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Original article

Long-term outcomes of adults with features of VACTERL association

Manu S. Raam [a,b,1], Daniel E. Pineda-Alvarez [a], Donald W. Hadley [c], Benjamin D. Solomon [a,*]

[a] Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Building 35, Room 1B207, 35 Convent Drive MSC 3717, Bethesda, MD 20892-3717, USA
[b] HHMI-NIH Research Scholars Program, Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815-6789, USA
[c] Social and Behavioral Research Branch, National Human Genome Research Institute, National Institutes of Health, Building 31, Room B1B37, 31 Center Drive MSC 2073, Bethesda, MD 20892-2073, USA

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ABSTRACT

VACTERL association involves the presence of specific congenital, multi-organ malformations that tend to co-occur. Clinical and research efforts typically center on pediatric patients, and there is a scarcity of information in the literature regarding VACTERL-related issues and outcomes in adulthood. We describe here 11 adults with features of VACTERL association ascertained through our research study on the condition. In our cohort of adult patients, approximately 25% of medically significant malformations that are component features of VACTERL association, including 40% of vertebral, 50% of cardiac, and 50% of renal anomalies, were not identified during childhood. Additionally, medical sequelae of many of the primary malformations identified in infancy or early childhood persist or are first reported in adulthood. These sequelae can involve challenging medical and surgical management in adulthood. As most adults with VACTERL association are not specifically followed for VACTERL-related issues, a more uniform diagnostic work-up and a low threshold for investigation of medical sequelae of the primary disorder may enhance the quality of clinical management in these patients.

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1. Introduction

VACTERL association, estimated to occur in approximately 1 in 10,000 live births [7], is a recognizable group of congenital malformations that tend to coexist in a single patient. In 1973, Quan and Smith initially named the condition VATER association, which included vertebral defects (V), anal atresia (A), tracheoesophageal fistula (TE) with esophageal atresia, renal defects (R), and radial dysplasia (R) [26]. The condition was soon redefined as VACTERL association, with the inclusion of cardiac defects (C) and additional limb anomalies (L) [23,26,35]. Uncertainty persists regarding exact diagnostic criteria. For example, some studies, such as the relatively large clinical series described by Weaver et al. in 1986 [39], required the presence of two component features for diagnosis, while others, including a follow-up study on that series [40], require at least three component features [3,4,14,29]. While several genetic causes have been implicated in a small number of human patients or in animal models [6,11,16,27,30,34,36], evidence of causality has not been uniform, and no consistent etiology has been identified.

Because VACTERL association is defined by congenital anomalies, clinical and research efforts tend to center around pediatric patients. Several large studies have obtained patient information from databases on congenital malformations in infants [3,4,14,15,29]; other sizeable cohorts have been described by pediatric geneticists or by pediatric surgical specialists, and focus mainly on infants and children [7,32,39]. While the outcomes of each of the component features have been studied separately, we located only one study examining long-term prognosis of adults with VACTERL association [40]; this study included many patients previously described as children, some of whom were ultimately found to have alternate diagnoses. The results of this study highlighted the fact that while patients with “classical” VACTERL association may have medical challenges, long-term outcomes generally tend to be positive [40].

Despite this, in our experience, many children diagnosed with VACTERL association are seen by pediatric geneticists and other

Abbreviations: ASD, atrial septal defect; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EA, esophageal atresia; GER, gastroesophageal reflux; TEF, tracheoesophageal fistula; UTI, urinary tract infection; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with esophageal atresia, renal defects, limb anomalies; VATER, vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, renal defects, radial dysplasia; VSD, ventricular septal defect.

* Corresponding author. Tel.: +1 (301) 451 7414; fax: +1 (301) 496 7184.
E-mail addresses: raamm@ccf.org (M.S. Raam), pinedaad@mail.nih.gov (D.E. Pineda-Alvarez), dhadley@nhgri.nih.gov (D.W. Hadley), solomonb@mail.nih.gov (B.D. Solomon).
[1] Present address: Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, 9500 Euclid Avenue Mail Code NA24, Cleveland, OH 44195-0001, USA.

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pediatric specialists, but are not followed for issues related to VACTERL association in adulthood. The paucity of information regarding VACTERL-related issues that persist or begin in adulthood is becoming increasingly problematic: children with VACTERL association now survive to adulthood more frequently than do children diagnosed decades ago, due to increased availability and quality of surgical treatments for TE fistula [9,18,25], imperforate anus [24,28], and congenital heart defects [8], as well as enhanced ventilatory support, neonatal anesthesia, and intensive care management [9,18]. Treatment of adults with VACTERL association is also complicated by the fact that although recurrence has been demonstrated in some families [2,22,32], the majority of patients do not have an affected relative whose medical care can highlight pertinent clinical issues [16].

Our research shows that many medically significant malformations may not be ascertained until after a patient's care has moved beyond the pediatric realm. Additionally, sequelae of malformations identified in infancy may not appear until later in life.

To address the need for information regarding clinical issues in adults with features of VACTERL association, we describe 11 adult patients diagnosed with VACTERL association.

2. Materials and methods

Over the course of approximately two years, our IRB-approved research protocol at the National Human Genome Research Institute (National Institutes of Health, Bethesda, MD, United States) has accumulated a cohort of 107 patients, consisting of fetuses, infants, children, and adults previously diagnosed with multiple features of VACTERL association. Inclusion criteria for the overall research study includes at least one of the following: at least three core component features of VACTERL association, at least two core component features and another congenital anomaly, or at least two core component features and a first-degree relative with at least one component feature. Patients were excluded if, either at first screening, or on later analysis, they were felt to likely meet criteria for an overlapping condition, either because of clinical features or results of genetic testing.

From this cohort, 11 adult patients were identified, with appropriate consent obtained from participants. All patients described here had been previously diagnosed or suspected to have VACTERL association (in Patients 1 and 10, who both had affected relatives, formal diagnosis was made upon participation in the study along with their affected family members). Participants were referred by clinicians or self-referred. Eight of the 11 patients were available to be contacted via telephone and/or e-mail for an extensive medical history. Six of the 11 patients, indicated by an asterisk (*) in Section 3.2, were additionally seen in person at the National Institutes of Health. For patients not seen in person, the telephone interview was supplemented by review of all available medical records provided by patients as well as those provided by referring clinicians in order to validate patient-reported information.

3. Results

3.1. Aggregate results

Eleven patients (10%) out of our total cohort of 107 patients with features of VACTERL association were adults (see Table 1 for a summary of adult patients and Fig. 1 for illustrations of selected findings). The adult group included five males and six females, with ages ranging from 28 to 64 years (mean 40 years). The average height in males was 170.2 cm; the average height in females was 159 cm. Eight patients (73%) demonstrated three or more component features of VACTERL association. Two patients (18%) had two component features of VACTERL association as well as clinical evidence of likely renal anomalies, but no further proof of that type of malformation. One patient (9%) had only two component features. In terms of specific component features, 10 patients (91%) had vertebral malformations, 5 (45%) had imperforate anus/anal atresia, 4 (36%) had cardiac malformations, 6 (55%) had a tracheoesophageal fistula (TEF), 4 (36%) had clear evidence of renal anomalies, and 4 (36%) had limb malformations. Three patients (27%) had genital malformations.

Five of the 11 patients (45%) were diagnosed with VACTERL association in childhood, and 8/11 (73%) were diagnosed at least 10 years before participation in our study. While the presence of imperforate anus/anal atresia, TEF, and limb anomalies were all diagnosed in infancy, vertebral anomalies were not diagnosed until adolescence/adulthood in 40% (4/10) of the patients with vertebral anomalies, cardiac anomalies were not diagnosed until adulthood in 50% (2/4) of patients with cardiac malformations, and renal anomalies were not diagnosed until adulthood in 50% (2/4) of patients with renal anomalies. Overall, 24% (8/33) of the core component features of VACTERL association in this cohort were not diagnosed until after childhood.

Karyotype testing was performed, with a normal result, in 1 patient (9%); microarray analysis (Illumina Omni1-Quad BeadChip) was performed, with a normal result, in 4 patients (36%); and no genetic testing had been reportedly performed (or known) for 6 patients (55%). No patients had evidence of developmental delay or neurocognitive impairment, or specific evidence for hydrocephalus. No patients described here had features highly suggestive of an alternate diagnosis.

Apart from Patients 1 and 2, who were father and daughter, patients were unrelated to each other. Patient 10 was the only other patient with a relative who also had VACTERL association. In Patients 1 and 2, inheritance appeared to be autosomal dominant, while X-linked inheritance was most likely in Patient 10's family. Patient 5 has multiple relatives with features of VACTERL association, though complete details are not available as the patient was adopted.

In terms of adult sequelae, 6 patients (55% of the total patient cohort, and 60% of the patients with vertebral anomalies) reported back pain associated with vertebral malformations. Five patients (45% of the total cohort and 100% of patients with imperforate anus/anal atresia) had adult sequelae of imperforate anus/anal atresia. Five patients (45% of the total cohort and 4/6, or 67% of those with TEF) reported dysphagia and/or reflux associated with TEF, as one patient who reported this issue did not have a TEF. Three patients (27% of the total cohort and 50% of patients with TEF) had pulmonary symptoms consistent with reactive airway disease, and 5 (45% of the total cohort, with 75% of patients who had a clear renal anomaly) had a history of UTIs and/or nephrolithiasis likely related to subtle renal anomalies, though only 1 (9% of the total cohort and 25% of patients with renal anomalies) had evidence of impaired renal function.

3.2. Individual patient descriptions

3.2.1. Patient 1*

Patient 1 is a 64-year-old male with VACTERL association with vertebral, cardiac, and possible renal anomalies. Adult sequelae include a ureteral stricture requiring surgical correction and numerous episodes of nephrolithiasis (>3000 stones) secondary to idiopathic hypercalciuria and resulting in renal papillary dilation, calyceal damage, and impaired renal function. At age 26, he began experiencing severe lower back pain, which was refractory to laminectomy, medication, and implantation of a spinal cord stimulator, and which greatly limits his activities. He also has a history of a resting tremor, multiple hernias, chronic obstructive pulmonary disease (COPD) ascribed to tobacco use, and pulmonary