UTIs.¹⁴ The relative role of these two mechanisms in causing CRF has not yet been clarified¹⁵ and may have changed over the last 30 years. The emphasis placed on the early diagnosis of VUR and UTIs since the 1970s may have reduced the incidence of acquired renal damage and, therefore, its impact on the genesis of CRF.^{4,16}

Although CRF registries have demonstrated the importance of VUR as a cause of renal impairment, they have not provided detailed demographic information concerning the affected patients. The aim of the present study was to describe the characteristics of patients with primary VUR who develop CRF, with special attention to sex-specific differences, in an attempt to improve our understanding of the factors responsible for renal failure. To this end, we used data provided by the Italkid Project, a prospective population-based registry of Italian children founded in 1990, which collects information of all patients with CRF born over the last 30 years, during which the policy of preventing scarring by means of early diagnosis and treatment of VUR became well established.

MATERIAL AND METHODS

The Italkid Project is a prospective population-based registry of Italian children with CRF, which was started in 1990 with the following inclusion criteria: (1) creatinine clearance < 75 mL/minute/1.73m² according to Schwartz's formula¹⁷ (or serum creatinine more than 3 standard deviations above the mean level for sex and age in the case of children aged < 1 year) and (2) an age of < 20 years at the time of registration. The organizational structure of the registry, the type of available information, and the data collection procedures have been described in detail elsewhere.³

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ANZDATA	Australia and New Zealand Dialysis and Transplant Registry	UTIs	Urinary tract infections
CRF	Chronic renal failure	VUR	Vesicoureteral reflux

Table. Associated renal and urologic abnormalities by sex

Renal/urologic abnormalities	Males (220)	Females (64)	P
Multicystic kidney (7) and agenesis (29)	24 (10.9%)	12 (18.7%)	.097
Other uropathies*	9 (4.1%)	1 (1.5%)	NS
Other conditions (cortical necrosis, stones)	0 (0%)	2 (3.1%)	NS
Total	33 (15.0%)	15 (23.4%)	

NS, Not significant.

*Pyeloureteral stenosis (n = 7), vesicoureteral junction stenosis (n = 2), complex uropathy (n = 1).

As of December 31, 2000, 1197 patients had been registered; the present study refers to all of the patients in whom primary VUR was reported as the main cause of CRF.

The data already available in the registry (sex, creatinine clearance, age at the time of registration, and major co-existing urologic abnormalities) were integrated with other information obtained by means of an additional study-specific questionnaire distributed in 1995-1997 to the physicians attending the patients with primary VUR. This additional information included: (1) age at VUR diagnosis; (2) the event leading to the diagnosis, according to the following pre-defined categorization: (a) UTI; (b) prenatal ultrasound report; (c) CRF; and (d) "other" (all the conditions not falling into any of the other three categories); (3) the grade of VUR at the time of diagnosis (according to the International Classification); and (4) the type and timing of therapy.

Statistical Analysis

The continuous variables were expressed as median values and interquartile ranges, and comparisons between the two sexes were made using the Mann-Whitney rank sum test. The discrete variables were compared using the χ^2 test.

RESULTS

Of the 1197 patients registered in the Italkid Project, 284 (25.7%) were affected by primary VUR: 220 of them (77.5%) were males, and their age at registration (median, 3.0 years; IR, 1.1-8.3) was significantly lower than that of the females (median, 7.9 years; IR, 3.0-11.4), whereas their creatinine clearance was not significantly different: median: 49.1 mL/minute/1.73m² (IR, 33.0-62.8 mL/minute/1.73m²) versus 54.0 mL/minute/1.73m² (IR, 40.2-65.0 mL/minute/1.73m²). The Table shows the major renal or urologic malformations associated with VUR and their sex-specific distribution: hypoplasia and wrinkled kidney were not included as they were not systematically reported because they were considered manifestations of reflux nephropathy. Renal agenesis combined with multicystic kidney (major co-causes of CRF) seems to be more common among females, although the difference is not statistically significant ($P = .097$).

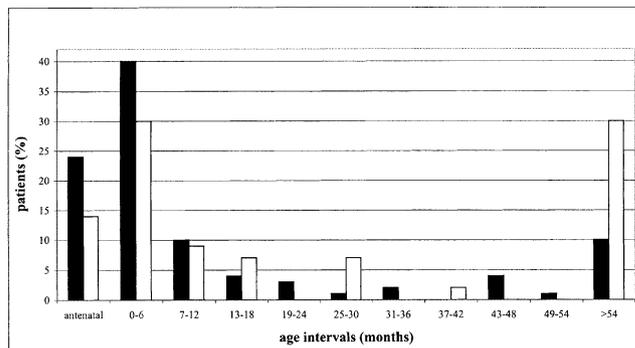


Fig 1. Frequency distribution of age (in months) at VUR diagnosis in 187 patients by gender (solid: males; blank: females). Median age at diagnosis: 3.0 months in males (n = 144) and 7.9 months in females (n = 43); $P = .045$.

Figure 1 shows the between-sex frequency distribution of age at VUR diagnosis in the 187 patients for whom the information was available. The diagnoses were generally made very early in life, particularly among the males, of whom 63% were diagnosed during the first 6 months of life as compared with 34% of the females ($P < .01$).

The events leading to the diagnosis of VUR, known in 191 patients, are shown in Figure 2. UTI represented the more frequent cause of diagnosis; prenatal reports were significantly more frequent among males than females ($P = .045$).

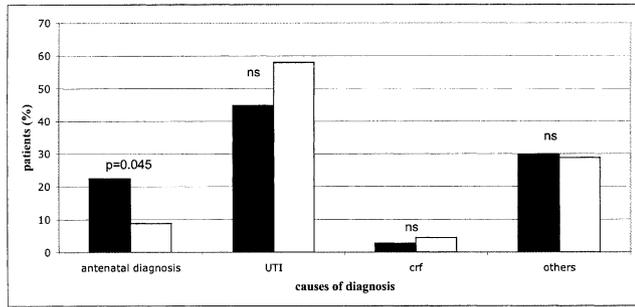
The degree of VUR (Fig 3) was reported for 179 patients (312 renal units). The VURs were usually bilateral; the unilateral cases were associated with renal agenesis, multicystic kidney, or contralateral obstructive uropathies. The majority (64%) of the VURs were grade IV or V in both sexes, and these were diagnosed earlier than the grade I to grade III cases ($P = .0001$); the median age at diagnosis was, respectively, 2 months (IR, 0-11 months) versus 9 months (IR, 3-51 months).

The therapeutic choice, at the time the survey was performed, was specified for 195 patients: 155 (79.5%) were surgically treated (95 within 6 months of diagnosis), thus making surgery the first-choice treatment.

DISCUSSION

The fact that the Italkid Project identifies primary VUR as a separate diagnostic category among the causes of CRF made it possible to study this group of patients in detail and to confirm that VUR is the principal cause of CRF in children.^{2,4} The Italkid data also indicate that VURs complicated by CRF mainly affect males, are generally severe, and are not currently burdened by a late diagnosis. On the other hand, it is likely that patients with a less severe grade of reflux usually will not end up in CRF and, consequently, are not recorded in the registry.

The striking prevalence of males in our population of CRF patients with VUR is a new finding that apparently conflicts with the data of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), one of the



*p<0.05

Fig 2. Events leading to the diagnosis of VUR in 191 patients by gender (147 males: *solid*, and 44 females: *blank*).

first CRF registries and one which, like Italkid, considers primary VUR as a single diagnostic category. The ANZDATA data indicate that the distribution of CRF secondary to reflux, <20 years of age, is similar in the two sexes.¹⁸ ANZDATA was started in 1972 and covers a heterogeneous population of adults and children with end-stage CRF born since 1949, thus including a period in which the disease was diagnosed later¹⁹ and treated less aggressively; on the contrary, the Italkid Project was started in 1990, is limited to pediatric patients born after 1975, and includes patients in pre-dialysis of varying degrees of creatinine clearance. The Italkid data are therefore not influenced by the progression of CRF, which may be different in the two sexes.²⁰ Thus, we believe that Italkid data better reflect the current morbidity of the disease. On the other hand, previous studies based on small patient series had already reported a more severe kidney involvement in males with VUR,^{21-23,27} but their findings are insufficiently representative because of the small number of patients studied, given the fact that severe renal damage and CRF is a rare complication of VUR. As it is a population-based CRF registry, Italkid collects the entire population of VUR patients who have developed renal failure, and therefore represents an optimum observatory for directly studying their characteristics.

Italkid patients developed CRF despite the generally early diagnosis of VUR. However, the diagnosis was established significantly later in females than in males, a previously known difference,²⁴ which has been attributed to the different age-incidence of UTIs in boys and girls.²⁵ We think that this difference may also reflect the greater severity of the disease in males, which can be responsible for its earlier clinical manifestation. This interpretation is indirectly confirmed by (1) the male prevalence in the Italkid registry despite the well-known higher incidence of VUR among females²⁶; (2) the earlier identification of CRF in males; and (3) the higher incidence of other concomitant CRF-causing diseases in females. These observations seem to corroborate the already suspected hypothesis of a between-sex difference in the nature of the reflux.^{5,21,27}

Earlier diagnoses also suggests that acquired renal damage played a limited role in the genesis of renal impairment, particularly in the large group of patients with an

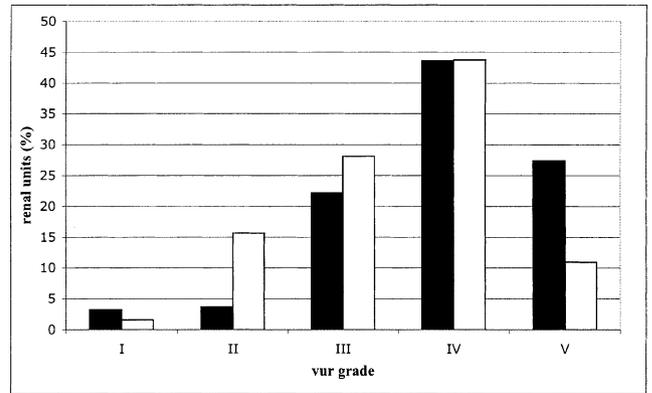


Fig 3. Degree of VUR in 312 renal units (248 males: *solid*, and 64 female: *blank*).

antenatal diagnosis and early management (20% of males). Although the clinical history of Italkid patients is not known in detail, 80% of them attended a major Italian pediatric nephrology center well experienced in this condition. Under these conditions, it is known that new renal lesions rarely occur, and disease outcome mainly depends on the lesions present at the time of diagnosis regardless of the type of treatment.^{28,29} Furthermore, the high percentage of surgical correction of reflux soon after diagnosis, besides documenting the still common assumption that reflux is important for UTIs and progressive damage of renal parenchyma, confirms that even this aggressive approach has not prevented renal failure in these patients. We believe that these observations are evidence that hypoplasia might have played an important role in the genesis of CRF. Our interpretation is supported by previous observations that VUR diagnosed on the basis of a prenatal ultrasound scan is often associated with renal hypodysplasia, particularly in asymptomatic male newborns affected by severe reflux (grade IV-V).^{5-9,11} In our cases, the VUR was generally grade IV or V, particularly in males; however, given the tendency of VUR to improve spontaneously with age,³⁰ it is possible that the milder cases (grade I-III) diagnosed later were also originally more severe.

Our data do not exclude the possible involvement of other factors in the pathogenesis of CRF. The role of co-existing nephro-uropathies is anything but negligible, and it can be speculated that the late diagnoses (>54 months) with undiagnosed previous UTI among some females might have played an important role in such cases.

The association between renal dysplasia and hypoplasia with urinary tract malformations, known as the CAKUT syndrome (Congenital Anomalies of the Kidney and Urinary Tract),³¹ may be the result of an alteration in ontogenesis involving both the kidney and the urinary tract. Hypoplasia also has been shown in an animal model as the consequence of the higher voiding pressure in males than in females in conjunction with VUR.³² This complex developmental process is controlled by the interaction of various genes, and the greater severity of VUR in males has led to a number of genetic hypotheses that still need to be investigated in detail (eg, X-linked genes, linkage disequilibrium).

In conclusion, the association between VUR and CRF is mainly observed in males; reflux was diagnosed early in life in many cases, nevertheless, the progression of kidney damage could not be prevented. This supports the growing doubts concerning the common assumption that females with frequent UTIs and a delayed diagnosis are at greater risk of CRF^{33,34} and points to the presence of parenchymal damage or hypoplasia before birth and to genetically determined disturbance of organogenesis associated to reflux, which mainly affects males. It cannot be excluded that the striking under-representation of females in the ItalKid registry, in comparison with the ANZDATA registry, is also the result of the more widespread and aggressive management of UTIs over the last 30 years, which could have led to an earlier detection of VUR than in the past. It is well known that females benefited from this reduction in age at VUR diagnosis more than males.¹⁹ It remains possible that VUR in females with primary unaffected kidneys leads to CRF in adulthood.

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APPENDIX

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