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Larsen syndrome: prenatal diagnosis – a report of three cases

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Summary

Larsen syndrome is a rare congenital skeletal malformation (one in 100,000 births) caused by a generalized mesenchymal connective tissue disorder. This disorder leads to a broad spectrum of anomalies. Major diagnostic criteria are multiple dislocations of large joints (especially knees), short metacarpals with cylindrical non-tapering fingers, and anomalous facial features. Clinical spectrum is variable and it ranges from mild to lethal forms. Genetic aspect is also variable; sporadic occurrence as well as autosomal dominant and recessive inheritance have been described. In this study, the authors report on their experience\ by presenting three cases of Larsen syndrome diagnosed by prenatal ultrasound.

Key words: Larsen syndrome; Multiple dislocations; Anomalous facial features; Prenatal ultrasound.

Introduction

Larsen syndrome is a very rare congenital syndrome (one per 100,000). It is characterised by multiple joint dislocations such as hip dislocation, genu recurvatum, clubfoot, and anomalous facial features, including prominent forehead, depressed nasal bridge, flattened face, micrognathia, and hypertelorism. Associated anomalies have been reported, including cleft palate, mental retardation, hydrocephalus, cardiac defects, and sensorineural/mixed hearing loss [1-3]. In addition to sporadic cases, both autosomal dominant and autosomal recessive patterns of inheritance are recognised [1].

Gene locus is 3p21.1-p14.1 [4]. It is a common connective tissue abnormality syndrome, which is accompanied by connective tissue abnormality and collagen formation disorder due to reduced alpha-1/alpha-2 chain ratio in type 1 collagen [5]. Prenatal diagnosis of Larsen syndrome may be challenging; therefore, the initial diagnosis has to be confirmed after birth [6]. For an appropriate treatment, collaborative practice between orthopaedics, plastic surgery, and rehabilitation is required. [7]

In this research paper, the authors report on three cases of Larsen syndrome.

Case Report

Case 1

A 28-year-old nulliparous woman was transferred to the present hospital at 29 weeks of gestation, because of fetal growth restriction (FGR). She had previously received antenatal care in a local clinic. Asymmetric FGR (<10 percentile) was diagnosed since the fetal abdominal circumference was about four weeks smaller than expected for gestational age on ultrasonography scan. Both of the fetal knee joints showed genu recurvatum (Figure 1), overlapping toe, and rocker-bottom feet with prominent calcaneus and convex rounded bottom to the feet. In addition, a small lower jaw and micrognathia with backwardly located lower lip in relation to the upper lip position were observed (Figure 2). Following the regular antenatal care, labour was induced at 41 weeks of gestation and a 2,860-gram female infant was delivered vaginally. Apgar scores at one and five minutes were 7 and 9 points, respectively.

Facial characteristics of the newborn included prominent forehead, depressed nasal bridge, and flat face. Additional findings included overlapped thumbs and a big toe, bilateral genu recurvatum, projected inner side of the feet, and rocker-bottom feet (Figure 3). Radiological findings showed hip joint dislocation, knee joint dislocation, and bilateral vertical talus of ankle joints. Additionally, a flexion contracture of metacarpalphalangeal joints on both thumbs was observed (Figure 3). A mild hydronephrosis was noticed in the left kidney. Both otolaryngological and ophthalmological examination showed no pathological findings.

A chromosome test showed a normal female karyotype (46, XX). Casts and splints were used to immobilise the infant's legs and fingers, and she is currently receiving an outpatient treatment for plaster replacement and rehabilitation.

Case 2

A 28-year-old primiparous (1-0-0-1) woman received antenatal care in a Eulji University Hospital due to twin pregnancy. A normal Quad test was obtained at 17 weeks of gestation. Ultrasonography scan was conducted at 29 weeks of gestation. The first fetus was in a breech presentation, and the second one was in transverse lie presentation. In the first fetus, both of the fetal knee joints were extended as Figure 1, and the right foot had a rocker-bottom deformity with a prominent calcaneus and a convex rounded bottom to the foot. The left foot was a club foot. The second fetus did not show any sonographic abnormality. A cesarean section was performed at 37+1 weeks of gestation and the first

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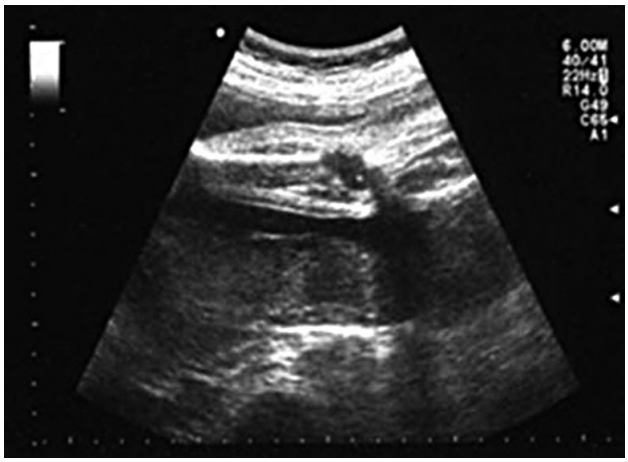

Figure 1. — Knee joint extension; genu recurvatum (Case 1).

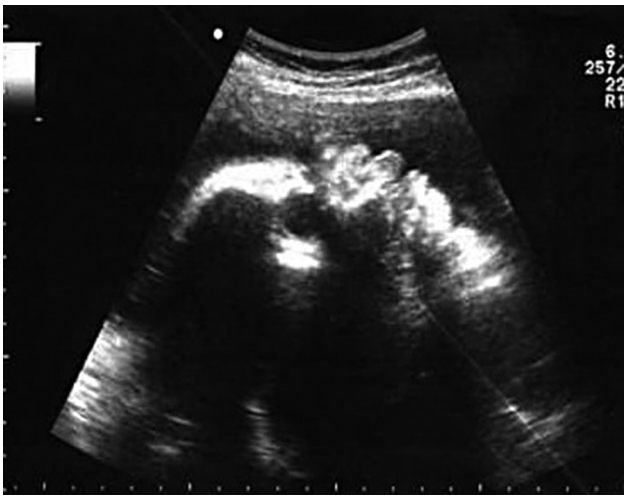

Figure 2. — Micrognathia, absent nasal bone (Case 1).

male infant weighting 2,370 grams was born. Apgar scores at one and five minutes were 3 and 5 points, respectively.

Neonatal findings and progress: The face of the newborn showed several specific features (prominent forehead, depressed nasal bridge, and a flat face). Additionally, dislocations of the left hip and both knees were observed. Both knees were genu recurvatum. The right foot had a vertical talus deformity, while the left showed characteristics of a club foot. A mild pelviectasis was observed in the left kidney, whereas echocardiography, otolaryngological and ophthalmological examinations did not reveal any pathological findings. Hip joint dislocation, knee joint dislocation, and bilateral vertical talus of ankle joints were shown on radiologic studies. A chromosome test showed a normal male karyotype (46, XY). Casts and splints were used to immobilise infant's legs and fingers, and he is currently receiving an outpatient treatment for plaster replacement and rehabilitation.

Case 3

A 32-year-old nulliparous woman, without any specific details or genetic diseases in her paternal or maternal history, had received antenatal care in a local clinic. She was transferred to the present hospital at 26 weeks of gestation because of sonographic suspected fetal club feet and hands. Additionally, a fetal growth restriction (< 10 percentile) was observed. The fetus had bilateral club feet, and the right foot showed a dorsal hyperflexion, as well as both fetal wrists. A cesarean section was performed because of preterm labour at 33+4 weeks of gestation. A male infant, weighting 1,160 grams was born. Apgar scores at one and five minutes were 3 and 5 points, respectively. Immediately after birth, the infant was intubated and transferred to the neonatal intensive care unit for supportive ventilation care.

Neonatal findings and progress: The face of the newborn showed some specific features (prominent forehead, depressed nasal bridge, and a flat face), while the right wrist resembled a claw hand, where all fingers were hyperflexed and contractured,with syndactyly of the left third and fourth fingers. Moreover, dislocation of hips, knees, and wrists were observed, as well as a bilateral genu recurvatum, and a bilateral clubfoot. Thoracic spine kyphosis was also diagnosed (Figure 4).

Radiological findings: Hip joint dislocation, knee joint dislocation and bilateral vertical talus of ankle joints were shown, as well as a metacarpalphalangeal joint flexion contracture of the right hand. Echocardiographic examination revealed a small atrial septal defect (ASD) secundum 1.1 mm in size and a mild regurgitation of tricuspid valve, while ophthalmological examination did not show any pathological findings.

Chromosome test showed normal male karyotype (46, XY). Cytogenetics and microarray testing results were also normal. Casts and splints were used to immobilise infant's legs and fingers, a tracheostomy was performed, and he is currently receiving rehabilitation.

Discussion

Larsen syndrome was first described in 1950 as a composite of characteristic facial features and multiple joint dislocations. [1] This disease is characterised by congenital skeletal dysplasia accompanied by multiple joint dislocations and characteristic facial deformities. The characteristic features of skeletal anomalies include bilateral hip and elbow dislocations, genu recurvatum, club foot, and short metacarpal bone (cylindrical finger). Typical facial features include prominent forehead, depressed nasal bridge, round faces, micrognathia, and hypertelorism. In addition to the typical features, a cleft palate, hydrocephalus, cervical kyphosis, etc. have also been described [1-3].

Larsen syndrome occurs in one in every 100,000 births, whereby most cases are autosomal dominant, although some autosomal recessive cases have been described. Sporadic cases have also been reported [1]. Some reports argue that an autosomal recessive pattern of inheritance is likely to provoke more severe or fatal anomalies [1]. Gene locus is on chromosome 3p21.1-p14.1 [4].

It has been reported that this disease is caused by a connective tissue abnormality and collagen formation disorder due to reduced alpha-1/alpha-2 chain ratio in type 1 of collagen. [5] According to the tissue biochemical test and electron microscopic study, the disease is caused by connective tissue abnormality which provokes collagen fibre dysmaturation and the lack of mature collagen bundles [8].

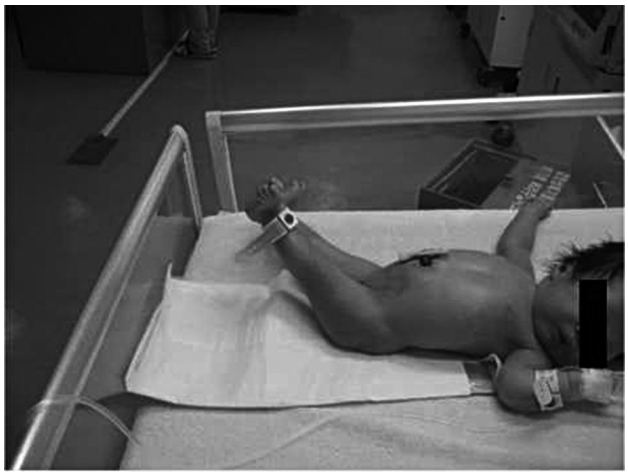

Figure 3. — Postnatal appearance with knee joint hyperextension and anomalous craniofacial features (Case 1).

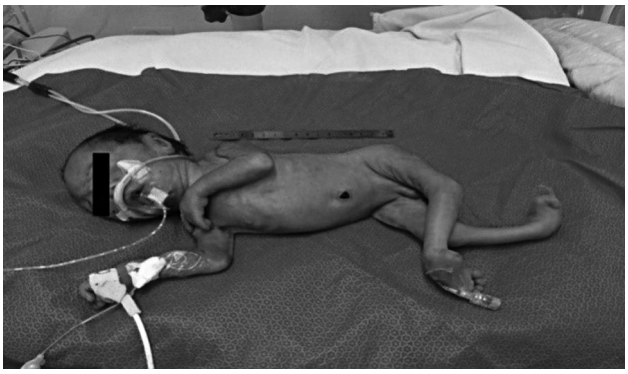

Figure 4. — Postnatal appearance with knee joint hyperextension and anomalous craniofacial features (Case 3).

A complete anal agenesis and bifid uterus were detected at autopsy of patients with Larsen syndrome. The cul-de-sac filled with meconium in descending colon, overall colon discolouration due to anal agenesis, and its extension or enlargement due to the accumulation of meconium were observed. Bifid uterus is a kind of a combined rectourethral defect occurring at early embryonic development, and it is caused by a fusion of undivided urorectal septum with cloacal membrane. It is suggested that anal agenesis and bifid uterus are caused by malformations of cloaca and urorectal septum [9].

When referring to the cardiovascular anomalies, cardiac muscle defects, patent ductus expansion, twist of brain and abdominal aorta, etc. have been described [10-12]. Regarding the respiratory malformations, the disease affects the cartilaginous structure in the bronchus, causing the narrowing of the cartilage ring to one-third of the lower bronchi, which finally leads to stenosis. Tracheomalacia accompanied by a collapse of bronchi, laryngomalacia, and brochomalacia have also been reported [13-15]. In terms of the nervous system malformations, it has been confirmed that hydrocephalus was caused by cerebrospinal fluid circulation failure in the outlet to the fourth ventricle and the subarachnoid space. Although the cause is not clearly identified, a mineralisation in the rear edge of foramen magnum is considered to play an important role. In addition, the midfacial malformation including midfacial flattening, hypertelorism, and cleft palate can be described as dysraphism which is the possible cause of hydrocephalus [16].

The joint deformities are characterised with ossicular joint abnormalities, and therefore, children with this disease may show conductive hearing loss without evidence of otitis media. Bilateral residual conductive hearing loss and functional ventilation tubes are the result of ossicular abnormality or ossicular dislocation, as well as multiple joint dislocations shown in Larsen syndrome [17].

Prenatal diagnosis of this disease may be challenging; nevertheless, the presence of multiple joint dislocations and characteristic facial abnormalities at prenatal ultrasound may facilitate diagnosis. It has been reported that the diagnosis is more likely to be achieved if similar findings are observed in parents [6]. If the father presents with mild malformation, this suggests autosomal dominant expression. However, it remains uncertain whether these symptoms are caused by cellular mosaicism, special mutation, or genetic background [7, 18]. In this case, definite diagnosis could be made after birth, whereby genetic counselling plays an important role.

Several conditions should be considered in the differential diagnosis of Larsen syndrome: arthrogryposis multiplex congenita, Pena-Shokeir syndrome, cerebro-oculo-facio-skeletal syndrome (COFS), etc. Arthrogryposis multiplex congenita can be excluded if normal facial appearance and internal organs are observed [19]. Pena-Shokeir syndrome is characterised by polyhydramnios, short umbilical cord, and intrauterine growth retardation. COFS syndrome can be identified by microcephaly, flexion contractures, and central nervous system abnormalities [18]. In such cases, pregnancy can be terminated before fetus gains viability. The postnatal treatment varies depending on the affected region. Suggested treatment procedures for multiple joint dislocations are cast immobilization, splints, supporting devices, physical therapy, and surgery. Furthermore, neurological complications can be avoided by early diagnosis and surgical correction of cervical kyphosis. Surgical treatment of inner ear bone structures may improve hearing, while cleft palate and cleft lip can be treated with speech therapy or surgery.

Respiratory problems can be treated with chest physical therapy, tracheostomy, and a respirator [7]. The therapeutic success depends on the degree of abnormalities (e.g. tracheomalacia), pulmonary insufficiency, and cervical kyphosis [15].

In the present study, the authors presented three cases

where genu recurvatum, overlapping toes, and rocker-bottom feet were detected by prenatal ultrasonography at 30 weeks of gestation, and the fetus was diagnosed with Larsen syndrome after birth. Therefore, they aimed to report and discuss their findings together with a literature review.

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