International Journal of Medical, Medicine and Health Sciences
ISSN: 2517-9969
Vol:9, No:2, 2015

Two Cases of VACTERL Association in Pregnancy with Lymphocyte Therapy

Seyed Mazyar Mortazavi, Masod Memari, Hasan Ali Ahmadi, Zhaleh Abed

***Abstract*—**VACTERL association is a rare disorder with various congenital malformations. The aetiology remains unknown. Combination of at least three congenital anomalies of the following criteria is required for diagnosis: vertebral defects, anal atresia, cardiac anomalies, tracheo-esophageal fistula, renal anomalies, and limb defects. The first case was 1-day old male neonate with multiple congenital anomalies was bore from 28 years old mother. The mother had history of pregnancy with lymphocyte therapy. His anomalies included: defects in thoracic and lumbar vertebral, anal atresia, bilateral hydronephrosis, atrial septal defect, and lower limb abnormality. Other anomalies were cryptorchidism and nasal canal narrowing. The second case was born with 32 weeks gestational age from mother with history of pregnancy with lymphocyte therapy. He had thoracic vertebral defect, cardiac anomalies and renal defect. diagnosis based on clinical finding is VACTERL association. Early diagnosis is very important to investigation and treatment of other coexistence anomalies. VACTERL association in mothers with history of pregnancy with lymphocyte therapy has suggested possibly of relationship between VACTERL association and this method of pregnancy.

***Keywords*—**Anal atresia, tracheo-esophageal fistula, atrial septal defect, lymphocyte therapy.

I. Introduction

VACTERL association, also named as VATER, VACTER, and VACTERLS associations was firstly named in 1973 by American physicians David Weyhe Smith and Linda Quan to explain a combination of some specific birth defects [1]-[4]. VACTERL is a descriptive acronym where each letter represents a birth defect. Thus, V denotes the vertebral defects, A indicates for anal atresia, C is for cardiac defects, TE for tracheoesophageal fistula, R for renal anomalies, L stands for limb abnormalities and S indicates single umbilical artery. In the beginning of knowing and understanding the disease, it was constituted from four congenital defects and termed as VATER. Years later, the other cases, i.e. cardiac defects (C), limb abnormalities (L) and single umbilical artery (S) were added to its abbreviation. VACTREL association is rarely combined with genital anomalies [5]. Among the mentioned defects, the most common were congenital heart defects with 73.3% and vertebral second with 66.6% [4]-[10]. It is documented that the incidence of the mentioned associated anomalies ranges from about 30% to 60% for low lesions and around 70% for high lesions [11]-[13].

Since there is no clear pathological relationship between these different symptoms, VACTERL is labelled an association and not a syndrome. The association is a disorder affecting multiple organ systems or multiple median and para-median structures [11], [12]. This disease is known as a fairly common pattern of human malformations, happening in nearly 1.6 per 10,000 births. Some studies also estimated that the incidence of the disease is 1 to 10000 to 40000 [14], [15]. It is rarely seen more than once in one family. The congenital malformations usually seen in such cases are one of the main reasons of death and disabilities during prenatal period.

For diagnosis, at least three cases of the six cases should be occurred. It seems that these anomalies occur in the first 4 weeks of life [16] with mesodermal origin [17]. From disease causation point of view, in some cases, the main reason of these malformations is unknown, including several non-accidental congenital anomalies that there is no special aetiology for them [1]-[7]. For some fraction of patients, there is evidence for familial clustering suggestive of inherited factors [18], [19]. It is reported that, roughly 90% of VACTERL association cases take place sporadically, while 10% of cases include familial inheritance [18]. The vast majority of genetic causes described in humans have been reported in isolated individuals or families and overall account for only a small percentage of patients with VACTERL association.

Now, there is no accurate genetic mechanism to explain the disease. Some experts believe that deletion of a small area of genetic material on the long arm of chromosome No. 16 is involved in this disease. Here, there are 4 known genes as $FOXF_1$, $FOXC_2$, MTHFSD and $FOXL_1$. Investigations show that mutation in $FOXF_1$ gene will result in lung diseases, mutation in $FOXC_2$ gene will result in defects of spine and simultaneous mutation in $FOXF_1$ and $FOXC_2$ will result in kidney abnormalities. Defects in chromosomes Nos. 13 and 17 are involved in VACTERL association [16].

Some reports have suggested that this defects may occur more in children of mothers who taken the cholesterol-lowering statin drugs [20]. some study reported an increased risk for anorectal malformations and VACTERL association among children born after assisted reproduction techniqes [21], [22]. Besides, the disease is often sporadic and its outbreak is more in mothers suffering from diabetes [16]. VACTERL association, however, is most likely caused by multiple parameters. As mentioned, multiple genetic and environmental issues play a role in determining the risk of

Seyed Mazyar Mortazavi MD, Neonatologist, is with the Sarem Cell Research Center -SCRC of Sarem Women's Hospital, Tehran, Iran (corresponding author: Phone: 989144191937; e-mail: mazy_mor@yahoo.com).

Masod Memari MD, Pediatrician, is with the Sarem Cell Research Center -SCRC of Sarem Women's Hospital, Tehran, Iran. (e-mail: masood_memari@yahoo.com).

Hasan Ali Ahmadi, MD, and Zhaleh Abed, BSc, are with the Sarem Cell Research Center -SCRC of Sarem Women's Hospital, Tehran, Iran.

evolving this disorder and how severe the disorder will be in an individual.

II. Description

The first case is a 1-day neonate, was bore from a 28 years old mother by caesarean section. The mother had history of 7 years of infertility, who is pregnant with lymphocyte therapy. The parents were not relatives and the mother had history of hypothyroidism and used levothyroxine during pregnancy. The mother did not mention to history of diabetes, blood pressure, or congenital malformations in the family.

The neonate had good Apgar score at birth and has been transferred to nursery. In examination of lower extremities, both hips were dislocated and the joints were located as hyper flexion. As shown in Fig. 1, the right knee was dislocated and joints of both knees had hyperextension and some degrees of arthrogryposis. In the left ankle, clubfoot and in the right ankle, calcaneus valgus was seen. Toes were normal. There are no abnormalities in upper limb. In the examination, male genitalia were with natural phallus. Right testis was undescended and touched in inguinal canal. Left testis was into the scrotum. The anus was closed.

During examination of nose about choanal atresia, the nasogastric tube was passed easily from the left nostril, but 8 french catheter did not pass from the right nostril. Finally, 6 french catheter passed it, which indicated stenosis of right nostril.

In the chest radiograph, which is done by nasogastric tube, esophageal atresia was not seen. As shown in Fig. 2, there is severe involvement between the thoracic and lumbar spine as multiple hemi vertebra, hypoplastic vertebral and scoliosis. Considering several involvements and probable cardiac anomalies, echocardiography was done for the patient, in which small PDA (patent ductus arteriosus) was reported. In renal ultrasound, bilateral renal pelvic dilatation was seen. Trans-fontanel ultrasonography was normal.

In the third day of hospitalization, in abdominal radiography, air of the intestine reached the rectum; so, possible obstruction of the digestive tract was rollout in other areas. The neonate was transferred to the operating room and colostomy was placed for him. At that day, both foot of the neonate was putted in cast to correct the knee deformity and clubfoot. Two days later, the neonate was discharged.

The second case was a male with 32 weeks gestational age that is born with caesarean section due to breech position and severe oligohydraminios. The mother had history of infertility, and was pregnant with lymphocyte therapy. She had history of hypothyroid and used levothyroxine during pregnancy.

The neonate had good Apgar score at birth. In the first minutes, he was suffering from respiratory distress, which the intubation was performed for him and connected to ventilator. Chest radiography showed pulmonary hypoplasia. A dose of surfactant was administered to the neonate. In the examination, organs were normal. There was no anal atresia or choanal atresia. The genitalia were normal.

In the chest radiography, there was vertebral involvement as thoracic scoliosis and hemi vertebra. Nasogastric tube was seen in the stomach and esophageal atresia was rejected. In renal sonography, renal hypoplasia was seen. Considering vertebral defects and risk of cardiac anomalies, echocardiography was done for the patient, in which small PDA, small ASD_2 (atrial septal defect), severe PH (pulmonary hypertension) and TR (tricuspid regurgitation) were reported.

In the third day of hospitalization, the neonate was suffering from pneumothorax and stated under HFO mode. Finally, the neonate was died at the age of six days due to respiratory failure.

III. Discussion

%70 of the neonates, who suffering from VACTERL, have three symptoms; %25 have 4 symptoms and %10 have 5 symptoms. The first case, suffering vertebral involvement, anal atresia, cardiac involvement, renal involvement, and extremity involvement, had 5 main symptoms and the second case, suffering spine anomalies, cardiac involvement, and renal involvement, had 3 main symptoms.

Fig. 1 Dislocation of knee joint and clubfoot in the left ankle

Spine anomalies were seen in %70 of cases, which is often as hemi vertebra, hypoplastic vertebral and extra vertebral. Cardiac involvement is seen in %75 of cases. The most common demonstrations are VSD, TOF, ASD and coarctation of the aorta. Extremity involvement is often as upper limbs, including anomalies of the thumb and radius bone, which could be unilateral or bilateral.

In the said cases, there was no upper limbs involvement; the only severe lower extremity involvement was seen in the first case that is included in non-common cases.

There are some non-common symptoms in VACTERL association; these symptoms in the first case include genitalia anomalies (cryptorchidism) and narrowing of the nasal passage.

Previous studies have shown that Infants born after In Vitro Fertilisation (IVF) have an increased risk for a congenital malformation [23]. An association between neural tube defects and ovarian stimulation with Clomiphene citrate has been discussed for a very long time [24].

Interestingly, in these cases history of mother infertility and pregnancy by IVF and lymphocyte therapy were seen. Considering that the cause of this disease is not completely understood, lymphocyte therapy may have a role in causing the disease. In other studies that examined mother problems in causing the disease, relationship between diabetes and this disease was confirmed.

Fig. 2 Multiple hemi vertebra, hypoplastic vertebral and scoliosis with ribs deformity

In order to manage treatment of VACTERL patients, there should be close cooperation between neonatologists and other fields, such as orthopaedics, surgery and paediatric cardiologists. The first priority in treating these patients is to control cardiorespiratory problems, and then gastrointestinal and orthopaedic problems should be corrected. Most of these neonates are born with low birth weight and in general, they have not adequate weight gain, but finally, they have normal intelligence and evolution.

IV. Conclusion

In VACTERL patients, all aspects of possible anomalies should be considered. Here, additional cases of disease may be found that sometimes there is inevitable need for faster treatment. It seems that in study of the cause of disease, in addition to genetic factors, motherhood issues should be considered. Lymphocyte therapy to induce pregnancy may have a relationship with cause of the disease; further studies are required to prove.

Acknowledgment

This study was supported by Sarem Cell Research Center - SCRC of Sarem Women's Hospital, Tehran, Iran.

References

[1] Richard J. Martin. Avray A. Fanaroff. Michele C. Walsh. Neonatal – perinatal medicine disease of fetus and infant. 9th ed. Vol. 2, Richard J, Ed. Mosby, 2011, p. 532.
[2] S.A. Temtamy, J.D. Miller. Extending the scope of the VATER association: definition of the VATER syndrome. J Pediatr, 85 (1974), pp. 345-349.
[3] Khoury MJ, Cordero JF, Greenberg F, James LM, Erickson JD. A population study of the VACTERL association: evidence for its etiologic heterogeneity. Pediatrics, 71 (1983), pp. 815–820.
[4] Rittler M, Paz JE, Castilla EE. VACTERL association, epidemiologic definition and delineation. Am J Med Genet, 63 (1996), pp. 529–536.
[5] MakatoKomura, Yutaka Kanamori, Masahiko Sugiyama, Tetsuya Tomonaga, Kan Suzuki, Kouhei Hashizume, and Keigo Goishi. A femaile Infant who had both complete VACTERL association and MURCS association: Report of a case. Surg Today (2007) 37:878-880.
[6] Kallen K, Mastroiacovo P, Castilla EE, Robert E, Kallen B. VATER non-random association of congenital malformations: study based on data from four malformation registers. Am J Med Genet, 101 (2001), pp. 26-32.
[7] Czeizel A, Ludanyi I. An aetiological study of the VACTERL-association. Eur J Pediatr, 144 (1985), pp. 331-337
[8] Solomon BD. VACTERL/VATER Association. Orphanet J Rare Dis, 6 (2011), p. 56.
[9] Solomon BD, Bear KA, Kimonis V, de Klein A, Scott DA, Shaw-Smith C. Clinical geneticists' views of VACTERL/VATER association. Am J Med Genet A, 158A (2012), pp. 3087-3100.
[10] Serpil A, Birsen G, Isilay K, and Ahmet D.Is duane retraction syndrome part of the VACTERL association? Clinical Ophthalmology. 2013; 7, pp 581- 585.
[11] Endo M, Hayashi A, Ishihara M, Maie M, Nagasaki A, Nishi T, Saeki M. Analysis of 1,992 patients with anorectal malformations over the past two decades in Japan. Steering Committee of Japanese Study Group of Anorectal Anomalies.J Pediatr Surg, 34 (3) (1999), pp. 435–441.
[12] Javid PJ, Barnhart DC, Hirschl RB, Coran AG, Harmon CM. Immediate and long-term results of surgical management of low imperforate anus in girls. J Pediatr Surg, 33 (2) (1998), pp. 198–203.
[13] Pakarinen MP, Rintala RJ. Management and outcome of low anorectal malformations. Pediatr Surg Int, 26 (11) (2010), pp. 1057–1063.
[14] Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL Association: Review of genetics and epidemiology. J Med Genet. 2006;43, pp 545–54.
[15] Sarada D, Aparna G, Suma D, Muralidhar R, Krupadanam K, anasuya K.VACTERL association with less common cardiac and tracheal defects- A case report. International Journal of Research and Development of Health. April 2013;Vol 1(2).
[16] Charles Shaw-Smith. Genetic factors in esophageal atresia, tracheo-esophageal fistula and the VACTERL association: Roles for *FOXF1* and the 16q24.1 FOX transcription factor gene cluster, and review of the literature. Eur J Med Genet. Jan 2010; 53, pp 6–13.
[17] Padma S, Shanmuga P, Sonik B. A case of VACTERL and non-VACTERL association without the "V and L".Indian Journal of Nuclear Medicine.24- Jun- 2014.V 29, pp 46-49.
[18] Brown AK, Roddam AW, Spitz L, Ward SJ. Oesophageal atresia, related malformations, and medical problems: a family study. Am J Med Genet 1999, 85, pp 31-37.
[19] Solomon BD, Pineda-Alvarez DE, Raam MS, Cummings DA: Evidence for inheritance in patients with VACTERL association. Hum Genet 2010, 127, pp 731-733.

[20] Salati SA, Rabah SM. VACTERL association. Online J Health Allied Scs. 2010;9(2), p 15.
[21] Nadine Zwink, Ekkehart Jenetzky, Eberhard Schmiedeke, Dominik Schmidt, Stefan Marzheuser, Sabine Grasshoff Derr. Assisted reproductive techniques and the risk of anorectal malformations: a German case-control study. Orphanet Journal of rare diseases 2012, 7:65.
[22] Chih-Ping Chen, Tung-Yao Chang, Yi-Yung Chen, Schu-Rern Chern, Jun-Wei Su, Wayseen. VACTERL association with hydrocephalus in a fetus conceived by in vitro fertilization and embryo transfer. Taiwanese Journal of Obstetrics and Gynecology. Volume 52, issue 4, December 2013, Pages 575-579.
[23] A. Ericson and B. Kallen. Congenital malformations in infants born after IVF: a population-based study. Human Reproduction Vol.16, No.3 pp. 504–509, 2001.
[24] Greenland S. Ackerman DL. Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. Fertil Steril. 1995 Nov;64(5):936-41.

Dr. Seyedeh Maziyar Mortazavi received his specialty in Pediatrics from Semnan University of Medical Sciences in January 2000 and his sub-specialty in Pediatrics from Shiraz University of Medical Sciences, Iran in August 2009. He worked in different hospital in different locations of Iran such as Amiralmomenin Hospital (Boushehr), Dr. Sajjadi Hospital (Hadishahr) and Taleghani Hospital (Tabriz) for several years. In April 2012, he then joined to Sina Hospital (Ahvaz), Iran and worked as NICU Technical Manager. Besides, he served as Assistant Professor in Pediatrics Group of Sina Hospital. Currently, he is the NICU Technical Manager and the manger of Children's section of Sarem women`s hospital, Tehran, Iran. He has been contributed and reported his researches to several national and international conferences. His areas of specific interest and expertise include prematurity care and brain sonography. He is a member of the Sarem Cell Research Center. He is also collaboration with Jondi Shapoor Medical Journal as a reviewer.