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Prenatally Diagnosed and Surviving Patient with Jarcho-Levin Syndrome: Case Report with Literature Review

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Jarcho-Levin syndrome is a congenital disorder characterized by several vertebral and costal anomalies. Other abnormalities have also been described, including neural tube defects, Arnold-Chiari malformation, renal/urinary tract abnormalities, hydrocephalus, hydroureteronephrosis, and meningomyelocele. We describe a spondylocostal dysplasia form of Jarcho-Levin syndrome that was prenatally diagnosed at 11 weeks of gestation and surviving. Although the patient had sporadic-type Jarcho-Levin syndrome, with normal karyotype and no family history of disease, the assessment of inheritance patterns and genetic counseling for the parents was important to inform them about the potential risks.

Key Words: Jarcho-Levin syndrome, Prenatal diagnosis, Scoliosis, Ultrasonography

Introduction

Jarcho–Levin syndrome was first described in 1938, and is a rare genetic disorder.[1] It is characterized by short-trunk skeletal dysplasia with vertebral and rib anomalies, leading to respiratory insufficiency, and has an incidence of 1 per 40,000 births. Approximately 400 cases have been described in the worldwide literature, five of which are from Korea.[2–6] None of the cases reported in Korea were diagnosed prenatally, and four cases with prenatally diagnosed Jarcho–Levin syndrome were aborted.[7–10] We report a prenatally diagnosed and surviving patient with Jarcho–Levin syndrome.

Case

A 26-year-old woman (gravida 0, para 0) was referred for evaluation. She had a three-quarter pack-year smoking history, but stopped at about 12 weeks of gestation. She had moderate obesity (body mass index, 33.79 kg/m^2). The maternal and paternal medical and family histories were unremarkable. Prenatal ultrasound at 11 weeks of gestation showed incomplete development of one side of a vertebral body, resulting in a wedge shape around the T11 area, and thickened nuchal translucency (3.2 mm). Targeted sonographic examination at 14 weeks of gestation demonstrated displacement and rotation of the heart into the right side of the chest, with a thoracic hemivertebra, short crown-rump length, and suspected absence of the left kidney (Fig. 1).

A female infant was born at 37^{+2} weeks of gestation by cesarean section (birth weight, 3,164 g). The Apgar scores were 7 and 9 at 1 and 5 minutes, respectively. The infant had a short neck, accessory nipples on the left side, and grossly abnormal left rib cage (Fig. 1). The abdomen was protuberant, and there was a single umbilical artery. At about

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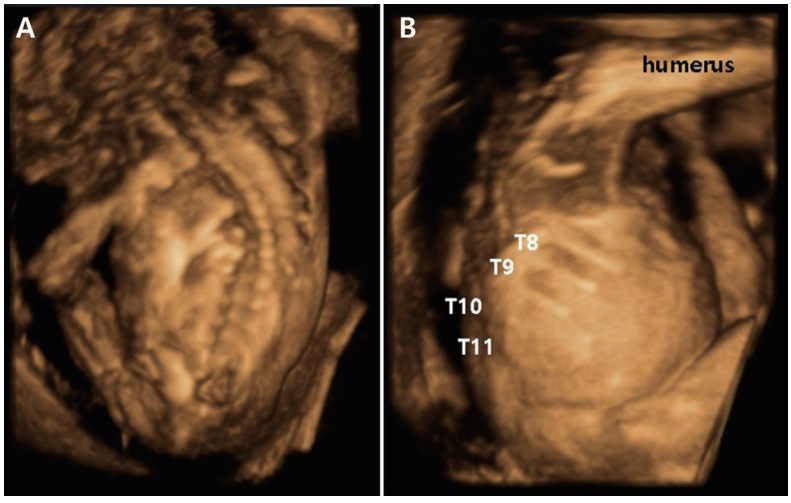

Fig. 1. Three-dimensional posterior image of the affected fetus at 14 weeks of gestation. (A) Kyphoscoliosis of the spine. (B) Absence of the T10 and T11 ribs in the left lateral thoracic cage.

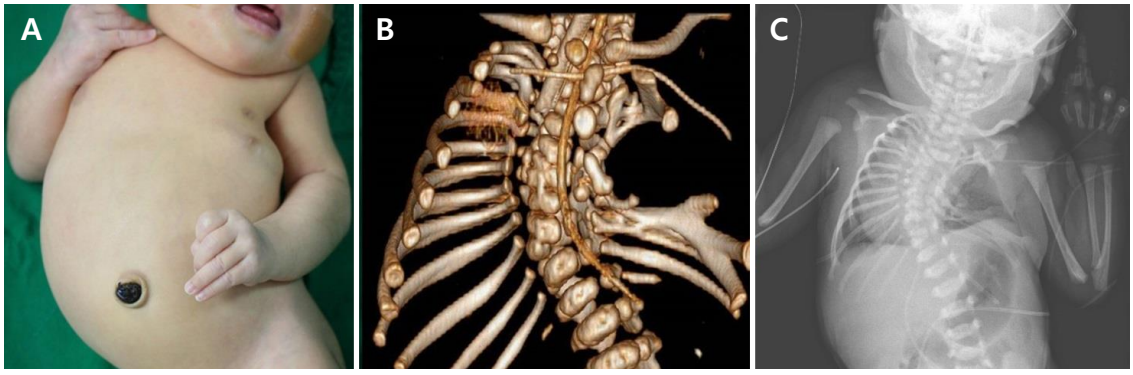

Fig. 2. Gross and computed tomography (CT) images of the infant. (A) The infant has a short neck, accessory nipples, and abnormal rib cage on the left side. (B) Three-dimensional spinal CT shows left T1, T2, and T10 hemivertebrae and a fusion anomaly in T6 and T7, with lateral wedging and scoliosis of the thoracic spine with convexity to the right. (C) Chest anteroposterior image shows dextrocardia and abnormal rib cage on the left side.

2 hours after birth, the infant was intubated and began to receive ventilator care owing to respiratory difficulty due to rib cage abnormality. On day 3, she briefly tolerated extubation and required supplemental oxygen; however, she required re-intubation for tachypnea, dyspnea, and desaturation on day 8. She was extubated after administration of antibiotics for 7 days.

Chest and abdominal radiographs revealed multiple vertebral deformities with hemivertebrae, scoliosis in the thoracolumbar spine, and absence of third to seventh ribs on the left side. The heart was displaced farther right owing to the vertebral and rib defects. Dynamic 3-dimensional computed tomography (CT) of the spine revealed left T1, T2, and T10 hemivertebrae and a fusion anomaly in T6 and T7, with lateral wedging (Fig. 2). Echocardiography showed no anomalies except for isolated dextrocardia owing to the thoracic deformity. On abdominal and pelvic CT, the left kidney was not visible in the left renal fossa and an ectopic kidney was not visible in the pelvis; thus, the contralateral right kidney had compensatory hypertrophy. Cranial ultrasound was normal. Chromosomal studies with GTG-banding showed normal results (46,XX). No mutation was detected in the coding region of the *MESP2* gene.

After extubation, the infant could take food well, showed no desaturation, and was discharged at 27 days of age (weight, 3,130 g). However, she was readmitted at 5 months of age because of severe cough, fever, and respiratory difficulty. She was treated for pneumonia for 16 days. The duration of treat-

ment was longer because of the rib cage abnormality, but she was discharged without respiratory problems. She has severe scoliosis; however, neurologic examination at 4 years of age showed normal results. She is being followed by pediatric, orthopedic, and thoracic surgeons.

Discussion

Jarcho-Levin syndrome is a rare genetic disorder. Mutations in the delta-like 3 (DLL3) gene on chromosome 19, and the *LFNG*, *HES7*, and *MESP2* genes, which are important components of the notch signaling pathway, are responsible for the development of spondylocostal dysostosis in the Jarcho-Levin syndrome.[11,12] Our case was sporadic, without a family history or genetic abnormality (no mutation of the *MESP2* gene, with other gene tests unavailable in Korea). The mother had been smoking in the first trimester, which might have affected the development of vertebrae and ribs in the infant. The association between Jarcho-Levin syndrome and maternal smoking has not yet been reported. However, a significant positive association between maternal smoking and congenital malformations has been reported in various studies. For example, maternal smoking has been reported to increase the risk of musculoskeletal defects in an infant by 16%.[13]

Jarcho-Levin syndrome reportedly presents with various clinical signs, with most cases being postnatally diagnosed. However, prenatally diagnosed Jarcho-Levin syndrome is rare, especially in the absence of a family history. All cases of Jarcho-Levin syndrome diagnosed during the first trimester have involved termination of pregnancy.[7-10] Most cases showed increased fetal nuchal translucency thickness,[7,10] although a case with normal thickness was also reported.[8]

Solomon et al.[14] classified Jarcho-Levin syndrome into 2 subtypes based on survival rate, inheritance pattern, and extent of skeletal anomalies, which helps to establish the prognosis and understand this disorder. First, spondylothoracic dysostosis (STD), an autosomal recessive disorder associated with *MESP2* gene mutation, is characterized by posterior symmetric fusion of the ribs and defects of vertebral development, resulting in a crab-like or fan-like appearance.[15] There are no intrinsic rib defects. In STD, death may occur because of pulmonary insufficiency or pneumonia.[16] Second, spondylocostal dysplasia (SCD), an autosomal dominant and recessive disorder, shows intrinsic rib anomalies such as bifurcation and broadening.[14] Patients with SCD are known to have mutations in the *DLL3* gene on chromosome 19. However, the karyotypes of almost all such patients are typically normal. Biochemical assays and chromosome banding studies are not available for diagnostic confirmation, and evaluation of distinctive clinical and radiological features is preferable.

The anomalies associated with Jarcho-Levin syndrome are complex congenital heart disease, and urogenital and anal anomalies. Patients with musculoskeletal anomalies are more likely to have genitourinary anomalies, because both the musculoskeletal and genitourinary systems have a mesodermal origin. Rai et al.[17] reported that 26.7% of patients with congenital vertebral abnormalities also have genitourinary abnormalities, the most frequent being unilateral renal agenesis. The two reported patients in Korea had renal anomalies (fused kidneys and an intrathoracic kidney).[4,6] In particular, rib dysplasia and hemivertebra on the left side might have been associated with additional defects of the left side in our case, involving both mesodermal origin, with renal agenesis, and ectodermal origin, with accessory nipples.

We report an SCD form of Jarcho-Levin syndrome that was prenatally diagnosed. Although the Jarcho-Levin syndrome in our case was sporadic, with normal karyotype and no family history, the assessment of the inheritance patterns and suggestion of genetic counseling to the parents was necessary to inform them about the potential risks. Since Jarcho-Levin syndrome is associated with a high risk of respiratory difficulty, we recommend that an affected infant should be transferred to a hospital with a neonatal intensive care unit if prenatal ultrasonography reveals rib and vertebral defects.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This case was reviewed and approved by the Institutional Review Board of Chung-Ang University (IRB No. 1707-015-16086).

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