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An approach to the identification of anomalies and etiologies in neonates with identified or suspected VACTERL (vertebral defects, anal atresia, tracheo-esophageal fistula with esophageal atresia, cardiac defects, renal and limb anomalies) association

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Keywords

VACTERL; VACTERL association; VATER; VATER association

VATER association was first described in the early 1970s as the non-random co-occurrence of congenital malformations including: Vertebral defects, Anal atresia, Tracheo-Esophageal fistula (TEF) with or without esophageal atresia (EA), and Radial and Renal dysplasia.[1] Following initial reports, it was suggested that "V" should include Vascular anomalies (including single umbilical artery). Cardiac malformations ("C") and Limb ("L") anomalies other than radial anomalies were also added, such that the term "VACTERL" became the most common descriptor, despite variable evidence for the inclusion of features such as cardiac or renal anomalies.[2–6] The presence of VACTERL association, which usually

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requires at least 3 component features and the absence of evidence for an overlapping condition, is estimated to occur in approximately 1/10,000–1/40,000 live births.[7, 8]

Just as there are challenges in defining the condition, there is no standard approach for the initial diagnostic work-up of a neonate with identified or suspected VACTERL association. This can be problematic: missed manifestations may obfuscate the etiological work-up[8]; delay medical interventions, potentially contributing to higher morbidity and mortality[9]; result in less informed and effective counseling.

To attempt to address these issues, we assembled a multi-disciplinary group of clinicians and researchers whose expertise focuses on VACTERL association and/or its individual component features. Following review of the literature, and based upon our collective experience, we offer suggestions for the evaluation of individuals identified or suspected to have VACTERL association.

Literature Search

We conducted a PubMed-based literature search for case reports and collections of patients identified or suspected of having VACTERL association and/or associated component features. Search terms included the following: Anal atresia; Anorectal malformations; Cardiac anomalies; Cardiac malformations; Cardiovascular anomalies; Cardiovascular malformations; Esophageal atresia; Genitourinary anomalies; Genitourinary malformations; Imperforate anus; Limb anomalies; Limb malformations; Radial anomalies; Radial dysplasia; Renal anomalies; Renal malformations; TEF; Tracheo-esophageal fistula; VACTERL; VATER; Vertebral anomalies; Vertebral malformations. Only articles describing human patients were considered, and articles were excluded if they did not pertain to component features specifically seen in VACTERL association.

SUGGESTED DIAGNOSTIC APPROACH

Patient criteria: to whom does the suggested diagnostic approach apply?

Individuals with any two component features of VACTERL association or either TEF/EA or ARM are frequently found to have additional VACTERL-type anomalies.[10–12] These additional anomalies may be difficult to detect without a high index of suspicion and/or specific testing. We suggest that our approach be applied to all individuals with at least 2 component features of VACTERL association, and all individuals in whom TEF/EA or ARM is diagnosed. Following the diagnostic work-up suggested here, the presence of VACTERL association is typically considered when at least three component features are present and there is no alternate causal explanation. Another view weights the component features differently, requiring the presence of at least one “core” feature: anorectal malformations (ARM) and/or TEF/EA in addition to at least two other component features.[7, 8]

Additional considerations

We discuss each feature individually, though many tests may be relevant to more than one organ system. After the identification of component features, further work-up and/or treatment will largely depend on the type and severity of the identified malformation, and may therefore vary widely. We also offer diagnostic suggestions based on current etiologic knowledge (; available at www.jpeds.com).

It is important to emphasize several points at the outset. First, the suggested approach should be performed in concert with routine newborn screening (i.e., hearing and blood-based screening). In addition to its general benefits, newborn screening can detect clinically

significant findings that may occur in conditions in the differential diagnosis, such as hearing impairment in Townes-Brocks syndrome.[8] Second, although a range of practitioners may perform the suggested work-up, the involvement of a clinical geneticist is optimal. Finally, though the suggested work-up is intended for the neonatal period, the approach might also be applied to an individual who is first recognized as having features of VACTERL association at an older age (which is not uncommon).[9]

Vertebral anomalies

Description—Vertebral anomalies, described in 60–90% of affected individuals, can affect any of the vertebrae, may involve single or multiple vertebrae, and may vary in severity.[7, 12, 13] Characteristic vertebral anomalies include segmentation defects and may be accompanied by rib anomalies and/or abnormal spinal curvatures.[12, 13] The presence of congenital costovertebral anomalies may require orthopedic tracking, as well as medical/surgical interventions. Surgical interventions are indicated at the earliest age-appropriate time related to the specific procedure.[9, 14–17]

In addition to frank vertebral anomalies, tethered spinal cord may occur, especially in those with caudal features such as ARM and/or urogenital anomalies.[18–21] Tethered spinal cord may co-occur with anomalies such as terminal filum or conus medullaris lipomas, intramedullary ependymal cysts, meningomyelocele, and syringohydromyelia.[18, 20] A tethered spinal cord can cause significant morbidity by impacting neurological function, including related to continence. Early detection of tethered cord, allowing timely surgical treatment, has shown a significant outcome benefit (though the benefit may differ in symptomatic vs. asymptomatic patients).[22, 23]

Initial work-up—The initial X-rays to detect vertebral anomalies should include dedicated sacral views to allow inference of the degree of caudal regression (through sacral ratio calculation), which can inform continence-related prognosis.[24] Further imaging, such as with magnetic resonance imaging (MRI) or three-dimensional computed tomography (CT) may be necessary to delineate complex malformations, though issues related to radiation exposure and sedation risk should be considered.[25]

A peripheral neurological/muscle examination, including assessment of reflexes (deep tendon and primitive), assessment of muscle tone (including rectal), and response to tactile stimulation can elucidate signs of spinal cord pathology related to tethered cord and/or other vertebral anomalies.[26] Imaging to detect the presence of a tethered spinal cord should also be part of the initial work-up. MRI is the most sensitive modality, but ultrasound is considered an adequate screening tool and has the advantage of being readily available, efficient, affordable, and avoids sedation. Because of the advantage of ultrasound, MRI may be reserved for patients with X-ray identified lower spinal anomalies.[18] The choice between MRI and ultrasound may also be influenced by availability, cost, and the timing of testing. In general, ultrasound to evaluate tethered cord may be performed up to approximately three months of age.[18]

Anorectal Malformations

Description—ARM, which are frequently accompanied by genitourinary (GU) anomalies (including complex cloacal malformations), are reported in 55–90% of affected individuals.[7, 13, 24, 27]

The timing and surgical approach can differ dramatically depending on the ARM type and related anomalies such as GU malformations. Early detection of ARM and GU anomalies is also critical in preventing GU infections and preserving renal function.[24, 27]

Initial work-up—Individuals should undergo careful physical examination and observation for signs of ARM and accompanying GU anomalies (e.g., abdominal mass in hydrocolpos). This examination should attempt to delineate the type of ARM/GU anomaly, including signs of recto-urinary fistulas, which may warrant further studies. In unclear circumstances, a cross-table lateral X-ray may help assess distal rectal anatomy, including for signs of ARM (e.g., an air column in the distal rectum).[24] In the case of a known ARM, a prone cross-table lateral pelvic X-ray (invertogram) may help judge the proximity of the distal rectum to the perineal skin, which can guide neonatal treatment in terms of the choice of anoplasty or colostomy.[24, 27]

An abdominal ultrasound should be performed to assess for accompanying GU anomalies.[24, 27] Fluids and nutrition should be administered intravenously, and a nasogastric/orogastric (NG/OG) tube should be placed to keep the stomach decompressed to decrease the risk of vomiting and related aspiration.[24]

Cardiac malformations (and cardiovascular anomalies)

Description—Cardiac malformations have been reported in 40–80% of affected individuals, ranging from subtle anomalies, including vascular anomalies, that may not be clinically significant to complex malformations necessitating multiple surgical and long-term medical interventions.[7, 13] In addition to medical/surgical interventions, cardiovascular anomalies may warrant specific inpatient cardiac monitoring and precautions, and may impact the overall care plan, including the timing and approach to other surgeries.[28–30] The presence of cardiovascular malformations may affect the anesthetic plan.[31] Patients with mild or severe congenital heart anomalies, such as occur in VACTERL association, may also be at risk of supraventricular and ventricular arrhythmias.[32]

Initial work-up—Trans-thoracic echocardiogram may detect and characterize cardiac malformations. An ECG may identify electrical disturbances not ascertained by echocardiogram.[32]

Depending on the results of the echocardiogram, additional techniques, such as cardiac MRI, may be necessary. If surgical interventions are planned, careful delineation of any accompanying vascular anomalies is indicated (e.g., with Doppler ultrasound of the affected area and/or echocardiogram; in complex cases, studies such as MR angiogram should be included).[30, 33, 34]

Tracheo-esophageal fistula with/without esophageal atresia

Description—A variety of TEF/EA types have overall been described in 50–80% of individuals with VACTERL association.[7, 13] Early interventions, including those related to fluid and nutrition management, can decrease complications (eg, aspiration).[35]

Initial work-up—As with certain other component features, an important initial step is physical examination and observation, including an attempt to pass an NG/OG tube.[35–37] Clinical findings (e.g., increased oral secretions/choking during feeding, failure to pass an NG/OG tube) can be supported by radiological diagnostic clues, such as NG tube coiling or an absent gastric bubble on X-ray.[37] These X-rays should be performed with an NG/OG tube in place - even if it meets resistance on placement - to help show the defect's location. Further imaging, such as contrast studies, is rarely required unless there is a clear clinical indication related to patient presentation or medical history. Reasons in the medical history might include gestational polyhydramnios because of fetal inability to swallow amniotic fluid.[38] The echocardiogram can evaluate anomalies of the heart and large vessels in preparation for surgical repair.[39]

Of note, H-type TEF diagnosis can be difficult, as there is normal NG/OG placement and gastric bubble, and the infant may present only with findings such as choking/respiratory distress with feeds. In this instance, a swallow study or rigid bronchoscopy may be required.[40] As with ARM, fluids and nutrition should be given intravenously.

Renal anomalies

Description—Renal anomalies, which may be accompanied by ureteral and GU anomalies, have been described in 50–80% of affected individuals.[7, 13] With severe anomalies that compromise renal function, renal transplant may be eventually required.[41] However, early diagnosis and management may preserve function via prevention of infection and management of vesico-ureteral reflux (VUR). Optimizing adequate bladder emptying is especially important in obstructive hydronephrosis.

Initial work-up—Further testing after renal ultrasound, such as a voiding cystourethrogram, serial ultrasound testing, and renal function studies (e.g., mercapto-acetyl-triglycine (MAG3)/furosemide scan), may be required in the presence of renal anomalies or if there is other evidence of manifestations such as VUR.[42–44] In addition, individuals with VACTERL association frequently have GU anomalies.[45] Physical examination may yield findings warranting further medical/surgical interventions.[27, 45]

Limb anomalies

Description—Radial anomalies were first described as a defining feature, but a wider variety of limb anomalies has been reported in 40–55% of affected individuals.[7, 13] The identification of limb anomalies can help plan interventions, including early physical therapy and eventual surgery.[46]

Initial work-up—Physical examination to assess for limb anomalies affecting any of the limbs, in addition to isolated radial anomalies should be part of the overall assessment. If limb anomalies are suspected/detected, radiologic studies (initially with X-rays) can be performed.

Hydrocephalus

Description—VACTERL with hydrocephalus (VACTERL-H), often due to aqueductal stenosis, may be a distinct condition or may represent a continuum with “more general” VACTERL.[7] The condition has been reported with X-linked inheritance in some families, though other inheritance modes have been described.[47–49] Genetic causes are known in some instances; these include mutations in *ZIC3*, or as a manifestation of Fanconi anemia due to *FANCB* or *FANCD1* mutations.[50–52] Surgical interventions (including shunting) may be beneficial to treat hydrocephalus. Such interventions may improve outcomes, including related to neuro-developmental sequelae.

Initial work-up—A cranial ultrasound in infancy can be used to detect hydrocephalus.[53]

Additional work-up (including medical/family history, physical examination, other testing)

Description—The causes of VACTERL association remain largely unknown, though scattered case reports have identified etiologies, as well as non-genetic risk factors (e.g., maternal diabetes mellitus).[7, 54–56] Although VACTERL association is usually sporadic, a relatively small number of familial cases have been described, and there may be an over-representation of VACTERL-type anomalies in relatives of probands.[57, 58] A thorough family history can help with the differential diagnosis (e.g., the possibility of other conditions may be raised) and can help inform discussions regarding recurrence risks.[8]

In addition to VACTERL-type anomalies, malformations affecting diverse organ systems have been described.[7] Even though none is common enough to warrant standard testing, clinicians should be aware that other congenital anomalies may co-exist, and have a low threshold for further related investigations.

Initial work-up—A medical and family history and physical examination by a clinical geneticist and genetic counselor may reveal clues to direct genetic testing as well as prompt further investigations related to specific findings.

As large-scale sequencing becomes increasingly available and accurate, techniques such as whole-exome/genome sequencing, or parallel sequencing of many genes, may be an efficient way to interrogate multiple genes and search for novel disease causes.[55, 59]

In addition to sequencing, analysis for causative copy-number variants (CNVs) (such as with high-density microarray) is warranted, as a small proportion of individuals can be identified with causal deletions or duplications and because such cytogenomic studies are generally indicated for individuals with multiple congenital anomalies. The frequency of de novo CNVs in individuals with VACTERL association is low (<5%), but CNVs that act as putative genetic susceptibility factors may be identified.[60] If a high-density microarray is not available, a standard, high-resolution karyotype is still indicated, as some conditions that include features of VACTERL association, and which may be difficult to identify clinically especially in the prenatal/neonatal period, can be diagnosed by karyotype and/or related cytogenomic studies (e.g., some trisomies).

A small proportion (especially those with radial ray abnormalities) of individuals may have Fanconi anemia, and testing through chromosomal breakage studies, such as diepoxybutane (DEB) assay, is indicated in all individuals with VACTERL association.[8, 61]

A peripheral blood CBC may inform the differential diagnosis, such as related to thrombocytopenia-absent radius syndrome.[62] Some hematologic anomalies (e.g., thrombocytopenia) may also affect management.

Finally, in addition to the other recommendations, early intervention services can be beneficial for many neonates VACTERL association-type anomalies. Patients may not be considered to be impaired at diagnosis but are at risk of disability and in the United States would qualify for services under the individuals with Disabilities Education Act (PL99–142). If available, a pediatric physiatrist should follow the infant every 3–6 months to monitor for signs of impairment and disability, oversee rehabilitation, and prescribe adaptive equipment.

Other diagnostic possibilities

A thorough clinical work-up may suggest the presence of a testable disorder, as many disorders overlap or include features of VACTERL association; in many of these conditions, the genetic causes are known and clinical testing is available[8] Patients may also demonstrate features of VACTERL association due to relatively large genomic imbalances, such as may be detected by microarray, though many of these patients will demonstrate additional, distinct findings.[60, 63] Finally, free web-based algorithms are available that can help generate a differential diagnosis based on specific patient features.[64]

DISCUSSION

The relative rarity and wide spectrum of VACTERL association challenges the ability to have a “gold standard” case definition. We nonetheless expect that this algorithm can be

beneficial to a diverse group of medical practitioners. The suggested work-up may involve considerable expense, but applying this algorithm early in life may ultimately decrease morbidity as well as costs to the health care system. Further research is necessary to determine the optimal cost-benefit ratio. Though the phenotypic spectrum is becoming better understood, the causes of VACTERL association remain largely elusive. Our research groups, as well as others, are currently leveraging new genomic research methods in order to search for genetic explanations of VACTERL association. This can be a lengthy process, but when these causes have been unraveled, they may improve understanding about the disease process specifically, basic developmental processes in general, and allow more informed genetic counseling. Understanding the causes of VACTERL association may lead to more specific clinical algorithms. For example, individuals who are known to have a mutation in one gene may be at higher risk for severe cardiac malformations, and others, with a mutation in a different gene, may be more prone to genitourinary and renal anomalies. Being able to categorize patients genetically may allow the practice of genomic medicine by enabling more individually-tailored medical plans.

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Abbreviations

AP	Anterior-Posterior
ARM	Anorectal Malformations
AXR	Abdominal X-ray
CBC	Complete Blood Count
CNV	Copy Number Variant
CT	Computed Tomography
CXR	Chest X-ray
DEB	Diepoxybutane
EA	Esophageal Atresia
ECG	Electrocadiogram
GU	Genitourinary
MAG3	technetium-99m mercaptoacetyltriglycine
MR	Magnetic resosance
MRI	Magnetic Resonance Imaging
NG	Nasogastric
NPO	nil per os
OG	Orogastric

TEF	Tracheo-esophageal Fistula
US	ultrasound
VACTERL	Vertebral defects, Anal atresia, Cardiovascular anomalies, Tracheo-esophageal fistula with or without Esophageal atresia, Renal anomalies, Limb anomalies
VATER	Vertebral defects, Anal atresia, Tracheo-esophageal fistula with or without Esophageal atresia, Radial and Renal dysplasia
VACTERL-H	VACTERL with Hydrocephalus
VUR	Vesicoureteral reflux
VCUG	Voiding Cystourethrogram
XR	x-ray

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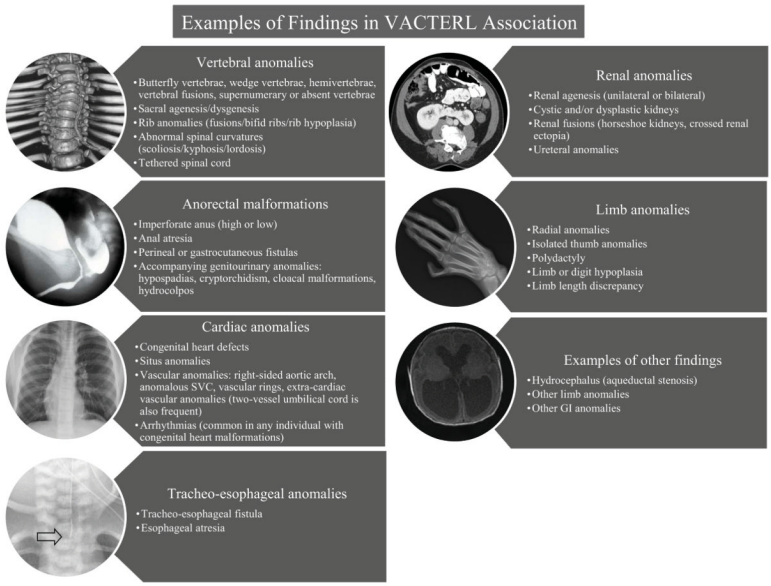

Figure 1.

Examples of findings in VACTERL association. The images in the circles represent radiological examples of findings. Vertebral anomalies: 3-D CT reconstruction showing thoracic segmentation anomalies; Anorectal malformations: contrast imaging showing a rectoprostatic urethral fistula in a patient with an anorectal malformation; Cardiac anomalies: chest x-ray showing a midline heart in a patient with situs anomalies as part of VACTERL association; Tracheo-esophageal anomalies: x-ray showing the position of feeding tube placement (arrow) due to a tracheal pouch; Renal anomalies: axial view from an abdominal CT showing a horseshoe kidney; Limb anomalies: skeletal anomalies affecting the right radius, wrist, and thumb; Examples of other findings: axial view from a brain MRI showing hydrocephalus (due to aqueductal stenosis) Abbreviations: 3-D: three-dimensional; CT: computed tomography; GI: Gastrointestinal

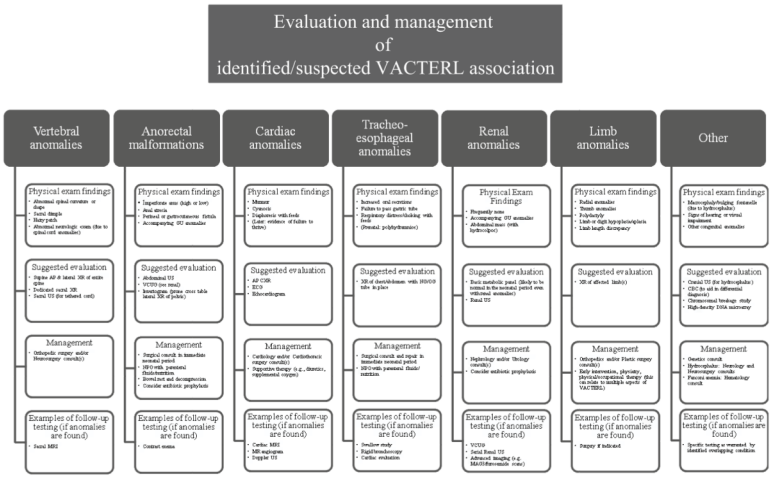

Figure 2.
Graphical representation of suggested algorithm for neonates affected with VACTERL association.