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BRIEF REPORT

Choni Rinat · Amicur Farkas · Yaacov Frishberg

Familial inheritance of crossed fused renal ectopia

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Abstract A family with dominant inheritance of a rare renal malformation is reported. The father and one son had left crossed fused ectopic and dysplastic kidneys and another son had a horseshoe kidney and vesicoureteral reflux. We discuss various potential pathogenetic mechanisms and propose that a defect in the timing of the proper reciprocal induction of the ureteric bud and the metanephric blastema is involved.

Keywords Crossed fused renal ectopia · Horseshoe kidney · Familial · Autosomal dominant

Introduction

Crossed (fused) renal ectopia is a rare renal anomaly (estimated incidence 1:1300–1:7500) [1, 2] in which both kidneys are located on the same side (either fused or not) with two separate ureters inserting into the bladder on opposite sides. We report a family with a presumably dominant inheritance of renal malformations: the father and one son had left crossed fused ectopic and dysplastic kidneys and another son had a horseshoe kidney and vesicoureteral reflux.

Case report

The proband was born at 36 weeks gestation (birth weight 2200 g) to non-consanguineous parents of Jewish-Iranian descent. A right kidney could not be visualized on prenatal ultrasound and an examination performed on the 1st day of life revealed left crossed fused ectopic kidneys with hydronephrosis and echogenic thin parenchyma in both kidneys. VCUG did not demonstrate vesicoureteral reflux or bladder outlet obstruction. There was no evidence of other congenital malformations. His renal function was compromised, with a serum creatinine level of 1.6 mg/dl. He underwent pyeloplasty of both moieties and ureteroureterostomy at the age of 1 month. Histological examination revealed an atretic ureter of the crossed kidney. Subsequently, his overall renal function markedly improved (serum creatinine 0.7 mg/dl) and at the time of writing he has been developing reasonably well. His father was found, at the age of 9 years, to suffer from hypertension with normal renal function. Imaging studies including angiography revealed left crossed ectopia. Renal function slowly deteriorated and his latest serum creatinine level was 1.6 mg/dl with a corresponding creatinine clearance of 40 ml/min.

A 28-month-old male sibling was found on abdominal ultrasound to have a horseshoe kidney, and a VCUG revealed right grade 3–4/5 vesicoureteral reflux without bladder outlet obstruction. The mother and two older siblings were healthy.

Discussion

Several renal and urologic malformations including refluxing or obstructive uropathies as well as dysplastic kidneys are commonly found in a familial pattern [3, 4]. Nevertheless, only two descriptions of familial crossed renal ectopia have previously been published. The first family is composed of a mother and child with crossed ectopia: the child on the right side and the mother on the left, while the maternal grandmother had an incomplete duplication of the left kidney [5]. The random occurrence of various renal malformations was postulated. The second description is of monozygotic twins with crossed renal ectopia [6].

Crossed renal ectopia has also been associated with various genetic disorders, further emphasizing the genetic background of this malformation. Goswami described crossed ectopia with pelvic malignant lipomatosis and an entire chromosomal translocation involving chromosomes 1 and 6 [7]. Acro-renal-ocular syndrome is an inherited disorder in which the renal malformations may include crossed renal ectopia [8].

In order to delineate the possible pathogenetic mechanisms related to this case, a brief review of normal renal

C. Rinat · Y. Frishberg (✉)
Division of Pediatric Nephrology, Shaare Zedek Medical Center and the Hebrew University-Hadassah School of Medicine,
PO Box 3235, Jerusalem 91031, Israel
e-mail: yaacov@md2.huji.ac.il
Tel.: +972-2-666-6144, Fax: +972-2-655-5689

A. Farkas
Department of Urology, Shaare Zedek Medical Center,
Jerusalem,Israel

morphogenesis is necessary. Formation of the metanephros, the developing kidney, depends on the existence of both the ureteric bud, which emerges from the lower portion of the mesonephric (Wolffian) duct, and the metanephric blastema, a poorly defined mesodermic tissue. By virtue of reciprocal induction, both tissues develop and propagate towards each other, merging to form the mature kidney and urinary tract. Normal development will not occur if either limb does not function properly or if there is failure of the distinct spatiotemporal relationship between them.

Cook and Stephens, searching for a plausible pathogenetic explanation for crossed ectopia, suggested that overbending and rotation of the caudal end of the developing embryo [9] may result in the inability of the ureteric bud to communicate with the more distant ipsilateral metanephric blastema. It would then be attracted to the now closer contralateral side. Their theory was supported by a study showing that inducing scoliosis in embryos resulted in a markedly high incidence of crossed kidneys [10]. Furthermore, there is an increased prevalence of crossed ectopia among patients with scoliosis [11, 12].

The insertion of two ureteric buds, one ipsilateral and one contralateral, to the same metanephric blastema will lead to the formation of two kidneys. This is implied from a study showing that pharmacological induction of supernumerary ureteric buds was responsible for the formation of multiple kidneys [13].

In crossed ectopia, it is obvious that one side is normal, while on the other side the ureteric bud failed to communicate with the ipsilateral metanephric blastema but managed to do so with the contralateral one and formed a kidney. We can therefore postulate that the ureteric bud is competent and the weak link is the metanephric blastema.

In familial cases and in the absence of skeletal malformations, it is unlikely that bending and rotation of embryos will reoccur accidentally. A genetically induced mechanism accounting for the attraction of a ureter to the contralateral blastema must be considered. To the best of our knowledge, none of the knock-out models of genes involved in kidney morphogenesis has resulted in crossed renal ectopia [14]. We therefore suggest a hypothetical pathogenetic mechanism that, in addition to explaining the familial occurrence, takes into account the existence of two phenotypes in one family (crossed ectopia and horseshoe kidney).

We propose that the pathogenesis involves a timing defect. Normal morphogenesis requires the coexistence of competent inducible constituents which are under strict temporal control. We assume that normally there is a small time difference between the induction of the two kidneys. This programmed time-lag prevents a message sent by one metanephric blastema being accepted by the contralateral ureteric bud. If as a result of a genetic error the time-lag malfunctions, the metanephric blastema will develop either too early or too late, and consequently will be non-synchronous with its corresponding ureteric bud. With late development of the metanephric blastema, the ureteric bud will find no “partner” on the same side and, by default, will be attracted to the contralateral side. The insertion of a second ureteric bud into the metanephric blastema results in the formation of a distinct kidney, in addition to the normal one. The two kidneys which develop on the same side may fuse and the two ureters might cross each other. If, on the other hand, premature development of the metanephric blastema occurs, the ureteric buds will be attracted by the two blastemas simultaneously. This will result in a marked proximity of the newly developing kidneys forming a unified renal entity termed horseshoe kidney. This pathogenetic mechanism implies a non-synchronous expression of a given gene in symmetric organs. A similar concept has been described in genes that govern the left-right determination [15] and in those accounting for hemihypertrophy.

Although a number of genes have already been associated with normal renal morphogenesis, many of the regulatory steps in this process have yet to be elucidated. Future studies in experimental animal models or in human embryos will hopefully shed light on the mechanisms responsible for defined renal malformations.

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