VACTERL Association with Meningomyelocele Combined with Trisomy 18 Syndrome

Yu Kyong Kim, M.D., Ji Hoon Lee, M.D., Ga Won Jeon, M.D., and Jong Beom Sin, M.D.

Department of Pediatrics, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

ABSTRACT

Vertebral, anal, cardiac, tracheo-esophageal, renal, and limb(VACTERL) association is defined as the presence of at least three of the above-mentioned six manifestations. An estimated incidence of the VACTERL association is 1 in 20,000 to 35,000 live births although the diagnostic criteria vary. The VACTERL association is highly heterogeneous in clinical presentation. It may represent a spectrum from the less severely affected to the more severely affected. Diagnosis is difficult because of the number of disorders that have overlapping features with trisomy 13 syndrome, trisomy 18 syndrome, trisomy 21 syndrome, Feingold syndrome, and so on. The incidence of trisomy 18 syndrome, a type of a chromosomal disorder, is estimated to be 1 in 6,000-8,000 live births. It includes characteristic craniofacial anomalies, clenched hand with overlapping of index finger over third, fifth finger over fourth, underdeveloped thumbs, short sternum, cardiac anomalies such as ventricular septal defect, and renal anomalies such as horseshoe kidney. Approximately over 50% of infants with trisomy 18 syndrome live less than one week. In 1983, Khoury et al. reported VACTERL association combined with trisomy 18 syndrome. Here, we report a case of a low birth weight female infant with VACTERL association, whose second diagnosis is Edward syndrome, and that she also has another combined anomaly, meningomyelocele. To the best of our knowledge, this is the first reported case of VACTERL association with meningomyelocele combined with trisomy 18 syndrome in Korea.

Key Words: VACTERL association, Meningomyelocele, Trisomy 18

INTRODUCTION

The congenital malformations; vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheo-esophageal fistula (TE), renal anomalies (R), and limb abnormalities (L)^{1,2)} combine to form the VACTERL association. The VACTERL association can be diagnosed by the presence of at least three features of VACTERL association as mentioned above³⁾. The

Received: 22 August 2013

Revised: 23 September 2013

Accepted: 3 October 2013

Correspondence to:

Ga Won Jeon, M.D.

Department of Pediatrics, Busan

Paik Hospital, Inje University

College of Medicine, 633-165

Gaegum 2-dong, Busan 614-735,
Korea

Tel: +82-51-890-6497

Fax: +82-51-895-7785

E-mail: iamgawon@hanmail.net

Copyright(c)

By Korean Society of Neonatology.

All right reserved.

This is an Open-Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

most common case of VACTERL association is the three defect combinations of congenital malformations, such as vertebral, cardiac, and renal defects⁴. In a previous study, the associated diseases with VACTERL association are trisomy 13 syndrome⁵, trisomy 18 syndrome⁵, trisomy 21 syndrome⁶, Mullerian aplasia syndrome⁵, Chiari malformation⁴, and so on.

The trisomy 18 syndrome includes characteristic craniofacial anomalies, clenched hand with overlapping of index finger over third, fifth finger over fourth, underdeveloped thumbs, short sternum, cardiac anomalies such as ventricular septal defect, and renal anomalies such as horseshoe kidney⁷.

In 1983, Khoury et al.⁵ reported VACTERL association combined with trisomy 18 syndrome. Later, there were no reported cases of VACTERL association combined with trisomy 18 syndrome. We now present a low birth weight female infant with VACTERL association, whose second diagnosis is Edward syndrome, and that she also has another combined anomaly, meningomyelocele. To the best of our knowledge, this is the first reported case of VACTERL association with meningomyelocele combined with trisomy 18 syndrome in Korea.

CASE REPORT

A female infant, weighing 1,750 g at 39 weeks and 5 days, was delivered by caesarean section because of prenatally detected huge mass in the sacral area at 20 weeks of gestation. Her mother was 41 years old and her father was 42 years old. Her mother's obstetric history was gravid 4, para 1. Prenatal ultrasonography

of the patient detected intrauterine growth restriction, polyhydramnios, cardiac anomaly, huge sacral mass, and sacral hypogenesis at 20 weeks of gestation. Amniocentesis was recommended because of advanced maternal age and multiple anomalies of the patient. The parents refused amniocentesis and wanted to continue the pregnancy.

At birth, she had respiratory difficulty and required ventilator care. Apgar scores were 4 at 1 min and 7 at 5 min. Her weight was 1,750 g (<10th percentile), height was 39 cm (<10th percentile), and head circumference was 29.5 cm (<10th percentile). She was presented with a 6.0 × 7.0 × 7.0 cm sized protruding mass on the lumbosacral area suspected to be meningomyelocele, prominent occiput, clenched hand with overlapping of index finger over third, fifth finger over fourth, clinodactyly and polydactyly of fingers, locker bottom feet, dorsiflexed big toe, prominent heels, and syndactyly of toes (Figure 1). Orogastric tube was not advanced, and the chest radiographs revealed coiled orogastric tube in the proximal blind end of esophagus. Chest computed tomography (CT) showed proximal blind end of esophagus at the level of the aortic arch and fistula connecting distal esophagus with trachea at the level of the bifurcation, revealed tracheo-esophageal fistula, type A⁸) (Figure 2). The horseshoe kidney was incidentally found in the CT scan (Figure 2). On spine magnetic resonance imaging, sagittal T2-weighted image showed meningomyelocele, sacral hypogenesis, and truncated cord (Figure 3). She had cardiac defects such as 2 mm sized atrial septal defect, 4.1 mm sized peri-membranous ventricular septal defect, 4.3 mm sized large patent ductus arteriosus, and pulmonary hypertension on echocardiography.

Figure 1. Photographs of patient. (A) A 6.0×7.0×7.0 cm sized protruding mass on lumbosacral area suspected to meningomyelocele. (B) Locker bottom feet, dorsiflexed big toes, and syndactyly of toes. (C) Clenched hand with overlapping of index finger over third, fifth finger over fourth, clinodactyly, and polydactyly of fingers.

Figure 2. Chest computed tomography. (A) Chest computed tomography(CT) images showing proximal blind end(arrow) of esophagus at the level of the aortic arch. (B) Fistula(arrowhead) connecting distal esophagus with trachea at the level of the bifurcation, tracheo-esophageal fistula, type A. (C) A CT scan showing horseshoe kidney.

Figure 3. Spine magnetic resonance imaging. (A) Sagittal T2-weighted image shows meningocele which expanded underlying subarachnoid space and sacral hypogenesis (arrow), truncated cord (arrowhead). (B) Axial T2-weighted image shows meningocele.

She was diagnosed with VACTERL association with five defects, namely vertebral defects, cardiac malformations, tracheo-esophageal fistula, renal anomalies, and limb abnormalities. A high-resolution chromosomal analysis performed on peripheral blood did not show any anomalies other than trisomy 18. She was diagnosed with VACTERL association with meningocele, whose second diagnosis was Edward syndrome. Her parents wanted conservative treatment and refused any operative treatments for multiple anomalies. She died on the 6th postnatal day.

DISCUSSION

The VACTERL association was first described in 1972, by Quan and Smith¹⁾. It includes multiple congenital malformations:

vertebral defects (V), anal atresia (A), cardiac malformations (C), tracheo-esophageal fistula (TE), renal anomalies (R), and limb abnormalities (L). It is diagnosed by the presence of at least three features of the above mentioned malformations¹⁻³⁾. In 2011, Solomon et al.⁹⁾ reported that 79% cases had three defects and 7% cases had four defects. The most common three defects were vertebral, cardiac, and renal anomalies, and there were accompanying anomalies in patients with VACTERL association. Cardiac malformations are present in 80%, vertebral defects in 78%, renal anomalies in 72%, anal atresia in 55%, tracheo-esophageal fistula in 52%, and limb anomalies in 47% of cases⁴⁾. Our patient had five defects, vertebral defects, cardiac malformations, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.

VACTERL association is highly heterogeneous in clinical

presentation and etiology²⁾. It may represent a spectrum from the less severely affected to the more severely affected. Diagnosis is difficult due to the number of disorders that have alternate and overlapping features with VACTERL, such as Feingold syndrome, CHARGE syndrome, CATCH22 syndrome, Townes-Brocks syndrome, Pallister-Hall syndrome, Holte-Oram syndrome, Fanconi anemia, and so on¹⁻³⁾. Feingold syndrome is different from VACTERL association in brachymesophalangy, microcephaly, cognitive impairment and *V-Myc Myelocytomatosis Viral Related Oncogene, Neuroblastoma Derived* mutation; CHARGE syndrome in colobomata, choanal atresia, and *chromodomain helicase DNA binding protein 7* mutations; CATCH22 syndrome in deletion of 22q11.2, and hypocalcemia; Townes-Brocks syndrome in dysplastic ears, hearing loss, and *sal-like 1* mutations; Pallister-Hall syndrome in hypothalamic hamartoma, bifid epiglottis, and *GLI family zinc finger 3* mutations; Holte-Oram syndrome in *T-box 5* mutations; and Fanconi anemia in hematologic anomalies^{1,2)}.

An estimated incidence of the VACTERL association is 1 in 20,000 to 35,000 births although the diagnostic criteria may vary^{3,4)}. Genetic causes of VACTERL association account for only a small percentage of patients. The VACTERL association is very heterogeneous in etiology, and there are diverse mutations in homeobox D13, phosphatase and tensin homolog, zic family member 3, interstitial deletions of chromosome 17 (del(17)(q22q23.3)) and so on^{2,9,10)}. In our patient, the high-resolution chromosomal analysis was reported to be normal other than trisomy 18.

The VACTERL association can be associated with trisomy 13 syndrome⁵⁾, trisomy 18 syndrome⁵⁾, trisomy 21 syndrome⁶⁾, Mullerian aplasia syndrome⁵⁾, Chiari malformation⁴⁾, and so on. In 1983, Khoury et al.⁵⁾ reported VACTERL association with trisomy 18 syndrome in two patients. Patients with isolated esophageal atresia or tracheo-esophageal fistula associated with trisomy 18 syndrome had also been reported¹¹⁻¹³⁾.

The trisomy 18 syndrome or Edwards syndrome is a chromosomal disorder caused by the presence of an extra chromosome 18, full, mosaic trisomy, or partial trisomy 18q. The incidence is estimated to be 1 in 6,000-8,000 live births⁷⁾. The prevalence of trisomy 18 syndrome increase with the increasing maternal age^{14,15)}. In this case, as the mother of the patient was 41 years old, she was recommended amniocentesis, but she refused and continued the pregnancy. Approximately 50% of infants with trisomy 18 syndrome live less than one week, and only

approximately 5-10% of infants survive beyond the first year, who are mostly mosaic trisomy or partial trisomy 18q¹⁶⁾. Recently, most infants with trisomy 18 syndrome are prenatally diagnosed^{7,16)}. Trisomy 18 syndrome includes characteristic fetal growth retardation, polyhydramnios, craniofacial anomalies, meningomyelocele, clenched hand with overlapping of index finger over third, fifth finger over fourth, underdeveloped thumbs, short sternum, ventricular septal defect or horseshoe kidney^{7,15)}.

We report a low-birth weight female infant with VACTERL association with five features, and another combined anomaly, meningomyelocele, whose second diagnosis is Edward syndrome.

REFERENCES

- 1) Shaw-Smith C. Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology. *J Med Genet* 2006;43:545-54.
- 2) Solomon BD. VACTERL/VATER association. *Orphanet J Rare Dis* 2011;6:56.
- 3) Agochukwu NB, Pineda-Alvarez DE, Keaton AA, Warren-Mora N, Raam MS, Kamat A, et al. Analysis of FOXF1 and the FOX gene cluster in patients with VACTERL association. *Eur J Med Genet* 2011;54:323-8.
- 4) Solomon BD, Pineda-Alvarez DE, Raam MS, Bous SM, Keaton AA, Velez JI, et al. Analysis of component findings in 79 patients diagnosed with VACTERL association. *Am J Med Genet A* 2010;152a:2236-44.
- 5) Khoury MJ, Cordero JF, Greenberg F, James LM, Erickson JD. A population study of the VACTERL association: evidence for its etiologic heterogeneity. *Pediatrics* 1983;71:815-20.
- 6) Solomon BD, Bous SM, Bianconi S, Pineda-Alvarez DE. Consideration of VACTERL association in patients with trisomy 21. *Clin Dysmorphol* 2010;19:209-11.
- 7) Cereda A, Carey JC. The trisomy 18 syndrome. *Orphanet J Rare Dis* [serial online]. 2012;7:[81]. Available from: URL: <http://www.ajrd.com/content/7/1/81>.
- 8) Khan S, Orenstein SR. Esophageal atresia and tracheoesophageal fistula. In: Kliegman RM, Stanton BF, Geme JS, Schor NF, Behrman RE, editors. *Nelson textbook of pediatrics*. 19th ed. Philadelphia: Elsevier Saunders, 2011;1262-3.
- 9) Solomon BD, Bear KA, Kimonis V, de Klein A, Scott DA, Shaw-Smith C, et al. Clinical geneticists' views of VACTERL/VATER association. *Am J Med Genet A* 2012;158a:3087-100.
- 10) Felix JE, Tibboel D, de Klein A. Chromosomal anomalies in the aetiology of oesophageal atresia and tracheo-oesophageal fistula. *Eur J Med Genet* 2007;50:163-75.

- 11) Torfs CP, Curry CJ, Bateson TF. Population-based study of tracheoesophageal fistula and esophageal atresia. *Teratology* 1995;52:220-32.
- 12) Depaepe A, Dolk H, Lechat MF. The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. EUROCAT working group. *Arch Dis Child* 1993;68:743-8.
- 13) Robert E, Mutchinick O, Mastroiacovo P, Knudsen LB, Daltveit AK, Castilla EE, et al. An international collaborative study of the epidemiology of esophageal atresia or stenosis. *Reprod Toxicol* 1993;7:405-21.
- 14) Snijders RJ, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age- and gestation-specific risk for trisomy 21. *Ultrasound Obstet Gynecol* 1999;13:167-70.
- 15) Viora E, Zamboni C, Mortara G, Stillavato S, Bastonero S, Errante G, et al. Trisomy 18: Fetal ultrasound findings at different gestational ages. *Am J Med Genet A* 2007;143:553-7.
- 16) Rasmussen SA, Wong LY, Yang Q, May KM, Friedman JM. Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics* 2003;111:777-84.

Trisomy 18 증후군과 척수수막류를 동반한 VACTERL Association

인제대학교 부산 백병원 소아청소년과
김유경 · 이지훈 · 전가원 · 신중범

VACTERL association은 척추기형, 직장항문기형, 심장기형, 기관식도기형, 콩팥기형, 사지기형의 여섯 가지 선천기형 중 최소 세 가지 이상이 나타나는 경우에 진단할 수 있다. 생존 출생아 20,000-35,000명 중 1명의 비율로 매우 드물게 발생하는 질환이며 임상양상이 매우 다양하고 trisomy 13 증후군, trisomy 18 증후군, trisomy 21 증후군, Feingold 증후군 등과 임상 양상이 중복되기 때문에 진단이 어렵다. trisomy 18 증후군(에드워드 증후군)은 특징적인 안면 모습, 특징적인 손발의 이상, 심실중격결손과 같은 심장기형, 마제신과 같은 콩팥 기형을 동반하며 50% 이상이 1주일 이내에 사망한다. 1983년에 VACTERL association 이 trisomy 18 증후군에 동반된 증례보고가 있었으나, 이후에는 보고된 바가 없다. 저자들은 고령산모에서 부당경량아로 태어난 여아에서 VACTERL association과 척수수막류를 동반하며, trisomy 18 증후군을 진단한 증례를 경험하였기에 이를 보고하는 바이다.