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Failure to Thrive and Multiple Anomalies in a Newborn : Edwards Syndrome

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= Abstract =

Key Words : *Chromosome, Edwards syndrome, Trisomy 18 syndrome, Malformation syndrome, Newborn*

CASE HISTORY

A 3 hour-old male baby was admitted to the Neonatal Intensive Care Unit of Sowha Children's Hospital due to low birth weight.

He was delivered to a 32 year-old mother by normal vaginal delivery at a local obstetric clinic at 39 weeks' gestational age with birth weight of 1,850gm. There was no history of premature rupture of membrane or maternal fever before delivery.

On admission, his vital signs were as follows: BP 60/40 mmHg, respiration rate 40/min, heart rate 120/min, body temperature 36℃. He was pale in appearance and weak in movement. The fontanelles were normotensive. The face was symmetrical. But micrognathia and low set ears were noted. His respiration was weak with a grade II/VI murmur audible at the left sternal border. There were 2 arteries and a vein in the umbilical cord. The baby had abnormally clenched fists and rocker-bottom feet. Moro reflex was weak.

Complete blood count findings on admission were as follows: WBC 17,600/mm^3 (band 2%, seg 42%, lymph 46%, mono 8%), hemoglobin 8.5 g/dl, hematocrit 25.7%, platelet 74,000/mm^3. Serum electrolytes and liver function tests were normal. Capillary blood gas showed pH 7.08, PCO_2 54.1 mmHg, PO_2 45.3 mmHg, BE -13.3 mmol/l. Prothrombin time was 20.9 seconds and activated prothrombin time was 58 seconds. Fibrinogen level was below 50 mg/dl, fibrin degradation product was positive and D-dimer was positive for 1 : 2.

Initial chest X-ray film showed pulmonary congestion with left ventricular enlargement and presence of air in the upper esophagus. Brain and kidney sonography showed hypoxic ischemic encephalopathy with right hydronephrosis and left renal ischemia.

Soon after arrival, he had substernal and subcostal retraction with weak respiration. Intubation was done. Bleeding from within the trachea and esophagus was noted. Vitamin K1, fresh frozen

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plasma and fresh packed blood cells were given. Gabexate mesylate was also given intravenously.

On the second day, his respiration became weaker and seizure of 1 minute duration was noted. Anticonvulsant was given, and the capillary blood gas during this time showed pH 7.05, PCO_2 37.9 mmHg, PO_2 52.0 mmHg, and BE -18mmol/l. Intermittent positive pressure ventilation was given to the patient. The ventilator was set at FiO_2 1.0, respiration rate 40/min, PIP 18 cmHg and PEEP 3 cmHg. Complete blood count showed WBC 18,600/mm^3 (band 1%, seg 27%, lymph 64%, mono 7%) hemoglobin 4.5 g/dl, hematocrit 14.4%, platelet 44,000/mm^3, prothrombin was >30 seconds, and activated prothrombin time was 109.4 seconds. Platelet concentrate and fresh packed blood cells were transfused, but platelet count still remained low (34,000/mm^3). Platelet was transfused again to become 78,000/mm^3.

There was no evidence of gross bleeding except those suctioned through the endotracheal tube. Stool was negative for occult blood. Blood, stool and urine cultures revealed no growth.

He did not show any improvement and was discharged against medical advice on the 5th hospital day. The patient died at home a few hours later.

DISCUSSION

Dr. Chang: This baby was born at term and weighed 1.85 kg which is below the 3rd percentile for the gestational age. He showed external dysmorphism, notably, low set ears, micrognathia, abnormal clenched fists, and rockerbottom feet. Other abnormalities suggesting the structural malformations are cardiomegaly and air in upper esophagus on chest X-ray, cardiac murmur and hydronephrosis. He showed respiratory distress, a weak Moro reflex, and seizure. He had bleeding from trachea and probable disseminated intravascular coagulopathy on the day of birth, and persistent metabolic acidosis. This is a clinical summary of this baby.

May we review the X-ray films at this time?

Dr. Kim (pediatric radiologist): An infantogram obtained on the day of birth demonstrates right sided diffuse air space disease with air bronchogram, distended air pocket in the upper esophagus, presence of gas in the abdomen, and relatively large heart. The 12th rib of right side is missing and the pelvis is relatively narrow. The follow up films obtained on the 2nd day and the 3rd day of life show decreased haziness of the right lung and clearing of the previous findings, but increased pulmonary vascularity throughout the lungs. The heart is still large, although was not progressively enlarged, suggesting that there is a large left to right shunt (Fig. 1). Brain sonography obtained at the first day of admission shows generalized increased parenchymal echogenicity. I think that it could be caused by hypoxic and ischemic cerebral injury.

Dr. Chang: May I ask some questions about the clinical history to Dr. Kim of Sowha Children's Hospital?

First, do you have any maternal history and perinatal history of the baby regarding Apgar score

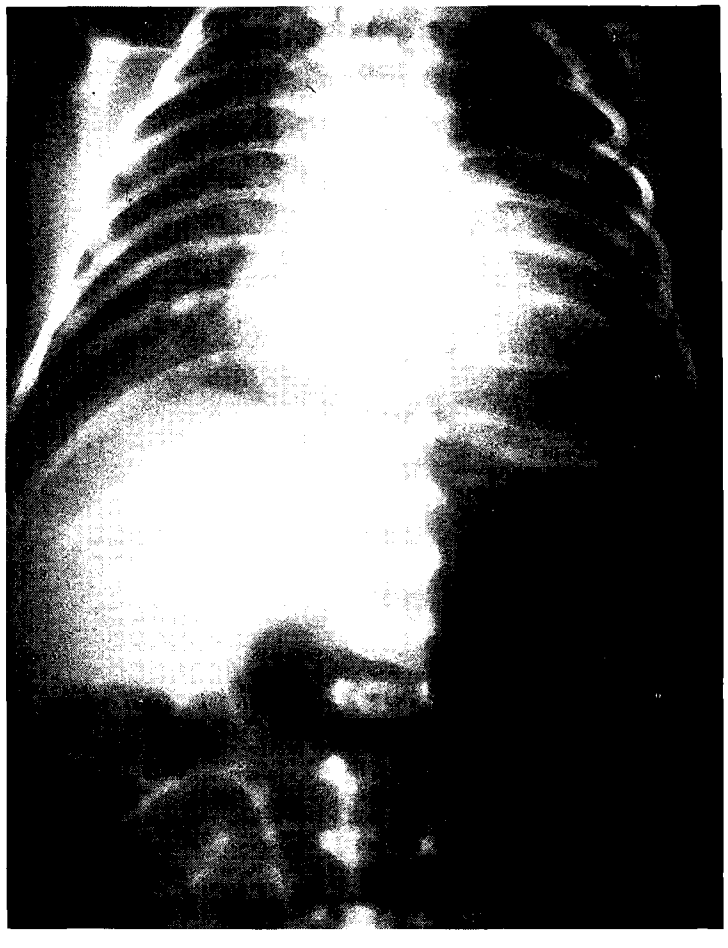

Fig. 1. Chest X-ray shows cardiac enlargement.

and whether the resucitation was performed at the delivery room or not? Second, do you know the facts that the amount of the oral secretion was profuse and insertion of feeding tube was difficult or impossible?

Dr. Kim,(Sowha Children's Hospital) : I heard that this pregnancy was complicated by polyhydramnios. And cardiopulmonary resucitation was not performed before transfer to our hospital. Immediately after the admission to our hospital, we found that the baby's oral secretion was very profuse. We tried to insert the feeding tube but failed.

Dr. Chang : Thank you. This term newborn infant is either of small for gestational age (SGA) or intrauterine growth retardation (IUGR). The term of SGA or IUGR is defined by birth weight below 10th percentile or more strictly, 3rd percentile in given race, gender, and gestational age. Although we cannot calculate the ponderal index in this case, physical findings including external dysmorphic features suggest that this baby had early or symmetrical intrauterine growth retardation, probably due to chromosomal anomaly or anomalad syndrome.

Air in the upper esophagus and presence of abdominal gas in the initial chest X-ray suggest the possibilities of upper esophageal atresia and distal tracheoesophageal fistula. Maternal polyhydramnios, profuse oral secretion, and difficulty in insertion of feeding tube strongly support it.

This baby had multiple localized structural defects that are thought to be due to a single cause, indicative of malformation syndrome. Many of the malformation syndromes or associations show constellations of clinical findings such as low set ears, micrognathia, rockerbottom feet, esophageal atresia with tracheo-esophageal fistula, and clenched hands. These are Edwards syndrome, Patau syndrome, Hutterite syndrome, Bowen-Conradi type and Pena-Shokeir syndrome. The last two are phyenotypically similar with Edwards syndrome and very rarely seen. But affected patients are normal in chromosome and inherited as autosomal recessive mode. Patau syndrome or 13 trisomy syndrome is characterized by microphthalmia, cleft lip and palate, and polydactyly. Edwards syndrome or 18 trisomy should be suspected when an affected person has five or more of the clinical findings with frequency of 50% greater and confirmed by chromosomal study (Hecht et al 1990). I am sure that this baby satisfies the major diagnostic criteria of Edwards syndrome. We can find 9 clinical findings with frequency of 50% greater in Edwards syndrome in this baby. They are failure to thrive, low-set ears, micrognathia, overlapping fingers, small narrow pelvis, hypotonia, heart murmur, rocker-bottom feet, and renal malformation including hydronephrosis. Prognosis of Edwards syndrome was reported to be very poor. Thirty percent of patients die by 1 month of age, 50% by 2 months, and 90% by 1 year. The usual causes of death were aspiration, apnea or congenital heart disease.

In this case diagnostic pivot is that this baby may have been asphyxiated perinatally although he was not resuscitated at the delivery room. Generally basic causes of asphyxia during labor and delivery are interruption of umbilical blood flow, failure of gas exchange across the placenta, inadequate perfusion of the placenta and failure to inflate the lungs adequately after birth. But without any other disturbing factors, a compromized fetus who is growth retarded like this case cannot further tolerate the transient intermittent hypoxia of normal labor. There are no informations about Apgar scores, cord blood pH of the baby. I am sure that this case had been suffered from perinatal asphyxia significantly. Supporting evidences are clinical findings of pallor, hypotonia, which are also explained by anemia and Edwards syndrome itself. Brain edema in neurosonography can be explained by hypoxic-ischemic cerebral injury.

Disseminated intravascular coagulation in the newborn can be caused by hypoxia-acidosis, infectious problems, various obstetric conditions such as abruptio placentae, and severe systemic diseases of the newborn such as necrotizing enterocolitis and shock. It is often initiated as an in utero event triggered by infection or hypoxia. I suspect that the primary event of disseminated intravascular coagulopathy (DIC) in this case could be hypoxia-acidosis due to antepartum and/or intrap-

artum asphyxia based on the fact that DIC in this baby was found from the 1st day of life without any clinical and laboratory evidence of perinatal infection. However, the persistent DIC in spite of the blood component infusion suggests that the sepsis was complicated during the hospital course.

Regarding the heart murmur in this case I have few comments. Heart murmur is noted in 33% of normal newborn infants examined on the first day of life. The vast majority of these murmurs are physiologic. However, since more than 90% of infants with Edwards syndrome have anomalies of cardiovascular system, pathological murmur should be considered in this case. Congenital heart diseases commonly associated with Edwards syndrome are patent ductus arteriosus, ventricular septal defect, atrial septal defect , valvular dysplasia more frequently, and complex lesions less frequently (Musewe *et al.*, 1990, van Praagh *et al.*, 1989). In this case there were no symptoms and signs of congestive heart failure such as tachycardia, tachypnea and hepatomegaly. Significant hypoxemia and cyanosis were not noted. Chest radiography revealed cardiomegaly with increased pulmonary vascularity during the first week of life. Therefore murmurs in this case must be pathologic. Acyanotic congenital heart disease with a large left to right shunt that can produce cardiomegaly in early newborn period is a possibility. Although large patent ductus arteriosus or ventricular septal defect is most commonly associated with Edwards syndrome, it cannot solely produce cardiomegaly with increased pulmonary vascularity within a few days of life because pulmonary vascular resistanc is not fully reduced at that time. So I consider the possibilities that there may be additional cardiac anomalies such as coarctation of aorta or aortic stenosis that can potentiate left to right shunt through the patent ductus arteriosus or ventricular septal defect.

Now, I would like to focus my discussion on the possible causes of the pulmonary edema seen in radiograph that was associated with respiratory distress within 24 hours of life (Table 1). First, pulmonary congestion caused by cardiovascular causes that may manifest as congestive heart failure within a day of life can be dismissed in this case. Second, among the exracardiac causes, less likely diagnoses include transient tachypnea of neuborn, respiratory distress syndrome, iatrogenic fluid overload, and neurogenic pulmonary edema. They are generally manifested as bilateral lung diseases. Congenital pneumonia is classified into transplacental pneumonia and postamnionitis pneumonia. X-ray findings of congenital pneumonia are diffuse homogeneous density similar to respiratory distree syndrome or coarse reticulonodular density or bronchopneumonia. Transplacental pneumonia caused by syphilis or listeriosis is preceded by maternal infection. Postamnionitis pneumonia is often associated with sepsis and commonly accompanied with predisposing factors, e. g., premature rupture of membrane of more than 24 hours, or premature labor. Causative agents are *group B streptococcus*, *E. coli*, enterococcus, *H. influenzae*, and *S. viridans*. Pulmonary hemorrhage is diagnosed by clinical manifestations of respiratory distress, bilateral or unilateral pulmonary alveolar haziness in chest radiograph and presence of blood in tracheal suction. In this case considering the fact of right dominant lung lesion with presence of blood in tracheal suction on the day of birth and no evidence of infection, we can suspect the main cause of initial and subsequent respiratory distress is pulmonary hemorrhage. I am sure that the pulmonary hemorrhage was complicated by asphyxia and DIC.

Onset of seizure in this case was within 72 hours of life. So I think that the seizure was a manifestation of hypoxic-ischemic encephalopathy in this case. Intracranial hemorrhage or intracranial malformations can be considered but is not likely.

Considering the fact that the baby showed downhill course despite of therapy with persistent metabolic acidosis and DIC I suspect that sepsis might have been complicated during the hospital course, although it was not the initial event of deterioration of the baby.

Clinical diagnosis (Dr. Chang):

1. Edwards syndrome
2. Esophageal atresia / distal tracheoesophageal fistula

3. Congenital heart disease
   : ventricular septal defect or patent ductus arteriosus, valvular dysplasia with corctation of aorta or aortic stenosis
4. Perinatal asphyxia with hypoxic-ischemic encephalopathy
5. Disseminated intravascular coagulation due to hypoxia-acidosis
6. Pulmonary hemorrhage
7. Hidden sepsis

Table 1. Causes of pulmonary edematous lesion with respiratory distress in the newborn within 24 hours of life

A. Cardiovascular causes
1. Left heart obstructive lesions(eg. Severe AS)
2. Pulmonary venous obstruction(eg. TAPVR, infracardiac type)
3. Excessive pulmonary blood flow(eg. TA with transposition)
4. Nonstructural heart disease
1) Myocarditis
2) Asphyxia in the newborn(acute LV failure)
B. Extracardiac causes
1. Transient tachypnea of the newborn
2. Pneumonia congenital
3. Respiratory distress syndrome of the newborn
4. Iatrogenic fluid overload
5. Neurogenic pulmonary edema
6. Pulmonary lymphangiectasia
7. Pulmonary hemorrhage

AS : Aortic stenosis TAPVR : Total anomalous pulmonary venous return
TA : Truncus arteriosus LV : Left ventricle

PATHOLOGICAL FINDINGS

Dr. Chi : This patient was brought to Sowha Children's Hospital after death at home. The postmortem examination was done at Seoul National Children's Hospital within 24 hours after his demise. Chromosome study was done in two separate occasions at two different institutions including our Department. The results were identical to be 47, XY, +18.

On external examination he had symmetrical growth retardation. The head showed micrognathia (receded chin), low-set ears, flat nasal bridge and prominent occiput. Extremities were symmetric. Both hands showed flexion deformity of the 2nd, 3rd and 4th fingers showing overlappings of index fingers over the third and fifth finger over the fourth. These findings are often called clenched hands. No simian crease was noted. Rocker bottom feet were noted.

Internal examination disclosed many other anomalies involving several organ system. The esophagus ended blindly at proximal one thirds, and there was a communication of distal esophagus to the carina of the trachea. The heart showed enlargement. The major vessels were normally oriented, and the ductus arteriosus was patent. There was atrioventricular septal defect, 0.5cm in size (Fig. 2). The lungs showed diffuse consolidation. There was massive alveolar hemorrhage. A focus of necrotizing vasculitis with bacterial colonies was woted in the lung. The right kidney showed hydronephrosis due to ureteropelvic junction obstruction. Both kidneys showed microcystic change through the cortices without features of dysplasia. Acute tubular necrosis was also noted (Fig. 3). Meckel's diverticulum was found. There were multiple hemorrhage in the mucosa of stomach, esophagus, testis, retina and brain, representing disseminated intravascular coagulopathy. Histological examination of entire organs and tissue showed several fibrin platelet thrombiinblood vessels. Necrotizing esophagitis and tracheitis were also noted. Blood culture grew *Pseudomonas aeruginosa*. The brain showed scattered pyknotic neurons in the brain and spinal cord, indicative of hypoxic-ischemic encephalopathy. The eyeball showed proliferative angioretinopathy.

In summary, this patient died of septicemia associated with necrotizing enterocolitis and multiple malformation syndrome.

Pathological Diagnosis

Trisomy 18 (Edwards) syndrome
- —Intrauterine growth retardation
- —Esophageal atresia with tracheo-esophageal

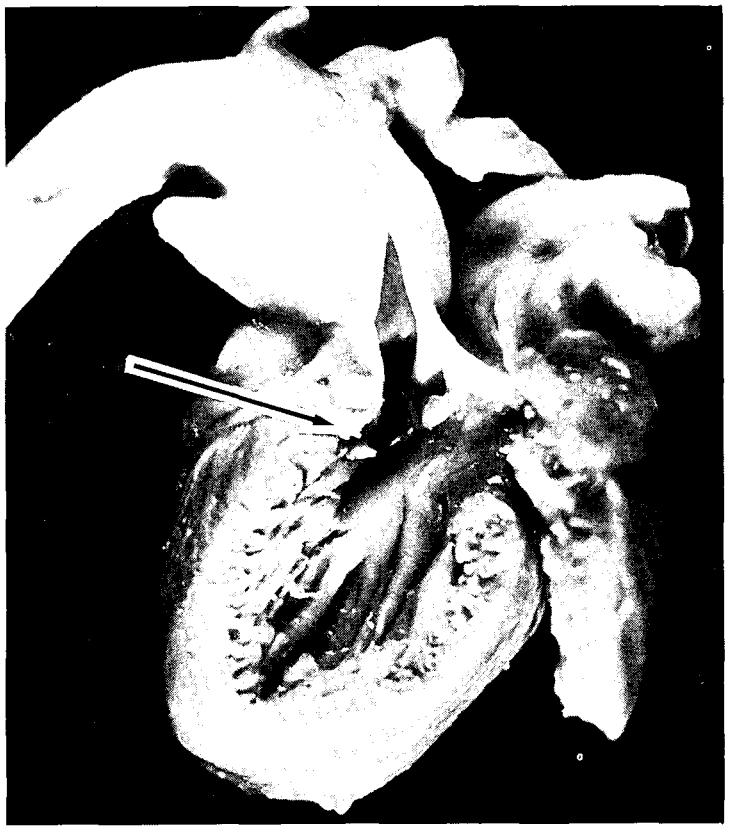

Fig. 2. The heart shows a large ventricular septal defect (arrow) seen in the left ventricle.

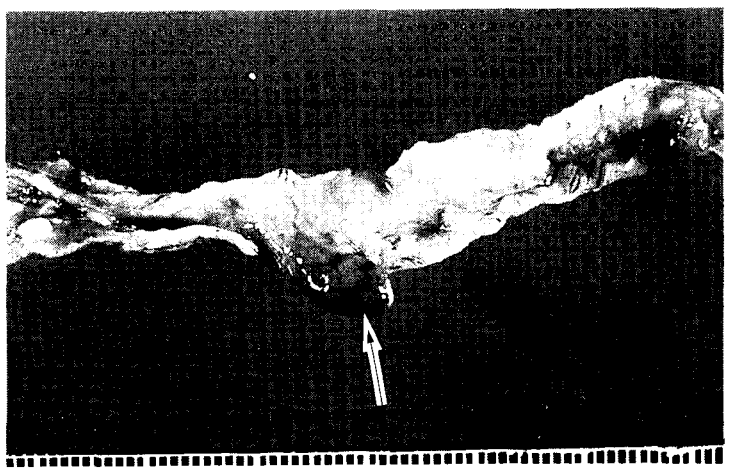

Fig. 3. Small intestinal segment shows mucosal hemorrhage and a Meckel's diverticulum (arrow).

fistula
- Atrioventricular septal defect and patent ductus arteriosus
- Micrognathia
- Low set ears
- Rocker bottom feet
- Clenched hands

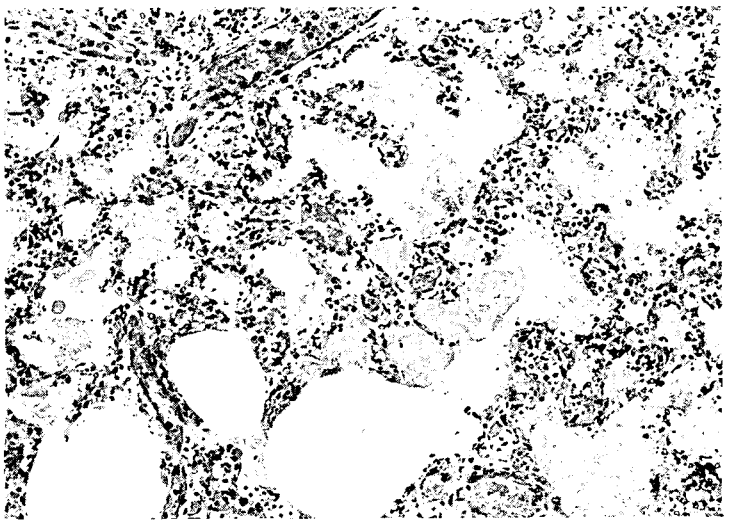

Fig. 4. Lung section showing intra-alveolar hemorrhage and edema.

- Absent 12th rib, right
- Microcystic change, kidney
- Heteropelvic junction obstruction and and hydronephrosis, right
- Single umbilical artery
- Meckel's diverticulum

Neonatal Hypoxidosis
- Hypoxic-ischemic encephalopathy
- Pulmonary edema and hemorrhage

Pseudomonas sepsis and disseminated intravascular coagulopathy
- Multiple hemorrhage in many organs and tissue
- Fibrin platelet thrombi
- Necrotizing enterocolitis

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