Significance of foetal autopsy in diagnosis of VACTERL association

J.P. Jessy[1], Rajesh Kumar[2], Anupriya Kaur[3], Kanchan Kapoor[4], Mahesh Sharma[4], Amandeep Kaur[5]

[1] *Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India*
[2] *Department of Anatomy, All India Institute of Medical Sciences, Patna, India*
[3] *Department of Paediatrics, PGIMER, Chandigarh, India*
[4] *Department of Anatomy, GMCH Chandigarh, India*
[5] *Department of Anatomy, AIIMS, Guwahati, India*

SUMMARY

VACTERL association occurs in 1 in 10000-40000 live births and is associated with vertebral defects, anal atresia, cardiac malformations, tracheoesophageal fistula, renal dysplasia and limb defects. A 19-week-old male foetus with antenatal diagnosis of foetal hydronephrosis on antenatal ultrasound in the left kidney was medically terminated and brought for foetal autopsy. No other malformation was reported on antenatal scan. On autopsy, facial abnormalities, upper and lower limb defects, coronal vertebral clefts and imperforate anus with a two vessel-umbilical cord were found. Both environmental and genetic factors are considered to be responsible for this association. The present case illustrates the importance of foetal autopsy for making a definitive diagnosis in the missed sonographic findings like anal atresia and absence of upper- and lower-limb bones.

Key words: VACTERL association – Malformation – Atresia – Dysplasia

INTRODUCTION

VACTERL association refers to statistically non-random co-occurrence of a group of congenital malformations. VACTERL stands for Vertebral defects, Anal atresia, Cardiac malformations, Tracheoesophageal fistula (TEF) with oesophageal atresia, Radial/Renal dysplasia, Limb defects. Various possible explanations considered for the occurrence of these malformations in a non-random fashion are: (1) chronic teratogenic influence throughout the period of embryogenesis; (2) an inaugural malformation which secondarily disturbs development of other anatomical structures –the so-called malformation sequence or cascade; (3) disturbances in molecular pathways or mutations of single genes; (4) disturbances in the developmental process that is essential to all systems affected (Stevenson et al., 2013).

Various environmental agents form a plausible explanation for induction of the malformation during the first trimester. Early gestational exposure to drugs like thalidomide for long term affects multiple anatomical systems like craniofacial, cardiac, and gastrointestinal structures other than the limb abnormalities. Other predisposing factors include maternal

Corresponding author:
Dr Jessy J.P. Assistant Professor, Department of Anatomy, First Floor, Academic block, All India Institute of Medical Sciences, New Delhi – 110029 India. Mobile: +918427990925. E-mail: jesjp07@gmail.com

Submitted: July 5, 2022. **Accepted:** September 3, 2022

https://doi.org/10.52083/WINX3037

diabetes, which causes oxidative stress, mitochondrial dysfunction and disturbance in key development pathways (Stevenson et al., 2013).

CASE REPORT

A 19-week-old male foetus with antenatal diagnosis of foetal hydronephrosis on antenatal ultrasound in the left kidney was medically terminated and brought for foetal autopsy. No other malformation was reported on antenatal scan. The mother was a 25-year-old primigravida with history of treatment for thyroid disorder for 3-4 months of pregnancy. The mother did not have any other significant medical history or any other history of drug intake. Informed consent was taken from the parents before performing the autopsy.

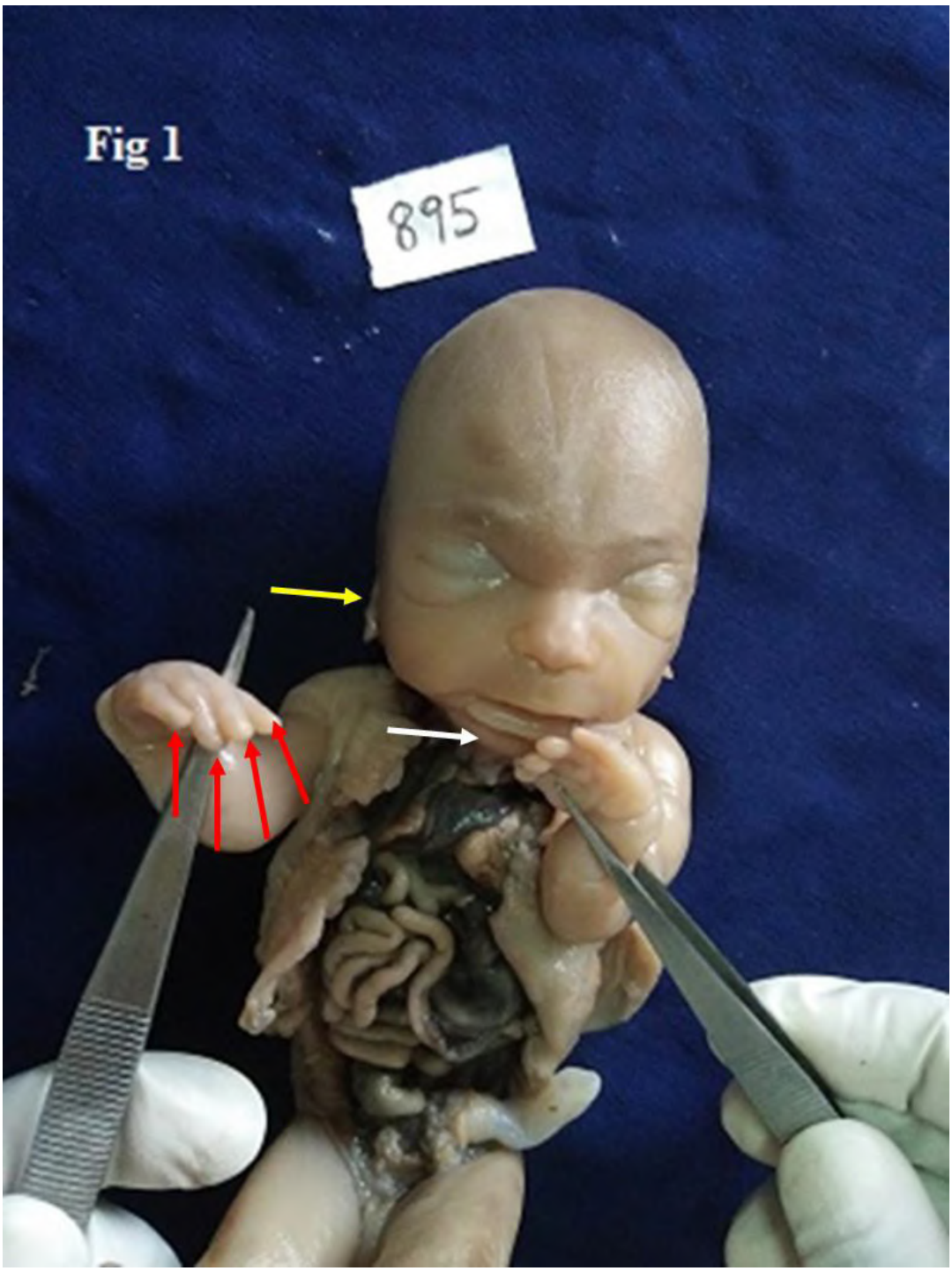

Fig. 1.- Showing bilateral meromelia and absent thumb (medial four digits are shown by red arrows), facial features - mild retrognathia (white arrow) with bilateral low set ears (yellow arrow).

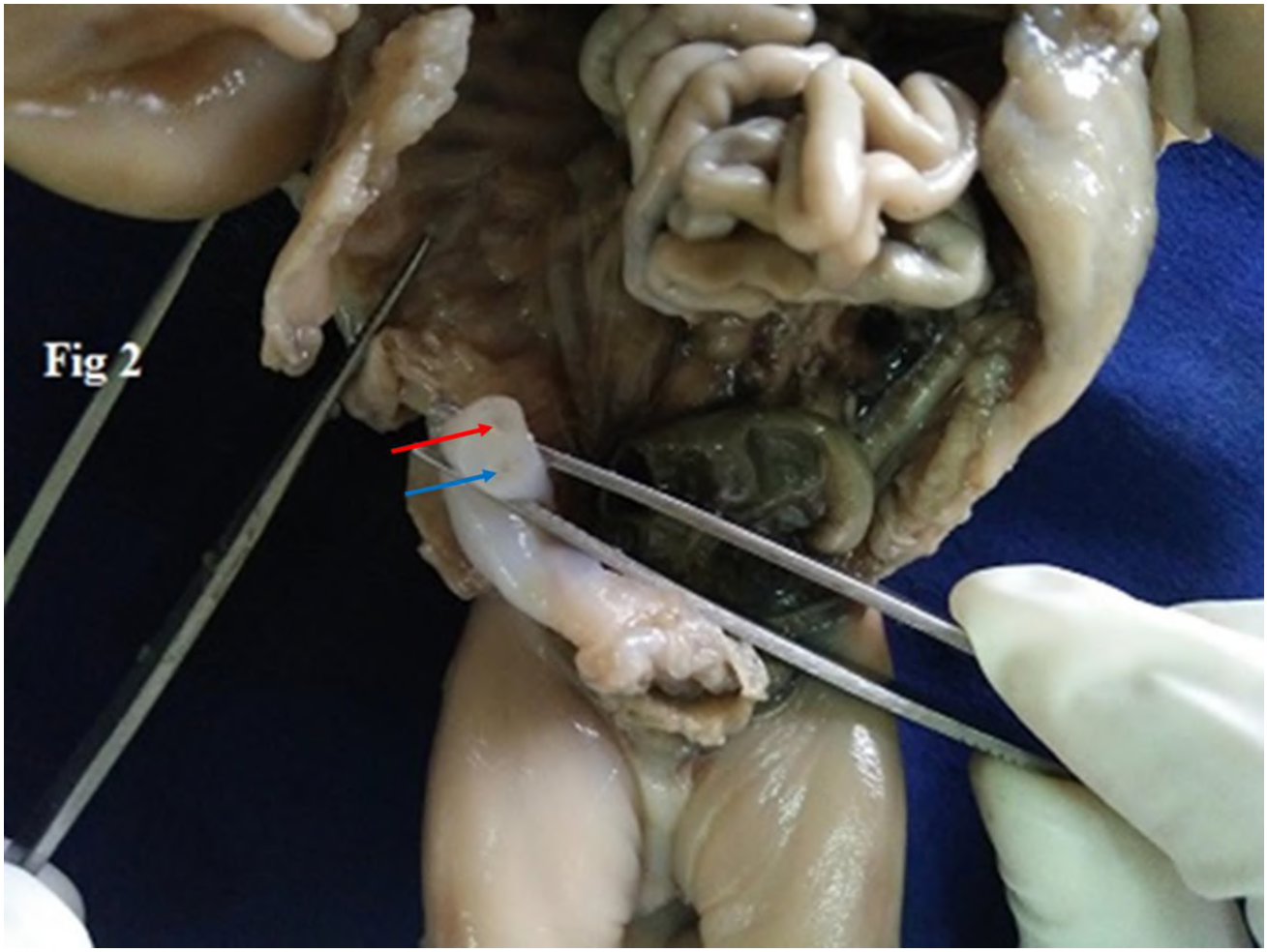

Fig. 2.- Showing 2 vessels umbilical cord (umbilical vein by red arrow and umbilical artery by blue arrow).

On further investigation, external examination showed that the 19-week-old male foetus had bilateral meromelia with absent thumb (Fig. 1). The umbilical cord consisted of 2 vessels (one umbilical artery and one umbilical vein) (Fig. 2). There was also absence of anal opening: a 1x1-cm depression was present in the anorectal region (Fig. 3). Facial features showed mild retrognathia with bilateral low set ears. Post-termination skeletal survey showed (Fig. 4) bilateral absence of radius, absence of left fibula and coronal clefts in multiple thoracic vertebrae. On internal examination, the gastrointestinal system showed blindly-ending large intestine distended with meconium (Fig. 5). The urinary system was normal. Tracheoesophageal fistula was not detected and there was no cardiac malformation.

DISCUSSION

The incidence of VACTERL association is estimated to be approximately 1 in 10,000 to 1 in 40,000 live-born infants (Jangle et al., 2014). VACTERL association is a term applied to sporadic, non-random association of specific birth defects (Stevenson et al., 2013). However, there is also strong clinical and genetic evidence for causal heterogeneity in patients with VACTERL association (Solomon et al., 2011). There should be at least three out of the following six findings for confirmed diagnosis of VACTERL association (Jangle et al., 2014).

V- Vertebral anomalies: hypoplastic (small) vertebrae or hemivertebra (where only one half of the bone is formed). About 70% of patients with VACTERL association will have vertebral anomalies.

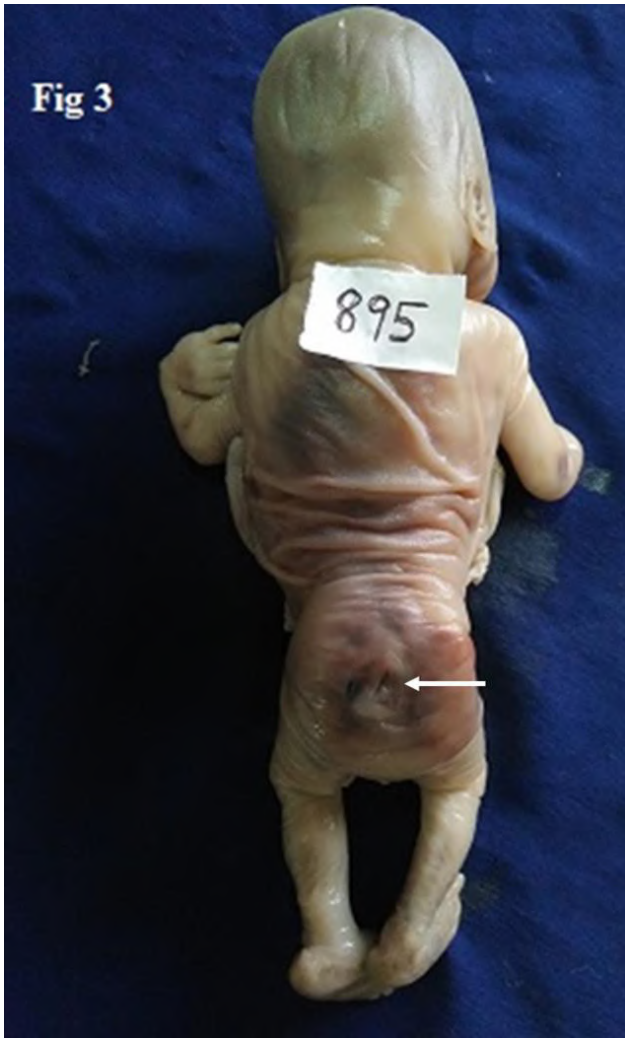

Fig. 3.- Showing absence of anal opening, 1x1 cm depression (white arrow) present in the anorectal region.

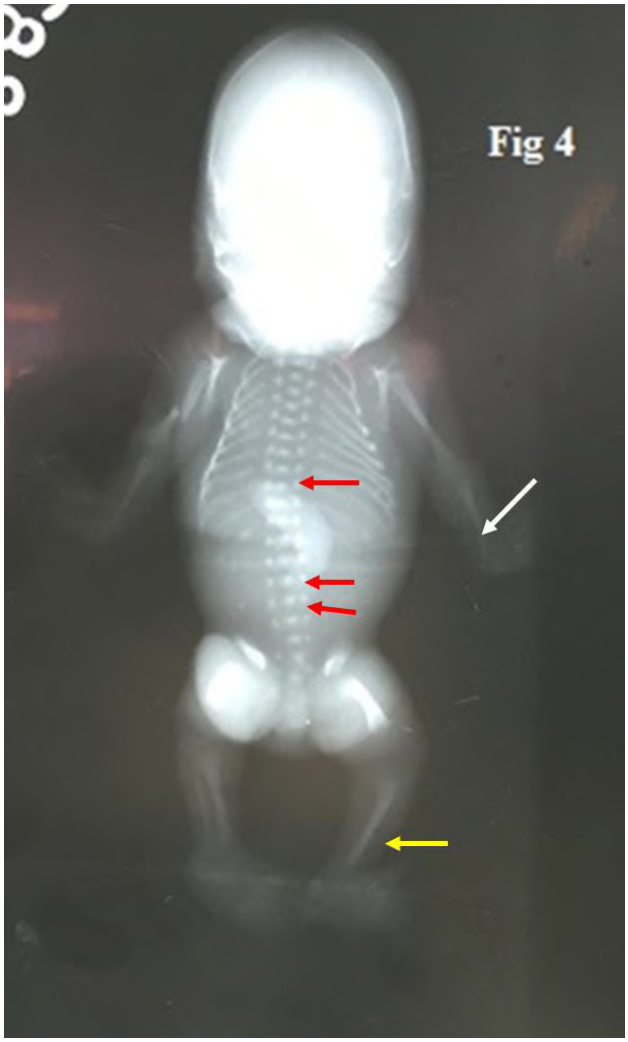

Fig. 4.- Showing bilateral absence of radius (white arrow), absence of left fibula (yellow arrow) and coronal clefts in multiple thoracic vertebrae (red arrows).

A- Anal atresia or imperforate anus is seen in about 55% of patients with VACTERL association.

C- Cardiovascular anomalies: these are present in up to three-quarters of patients with VACTERL association and the most common are ventricular septal defects, atrial septal defects and Tetralogy of Fallot.

T-E- Tracheoesophageal fistula: oesophageal atresia with tracheoesophageal fistula (TE fistula) is seen in about 70% of patients with VACTERL association.

R- Renal (Kidney): renal defects are seen in half the patients with malformation of one or both kidneys or obstructive uropathy.

Limb defects: limb defects are seen in up to 70%, which include absent or displaced thumbs, polydactyly, syndactyly and forearm (including radial aplasia) and leg defects.

Various authors have found a variable number of anomalies in patients with this association. Some of the recent reports with anomalies found by different authors have been tabulated (Table 1). Cardiac malformations have been reported in approximately 40-80% of patients with VACTERL association, while tracheo-oesophageal fistula have been found in 50-80% of cases (Weaver et al., 1986; Solomon et al., 2010). In this case report, tracheal-oesophageal fistula and cardiac anomalies were not present. The exact cause of the presence of particular anomalies associated with VACTERL has not been clearly found yet. It has been referred to various genetic or developmental defects during different stages of the embryo (Kim et al., 2001a, b). Familial clustering has also been

seen in variable number of cases (Solomon et al., 2010).

Since there are no major genes for this condition, and also its phenotypes are too heterogeneous to be defined as a syndrome, it is still referred to as an 'association'. Previous studies have observed that 90% of the patients diagnosed with VACTERL association had three or fewer phenotypes (referred to as VACTERL-like association) and <1% of patients had all six anomalies (Chen et al., 2016). It has been observed that multiple embryological processes are disturbed in the genesis of VACTERL malformations. Abnormal timing of molecular oscillator known as segmentation clock results in mal-segmentation of the vertebrae. Mesodermal proliferation and migration, epithelial-mesenchymal interactions and programmed cell death are observed to be involved in atresia of the oesophagus and anus. Failure to lay down, condense or chondrify the anlage of the radius is involved in radial aplasia. Failure of development of ureteric bud or primary failure of the metanephric mesenchyme in the early five week results in renal agenesis and the abnormal development of mesonephros/ mesonephric duct leads to lower urinary defects.

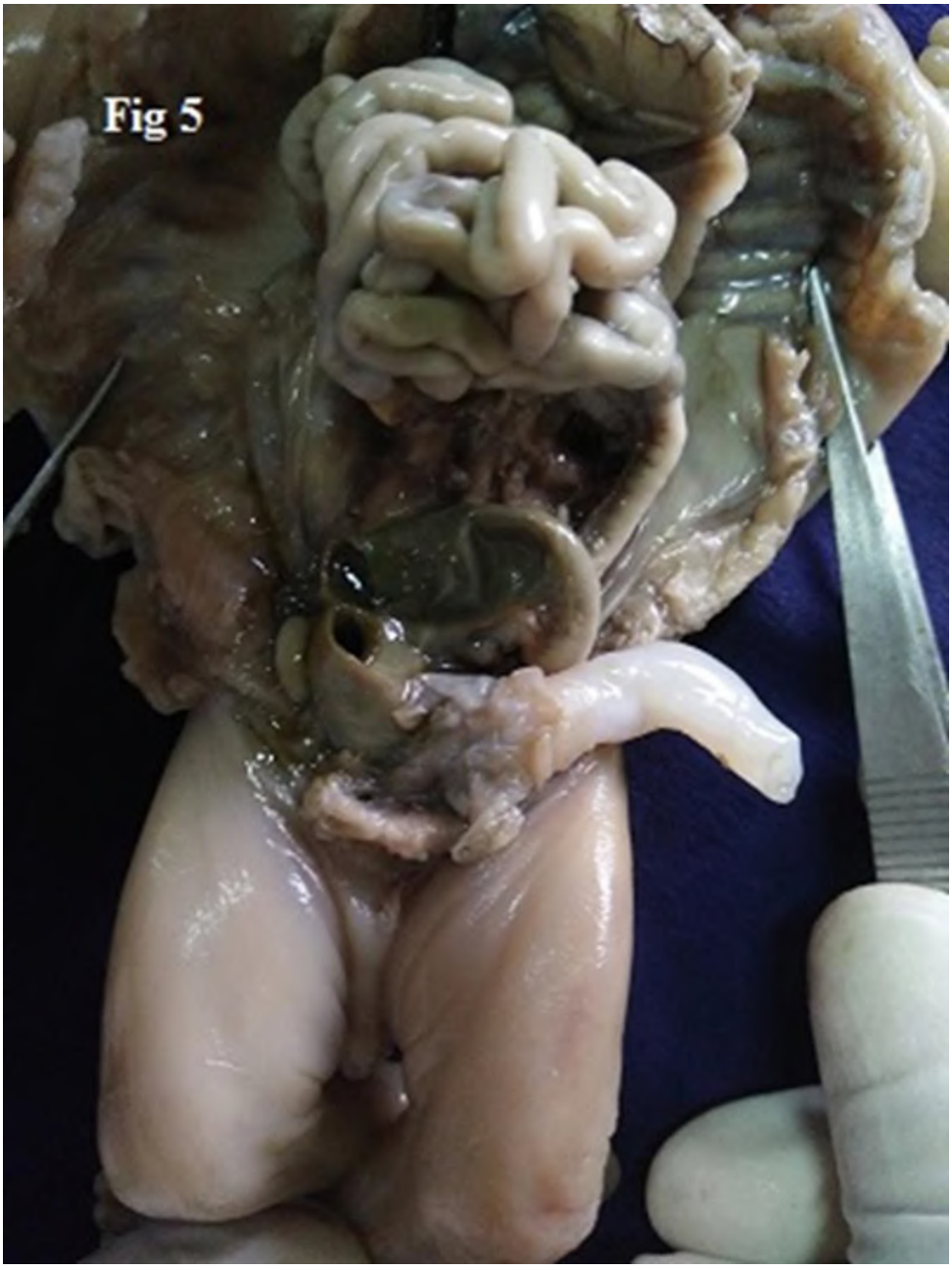

Fig. 5.- Internal examination: gastrointestinal system showing blindly ending large intestine distended with meconium.

Table 1. Various malformations found in patients with VACTERL association.

Authors	Anomalies found in VACTERL
Walsh et al., 2001	All six anomalies
Komura et al., 2007	All six anomalies
Harris et al., 2009	Abdominal wall hernia, imperforate anus, vestibular fistula, absent right rib, vertebral anomalies, tethered cord, syringomyelia, cardiac anomalies, absence of tracheoesophageal fistula
Salati et al., 2010	Anomalies involving cardiac, skeletal (vertebrae, limb) and renal system
Shah et al., 2004	All six anomalies with Prune Belly syndrome
Obeidat et al., 2019	Imperforate anus, tracheoesophageal fistula, esophageal atresia, and left renal agenesis with unicornuate uterus
Tongsong et al., 2001	All six anomalies
Cunningham et al., 2013	No statistically significant association between CHD severity and the presence or absence of other VACTERL component features, specifically anorectal malformation or tracheo-esophageal fistula; CHD presence also did not correlate with the presence of tracheo-esophageal fistula or anorectal malformation
Yang et al., 2019	Multiple airway abnormalities including bridging bronchus, airway malacia, and complete tracheal rings with VACTERL
Pariza et al., 2021	Scoliosis, imperforate anus, common truncus arteriosus, tracheoesophageal fistula, polycystic kidneys, with short right ureter, lower limb hypoplasia, micrognathia, hygroma, duodenal atresia, and cloacal malformation, with an aberrant omphalomesenteric duct
Puvabanditsin et al., 2016	Vertebral anomalies, anal and urethral atresia, esophageal atresia with tracheoesophageal fistula (TEF), renal agenesis, pulmonary hypoplasia, genital and sacral appendages, and a single umbilical artery
Chen et al., 2013	Small cerebellum, ventricular septal defect, single umbilical artery, scoliosis, right club hand, radial aplasia, renal agenesis and imperforate anus.
Nakaya et al., 2017	Non-functioning right kidney with VUR, hemidiaphragmatic eventration, ventricular septal defect (VSD) with tetralogy of Fallot, cryptorchidism, and hyperdactylia
Pelluard-Nehmé et al., 2007	Single umbilical artery, dextroposition of heart, Butterfly-shaped vertebrae, hemivertebrae, fused cervical vertebrae, left diaphragmatic hernia, anal imperforation, hypospadias and amelia of left upper limb
Endoh et al., 2008	VACTERL association with a cleft hand
Ünal et al., 2008	VACTERL association, arachnoid cyst in sylvian fissure and corpus callosum agenesis

The common cardiac anomalies in VACTERL association are ventricular and atrial septal defects and Tetralogy of Fallot occurring due to abnormal development of the cardiac septa, results in cardiac malformation (Stevenson et al., 2013). The thoracic vertebrae are most commonly affected, followed by cardiac, tracheoesophageal structures and forearm bones followed by anorectal structures in the end (Stevenson et al., 2013).

The ZIC3 gene has been shown to cause X-linked VACTERL association. Various types of ZIC3 mutations have been reported to be responsible for both VACTERL or VACTERL-like association. Anal atresia is present in most patients with ZIC3 mutations; vertebral anomalies are not commonly observed and demonstrated phenotypic variability (Chen et al., 2016). Mitochondrial dysfunction is one of the aetiological factors of VACTERL association but seen in small proportion of affected individuals (Siebel et al., 2013). SHH gene plays a significant factor, as the key inductive signal in patterning of the ventral neural tube, the anterior-posterior limb axis and the ventral somites. In humans, SHH mutation has been observed to cause more severe VACTERL phenotypes (Chen et al., 2016).

Prenatal and postnatal growth deficiency, laryngeal stenosis, ear anomaly, large fontanels, lower limb defects, rib anomalies, external genital defects, single umbilical artery (SUA), and tethered cord are less frequently seen with VACTERL association (Yang et al., 2019). The present case presented with intestinal and lower

limb abnormalities, which is a rare association. In the present case, because of the presence of limb defects, coronal vertebral clefts and imperforate anus, we label this constellation of birth defects as VACTERL association and can be because of the A3243G point mutation in mtDNA (Damian et al., 1996). The present case also highlights the importance of doing foetal autopsies, as some anomalies in our case were missed on antenatal scan and the exact diagnosis of VACTERL was possible only after the autopsy.

Genetic counselling was provided to the affected couple, as in 90% of the cases this association is sporadic with minimal risk of recurrence. However, in 10% of the cases it is seen that first-degree relatives are affected with either isolated or multiple components of VACTERL association. Hence, review of the family members for features of VACTERL was advised along with focus on polyhydramnios, absent gastric bubble and single umbilical vessel on antenatal scan in subsequent pregnancies.

CONCLUSION

VACTERL is a relatively common congenital malformation syndrome. However certain features of VACTERL association, such as anorectal malformation and tracheoesophageal fistula are often missed during prenatal imaging. Hence, foetal autopsy contributes significantly to the diagnosis of VACTERL association.

Limitation- Karyotyping and other genetic analysis were carried out neither in reported case nor in family or close relatives. Genetic analysis should be done in these types of cases to explore the genetic basis in detail.

ACKNOWLEDGEMENTS

Authors acknowledge the family for giving consent to carry out this study for the benefit of scientific world. Results from such research can potentially increase mankind's overall knowledge that can then improve patient care. Therefore, the family deserves our highest gratitude.

REFERENCES

CHEN CP, CHANG TY, CHEN YY, CHERN SR, SU JW, WANG W (2013) VACTERL association with hydrocephalus in a fetus conceived by in vitro fertilization and embryo transfer. *Taiwanese J Obstet Gynecol*, 52(4): 575-579.

CHEN Y, LIU Z, CHEN J, ZUO Y, LIU S, CHEN W, LIU G, QIU G, GIAMPIETRO PF, WU N, WU Z (2016) The genetic landscape and clinical implications of vertebral anomalies in VACTERL association. *J Med Genet*, 53(7): 431-437.

CUNNINGHAM BK, HADLEY DW, HANNOUSH H, MELTZER AC, NIFORATOS N, PINEDA-ALVAREZ D, SACHDEV V, WARREN-MORA N, SOLOMON BD (2013) Analysis of cardiac anomalies in VACTERL association. *Birth Defects Res A Clin Mol Teratol*, 97(12): 792-797.

DAMIAN MS, SEIBEL P, SCHACHENMAYR W, REICHMANN H, DORNDORF W (1996) VACTERL with the mitochondrial np 3243 point mutation. *Am J Med Genet*, 62(4): 398-403.

ENDOH N, IGAWA HH, SUGIHARA T (2003) VACTERL association with a cleft hand. *Congenital Anomalies*, 43(3): 180-183.

HARRIS K, DORN C, BLOOM B (2009) Lumbocostovertebral syndrome with associated VACTERL anomaly: a neonatal case report. *J Perinatol*, 29(12): 826-827.

JANGLE SH, GINDODIA KR, SIDDIQUI MM (2014) A case report of VACTERL association and management of its renal component. *Int J Health Sci Res*, 4: 305-309.

KIM JH, KIM PCW, HUI CC (2001a) The VACTERL association: lessons from the Sonic hedgehog pathway. *Clin Genet*, 59(5): 306-315.

KIM PC, MO R, HUI CC (2001b) Murine models of VACTERL syndrome: Role of sonic hedgehog signaling pathway. *J Pediat Surg*, 36(2): 381-384.

KOMURA M, KANAMORI Y, SUGIYAMA M, TOMONAGA T, SUZUKI K, HASHIZUME K, GOISHI K (2007) A female infant who had both complete VACTERL association and MURCS association: report of a case. *Surg Today*, 37(10): 878-880.

NAKAYA T, HYUGA T, TANAKA Y, KAWAI S, NAKAI H, NIKI T, TANAKA A (2017) Renal dysplasia characterized by prominent cartilaginous metaplasia lesions in VACTERL association: A case report. *Medicine (Baltimore)*, 96(15): e6499.

OBEIDAT RA, ALESHAWI AJ, TASHTUSH NA, ALSARAWI H (2019) Unicornuate uterus with a rudimentary non-communicating cavitary horn in association with VACTERL association: case report. *BMC Women's Health*, 19(1): 1-5.

PARIZA PC, STAVARACHE I, DUMITRU VA, MUNTEANU O, GEORGESCU TA, VARLAS V, BOHÎLȚEA RE (2021) VACTERL association in a fetus with multiple congenital malformations–Case report. *J Med Life*, 14(6): 862.

PELLUARD-NEHMÉ F, BAUDET C, CARLES D, ALBERTI EM, DELRUE MA, LACOMBE D (2007) A new case of VACTERL association with unilateral amelia of upper limb. *Clin Dysmorphol*, 16(3): 185-187.

PUVABANDITSIN S, VAN GURP J, FEBRUARY M, KHALIL M, MAYNE J, AI MCCONNELL J, MEHTA R (2016) VATER/VACTERL association and caudal regression with Xq25-q27. 3 microdeletion: A case report. *Fetal Pediat Pathol*, 35(2): 133-141.

SALATI SA, RABAH SM (2010) VACTERL association. *Online J Health Allied Sci*, 9(2).

SHAH D, SHARMA S, FARIDI MMA, MISHRA K (2004) VACTERL association with Prune-Belly syndrome. *Indian Pediat*, 41(8): 845-847.

SIEBEL S, SOLOMON BD (2013) Mitochondrial factors and VACTERL association-related congenital malformations. *Mol Syndromol*, 4(1-2): 63-73.

SOLOMON BD (2011) Vacterl/Vater association. *Orphanet J Rare Dis*, 6(1): 56.

SOLOMON BD, PINEDA-ALVAREZ DE, RAAM MS, CUMMINGS DA (2010a) Evidence for inheritance in patients with VACTERL association. *Human Genet*, 127(6): 731-733.

SOLOMON BD, PINEDA□ALVAREZ DE, RAAM MS, BOUS SM, KEATON AA, VÉLEZ JI, CUMMINGS DA (2010b) Analysis of component findings in 79 patients diagnosed with VACTERL association. *Am J Med Genet A*, 152(9): 2236-2244.

STEVENSON RE, HUNTER AGW (2013) Considering the embryopathogenesis of VACTERL association. *Mol Syndromol*, 4(1-2): 7-15.

TONGSONG T, CHANPRAPAPH P, KHUNAMORNPONG S (2001) Prenatal diagnosis of VACTERL association: a case report. *J Med Assoc Thailand*, 84(1): 143-148.

ÜNAL S, KIBAR AE, ÖZAYDIN E, KARADAG N, BALCI S (2008) A new case of VACTERL association with congenital arachnoid cyst. *Clin Dysmorphol*, 17(3): 221-222.

WALSH LE, VANCE GH, WEAVER DD (2001) Distal 13q deletion syndrome and the VACTERL association: case report, literature review, and possible implications. *Am J Med Genet*, 98(2): 137-144.

WEAVER DD, MAPSTONE CL, YU PL (1986) The VATER association: Analysis of 46 patients. *Am J Dis Children*, 140(30): 225-229.

YANG L, LI S, ZHONG L, QIU L, XIE L, CHEN L (2019) VACTERL association complicated with multiple airway abnormalities: A case report. *Medicine (Baltimore)*, 98(42): e17413.