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Prenatal diagnosis of Larsen syndrome caused by a mutation in the filamin B gene

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Larsen syndrome [OMIM 150 250] is an autosomal dominant skeletal dysplasia characterized by craniofacial features, large-joint dislocations and abnormalities of the extremities. Craniofacial anomalies include hypertelorism, prominence of the forehead, a depressed nasal bridge and a flattened midface. Dislocation of the large joints (knees, hips, elbows, tibio-tarsal) including anterior dislocation of at least one of the knees are the main features. The limb abnormalities include a very characteristic tapering aspect of the distal humerus. Other occasionally seen findings include short stature, cleft palate, and extraskeletal manifestations include bilateral testicular ectopy, retinal lesions and bilateral macular dysplasia, deafness, cardiac abnormalities (ventricular septal defect) and tracheomalacia.

Heterozygosity for mutations in the gene encoding the filamin B (*FLNB*) located at chromosome 3p14.3 have been identified in a wide spectrum of osteochon-drodysplasias, including Larsen syndrome, atelosteogenesis type III (AOIII) and I, boomerang dysplasia and spondylocarpotarsal syndrome (Krakow *et al.*, 2004). Filamin B is a cytoskeletal protein essential in modulation of the cellular cytoskeleton and has functions in signal transduction, cell division motility and transport of small molecules.

Diagnosis of Larsen syndrome is usually made in the postnatal period. The prognosis is highly variable and occasionally lethal. Complications include multiple orthopedic abnormalities, instability of the cervical spine, pulmonary hypoplasia and neonatal tracheomalacia. Prenatal

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diagnosis of Larsen syndrome has been reported in few instances and is still challenging. Most of these previous cases were diagnosed following targeted ultrasound examination because of a positive family history. Herein, we report the prenatal diagnosis of a *de novo* case of Larsen syndrome inherited from unaffected parents. Clinical examination and molecular analysis confirmed the diagnosis after birth.

A healthy 22-year-old woman (gravida 2, para 1) originating from Gabon, referred for a tertiary-targeted ultrasound examination after initial ultrasound screening indicated severe micromelia. Consanguinity was denied and there was no relevant personal medical history. Sonography performed at 22 weeks of gestation showed abnormalities in the facies, shortened limbs with tapering distal humeri, and multiple dislocations with an unusual finding of hyperechogenic areas resembling punctuated lesions, that initially suggested a diagnosis of rhizomelic chondrodysplasia punctata. Subsequent sonographies performed between 22 and 31 weeks of gestation showed the following features: (1) dysmorphic facies with flattened profile, depressed nasal bridge, prominent and high forehead and exophthalmia with hypertelorism and mild micrognathia, (2) limb abnormalities including rhizomelic micromelia of the upper limbs (amputated, short and frayed humeral aspect), asymmetry of the forearm and leg bones, equinovarus and multiple subluxations of the large joints (shoulders, elbows, hips and ankles) (Figure 1a), (3) a narrow thorax and polyhydramnios. These features suggested the prenatal diagnosis of Larsen syndrome. The mother delivered via vaginal delivery, after declining cesarean section, of an affected female infant, with apgar scores of 10/10, and normal postnatal measurements: weight 3070 g, head circumference 33 cm, and height 51 cm.

At birth, physical examination confirmed the prenatal findings, especially the facial features and joint dislocations. Radiological examination showed dislocations at the elbows, hips and knees, as well as wide, short metacarpals, short tapering humeri (Figure 1b), and widely spaced iliac bones. Skeletal radiographies confirmed the rhizomelic involvement predominating of the humeri. The femurs were slightly curved, while the tibia and fibula were normal (data not shown). Coronal clefts were noted in the cervical and lumbar spine. The radiographic findings were characteristic of Larsen syndrome and confirmed the prenatal findings and diagnosis. During the first few weeks of life, she had multiple episodes of respiratory compromise and succumbed to pulmonary edema.

Standard karyotyping was performed by conventional methods on metaphase spreads prepared from amniocytes and showed a 46,XX karyotype. Genomic DNA was extracted from cultured amniocytes using a standard protocol. *FLNB* polymerase chain amplification reactions and sequence analysis were performed using previously published conditions (Krakow *et al.*, 2004). Heterozygosity for a missense mutation, c.502G> A (p.Gly168Ser) was identified.

Prenatal diagnosis of Larsen syndrome is still challenging, partly because of the broad spectrum in presentation of clinical abnormalities. Several cases have nonetheless been reported in families with a positive history of Larsen syndrome (Mostello *et al.*, 1991; Rochelson *et al.*, 1993). In some cases, other congenital nonskeletal abnormalities detected by ultrasound were seen in Larsen syndrome: neurological abnormalities (Shih *et al.*, 2004), brain dysplasia with severe psychomotor retardation (Yamaguchi *et al.*, 1996) and oligoamnios (Rizk *et al.*, 2006). In the present case, the prenatal diagnosis was based on a combination of skeletal abnormalities. The clinical picture, along with other findings, raised two main possible diagnoses: Larsen syndrome and AOIII. Differential diagnosis between Larsen syndrome and AOIII can be difficult. As Larsen syndrome, AOIII is a bone dysplasia inherited in an autosomal dominant fashion. Larsen syndrome and AOIII may represent a continuous clinical spectrum of disease since many clinical and radiological signs are common to the two conditions and both result from mutations in the gene that encode filamin B (Krakow *et al.*, 2004; Farrington-Rock *et al.*, 2006). A shortened and tapering aspect of the humerus,

dislocations of the large joints, a rhizomelia and equinovarus have been described in both syndromes. Fibula aplasia, described in AOIII but not in Larsen syndrome aids in distinguishing the two syndromes and our patient had normally formed fibulas. Prenatal diagnosis of both disorders remains difficult when the characteristic findings are not detected by ultrasound (Rochelson *et al.*, 1993; Becker *et al.*, 2000; Tongsong *et al.*, 2000) and familial history is negative (Becker *et al.*, 2000).

In this fetus, a p.Gly168Ser missense mutation in exon 2 of the *FLNB* gene was identified. Mutations responsible for Larsen syndrome are clustered, one cluster occurs in the region of the gene encoding the second calponin homology domain and the other in the region encoding filamin repeats 13–17 surrounding the first hinge of the molecule (Farrington-Rock *et al.*, 2006). The p.Gly168Ser mutation has been previously identified in one family with Larsen syndrome and in two individuals with AOIII (Farrington-Rock *et al.*, 2006; Bicknell *et al.*, 2007). The family with Larsen syndrome presented with midface hypoplasia, elbows and hips dislocations, clubfoot, scoliosis, vertebral fusion, spatulate fingers and distal tapering of humerus. One patient with AOIII displayed shortened and distally tapered humeri and shortened femora and died neonatally, in contrast to the other patient who only had distally tapered humeri and survived beyond the neonatal period.

Prenatal diagnosis of Larsen syndrome allows multidisciplinary management to evaluate the prognosis, to plan obstetric and neonatal pediatric management and to decide on the medical and surgical treatment. Cesarean section should be considered the preferred mode of delivery because of the risks of trauma during vaginal delivery (multiples subluxations) and especially the risk of death resulting from cervical spinal instability (Becker *et al.*, 2000; Tongsong *et al.*, 2000). Considering the variability in prognosis and the potential neurological abnormalities, the decision to pursue or terminate the pregnancy should be discussed with the couple (Shih *et al.*, 2004). The long-term prognosis of children with Larsen syndrome is variable and demands aggressive orthopedic management. Many of these individuals go on to have productive lives with normal fertility (Tongsong *et al.*, 2000). In contrast, the outlook can be very poor in the severe forms. Death can occur due to cardiorespiratory arrest following brain stem compression due to subluxation of the cervical spine. Respiratory complications are also frequent, with recurrent infections, as in our patient. Most importantly, prenatal ultrasound findings include midface hypoplasia, mild micrognathia, rhizomelia, tapering humeri, and equinovarus; the diagnosis of Larsen syndrome should be considered. Finally, final diagnosis by clinical and radiographic analysis, and confirmation by mutational analysis, are crucial for accurate genetic counseling.

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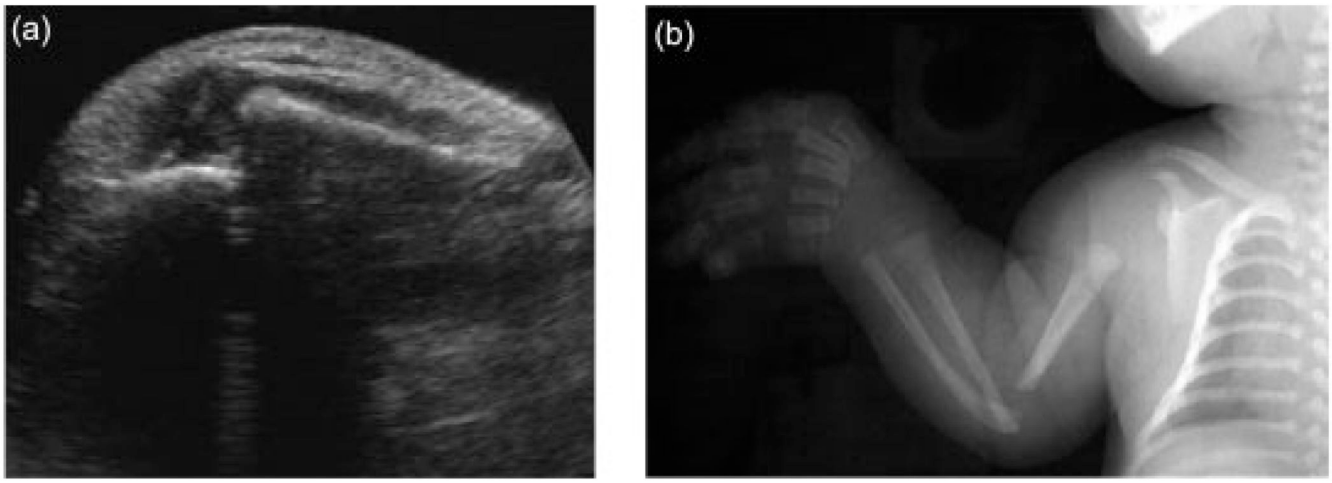

Figure 1.
(a) Sonographic view showing dislocation of the hip. (b) Radiograph showing the shortened and tapering distal humerus