VACTERL Association with Meningomyelocele Combined with Trisomy 18 Syndrome

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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) 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 above. The
most common case of VACTERL association is the three defect combinations of congenital malformations, such as vertebral, cardiac, and renal defects. In a previous study, the associated diseases with VACTERL association are trisomy 13 syndrome, trisomy 18 syndrome, trisomy 21 syndrome, Mullerian aplasia syndrome, Chiari malformation, 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 kidney.

In 1983, Khoury et al. 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 A (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, prominent heels, and syndactyly of toes. (C) Clenched hand with overlapping of index finger over third, fifth finger over fourth, clinodactyly, and polydactyly of fingers.
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 meningomyelocele, 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 Smith. 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 malformations. In 2011, Solomon et al. 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 cases. 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 etiology. 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, Towne-Brooks syndrome, Pallister-Hall syndrome, Holte-Oram syndrome, Fanconi anemia, and so on. 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 coloboma, choanal atresia, and chromodomain helicase DNA binding protein 7 mutations; CATCH22 syndrome in deletion of 22q11.2, and hypocalcemia; Towne-Brooks 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.

An estimated incidence of the VACTERL association is 1 in 20,000 to 35,000 births although the diagnostic criteria may vary. 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. 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 syndrome, trisomy 18 syndrome, trisomy 21 syndrome, Mullerian aplasia syndrome, Chiari malformation, and so on. In 1983, Khoury et al. reported VACTERL association with trisomy 18 syndrome in two patients. Patients with isolated esophageal atresia or tracheo-oesophageal fistula associated with trisomy 18 syndrome had also been reported. 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 births. The prevalence of trisomy 18 syndrome increase with the increasing maternal age. 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 18q. Recently, most infants with trisomy 18 syndrome are prenatally diagnosed. Trisomy 18 syndrome includes characteristic fetal growth retardation, polyhydranmios, craniofacial anomalies, meningo(myelo)cele, clenched hand with overlapping of index finger over third, fifth finger over fourth, underdeveloped thumbs, short sternum, ventricular septal defect or horseshoe kidney.

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

REFERENCES

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Trisomy 18 증후군과 척수수막류 동반한 VACTERL Association

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VACTERL association은 저주기형, 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 특정적인 안면 모양, 특정적인 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. 저작들은 고령산모에서 부당경량아로 태어난 여아에서 VACTERL association과 척수수막류를 동반하며, trisomy 18 증후군을 진단한 증례를 경험하였기에 이를 보고하는 바이다.