

VATER/VACTERL Association in Palestinian Children: A Case Report

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Abstract

VACTERL/VATER association is typically defined by the presence of at least three of the following congenital malformations: vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. This finding is supported by evidence linking all of the human disease genes for the VATER/VACTERL association identified to date, namely, FGF8, FOXF1, HOXD13, LPP, TRAP1, and ZIC3, with renal malformations. VATER association was first described in 1972 by Quan and Smith. We present here a 75 days male boy with cardiac (VSD, PDA), esophageal atresia, anal abnormalities (sacral dimple), and genitourinary (hypospadias and communicating hydrocele). Others abnormalities were detected ear deformity, sacral dimple and 13 pairs of ribs.

Introduction

VACTERL is a cluster of congenital malformations based on the non-random association of various congenital malformations in a single patient. In addition to these core component features, patients may also have other congenital anomalies [1]. Population-based epidemiological studies in Europe and the USA



Figure 1. Male infant aged 75 days has congenital heart disease (VSD & PDA), esophageal atresia, sacral dimple, genitourinary (hypospadias & communicating hydrocele). Others abnormalities (ear deformity & 13 pairs of ribs).

have reported a prevalence among infants of one in 10 000 to one in 40 000 live-born infants (approximately <1-9/100,000 infants) [2]. Most of the cases of VACTERL association occur sporadically; however, chromosomal abnormalities have also been described in a few cases [3]. Maternal diabetes, teratogenic drugs, physical stress and usage of oral contraceptives at the initial stages of pregnancy have been suggested as possible causes [4]. VACTERL is believed to result from an early embryonic insult, more specifically of blastogenic origin occurring during the first 4 weeks of embryogenesis, so the expected effects are primary, polytopic, developmental field defects [5] (Figure 1).

This early embryonic event can lead to different defects in various body systems. VACTERL/VATER association is an acronym for Vertebral anomalies (fusion, hypoplasia), Anorectal malformation, Cardiac malformations (ventricular septal defect (30%), patent ductus arteriosus (26%), atrial septal defect (20%) and transposition of great arteries (10%), Tracheoesophageal fistula with or without atresia, Renal anomalies (renal agenesis, hypoplasia or even cystic dysplasia) and Limb anomalies (usually involving the radial ray such as radial or thumb hypoplasia, either uni- or bilateral) [6,7]. To date, no unifying etiology for VACTERL/VATER association has been established, and there is strong evidence for causal heterogeneity [8,9,10]. The genetic etiology of VACTERL has not been elucidated and it is thought to be multifactorial, although some cases may be due to teratogenic exposure, such as maternal diabetes [11]. Some of the malformations make their appearance early in the embryological period; 23–30 days post conception, while others occur later in embryogenesis. There is overall no strong evidence for an increased incidence of VACTERL association in certain areas of the world or in specific ethnic populations [12]. The management of patients with VACTERL association can be complex and is directed at surgical correction of specific anomalies [7].

Discussion

A male baby was born at 40 weeks of gestational age through elective lower segment cesarean section to 24 years old, first degree consanguinity, fifth gravida mother. There was no history of birth defect in family. There was no significant history of any

infection, drug intake, diabetes mellitus, or radiation exposure during the pregnancy. The birth weight was 2.67 kg. He was operated at age of 3 days after confirming of esophageal atresia. At age of 75 days of his life was admitted to our hospital due to cough, dyspnea associated with poor feeding. Physical examinations reveal a loud, harsh, Pan-systolic murmur at third left parasternal intercostal space, posterior part of the chest show scar due to repair of esophageal atresia, external genital reveal hypospadias, communicating hydrocele. An abnormal ear lobe shape, position and with sacral dimple. Chest x-ray reveal cardiomegaly and 13 pairs of ribs, echocardiography reveal (ventricular septal defect, patent ductus arteriosus), abdominal ultrasound not detect any abnormalities, and Kidney and liver functions were normal studies (Figure 2). In our patient, we detect cardiac (VSD, PDA), esophageal atresia, genitourinary (hypospadias and communicating hydrocele) anal abnormalities (sacral dimple). Others abnormalities were detected ear deformity, sacral dimple and 13 pairs of ribs.



Figure 2. Chest x-ray of 75 days male patient reveal cardiomegaly and 13 pairs of ribs.

Vertebral anomalies, 70 percent of patients with VACTERL association will have vertebral anomalies and usually consist of hypoplastic, butterfly, wedge, fusion, supernumerary, absent or hemivertebrae and later in life, these vertebral anomalies may put the child at risk for developing scoliosis [6,7,10,13]. Anal atresia or imperforate anus is seen in about 55-90 percent of patients with VACTERL association. These anomalies often require surgery in the first days of life [10,13,14]. The most common heart defects are ventricular septal defects (30%), patent ductus arteriosus (26%), atrial septal defects (20%), Coarctation of aorta, transposition of great arteries (10%) and Tetralogy of Fallot. Less common defects are truncus arteriosus and transposition of the great arteries [10,15]. A number of subtypes of Tracheo-Esophageal Fistula (TEF) may occur, and may present with or without esophageal atresia. Overall, TEF occurs in approximately 50-80% of patients. Early signs of TEF include polyhydramnios or absent gastric bubble recognized prenatally, inability to pass nasogastric tubes immediately postnatally, or choking/swallowing in infancy [8,12]. Renal abnormalities include unilateral agenesis and less commonly ectopic, horseshoe kidney, cystic and/or dysplastic kidneys, sometimes accompanied by ureteral and GU anomalies [16]. In our case we found a rare urogenital finding as hypospadias.

Limb deformities have been reported in approximately 40-50% of patients, consist of ray abnormalities such as radial aplasia or hypoplasia, abnormal thumbs, preaxial polydactyly, syndactyly and humeral hypoplasia [12,17,18]. While the above malformations are considered to be the core component features, many other malformations have been described in affected patients [19,20]. Lautz and associated found that vertebral anomaly in 25.5%, anorectal malformation in 11.6%, congenital heart disease in 59.1%, renal disease in 21.8% and limb defect in 7.1%. and 33.4% had 3 or more anomalies and met criteria for a VACTERL diagnosis [21]. Among 52 patients with EA/TEF, 20 (38, 4%) had isolated EA and 7 (21, 8%) had a recognized etiology such a syndrome and therefore were excluded. Among 32 infants with EA and associated malformations, 15 (46, 8%) had VACTERL association. The most common anomalies were congenital heart defects (73, 3%), followed by vertebral anomalies (66, 6%). Many patients also had additional non-VACTERL-type defects. Single umbilical artery was the most common one followed by nervous system abnormalities and anomalies of toes [22]. In addition, to the above mentioned features, affected children may also exhibit less frequent abnormalities including growth deficiencies and failure to gain weight and grow at the expected rate (failure to thrive). Practically every organ system have been reported in association with VACTERL in lower frequency like facial asymmetry (Hemifacial microsomia), external ear malformations, lung lobation defects, intestinal malrotation and genital anomalies [23]. The combination of VACTERL abnormalities can present with some known chromosomal abnormalities, including trisomy 13, 18, and 5p-syndrome. Interstitial deletion of long arm of chromosome 6 (6q13-15) and long arm of chromosome 13 have been reported in few cases [24]. Recent research has shown that VACTERL could be caused by defective SHH (Sonic hedgehog pathway) signaling during human embryogenesis [25].

Differential diagnosis with Trisomy 13, trisomy 18, PHAVER syndrome, and Townes syndrome, CHARGE syndrome, Currarino syndrome, deletion 22q11.2 syndrome, Fanconi anemia, should be included in differential diagnosis (Table 1) [13,26,27].

Treatment is directed towards the specific symptoms that are apparent in each child, which often varies greatly. Many of the structural abnormalities (radial defects, cardiac defects, anal atresia etc.) require staged surgical corrections. Infants with this condition need to be managed by a multidisciplinary team including pediatricians, cardiologists, urologists, orthopedic surgeons, otorhinolaryngologists and clinical geneticist in order to have a reasonable life expectancy [24]. Prognosis for children with this condition depends on the severity of anomalies. Seventy five percent of these children die early in life [38]. With improvements in surgical techniques and in specialized neonatal and post-surgical facilities, these children have a much better outcome than reported previously. Nonetheless, even with optimal surgical management of cardiac defects, trachea-esophageal fistula, and limb abnormalities patients can face considerable medical challenges throughout life. Finally, despite significant morbidity associated with the component congenital malformations, it is also important to note that these patients

Table 1: Differential diagnosis: conditions with multiple features in common with VACTERL association

Condition	Features similar to VACTERL association	Features different from VACTERL association	Cause(s)	Reference(s)
Currarino syndrome	Sacral malformations, anorectal malformation.	Presacral mass	Heterozygous mutations/deletions of HLXB9	28,29
Fanconi anemia	Virtually all features of VACTERL association may occur; radial anomalies	Hematologic anomalies, Pigmentation anomalies	Recessive or X-linked mutations in multiple genes.	30, 31,32
CHARGE syndrome	Cardiac malformations, genitourinary anomalies; may also include TEF	Colobomata, choanal atresia, neurocognitive, growth impairment, ear anomalies, cranial nerve dysfunction, specific facial features	Heterozygous mutations in CHD7	33,34
Baller-Gerold syndrome	Radial anomalies, may also include anal anomalies	Craniosynostosis, skin anomalies	Heterozygous mutations in RECQL4	35
Holt-Oram syndrome	Cardiac malformations, limb malformations	Cardiac conduction disease (also reported in VACTERL association)	Heterozygous mutations in TBX5	36,37

do not typically display neurocognitive impairment [11,39]. The prognosis for growth and development in newborns who survive infancy is good. Most have normal intelligence and eventually achieve normal stature [40]. The recurrence risk of parents of a child with sporadic VACTERL association is 1% [41].

Conclusion

A high degree of suspicion and knowledge of various combinations of congenital anomalies must be kept in mind. VACTERL association is a condition characterized by nonrandom association of specific birth defects involving multiple organ systems. Occurrence is usually sporadic. Etiology is multifactorial. Diagnosis is essentially clinical and requires defects in at least 3 organ systems as mentioned previously. Multidisciplinary management is required for these cases, with staged surgical therapy being the mainstay of treatment. Medical and operative therapy is directed toward the specific malformations present. Since the exact genetic basis for this condition has not yet been established, parents with an affected child must be reassured that the recurrence risk in subsequent pregnancies is extremely low and if detected early in utero before viability, termination can be offered.

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