



Infant of a Diabetic Mother with Spondylocostal Dysostosis and Multiple Congenital Anomalies

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Abstract

Fetal development is adversely affected in infants of diabetic mothers. Poorly controlled diabetes in these mothers increases the incidence of congenital anomalies. The most common congenital anomalies are congenital heart disease, caudal regression syndrome, and central nervous system anomalies. The mortality rate of infants of diabetic mothers with cardiac malformations is higher. Jarcho–Levin syndrome, also known as spondylocostal dysostosis (SCD), is a rare genetic disorder with an unknown cause that manifests with respiratory failure, multiple spines, ribs, and other abnormalities. Here is a case of SCD with multiple congenital anomalies in the infant of a diabetic mother presented.

Keywords: Infant of a diabetic mother, spondylocostal dysostosis, congenital anomalies

Introduction

Jarcho-Levin syndrome is a rare genetic disorder characterized by respiratory insufficiency and multiple spine and rib abnormalities. It was first described by Jarcho and Levin in 1938. Spondylocostal dysostosis (SCD) and spondylothoracic dysostosis (STD) are the subtypes of Jarcho-Levin Syndrome, which show a hereditary picture. Autosomal dominant, autosomal recessive, and sporadic cases have been described in the literature (1, 2). The prevalence of this syndrome has been reported as 0.25/10.000. A developmental problem that occurs in a period between the 4th and 8th weeks of the fetal life is believed to be responsible for the pathogenesis, although its cause is not completely known. Multiple organ anomalies may accompany (3).

Diabetes is an important disease that affects fetal development during pregnancy and causes metabolic disorders in newborns. It may cause spontaneous abortion, preeclampsia, hypertension, polyhydramnios, hypoglycemia, and ketoacidosis in pregnant women and a variety of anomalies and complications such as macrosomia, intrauterine growth restriction, and preterm delivery in the fetus (4). Although maternal hyperglycemia is diminished by current pregnancy follow-ups, the morbidity of infants of diabetic mothers (IDM) still remains important. Studies have shown that the diagnosis rate of gestational diabetes mellitus (GDM) is 7.5%, and the prevalence of IDM is 5%. Among these IDM cases, 93% of them are born of mothers diagnosed with GDM and the remaining 7% comprise those born of mothers diagnosed with insulin-dependent diabetes mellitus (IDDM). It has been reported that the frequency of major anomalies and structural defects in infants of diabetic mothers is three to five times higher than that in healthy newborns (5). This article reports about an SCD case that sporadically developed in an IDM on the basis of pre-GDM and was accompanied by multiple congenital anomalies.

Case Report

A 38-week cesarean-born female infant of a 35-year-old mother (G4P4A0) was admitted to the neonatal intensive care and intubated due to the absence of spontaneous breathing. Family history revealed no blood relationship between the infant's mother and father, but the mother has been suffering from uncontrolled diabetes for 5 years. On physical examination, the infant's general condition was poor, and tachypnea (80/min), dyspnea, chest withdrawal, increased chest anterior–posterior diameter, irregular-looking costae, and scoliosis were noteworthy. Her body weight was 4,200 g (75 p), height was 49 cm (50 p), head circumference was 33 (50 p), body temperature was 36.5°C, pulse rate was 124/min, and oxygen saturation was 90% measured using a pulse oximeter. Detailed physical examination of the patient revealed that she had a short neck, a low nuchal hair line, discrete nipples, a narrow chest cage, internal rota-

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Figure 1. a, b. Short inclined neck, low nuchal hair line, discrete nipples, and limb shortness due to scoliosis and right fibula hypoplasia are seen in an SCD case in the figure
SCD: spondylocostal dysostosis

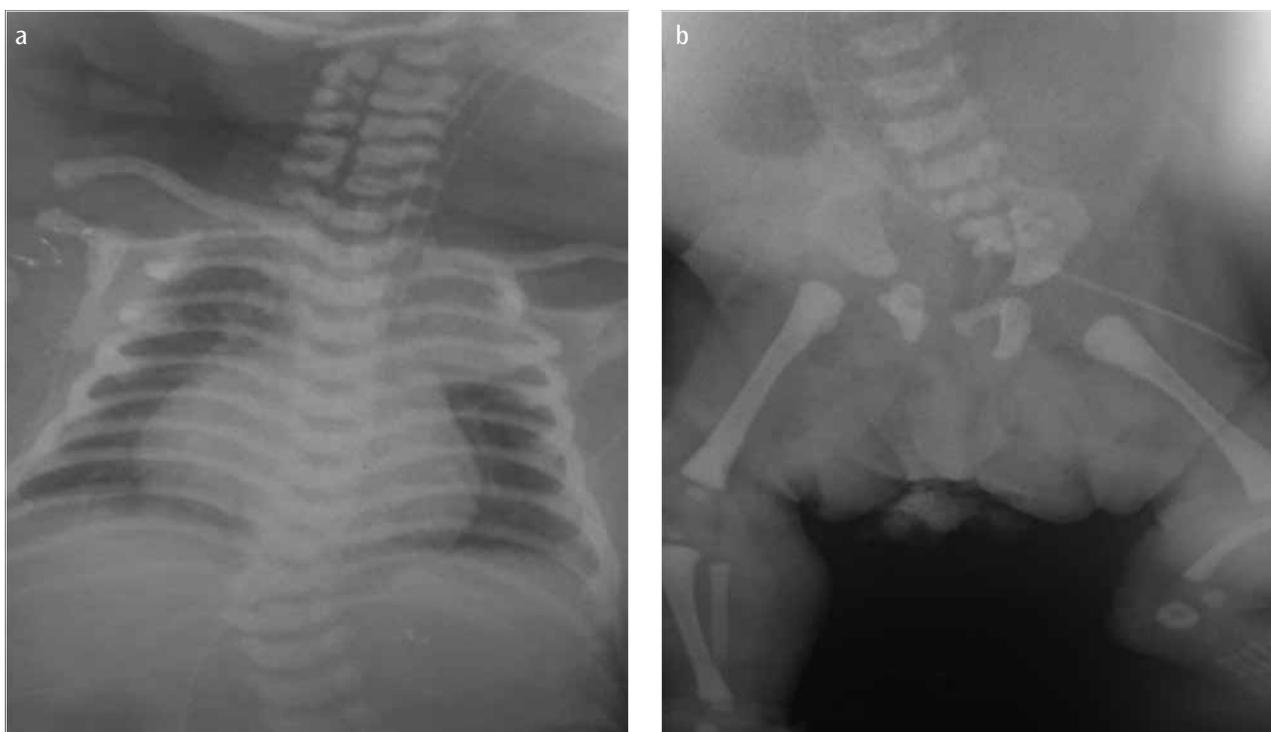


Figure 2. a, b. Figure 2a shows cervical and thoracic vertebral segmentation defects. Figure 2b shows sacral agenesis, right fibula agenesis, and tibial hypoplasia

tion anomaly in the right hand, and shortness in the right lower extremity (Figure 1a, b). In the radiological examinations, direct radiographs revealed hemivertebra in C1–C6 and T1–T8, marked scoliosis on the spine, agenesis on the right fibula, hypoplasia, and sacral agenesis on the right tibia (Figure 2a, b). Liver and kidney functions, serum electrolytes, and C-reactive protein levels were found within normal limits in the laboratory tests of complete blood count. While the level of HbA1c, which was examined because the patient was an IDM, was 6.8%, HbA1c level of the mother was 8.4%. Abdominal ultrasonography (US) revealed hepatomegaly and left renal agenesis, whereas transfontanel US and brain magnetic resonance imaging were within normal limits. Truncus arteriosus, complete AVSD, and hypertrophic cardiomyopathy (CMP) were observed in the echocardiography of the

patient along with systolic murmur in the cardiovascular system examination. Intravenous administration of furosemide 1 mg/kg/day and dobutamine 5 g/kg/min was started in the patient for heart failure. Chromosome analysis revealed a 46, XX karyotype. Mutation analysis could not be executed. Since the patient with cardiac anomalies had symptoms of syndromic genetic diseases, surgery was not considered. Finally, the infant was diagnosed with SCD based on multiple vertebral and costal anomalies and crab-like chest wall structure. Chest physiotherapy was applied to the patient during the follow-up, along with continuous intubation, for 2 months. However, the patient died on the postnatal 60th day due to recurrent pulmonary infection, respiratory failure, and heart failure. This case report was prepared after obtaining consent from the patient's parents.

Discussion

Jarcho-Levin syndrome is a rare unknown disorder of vertebral and costal formation (1). It comprises two types, including SCD, which is also known as Jarcho-Levin syndrome, and STD, which is known as Lavy–Moseley syndrome. SCD is a milder form characterized by autosomal dominant multiple vertebral segmentations, formation defects, and costal anomalies. In this syndrome, the appearance of the chest wall almost resembles a “crab” (6). STD is an autosomal recessive disorder showing block vertebrae and is characterized by segmentation, formation defects, and additional anomalies of the cervical, thoracic, and lumbar spine and has a higher mortality. Neural tube defects and cardiovascular, genitourinary, and parenchymal organ pathologies may accompany in both clinical pictures. Hydrocephalus, meningomyelocele, strabismus, spina bifida, bifid uvula, ASD, VSD, renal agenesis, polycystic kidney, diaphragmatic hernia, Sprengel deformity, and club foot are other reported anomalies (1, 7). It is believed that insufficient segmentation occurring in the somites during the 4th and 5th weeks of fetal life is responsible for the pathogenesis. Mutations in *DLL3*, *MESP2*, *LFNG*, *HES7*, and *TBX6* genes have been identified in the genetic etiology of patients with SCD (8). Although chromosome examinations were also performed in our case, genetic mutations could not be identified. Genetic etiology has not been defined in a majority of SCD patients, which suggests that other factors may be effective in addition to genetic heterogeneity. In fact, the presence of an uncontrolled pre-GDM status in the antenatal follow-up of our case supports that epigenetic factor may also be effective in addition to genetic heterogeneity. Diabetes in pregnancy is a health problem that is important nowadays due to increased fetal and neonatal risks. Genetic, teratogenic, maternal, and metabolic factors have been held responsible for the increase in congenital anomalies in the infants of diabetic mothers (4, 5). Although there is not enough information about the early pregnancy process, studies have shown that hyperproinsulin that occurs in the embryos of diabetic mothers causes a teratogenic effect. The effects of hyperinsulinemia and hyperglycemia in infants of diabetic mothers occur during organogenesis, especially in the first trimester (9). There are studies suggesting that mother’s poorly controlled diabetes and increased HbA1c levels in the first trimester of pregnancy play an important role in the prevalence of congenital anomalies, and studies have also been conducted for investigating the levels of maternal HbA1c, insulin, and C-peptide and the genetic basis in the third trimester. The increased HbA1c levels observed in our case, the mother’s uncontrolled pre-GDM status, and, in addition to genetic factors, the hyperinsulinemia and hyperglycemia support the development of multiple system anomalies. Low oxygen transport capacity of HbA1c that occurs in diabetic pregnancies is considered to be responsible for fetal tissue hypoxia, maternal metabolic acidosis, and hyperglycemia (9). Serum glucose levels in early gestation period, ketone bodies, and the changes in somatomedin inhibitors are also considered to be responsible for the development of malformations. Isolated congenital anomalies at a rate of 68%, a large number of congenital anomalies at a rate of 22%, and syndrome-diagnosed congenital anomalies at a rate of 10% are found in infants of IDDM mothers. Cardiovascular, central nervous system (CNS), musculoskeletal, genitourinary,

and gastrointestinal system anomalies are most commonly seen. While caudal regression syndrome is observed 200–400 times more, CNS malformations are observed 20 times more (10). In our case, caudal regression syndrome and multiple skeletal system anomalies depending on the lack of development of the sacrum were observed. Caudal regression syndrome may be a part of SCD as in our patient and it can also be seen in IDM. Multiple vertebral and costal anomalies and crab-like chest wall structures found in our case were an aid to make the diagnosis of SCD. The diagnosis of SCD was also based on clinical and radiological findings. CHARGE syndrome, VATER/VACTERL syndrome, and Klippel–Feil syndrome should also be considered for the definitive diagnosis.

Cardiac anomalies are also more common in the infants of diabetic mothers than in healthy newborn populations; reversible septal hypertrophy, transposition of the great arteries, double outlet right ventricle, ventricular septal defects, truncus arteriosus, tricuspid atresia, and ductus arteriosus are the most frequently detected anomalies (4, 10). In our case, truncus arteriosus type 1, complete AVSD, and hypertrophic CMP were detected, and surgery was not considered because of the large number of accompanying anomalies and the patient carried genetic syndrome findings. GDM and pre-GDM require close monitoring in pregnancy due to increased risks in terms of maternal and fetal monitoring. Congenital anomalies in the infants of diabetic mothers lead to severe morbidities. Therefore, blood sugar regulation before preconception is very important for diabetic patients. In our case, the mother was diagnosed with diabetes mellitus 5 years ago and she did not use her medicines regularly.

To our knowledge, no SCD case that developed sporadically on the basis of IDM has been reported in the literature. This case report is presented to discuss the possibility that uncontrolled GDM may also be a factor in the development of SCD and STD, besides genetic heterogeneity.

Informed Consent: Informed consent was obtained from patients who participated in this study.

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