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Analysis of Renal Anomalies in VACTERL Association

Bridget K. Cunningham^{1,2}, Alina Khromykh³, Ariel F. Martinez², Tyler Carney², Donald W. Hadley², and Benjamin D. Solomon^{*,2,3}

¹Department of Pediatrics, Walter Reed National Military Medical Center-Bethesda, Maryland

²Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland ³Inova Translational Medicine Institute and Department of Pediatrics, Inova Children's Hospital, Inova Health System, Falls Church, VA

Abstract

VACTERL association refers to a combination of congenital anomalies that can include: Vertebral anomalies, Anal atresia, Cardiac malformations, Tracheo-Esophageal fistula with esophageal atresia, Renal anomalies (typically structural renal anomalies), and Limb anomalies. We conducted a description of a case series to characterize renal findings in a cohort of patients with VACTERL association. Out of the overall cohort, 48 patients (with at least 3 component features of VACTERL and who had abdominal ultrasound performed) met criteria for analysis. Four other patients were additionally analyzed separately, with the hypothesis that subtle renal system anomalies may occur in patients who would not otherwise meet criteria for VACTERL association. Thirty-three (69%) of the 48 patients had a clinical manifestation affecting the renal system. The most common renal manifestation (RM) was vesicoureteral reflux (VUR) in addition to a structural defect (present in 27%), followed by unilateral renal agenesis (24%), and then dysplastic/multicystic kidneys or duplicated collected system (18% for each). Twenty-two (88%) of the 25 patients with a structural RM had an associated anorectal malformation. Individuals with either isolated lower anatomic anomalies, or both upper and lower anatomic anomalies were not statistically more likely to have a structural renal defect than those with isolated upper anatomic anomalies ($p=0.22$, $p=0.284$ respectively). Given the high prevalence of isolated VUR in our cohort, we recommend a screening VCUG or other imaging modality be obtained to evaluate for VUR if initial renal US shows evidence of obstruction or renal scarring, as well as ongoing evaluation of renal health.

Keywords

VACTERL; VACTERL Association; VATER; VATER Association; Renal Anomalies

BACKGROUND

VATER association was first described in 1973 as the statistically nonrandom co-occurrence of congenital anomalies: Vertebral defects, Anal atresia, Tracheo-Esophageal fistula (TEF)

*Corresponding author contact information: Inova Translational Medicine Institute Claude Moore Building 3300 Gallows Rd Falls Church, VA 22042 Phone: 703-776-6118 Fax: 703-776-6117 benjamin.solomon@inova.org.

with esophageal atresia (EA), Radial and Renal dysplasia (Quan and Smith, 1973). Cardiac malformations and Limb abnormalities were later included, and the condition was called VACTERL association (Quan and Smith, 1973; Nora and Nora, 1973; Tetamy and Miller, 1974; Nora and Nora, 1975; Khoury et al, 1983; Czeizel and Ludanyi, 1985; Rittler et al, 1996).

VACTERL association is estimated to occur in 1 in 10,000 live births. The most widely accepted definition requires the presence of at least three component features (CFs) (Botto et al, 1997; Rittler et al, 1997; Kallen et al, 2001; Solomon et al, 2014). Some groups describe the presence of an anatomically-based upper and lower group of VACTERL/VATER-related anomalies, with cardiac defects in the upper and renal anomalies in the lower group (Kallen et al, 2001). A consistent requirement is the absence of any clinical or laboratory-based evidence of an alternate diagnosis (Solomon, 2011).

In addition to other malformations, the renal/urinary system is also frequently involved, with at least some of the types of representative renal anomalies involving ureteral bud defects (Quan and Smith, 1973). Further, while the initial clinical focus is often directed at the obvious conditions that can be life-threatening in the neonatal period such as TEF/EA, anorectal malformations (ARM), or severe congenital heart defects (Solomon et al, 2014). Urinary anomalies, which are infrequently immediately life-threatening and may not be recognized without the request for specific imaging may be incompletely assessed (Kolon et al, 2000).

The aim of this study is to better characterize the renal manifestations (RM) in a cohort of VACTERL patients who have undergone a standardized evaluation. Questions include: are specific RMs frequently observed in patients with VACTERL association? Is there a statistically significant association between the type of RM and VACTERL phenotype? As there can be important clinical implications involving long-term sequelae of nonstructural renal anomalies (e.g., vesico-ureteral reflux), how prevalent are these findings in our cohort?

MATERIALS AND METHODS

This study was conducted through our National Institutes of Health (NIH)/National Human Genome Research Institute IRB-approved protocol on VACTERL association, with appropriate consent obtained from all participants. For the purpose of this particular inquiry (focusing on renal findings), patients were included if they had at least three CFs of VACTERL and had available renal imaging (abdominal ultrasound) performed either in person at the NIH Clinical Center (along with the rest of their participation in the study) or prior imaging documenting a structural renal defect(s). After requiring the presence of a structural renal anomaly to be present to account for the “R” in VACTERL, we then looked more broadly at RMs in the cohort, as clinically significant RMs (such as hydronephrosis) may occur without structural RMs.

RMs were classified as structural vs. nonstructural. We defined nonstructural RMs as isolated hydronephrosis or vesico-ureteral reflux (VUR). We further divided the cohort

based on the presence of anatomic findings. The upper group was defined by presence of TEF/EA or congenital heart defect (CHD), the lower group by the presence of ARM. If the patient had upper and lower features they were considered to have both.

Patients were excluded from the analyses described here if they were unable to come to NIH, if they had less than 3 CFs, if no renal imaging was available in the absence of a prior diagnosis of renal disease, or if they had clinical or laboratory-based evidence of an alternative diagnosis (supplementary Figure 1). We did not include isolated GU anomalies in our definition of renal anomaly (e.g., scrotal defects, hypospadias, cloaca, or recto-vestibular/recto-urethral fistulae).

Clinical evaluation included genetic/dysmorphic physical examination and medical/family history (all by BDS), medical photography, echocardiogram, electrocardiogram, chest x-ray, x-rays of the entire spine and limbs, complete abdominal ultrasound, complete blood count, complete metabolic panel, urinalysis, with other testing as clinically indicated based on specific manifestations. The molecular studies involved to attempt to discern the causes of VACTERL and related disorders include high-density microarrays, candidate gene sequencing, Fanconi anemia testing, and trio-based exome sequencing. None of the individuals described here have a known molecular or other known etiology for their VACTERL association-type findings.

Statistical analysis was performed using Fisher's exact test (2-sided) or chi-square analysis as appropriate. P-values < 0.05 were deemed statistically significant.

RESULTS

The overall VACTERL cohort consists of 220 patients, 62 of which were able to come to the NIH for full evaluation. Forty-eight patients met criteria for analysis. As described, none of these patients had an identified molecular etiology or other cause that would explain their condition. Thirty-three (69%) of these 48 patients had some type of anomaly affecting the renal system, which we further characterized as structural or non-structural. There was no significant difference regarding gender either in the overall cohort or in the group with RMs ($p=0.39$, $p=0.12$, respectively).

Four patients (12%) had a classification of upper VACTERL, 8 (24%) had lower, and 20 (61%) had a classification of both based on anatomic phenotype (Table 1). One patient (3%) had neither features of upper nor lower VACTERL using our described criteria with component features of vertebral anomalies, renal anomaly and limb anomaly. (See Table 2 for details of RM; see Supplementary table for full clinical details).

Of the total 48 patients, 25 (52% of the total patients, 76% of the 33 patients with RMs) had a structural RM, while 8 (17% of total patients, 24% of the 33 patients with RMs) had a nonstructural RM. Of the 25 patients who had a structural anomaly, 12 (48%) also had a coexisting nonstructural anomaly (VUR or hydronephrosis). The most common RM was VUR in addition to a structural defect (present in 27%), followed by unilateral renal agenesis (24%), and then dysplastic/multicystic kidneys (18%) and duplicated collecting

system (18%). Additional, anomalies in the cohort are further reported in Table 2. Examples of typical ultrasound findings are presented in Supplementary Figure 2.

Twenty eight (85%) of thirty three patients with RM had an associated ARM. Of the 28 patients with ARM, 13 also had VUR (46%) grade 2 or higher. Twenty-two (88%) of the 25 patients with a structural RM had an associated ARM. Anatomic classification was not statistically associated with the presence or absence of RMs.

DISCUSSION

Congenital renal anomalies occur in 1 in 500 live births (Nakanishi et al, 2003). The underlying cause(s) of VACTERL association (including renal anomalies) have long centrally implicated Hedgehog signaling (Ngan et al, 2013). The precise type of renal anomaly appears to depend on the level and nature of the genetic lesion in relation to Hedgehog signaling, and remains incompletely elucidated.

The overall prevalence of RM (69%) in our cohort is similar to other published studies (Uehlig et al, 1983; Weber et al, 1980). Similar to the Ahn et al study in 2009, most of our patients had a structural defect (68%) (see Table 2). The presence of an ARM (or features of lower VACTERL anatomic phenotype) was not statistically associated with co-existence of a structural RM ($p=0.11$).

The most frequent RM in our VACTERL cohort was VUR in conjunction with a structural renal anomaly. Interestingly, however, isolated VUR or hydronephrosis were also common, reported in 24% of patients when considered together. The high incidence of this nonstructural RM is similar to data published by Kolon et al in 2000, which reported that 63% of the studied cohort had underlying VUR in the setting of a normal renal US. The etiology of these nonstructural RM is unclear – some may result secondarily from malformations affecting other organ systems, such as an ARM or lower vertebral anomaly. However, it is also possible that these nonstructural RMs may represent an intrinsic anomaly in the renal system in patients within the broad and admittedly heterogeneous group of patients. It is likely that better answers will be provided with further knowledge about the underlying causes of VACTERL association and related conditions (Saisawat et al, 2013).

Several of our patients had a late diagnosis of VUR (remote from infancy) and others experienced life-long complications such as hypertension and renal dysfunction, including individuals who require renal transplant. This anecdotal evidence nonetheless has important clinical implications. Given the high prevalence of isolated VUR or hydronephrosis, we recommend a screening renal US as part of the initial evaluation in patients with suspected VACTERL association. If the US shows evidence of obstruction or scarring, further imaging such as VCUG and consultation is indicated.

VUR can predispose to urinary tract infections and renal scarring, leading to progressive renal damage and renal insufficiency. Specifically regarding the population described in this manuscript, and in accordance with current Academy of Pediatrics Clinical Practice Guidelines published in 2011 and reaffirmed in 2014, we recommend considering antibiotic prophylaxis in infants with recurrent febrile UTIs during the first year of life, in addition to

obtaining a VCUG. We recommend that families and practitioners be vigilant with regard to infections and that there be a low threshold to screening febrile infants for UTI as part of their initial evaluation for fever.

The severity of renal defects in our cohort ranged from self-resolving and/or of unclear clinical significance to requiring surgical interventions. It is important to note that the coexisting comorbidities associated with VACTERL association may impact the overall prognosis and outcome. Ahn et al reported long-term follow up data on 12 VACTERL patients with chronic kidney disease (CKD) stage 2-5 compared to age matched controls (similar urologic anomalies and CKD). This group found that VACTERL patients develop end stage renal disease (ESRD) more frequently, experience more complications with dialysis, may have a poorer transplant outcome and have more severe growth failure than other patients (Ahn et al, 2009). We feel that all VACTERL patients should undergo lifelong surveillance and monitoring of growth, blood pressure and renal function with close urologic follow up throughout childhood, as such monitoring is relatively easy and non-invasive, but can be important in recognizing and preventing sequelae.

The strengths of our study include a cohort of patients who were each examined in person by the same clinical geneticist and through the same study modalities. We were thus perhaps better able to exclude individuals with distinct underlying disease processes that resulted in phenotypic features similar to VACTERL. We also used stringent inclusion criteria (including the number of CFs) to allow a slightly more homogeneous population even within an extremely clinically heterogeneous disorder.

In addition to the small cohort, an important weakness of this study is selection bias. First, we accepted the standard definition of VACTERL association as requiring 3 CFs (of which one could be a renal anomaly). Second, we only included individuals with abdominal imaging, again potentially increasing our selection bias.. Last, for some individuals, we relied on reported history with regard to presence of specific RM due to prior surgical correction, isolated reflux or spontaneous resolution. We did not perform invasive imaging tests on any patient due to the risks and discomfort of these procedures. This potential bias may have falsely decreased the overall prevalence of RMs (specifically VUR) in our cohort.

While this study does not, by design, provide further evidence towards the questions of whether RMs are a defining feature of VACTERL association, the frequency of renal disease in our cohort lends support to it being an important medical consideration in patients with VACTERL association. Based on our experience, we recommend a screening renal US in all patients with a potential diagnosis of VACTERL association and additional VCUG or other imaging if there is evidence of scarring or obstruction. Individuals with VACTERL association should undergo regular evaluation of renal health throughout their lifetime and patients, families and practitioners should be aware of the risk of renal sequelae and complications related to VUR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Upper VACTERL (presence of congenital heart defect and or trachea-esophageal fistula), Lower VACTERL (presence of anorectal malformation), Both (features of both Upper and Lower VACTERL). Nonstructural renal defects include isolated VUR and isolated hydronephrosis without evidence of obstruction.

NIH VACTERL Cohort			
Total patients	48		
Renal patients	33	69%	
Male	21	64%	
Female	12	36%	
Type of Renal Manifestation			
Structural	25	76%	
Nonstructural	8	24%	
VACTERL Anatomic Description			
Upper VACTERL	4	12%	
Lower VACTERL	8	24%	
Both	20	61%	
Neither	1	3%	
Anatomic Classification and Renal Manifestations			
	Structural	Nonstructural	
Upper VACTERL	2	3	
Lower VACTERL	7	1	p=0.22
Both	15	5	p=0.28
Gender and Renal Manifestation			
	Structural	Nonstructural	
Male	16	5	p=0.70
Female	9	4	

Table 2

Type of Renal Manifestations. GU: Genitourinary; RM: Renal Manifestation. VUR: Vesico-ureteral reflux.

<u>Type of RM</u>	<u>Number affected</u>	<u>%</u>
VUR plus structural anomaly	9	27%
Unilateral renal agenesis	8	24%
Dysplastic/multicystic kidneys	6	18%
Duplicated collecting system	6	18%
Isolated VUR *	4 †	12%
Hydronephrosis without structural anomalies	4 †	12%
History of VUR without hydronephrosis	3	9%
Horseshoe kidney	3	9%
RM + associated GU anomalies **	3	9%
Renal atrophy or hypoplasia	3	9%
Ectopic (pelvic) kidney	2	6%
Isolated ureteral stenosis	1	3%

* Isolated VUR defined as grade 2 or higher.

** Associated GU anomalies were found in addition to documented or observed renal anomalies.

† Only patients meeting stricter criteria for VACTERL association are included (see Materials and Methods)