Clinical course, treatment and outcome of chronic kidney disease in VATER association

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Clinical course, treatment and outcome of chronic kidney disease in VATER association

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<ABSTRACT>

Clinical Course, Treatment and Outcome of Chronic Kidney Disease(CKD) in VATER Association

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Background: Renal anomalies occur in approximately 60% of VATER (nonrandom association of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with atresia, renal defects and radial limb dysplasia) patients. The renal anomalies can be associated with chronic kidney disease (CKD). With improved medical care, a large proportion of these patients are surviving into adulthood. However, longitudinal follow-up data regarding the management of kidney disease in these children do not exist.

Objective: To describe the course and outcome of kidney disease in VATER association patients and compare them to control patients with similar renal abnormalities but no VATER association

Design/Methods: The records of VATER patients with CKD stage 2-5 and age-matched controls with similar renal anomalies and CKD but no VATER association seen at the University of California San Diego from Jan 1980 to Dec 2005 were retrospectively reviewed. Statistical analysis was performed using SPSS v12.0.

Results: Fifty-four VATER (M:F 15:39) patients with renal involvement were identified, among which twelve(M:F 3:9) patients had CKD. The mean follow up period for the VATER patients was 15.0±1.4SE yrs, while the mean follow up period for the 12 controls was 11.9±2.1SE yrs. VATER patients had imperforate anus(91.7%), cardiac anomalies(66.7%), vertebral anomalies(50%), TEF(25%) and limb anomalies (25%). Eight VATER patients progressed to end-stage renal

disease(ESRD) compared to 4 controls (66.7% vs 33.3%). There was no significant difference in mean age at ESRD development (8.5±2.5 vs. 9.3±2.7SE yrs, $p>0.5$). Six VATER patients were dialyzed pre-transplant; 2 were on hemodialysis(HD) and 4 were begun on peritoneal dialysis (PD), but 3 were switched to HD within a few months due to complications(diaphragmatic leak, severe abdominal adhesions). Three controls were dialyzed without significant complications (2 on PD, 1 on HD). Seven VATER patients underwent renal transplantation compared to 4 controls. Mean creatinine clearance 2 years post-transplant was 65.8±6.3 in VATER patients vs. 87.8±7.1 ml/min/1.73m^2 in controls ($p=0.07$). VATER patients had a significantly lower mean height standard deviation score compared to controls (-2.34±0.41 vs. -1.27±0.24, $p<0.05$).

Conclusions: VATER association patients with CKD are predominantly female, have a high incidence of bladder abnormalities, develop ESRD more frequently, usually require HD as dialysis modality, experience more complications with dialysis, have a worse graft outcome 2 years post-transplant, and have more severe growth failure than controls.

Key words : VATER association, chronic kidney disease, short stature, transplant

Clinical course, treatment and outcome of chronic kidney disease in VATER association

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I. INTRODUCTION

VATER or VACTERL association refers to a group of congenital malformations that includes vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula with atresia, renal defects and radial upper limb dysplasia. The association was first described by Quan and Smith [1], and since then the description has been extended to include cardiac(C) and limb defects (L), with the resulting acronym of VACTERL [2, 3] . Temtamy et al. have suggested that the V in VATER could also include vascular defects such as ventricular septal defect(VSD) and single umbilical artery(SUA) [4].

Although some cases of VATER association have been found to be related to chromosomal trisomy and deletion defects [5], the VATER association is generally not related to a chromosomal abnormality. The anomalies appear to arise from developmental abnormalities of the mesoderm of the involved organs during early embryogenesis (<35 days), when the areas of formation of the lumbosacral spine, genitourinary tract and hindgut are in close proximity[6].

Renal anomalies are found in approximately 60% of VATER patients. Uehling et al. reported genitourinary involvement in 21 of 23 children with VATER association, including renal agenesis (7 cases), severe reflux (9 cases), crossed

fused ectopia (5 cases) and ureteropelvic junction obstruction (5 cases) [7]. Thirteen patients in their study required more than one surgical urologic intervention. Three patients progressed to renal failure and one patient had a renal transplantation.

Weber et al. reported renal malformations in 20 of 30 patients (67%) with VATER association, with the most common anomalies being renal agenesis (9 cases), unilateral hypoplasia and contralateral uretero-pelvic obstruction (4 cases), crossed renal ectopia (3 cases) and horseshoe kidney (2 cases) [8]. In their study, one patient died of renal failure and another of urinary sepsis at the age of 20 months.

Although renal anomalies occur at a high frequency in VATER association and managing these problems is a clinical challenge especially in the setting of multiple other medical issues, there is limited data on the clinical course of kidney disease in VATER association. The course of chronic kidney disease, the different management modalities, renal transplantation and its outcome, and growth in VATER association patients will be discussed.

II. MATERIALS AND METHODS

1. Subjects

The records of VATER patients with CKD stage 2-5 and age-matched controls with similar urologic anomalies and CKD but no VATER association seen at the University of California San Diego from Jan 1980 to Dec 2005 were retrospectively reviewed. The pregnancy and birth histories of the patients were obtained when available and all hospitalizations and operations were recorded.

2. Diagnosis and evaluations

The diagnosis of VATER association was made when more than 3 major organ systems were involved. The major organ systems included vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula with atresia, renal defects and radial upper limb dysplasia. Exclusion criteria in this study included patients with known chromosomal abnormalities or other disorders. All the patients underwent extensive evaluations, including ultrasounds, echocardiograms, voiding cystourethrograms and cystoscopy.

3. Formulas

Creatinine clearance (CrCl ml/min/1.73m^2) was estimated using both the Schwartz formula and the Cockroft-Gault formula:

1. If the patient had a weight less than 10kg, then [(0.45xheight in cm)/serum Cr][9].
2. If the patient was a female or prepubertal male with weight between 10 and 70 kg, then [(0.55xheight in cm)/serum Cr][9].
3. If the weight was greater than 70kg, then [(1.55xage+0.5Xheight in cm)/serum Cr][10].

Chronic kidney disease staging was performed according to K/DOQI guidelines[11]:

Table 1. Stages of chronic kidney disease

Stage	**Description**	**GFR (mL/min/1.73m^2)**
1	Kidney damage* with normal or	≥ 90

	increased GFR	
2	Kidney damage with mild decreased GFR	60-89
3	Moderate decreased GFR	30-59
4	Severe decreased GFR	15-29
5	Kidney failure	≤15 (or dialysis)

*Damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

Height standard deviation scores (SDS) were calculated by appropriate gender- or age-specific mean and standard deviation for the US population using the National Health and Nutrition Examination Survey (NHANES) III study (2000) of the National Center of Health Statistics. Since the 3rd percentile for age and gender corresponds to a height SDS of -1.88, the patients were categorized by height SDS<-1.88 and >-1.88.

4. Statistical analyses

Statistical analyses were performed using SPSS for Windows v. 12.0. Comparison of patient characteristics between VATER association patients and control patients was done by chi-square Fisher test and two-tailed Student's t-test. A p value < 0.05 was considered to be statistically significant.

III. RESULTS

1. Patient characteristics:

Fifty-four VATER patients with renal involvement were identified. Among these patients, 15 were male and 39 female. Twelve patients (22%) had CKD stage 2-5 and were the subjects of this study. The mean follow-up period was 15.0±1.4 SE years and all patients were diagnosed at birth. Six patients (50%) were delivered prematurely. Five (42%) were diagnosed prenatally with urological abnormalities. Two patients were diagnosed with oligohydramnios while 1 patient was diagnosed with polyhydramnios.

2. Extrarenal anomalies in VATER patients

There were multiple extrarenal anomalies observed in the VATER patients. The most common extrarenal anomaly was imperforate anus which occurred at an incidence of 92%, followed by cardiac anomalies, which was 67%. The most common cardiac anomalies were atrial septal defect and patent ductus arteriosus. Vertebral anomalies and limb anomalies occurred at 50% and 25% respectively. Limb anomalies included polydactyly, syndactyly and reduction deficiency.

Table 2. Extrarenal anomalies in VATER patients

	No. of Cases (%)
Vertebral anomalies	6 (50%)
Tracheo-esophageal fistula	3 (25%)
Imperforate anus	11 (92%)
Cardiac anomalies	8 (67%)
Ventricular septal defect	1 (13%)
Atrial septal defect	2 (25%)
Patent ductus arteriosus	2 (25%)
Dextrocardia	1 (13%)
Septal hypertrophy	1 (13%)
Limb anomalies	3 (25%)

3. Renal anomalies and intervention

Structural bladder anomalies were observed in 50% of the VATER patients. These anomalies included duplicated, enlarged, dysplastic and diverticulated bladders. Five patients had neurogenic bladders and 6 patients had cloacas. The high incidence of bladder dysfunction was such that most of the patients (92%) required vesicostomies or intermittent catheterizations. Most of the patients had combined multiple urologic anomalies with 5 patients (42%) having dysplasia and reflux and 3 patients (25%) having dysplasia, reflux and obstruction.

Table 3. Urogenital anomalies and intervention in VATER patients

	Structural bladder anomalies	Neurogenic bladder	Cloaca	Vesicostomy or catheterization
No. of patients (%)	6 (50%)	5 (41.7%)	6 (50%)	11 (91.7%)

Table 4. Other urological anomalies in VATER patients

	RF* only	**OS† only**	**DS‡ only**	**DS + OS**	**DS + RF**	**DS+OS + RF**
No. of patients (%)	1(8%)	1 (8%)	0	2 (17%)	5(42%)	3(25%)

RF*: reflux, OS†: obstruction, DS‡: dysplasia

Table 5. Summary of VATER patient renal characteristics

	Sex	**Renal anomaly**	**Urologic surgical intervention**	**Dialysis Modality**	**Transplant**
Patient 1	F	Bilateral hydronephrosis Neurogenic bladder Bilateral grade 5 reflux	Bladder augmentation Bilateral ureteral reimplant Vesicostomy		
Patient 2	M	Lt* kidney agenesis Rt. † VUR Dysplastic rt. kidney Urethrocutaneous fistula Chordee Rectourethral fistula Enlarged bladder	Cystostomy Chordee release		LRD‡ (pre-emptive)
Patient 3	M	Rt single dysplastic kidney Distal urethral duplication PUV Rt. grade V VUR Bladder diverticulum	Vesicostomy Rt. cutaneous ureterostomy	PD	LRD
Patient 4	F	Solitary rt. dysplastic kidney	Vesicostomy	PD then HD	LRD

		Lt. MCDK Stenotic urethra Cloaca	Rt. ureteroplasty and ureteroneocystostomy Urethroplasty		
Patient 5	F	Rt. MCDK Lt. moderate hydronephrosis Lt. VUR, Lt. UVJ obstruction Cloaca	Rt. nephrectomy Lt. ureter reimplant Bladder augmentation Mitrofanoff ileovesicostomy	HD	Cadaveric
Patient 6	F	Lt. kidney agenesis Rt. dysplastic kidney Grade 2 VUR			
Patient 7	F	Small rt. kidney Lt hydronephrosis, lt. VUR Neurogenic bladder Cloaca	Vesicostomy Mitrofanoff ileovesicostomy	PD then HD	Cadaveric
Patient 8	F	Cystic kidneys Lt. reflux Duplicated bladder Cloaca	Rt. loop ureterostomy	PD then HD	LRD

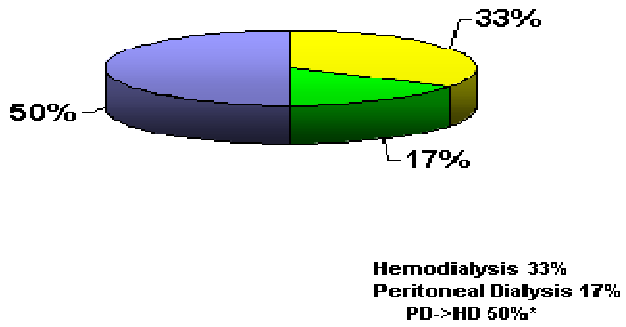
Patient 9	F	Bilateral reflux Cross fused ectopic kdney Deformed bladder Cloaca	Vesicostomy		
Patient 10	M	Small atrophic lt. kidney Rt. GII VUR Rt. Hydronephrosis Bulbar urethral stricture Chordee Neurogenic bladder	Vesicostomy Mitrofanoff transureteroureterostomy Bladder augmentation Release of chordee		
Patient 11	F	Neurogenic bladder Cloaca	Vesicostomy		LRD pre-emptive
Patient 12	F	Rt. UPJ obstruction Horseshoe kidney Lt. VUR Bladder diverticulum Neurogenic bladder	Bladder augmentation Rt. nephrectomy	HD	

Lt.*: Left, Rt.†: Right, LRD‡: living-related donor

4. Dialysis modalities

Six VATER patients were on dialysis. Two (33.3%) were on hemodialysis (HD), and 4 patients were initially on peritoneal dialysis (PD). 3 PD patients were switched to HD due to complications. One patient had a diaphragmatic leak, while two other patients had severe abdominal adhesions from multiple previous surgeries.

Figure 1. Dialysis modality in VATER patients



3 patients were switched to HD due to diaphragmatic leak and severe abdominal adhesions

5. Renal Transplant

Seven VATER patients were transplanted. Five patients (71.4%) received a living-related donor transplant, among which two were pre-emptive transplants. Two other patients received a deceased donor transplant. One patient on HD was unable to receive a transplant until the end of the study period. The time from diagnosis of end-stage renal disease (ESRD) to renal transplant was 9.1±3.2 SE mos. The mean creatinine clearance (CrCl) immediately post-transplant, 2 yrs post-transplant, and 5 yrs post-transplant was 88.4±8.4 SE, 65.8±6.4 SE, and 47.8±6.5 SE ml/min/1.73m^2 respectively.

Table 6. Transplant

Time from ESRD to renal transplant	9.1±3.2 SE mos
Tot. no of transplants	7 cases (87.5%)
Living-related donor transplant	5 cases (71.4%)
Deceased donor transplant	2 cases (28.6%)
Urologic interventions prior to transplant	6 cases (85.7%)
Graft failure	2 cases (28.6%)

Table 7. Mean serum Cr (mg/dl) and CrCl* (ml/min/1.73m^2) post-transplant

	Age at Transplant	Immediately post transplant	2 years post transplant	5 years post transplant
Patient 1	3.8 yrs	0.6 (81.6)	0.9 (66)	1.4 (47.1)
Patient 2	18.4 yrs	1.8 (53.5)	1.8 (53.5)	N/A†
Patient 3	11.1 yrs	0.8 (89.4)	1.2 (66.9)	1.5(54.8)
Patient 4	1.6 yrs	0.4 (113.4)	0.7 (71.7)	N/A†
Patient 5	2.9 yrs	0.4 (114.8)	0.5 (97.4)	0.9 (68.1)
Patient 6	8.1 yrs	0.8 (71.5)	1.0 (60.8)	1.9 (35.3)
Patient 7	7.7 yrs	0.6 (94.3)	1.4 (44.5)	2.1 (33.8)
Mean CrCl		88.4±8.4 SE	65.8±6.4SE	47.8±6.5SE

*CrCl: Creatinine clearance, †N/A: not available due to patient being less than 5 yrs post transplant

6. Growth in VATER patients

Eight (67%) VATER patients had a height SDS less than -1.88. For all these patients growth hormone was used with significant improvement in height SDS from -3.4±0.4 SE to -2.6±0.5 SE within 2 years.

Table 8. Growth in VATER patients

Height (Ht) SDS < -1.88	8 cases (66.7%)
Male	1 case (12.5%)
Female	7 cases (87.5%)

Growth hormone (GH) use	8 cases (66.7%)
Mean ht SDS before GH use	-3.4±0.4 SE
Mean ht SDS 2 yrs after GH use	-2.6±0.5 SE*

*difference in ht SDS pre and post GH use was 0.8±0.3SE, $p<0.05$

7. Comparison between VATER and control patients

VATER patients and age-matched controls with similar urologic anomalies but no VATER association were compared. The mean follow-up period was similar between the two groups (15.0±1.4 SE yrs vs. 11.9 ±2.1 SE yrs, p=0.23). The VATER patients were diagnosed earlier with CKD stage>2 compared to controls (3.8±1.7 vs. 9.4±1.8, p=0.06), although the mean age of reaching ESRD was similar for both groups. The number of patients who reached ESRD during the study period was greater in the VATER group, although this was not statistically significant. Most of the VATER patients were ultimately on HD, while one control patient was on HD. Although the VATER patients experienced several complications during PD, including diaphragmatic leak and severe abdominal adhesions that required them to switch to HD, none of the control patients experienced complications that required them to switch dialysis modalities. Seven VATER patients vs. four controls were transplanted and the mean CrCl 2 yrs post-transplant was 65.8±6.3 vs. 87.8±7.1 ml/min/1.73m^2 (p=0.07) respectively. The height SDS for VATER patients and control patients was -2.34±0.41 vs. -1.27±0.24 (p=0.02). VATER patients were significantly shorter than control patients.

Table 9. Comparison between VATER and control patients

	VATER	Controls	p-Value
M:F	3:9	5:7	
Mean follow-up	15.0±1.4 SE yrs	11.9 ±2.1 SE yrs	0.23
Mean age at diagnosis of CKD stage > 2	3.8±1.7	9.4±1.8	0.06

No. of ESRD pts	8/12 (67%)	4/12 (33%)	0.22
Mean age of reaching ESRD	8.5 ± 2.5 SE yrs	9.3 ± 2.7 SE yrs	0.82
Dialysis modality	HD: 2 PD then HD: 3 PD: 1	PD: 2 HD: 1	
No of transplant patients	7 /12 (58%)	4 /12 (30%)	
LRD	5(71.4%)	3(25%)	1.0
Mean CrCl			
6mos	72.3±10.8	100.7±8.4	0.1
2 yrs	65.8±6.3	87.8±7.1	0.07
Height SDS	-2.34±0.41	-1.27±0.24	0.02

IV. DISCUSSION

VATER association refers to a constellation of congenital malformations that includes vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula with atresia, renal defects and radial upper limb dysplasia. Although renal anomalies are found at a high frequency in VATER association, there are very few reports on the renal course in this subset of population, especially in pediatric patients. We followed our subjects over an extended period of time (15.0±1.4 SE yrs) and describe their renal anomalies, the course of their chronic kidney disease, dialysis modality and renal transplant course.

Among 54 VATER patients with renal disease at our center, twelve patients developed CKD stage 2-5 during the study period. Interestingly, we noted that although in VATER association, there is a greater predominance of males over females (52%)[12], the patients who had CKD in our study were predominantly female (75%). This observation may be due to the fact that the females had a high incidence of cloacas, which may have been the cause of urinary obstruction and therefore reduced renal function.

Multi-organ involvement in VATER patients greatly complicates medical care. In the study by Weber et al. of 30 infants with the VATER association, they reported that 21 of the patients (70%) required major surgeries on 2 organ systems, while 1 patient required major operative procedures on 3 organ systems[8]. Our patients also had multiple congenital anomalies, and these included imperforate anus(91.7%), cardiac anomalies(66.7%), vertebral anomalies(50%), and TEF(25%). Eleven patients in our study underwent surgery on more than 2 organ systems. In a study of 286 patients with VATER association[13], vertebral anomalies were found in 66.4% of the patients, comparable to 50% in our study. Esophageal atresia was found in 58.7%, which was at a higher incidence than our study, and cardiovascular defects in 47.6% of the patients. Imperforate anus also occurred at a high incidence of 82.5%. Interestingly there was a very high incidence of renal defects at 80.8%.

Fifty-percent of our subjects were born prematurely compared to 40% in

Weber's study and 42% were diagnosed prenatally with urological anomalies. Two patients had oligohydramnios while one patient had polyhydramnios. Early detection in the prenatal period may explain the high survival rate in our subject population compared to other published studies. Weber et al.[8] reported survival in 77% of their patients, while another study by Uehling et al. reported a similar survival rate of 78%[7]. There was no mention of the number of patients whose urologic anomalies were detected prenatally. All patients in our study were still surviving at the end of the study period. Warner et al. emphasized the importance of prenatal diagnosis in patients with urological anomalies[14], and this has significant implications especially for our study subjects who had complex urological issues, including cloacal anomalies. Urinary obstruction in the fetal period can cause long-term adverse complications[14]. In a study of 60 patients with cloacal anomalies, 50% developed CKD in childhood with 7% mortality due to renal failure. An early second trimester diagnosis of a cloaca especially is correlated with lung hypoplasia and impaired renal function[15]. These are important complications that the medical team should be aware of in preparing for perinatal care. Prenatal diagnosis would help prenatal counseling and help plan delivery of the patient in a facility with neonatal care intensive units and pediatric surgical facilities. With advancing technology, prenatal diagnosis of urological anomalies has improved remarkably, probably explaining the relatively high rate of prenatal diagnosis in our study.

Structural bladder anomalies were observed in 50% of the VATER patients with CKD. These anomalies included duplicated, enlarged, dysplastic and diverticulated bladders. Five patients had neurogenic bladders and 6 patients had cloacas. In total, 92% of the patients had bladder involvement, which required urologic interventions such as vesicostomies or intermittent catheterizations. Two patients underwent bladder augmentation, and five patients urinary diversion. The bladder anomalies may have played an important role in CKD progression in our patients. Renal failure can be induced by high pressure, noncompliant bladders. Many of our patients who were on intermittent catheterizations had problems with noncompliance, which may have led to backflow pressure on the kidney. Multiple

urinary tract infections were also a frequent complication among our patients. The bladder anomalies were also complicated by other renal problems.

The VATER patients with CKD had significantly complex urological issues (Table 5). Five patients (42%) had dysplasia and reflux, 3 patients (25%) had dysplasia, reflux and obstruction, and 2 patients (17%) had dysplasia and obstruction. Furthermore, there were urethral abnormalities such as stenotic urethra in 2 patients, urethrocutaneous fistula and chordee in one patient, and duplicated urethra in one patient. Fernbach[16] reported that 8 of 20 VATER patients had urethral anomalies, which included megalourethra, urethral duplication, anterior urethral valve, congenital stricture, and hypospadias. Due to the high incidence of urethral anomalies, the author recommended doing a voiding cystourethrogram on all males with VATER association even in the absence of clinical symptoms.

Uehling et al. in a study of 23 patients with VATER association found that similar to our study, their patients also had multiple renal anomalies[7]. Twenty-one patients had more than one type of renal involvement. The renal anomalies included renal agenesis (7 cases), severe reflux (9 cases), crossed fused ectopia (5 cases) and ureteropelvic junction obstruction (5 cases) [7]. Thirteen patients required more than one urologic surgical procedure. Four children underwent a vesicostomy in the first year of life for severe reflux, while 4 children had pyeloplasties for hydronephrosis and 4 others had ureteral reimplantations for reflux. Three patients required a nephrectomy and 2 underwent a urinary diversion. In our study, 2 patients underwent ureteral reimplants, one patient underwent ureteroplasty and ureteroneocystostomy, and six patients underwent urinary diversion.

In another study by Weaver et al. [12] of 46 patients with VATER association, 13 patients had renal agenesis, while sixteen patients had combinations of other renal anomalies. Four patients had horseshoe kidney, four had hypoplastic kidney, three had ureteropelvic junction obstruction, two had crossed renal ectopia, two had pelvic kidney, one had a duplicated collecting system, one had a caliceal diverticulum, and one had a multicystic dysplastic kidney. Three patients had

ureteral anomalies without associated renal defects. Two patients had a unilateral hydroureter and one had a blind pouch arising from the left ureter. Other ureteral anomalies included bifid ureter, bilateral ureteral agenesis, aplastic ureter, primary megaloureter, and unilateral triple ureter. No mention was made of bladder anomalies. These studies show the complex nature of the renal anomalies in VATER association.

Seven patients in our study progressed to ESRD during our study period. Thirty-eight percent of the patients who progressed to ESRD were 2-5 years of age versus 10.3% in the data released by the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). Patients 6-12 and 13-17 comprised 38% and 0% respectively, whereas in the NAPRTCS database, patients 6-12 and 13-17 comprised 30.7% and 38.5% respectively. The mean age of ESRD development was 8.5±7.1SD years. Therefore compared to the national US database, there was a higher percentage of patients developing ESRD at an early age. This may be explained by the high incidence of bladder abnormalities in our patients and also the multiple other medical issues that the patients experienced which may have adversely affected renal function.

Six VATER patients were on dialysis. Two (33.3%) were on hemodialysis (HD) and 4 patients were initially on peritoneal dialysis (PD). Peritoneal dialysis was initially chosen due to the many advantages it has for pediatric patients in general, with greater freedom to ambulate and less interruption of daily activities. However, 3 PD patients were switched to HD due to complications. One patient was switched to HD within four months because of the need for ileal conduit surgery of the urinary tract. Although an attempt was made to switch back to PD, this attempt failed due to multiple intra-abdominal adhesions. Another patient was on PD for two years but was switched to HD because of adhesions due to multiple abdominal surgeries, and episodes of peritonitis. One patient had a diaphragmatic leak, and was therefore switched to HD. For the 2 other patients who were on HD, PD was not even considered due to the patients having already had multiple abdominal surgeries. It appears that HD is the preferred modality for VATER patients due to the high incidence of intra-abdominal surgeries that these patients

have. In accordance with our study, Uehling et al. have also reported that the renal failure patients in their study also all underwent HD, although no mention is made on whether these patients required HD due to complications that prevented them from undergoing PD.

Other complications that these patients experienced during dialysis were line infections, catheter pulling, and peritonitis.

Seven VATER patients were transplanted. Five patients (71.4%) received a LRD transplant, among which two were pre-emptive transplants. Two other patients received a deceased donor transplant. The proportion of our patients who received a LRD transplant is consistent with the national database (NAPRTCS) that shows that LRD transplants accounted for a little under 60% of all pediatric transplants in 2005. The time from diagnosis of ESRD to renal transplant was 9.1±3.2 SE mos. Among the seven patients, six underwent urologic interventions, specifically urinary diversions, in preparation for transplant.

Patients who have congenital urologic anomalies have been shown to be at increased risk for urinary tract infection, surgical complications, graft dysfunction, and graft loss[17-19]. Some studies have suggested that patients who have a history of posterior urethral valves(PUV) and undergo renal transplantation have an increased bladder pressure that can lead to progressive graft dysfunction[17, 20]. There are conflicting reports on the management of the lower urinary tract before and after transplantation. Alfrey et al. reported that bladder augmentation before transplant caused increasing hydronephrosis and infection, and suggested takedown of bladder augmentation before transplant[21]. Another study also showed that patients with ESRD due to obstructive or reflux uropathy, who had undergone bladder augmentation, had a higher rate of metabolic acidosis and urinary tract infections after transplant[22]. Other studies, however, have shown that urinary tract reconstruction before transplantation is safe[20, 23, 24]. Koo et al. studied 18 patients with severe dysfunctional lower urinary tract anomalies that included PUV, urogenital sinus anomalies, prune-belly syndrome, completed bladder duplication, and ureterocele[24]. Eleven patients underwent bladder augmentation or continent urinary diversion, while 2 had intestinal conduit and 5 had a transplant into the

native bladder. They reported a patient survival of 100% and an allograft survival of 81% during a 4.4 yr follow-up period, which were similar to the values of all the children who underwent renal transplantation in their center. They therefore concluded that renal transplantation in patients with lower urinary tract dysfunction was successful, and that bladder reconstruction could be safely performed before and after transplant. DeFoor et al. also reported an overall graft survival rate of 82% in patients who underwent pre-transplant augmentation cystoplasty and continent reconstruction, concluding that lower urinary tract reconstruction was safe in children with ESRD[25]. In our study, all patients who underwent transplant had severe lower urinary tract anomalies. Six patients underwent urinary reconstruction prior to transplant and only 1 patient had graft failure (83% graft survival). Our results indicate that careful, staged urinary reconstruction before transplantation is relatively safe.

The mean creatinine clearance (CrCl) immediately post-transplant, 2 yrs post-transplant, and 5 yrs post-transplant was 88.4±8.4 SE, 65.8±6.4 SE, and 47.8±6.5 SE ml/min/1.73m^2 respectively. Compared to the NAPRTCS database, the mean CrCl immediately post-transplant and 2 yrs post-transplant was not statistically different. However, the mean CrCl 5 years post-transplant was significantly lower for patients with the same age at transplant in the NAPRTCS database. This indicates that the VATER patients had poorer graft function 5 years after transplant. Khositseth et al. reported no difference in graft function between kidney transplant recipients with obstructive and reflux uropathy compared to controls over a 10 year period[22]. This may indicate that factors other than urologic anomalies may influence graft function in VATER patients, especially since these patients had multiple other medical issues.

VATER patients have been noted to have growth deficiency. In a study of 31 VATER patients, 45% of the patients showed postnatal growth deficiency of at least -2SDS for the first 3 years of life or beyond[26]. Severe cardiac defect was correlated to the growth deficiency in 9 patients, but no cause for the growth deficiency in the other patients was noted. Khadilkar et al. found that VATER patients had normal serum insulin-like growth factor binding protein (IGFBP-3)

concentrations, and did not appear to have pituitary dysfunction[27]. Only one of their VATER patients had vertebral anomalies, and so this would not have explained the short stature.

In our study, 8 (67%) VATER patients had a height SDS less than -1.88. This was a significantly higher percentage compared to the NAPRTCS database, where CKD patients with a height SDS≤-1.88 comprised 35.8%[28]. Several factors can contribute to the short stature such as feeding difficulties, especially for patients with T-E fistula, multiple surgeries, and cardiovascular anomalies. However, we could not find a significant correlation between these factors and short stature for our patients. One limitation of our study is the small number of patients. With a larger study number, a more apparent cause may be uncovered. Surprisingly, for all these patients growth hormone was used with significant improvement in height SDS from -3.4±0.4 SE to -2.6±0.5 SE within 2 years. There has been no published report to date on the effect of GH on growth in VATER patients.

In order to observe the effect that the VATER association had on the course of renal disease, we identified age-matched controls with similar urologic anomalies to the VATER patients but without VATER association. The control patients had a mean follow-up period similar to the VATER association group (11.9 ±2.1 SE yrs vs. 15.0±1.4 SE yrs, p=0.23). The VATER patients were diagnosed earlier with CKD stage>2 compared to controls (3.8±1.7 vs. 9.4±1.8, p=0.06), although the mean age of reaching ESRD was similar for both groups. This observation may be due to the fact that the VATER association patients had other congenital defects that brought attention to their renal disease early in life (neonatal period), whereas the controls in a few cases were not even aware of having renal disease and presented with ESRD. The number of patients who reached ESRD during the study period was greater in the VATER group, although the difference was not statistically significant from the control groups. Most of the VATER patients were ultimately on HD, while one control patient was on HD. Although the VATER patients experienced several complications during PD, including diaphragmatic leak and severe abdominal adhesions that required them

to switch to HD, none of the control patients experienced complications that required them to switch dialysis modalities. Seven VATER patients versus four controls were transplanted and the graft function for the VATER patients was less than that of the controls with a mean CrCl 2 yrs post-transplant for the VATER patients being 65.8±6.3 versus 87.8±7.1 ml/min/1.73m^2 (p=0.07) for control. The height SDS for VATER patients and control patients was -2.34±0.41 vs. -1.27±0.24 (p=0.02), showing that VATER patients were significantly shorter than control patients.

The limitations of this study include a small subject number. Due to this limitation, we were unable to determine the prognostic factors for short stature and development of graft dysfunction. With a multi-center trial, there would be more data available that would provide statistically significant information. Due to improving medical care, we are observing that more VATER patients are surviving into adulthood. Since this population has complex medical needs, more longitudinal studies are required to provide guidelines on how to manage these patients.

V. CONCLUSION

VATER patients were predominantly female and had complex anomalies of the renal system that were complicated by multiple organ defects. They had a high incidence of bladder abnormalities, and developed ESRD early in childhood. Due to complications from multiple abdominal surgeries, these patients were usually unable to do PD and required HD as dialysis modality. VATER patients also seemed to have similar graft function initially compared to patients who had similar urologic anomalies but no VATER association; however, CrCl 2 yrs post transplant was worse (65.8±6.3 versus 87.8±7.1 ml/min/1.73m^2, p=0.07) compared to controls. VATER association patients with CKD had more severe growth failure than controls (-2.34±0.41 vs. -1.27±0.24, respectively (p=0.02)). Growth hormone use resulted in with significant improvement in height SDS from -3.4±0.4 SE to -2.6±0.5 SE within 2 years. Since there are very few reports on the renal course and complications of VATER association patients, many clinicians experience difficulties when treating these patients. By elucidating the clinical course, treatment, and outcome of kidney disease in VATER association patients, this study would contribute to awareness of the various complications that can arise during treatment of VATER patients, the modes of intervention that may be required, and the timing of these interventions.

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< ABSTRACT(IN KOREAN)>

VATER 증후군에서의 만성 신장 질환의 임상적 경과, 치료 및 결과

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배경
VATER 증후군은 척추결손, 쇄항, 심장 결손, 기관식도루, 신장 결손, 요측 상지 이형성증 등의 연관 질환이다. VATER 증후군의 약 60%에서 신장기형이 발견되며, 일부에서 만성신질환(chronic kidney disease, CKD)이 동반된다. 의학적 발전을 통해 최근에는 만성신질환을 동반한 VATER 증후군 환자의 상당수가 성인 연령까지 생존하지만, 이들의 신장 질환 관리에 관한 종단적 관찰 자료는 없다.

목적
VATER 증후군 환자의 신장 질환 경과 및 예후를 기술하고, 비슷한 신장질환을 동반하고 있지만 VATER 증후군이 아닌 대조군과 임상적 특징을 비교한다.

방법
1980 년 1 월부터 2005 년 12 월까지 University of California San Diego 병원에서 치료한 환자들을 대상으로 하였다. VATER 증후군 환자 중 만성 신질환 2 기~5 기에 해당되는 환자들의 의무 기록과, 동반된 신질환 및 연령을 기준으로 VATER 증후군 환자군과 서로 적합하게 선정된 대조군들의 의무 기록을 후향적으로 검토한 후, 두 환자군의 자료를 비교하였다. 통계 분석은 SPSS v12.0 을 이용하여 수행되었다.

결과
신장 결손을 가진 VATER 증후군군은 54 명(남: 여 = 15:39)이었으며 이 중 12 명(남:여 = 3:9)이 만성신질환을 동반하였다. 만성신질환 동반 VATER 증후군군의 평균 추적 기간은 15.0±1.4 년이었으며 대조군 12 명의 평균 추적 기간은 11.0±2.1 년이었다. VATER 증후군에서는 쇄항(91.7%), 심장 결손(66.7%), 척추 결손(50%), 기관식도루(25%) 및 사지 결손(25%) 등이 관찰되었다. VATER 증후군군 8 명과 대조군 4 명이 말기신질환으로 진행하였다(66.7% 대 33.3%). 말기신질환이 발생한 평균 연령은 두 군간

유의한 차이가 없었다(8.5%±2.5 대 9.3±2.7 년, $p>0.5$). VATER 증후군군 환자의 6 명이 이식전 투석을 받았으며, 이 중 2 명은 혈액투석, 4 명은 복막투석을 받았다. 복막투석을 시작한 4 명 중 3 명은 심각한 합병증(횡격막누출, 심한 복강 유착 등)으로 인해 투석 개시 수개월 이내에 혈액투석으로 전환하였다. 대조군으로서 투석을 실시한 3 명 중, 2 명은 복막투석을, 1 명은 혈액 투석을 받았으며 모두 심각한 합병증이 없었다. VATER 증후군군 중 7 명과 대조군 중 4 명이 신장을 이식받았다. 이식 후 2 년째 평균 크레아티닌 청소율은 VATER 증후군군에서 65.8±6.3 mL/min/1.73m^2 이었고, 대조군에서 87.8±7.1 mL/min/1.73m^2 이었다($p=0.07$). 평균 키표준편차점수는 VATER 증후군군에서 대조군에 비하여 통계적으로 유의하게 더 저하되어 있었다(-2.34±0.41 대 -1.27±0.24, $p<0.05$).

결론

만성신질환을 가진 VATER 증후군군 환자들은 주로 여자이었며, 방광이상을 보이는 경우가 많았다. 대조군에 비교하여 말기신질환을 잘 일으켰으며, 주로 혈액 투석을 필요로 하였고, 투석 중 더 많은 합병증이 발생하였으며, 이식 후 2 년째 신장 기능이 낮았고, 심한 성장 장애를 보였다.

핵심되는 말 : VATER 증후군, 만성신장질환, 저신장, 신장 이식