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Original Research Paper

VACTERL Association"- Interesting and Rare

Medical Science

KEYWORDS : VACTERL Association--Vertebral defects (V), imperforate Anus (A), Tracheo-Esophageal fistulas, Renal anomalies, Limb defects.

Dr. Sankappa. P. Sinhasan

MD, DNB (Pathology), MNAMS ,Associate Professor, Department of Pathology, Indira Gandhi Medical College and Research Institute (IGMC & RI), Pondicherry –605 009, Pondicherry. INDIA

ABSTRACT

Introduction: *The first report of VATER association was described in 1968, which includes a nonrandom association of Vertebral defects (V), imperforate Anus (A), Tracheo-Esophageal fistulas and Renal anomalies. This VATER association is further extended as VACTERL association with addition of Cardiac anomalies and Limb defects. A diagnosis of VACTERL is made if any three of the seven key features are present. The exact gene which causes these birth defects to occur is still a question of debate. Possibly a defect in blastogenesis has been suggested as etiology of this malformation.*

Material and Methods: *We collected retrospective data from histopathology section for a period of 7 years from January 2009 to December 2015. Total 51 baby autopsies are carried out during the study period. We have selectively collected babies which have been reported as VACTERL association and noted various anomalies of these cases. In the present article, we are reporting these three different cases, each having different components of VACTERL association.*

Conclusion: *All these three cases of our VACTERL association, we noted anal agenesis as a common finding. Each child with this condition can be truly unique, with defects being different from any other child. The purpose of this article is to provide more information about the VACTERL association thereby to gain a better understanding of the rare entity and improved treatment in near future.*

INTRODUCTION:

The first report of VATER association (Vertebral defects (V), imperforate Anus (A), Tracheo-Esophageal fistulas, Renal anomalies) was made in 1968[1]. The original VATER association has been extended as VACTERL association with addition of Cardiac anomalies and Limb defects.[1] Further modification include VACTERLS, or VATERS association with the 'S' standing for presence of Single umbilical artery. Approximately worldwide around 300 cases have been reported till date.[2] A diagnosis of VACTERL is made if any three of the seven key features of the association are present. In dysmorphology (the study of birth defects), the term "association" refers to non-random occurrence of two or more patterns of birth defects. The reason it is called an association, rather than a syndrome is that while all of the birth defects are linked, it is still unknown which genes or set of genes cause these birth defects to occur. A defect in blastogenesis has been suggested as a possible etiology of this malformation. Martinez-Frias et al proposed that combinations of anomalies of blastogenetic origin, such as VATER/VACTERL should be considered and called "polytopic field defects" instead of the generic term "association".[2,3]

Material and Methods:

We collected retrospective data from histopathology section for a period of 7 years from January 2009 to December 2015. Total 51 baby autopsies are carried out during the study period. Thorough external examination was made and photographs were taken if any congenital anomalies present. All these babies have been dissected taking standard I shaped incision from symphysis menti to pubic symphysis. Enblock dissections of organs were made with careful microdissection for presence of internal anomalies.

Results:

We have reported three cases of VACTERL association during the study period.

Case1:

A 28 year old Gravida 2 Para 2 presented with 28 weeks of amenorrhea to the Obstetrics department. The first pregnancy was uneventful, full term normal home delivery; alive and healthy male baby. There is no history of any medications (specially asked for lipid lowering agents or estrogen therapy). Patient is not diabetic. Regular ANC check-up was not get done till 28 weeks of gestation. Abdominal USG done at 28 weeks revealed large intra-abdominal cystic mass with probable diagnosis of cystic kidney disease was suspected. Hence, the pregnancy was terminated by induction of labor.

External examination: showed male baby with bloated abdomen (Fig 1), with peeling of skin over chest wall and right abdomen. Both the ears were low set and examination of hands showed polydactyly on right hand. Anal opening was not seen (Fig 2)

Fig 1: Showing huge distension of abdomen. Fig 2: Showing absent anal opening.

Volume : 5 | Issue : 10 | October 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Cut section of abdominal cavity revealed cystically dilated underlying structure which was identified as later as hugely distended urinary bladder, the wall of which was stretched and thinned-out (Fig 3). Approximately around 500 ml of straw colored fluid (urine) was drained out.

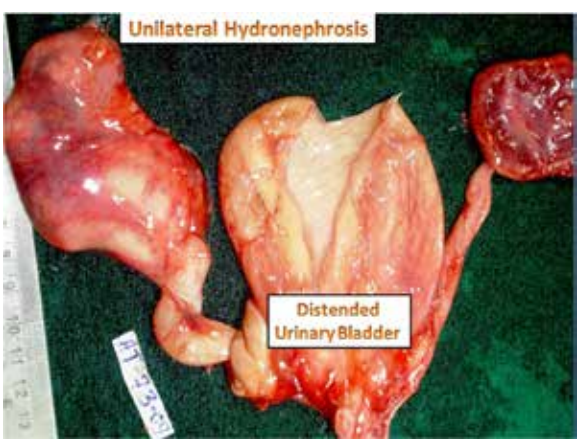

Fig 3: Distended urinary bladder. Fig 4: Bilateral hydroureters with right kidney showing hydronephrosis.

Examination of right kidney showed hydronephrotic change with thinned-out renal parenchyma. Both the ureters showed hydroureteric change (Fig 4). Spleen was absent. Descending colon showed dilatation throughout with accumulation of meconium in the lumen. It was ended blindly without continuity to anal canal. Right testis was found in the abdominal cavity and left testis in the inguinal canal with empty scrotal sac. The X-ray of baby revealed sacral agenesis (Fig 5).

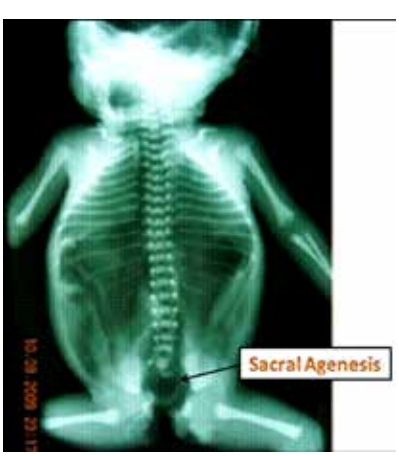

Fig 5: X- ray of baby showing sacral agenesis.

Microscopy from right kidney showed features consistent with hydronephrosis; sections from blind ended descending colon revealed congenital Hirschsprung's disease with absent ganglion cells and hypertrophied nerve bundles. Possibility of presence of congenital posterior urethral valve was considered causing renal complications which we couldn't be able to demonstrate. Diagnosis of VACTERL association was issued due to presence of three anomalies (Vertebral anomaly—sacral agenesis, Anal atresia and Renal anomalies).

Case 2: 23 year old Primi presented with history of 8 months amenorrhea. She was presented for the first time to hospital without prior ANC checkups. USG revealed IUGR with oligohydroamnios and multiple anomalies and suggested termination of pregnancy. The pregnancy was terminated by induction of labor and an anomalous stillborn male child delivered by breach presentation. Baby weighted 1640 gms and external examination of head showed low set ears. Right upper limb was short with presence of only one broad finger; Left upper limb was completely absent (unilateral Amelia) (Fig No 6). Right lower limb was normal in length and showed CTEV (congenital talipes equinovarus); left lower limb was short with presence of only three toes with maldeveloped foot.

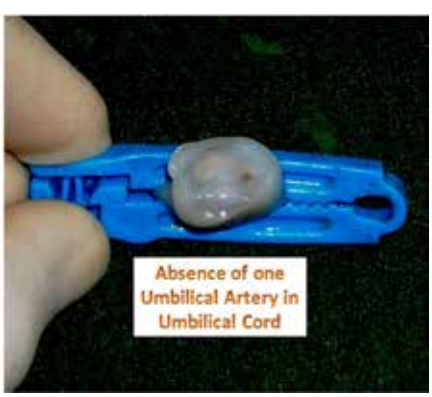

Fig 6: Completely absent left upper limb with deformed left lower limb. Fig 7: Absence of one umbilical artery in umbilical card.

Anal opening was absent. Scrotal sac was empty with bilateral undescended testes. Umbilical cord revealed presence of only two vessels (absence of one umbilical artery) (Fig 7). Microscopic examination umbilical cord confirmed the absence of an artery. Examination of the vertebral body at back showed scoliosis and lardosis, which was confirmed by X-ray of the baby. In view of presence of vertebral anomalies, with anal agenesis and limb anomalies, diagnosis of VACTERL association was issued.

Case 3: A 26 year old Para 2 Living 2 presented with history of 9 months amenorrhea. She was presented for the first time to hospital without prior ANC checkups. USG revealed baby with multiple anomalies and suggested termination of pregnancy. The pregnancy was terminated by induction of labor and an anomalous stillborn male child delivered by caesarian section.

On examination, baby weighted 2350 gms. Striking feature on external examination was hugely distended abdomen. Head examination showed low set ears. Left hand showed presence of polydactyly. Both the lower limbs were short in length and show peeling of skin. Anal opening was absent and micropenis was noted with absent scrotal sac and bilateral undescended testes. Umbilical cord revealed presence of only two vessels.

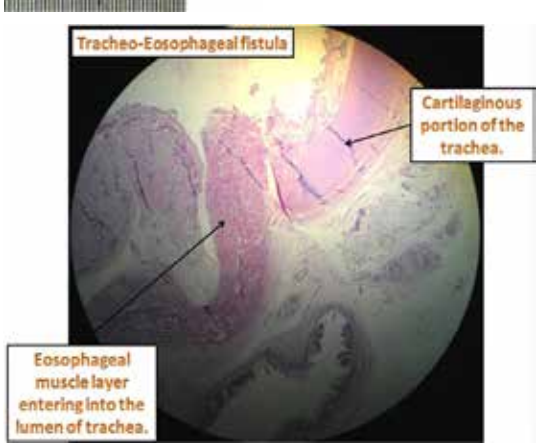

Fig 8: Distended urinary bladder with distal colon opening into bladder. Fig 9: Tracheo-esophageal fistula that was further confirmed by microscopic (Fig 10) examination (H & E, 4X magnification).

Internal examination revealed distended urinary bladder was seen with openings of distal colon and left sided ureter ending into the bladder sac (Fig 8). The distended urinary bladder showed thinned out muscular wall with openings of the distal colon ended blindly into the urinary bladder. Left kidney showed cystic change along with persistent fetal lobulations. Right kidney showed only persistent lobulations. The left ureter showed hydroureteric change. Both the testes were seen in the abdominal cavity. Internal examination revealed Tracheo-Esophageal fistula with esophagus opening into the middle third of the trachea (Fig 9). Microscopy confirmed the presence of tracheo-esophageal fistula in which esophageal muscle layer was seen entering into the lumen of trachea by seepage in the cartilaginous portion of the trachea (Fig 10). Testes were seen in the abdominal cavity. In view of presence of renal anomalies, anal agenesis, tracheo-esophageal fistula, diagnosis of VACTERL association was issued.

Discussion:

A nonrandom association of Vertebral defects (V), imperforate Anus (A), Cardiac anomalies (C) Tracheo-Esophageal fistulas (TE), Renal anomalies (R), and Limb defects (L) constitute VACTERL, diagnosis of which is made if any three of the seven key features are present.[1]

Incidence: The estimated birth prevalence of this non random association varies from 1:3,500 to 1.6 cases per 10,000 live births. It is rarely seen more than once in one family.[2]

Etiology/Molecular Genetics: VACTERL Association has not been attributed to any specific genetic defect. While VACTERL can arise in tandem with some chromosomal disorders, at this time, there is no known gene or set of genes that causes VACTERL, and its occurrence is probably due to combination of factors. It appears most often in sporadic cases. It is clear that the condition is caused by defects in the early embryonal development. However, it is not known whether a single or multiple genes are involved. Certain chromosomal abnormalities have been observed in a few patients. These include deletions in the long arm of chromosome 13, chromosome 6, and extra marker from chromosome 12. Many patients have also been seen to be trisomic for chromosome 18. Interestingly, infants born to diabetic mothers are more prone to be affected with VACTERL. Pathogenesis is suggestive of a defective mesodermal development during embryogenesis due to a variety of causes, leading to overlapping manifestations.[3]

The VACTERL association was also linked to inhibition of cholesterol synthesis and down-regulation of what is called the cholesterol-dependent sonic hedgehog morphogenetic pathway. This is a biochemical pathway in the shaping of the embryo that requires cholesterol. Case reports have suggested that the VACTERL association may possibly occur with increased frequency in children whose mothers have taken the cholesterol-lowering statin drugs in the first trimester of pregnancy. (These drugs are contraindicated in pregnancy.) Some authors report that prenatal rats exposed to Adriamycin demonstrated a similar series of anomalies. Unknown mitochondrial mutations also have been quoted by some studies.[4]

There are many different health issues one may face with a child who has VACTERL association. Apart from the defects themselves, children often have problems with growth and weight gain and may have multiple infections. While some have delayed development in the beginning due to many hospitalizations and illnesses, the majority of VACTERL children have normal intelligence. Other health issues occur as a result of individual defects.[3,4]

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Vertebral anomalies: About seventy percent of children will be born with anomalies of their vertebral column. Most are benign, but they can contribute to other problems. Some vertebral issues that are common are hemivertebrae (half formed vertebrae), butterfly shaped vertebrae, fused vertebrae, missing vertebrae, tethered spinal cord, Chiari malformation and scoliosis. For most children these anomalies cause few issues early in life, but scoliosis may become more significant later on.[3]

Anal anomalies: Another rarely talked about but profoundly important issue for children with VACTERL is imperforate anus. This is a topic all by itself, but in general, around fifty-five percent of children will be born with this defect, which ranges from having a misplaced anus to not having an anal opening at all. This defect is often the most difficult and shocking for parents to handle since it is such a taboo subject to talk about and also may result in significant problems related to stooling. This defect, however, is very serious and must be taken care of in the early days of life either though anoplasty (reconstruction of the anus), a pull-through procedure (colon is pulled through and reconnected to the anus), or colostomy (an opening in the abdomen that allows stool to be collected). Depending on the type of imperforate anus, correction may involve minimal surgery or full reconstruction through multiple surgeries.[3]

Cardiac anomalies: Cardiac issues are also common in VACTERL, and about seventy-five percent of VACTERL children are born with some type of cardiac condition. The spectrum can be endless but the more common defects are atrial septal defects, ventricular septal defects, or Tetralogy of Fallot. All children found to have VACTERL defects should be checked for cardiac problems regardless of whether a murmur is heard or not. Some children will require surgical repairs while minor defects may self-resolve or cause no ongoing problems.[3]

4,5. Tracheo-Esophageal anomalies: The T and E defects of VACTERL usually occur in tandem, typically in the form of a Tracheo-Esophageal Fistula or esophageal atresia, though other defects of the trachea or esophagus may be present. Esophageal atresia occurs when the stomach and esophagus do not connect with each other, while a fistula is an opening between the trachea and esophagus that should not be there. Children born with these defects typically require surgical repair of the trachea and esophagus, and can have serious ongoing gastric reflux disease that may require fundoplication surgery or a feeding tube. Some children also have significant respiratory issues, including tracheomalacia (a floppy trachea). Around seventy percent of children born with VACTERL will have these birth defects.[5]

6. Renal anomalies: Renal issues are also commonly found in children with VACTERL. Approximately fifty percent of children are affected, and one can find a large spectrum of kidney and urological problems. These defects can be severe, such as incomplete formation of one or both kidneys or obstruction of outflow of the urine, or more minor, like kidney reflux (backflow of urine). If these defects are corrected early in life, kidney failure may be prevented. Some children may require surgery or medication to deal with these anomalies.[3]

7. Limb anomalies: Limb issues vary widely, but affect about seventy percent of children. Some children have extra fingers or toes, fused digits, missing digits, clubbed feet or hands, or forearm abnormalities. Many can be corrected surgically, while others require ongoing adaptations throughout life.[3]

8. Other associated abnormalities: a. Failure to thrive, b. Short stature, c. Wide cranial suture

d. Large fontanel, e. Potter facies, f. Ear anomalies, g. Cleft palate,

h. Gastrointestinal anomalies: i. Malrotation, ii. Meckel diverticulum, iii. Duodenal atresia, iv. Pyloric atresia, v. Ileal atresia, vi. Pancreatic heterotopias, vii. Vermiform appendix agenesis, viii. Omphalocele, ix. Inguinal hernia.

i. Genital anomalies: i. Hypospadias, ii. Cryptorchidism, iii. Bifid scrotum, iv. Micropenis

Differential diagnosis: Nearly half of patients with tracheo-esophageal fistula will exhibit other VACTERL malformations. Down's syndrome has many similar features. Because VACTERL syndrome consists of anomalies of multiple systems, chromosomal disorders such as trisomy 18 and trisomy 13 must be excluded by karyotype study. Disorders characterized by the presence of vertebral, renal, and/or radial defects such as thrombocytopenia absent radius syndrome, Fanconi anemia, Robert's syndrome, Holt-Oram syndrome, Nager syndrome, caudal regression syndrome, sirenomelia, Müllerian duct, renal agenesis, upper limb, and rib abnormalities association, ectodermal dysplasia syndrome, and Jarcho-Levin syndrome should be considered. Associated anomalies are numerous; hydrocephalus is commonly associated.[5]

Prognosis: Overall poor prognosis, but depends on the particular association of anomalies. During the last several decades the literature has reflected a steady increase in the survival of infants with the VACTERL association. Today most children with the VACTERL association survive.[5]

Treatments: It will differ from child to child since children with VACTERL are all very unique, resulting in different health problems. The number of surgeries varies widely among children born with VACTERL. Some can have as few as three surgeries to fix defects, while others have as many as 60 or more, depending on the extent of the defects. While the defects of VACTERL never go away, through surgery, treatment, and acceptance they become more manageable. VACTERL is not consistent from child to child, and there never is a constant with ongoing surgeries and treatments.[6]

Conclusion: The purpose of this article is to provide more information about the VACTERL association thereby to gain a better understanding of the rare entity and improved treatment and genetic counseling. Each child with this condition can be truly unique, with defects being different from any other child. At present this condition is treated after birth with issues being approached one at a time. Termination of pregnancy can be offered before viability. Monthly sonographic monitoring of fetal growth and evaluation of the structural defects are recommended. Delivery in a tertiary center is required for prompt surgical repair and rehabilitation. The most common organ system involved is the urinary system with an upper urinary tract anomaly in more than 90% of cases. After birth patients with the VACTERL association should remain on antibiotic prophylaxis for urinary tract infection while awaiting the completion of screening. Urological follow-up is crucial since the majority of patients eventually require genitourinary intervention. Today, pediatric surgeons are more apt to correct cardiac and intestinal problems in these cases.

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