Familiar case of Larsen syndrome

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INTRODUCTION

Larsen syndrome is a rare, autosomal-dominant disorder characterized by flat face with hypertelorism, multiple large-joint dislocations, kyphoscoliosis and equinovarus or equinovalgus foot deformities. Case report. In this report a four-year-old female patient with Larsen syndrome is presented. A family history, disclosed that a father and an older brother were affected by the syndrome. We noted the clinical features of the disease associated with the presence of a FLNB mutation. The daughter is having significant psychomotor delay and severe clinical presentation compared with mildly delayed brother; the father presented with dysmorphic facial features and deformities of hands and foot only. Conclusion. In this study we present the family with Larsen syndrome and draw attention to the member with severe developmental delay and pronounced skeletal changes. Further reports and investigations are needed to better understand mechanisms and clinical spectrum of central nervous system involvement in patients with Larsen syndrome.

Key words: Larsen syndrome, nervous system involvement, cervical kyphosis

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Larsen syndrome was first described in 1950 as an entity comprising congenital large-joint dislocations and characteristic craniofacial abnormalities1. The incidence of Larsen syndrome is estimated to be 1 in 1000 000, but it is well recognized that diagnosis is problematic because of the wide variability in severity and clinical symptoms2.

Larsen syndrome is a rare, autosomal-dominant disorder characterized by the dislocations of hip, knee and elbow joints, with equinovarus or equinovalgus foot deformities. Spatula-shaped fingers, most marked in the thumb, are also present. Craniofacial abnormalities include hypertelorism, prominence of the forehead, a depressed nasal bridge and a flattened midface. Cleft palate and short stature are often associated characteristics. Spinal anomalies include scoliosis and cervical kyphosis, while cervical kyphosis can be associated with myelopathy. Supernumerally carpal and tarsal bones are a useful diagnostic feature in early childhood3.

There is clear evidence for an autosomal dominant form of Larsen syndrome, with multiple instances of male-to-male transmission being described in addition to linkage data that defines a locus at 3p21.1-14.1 Larsen syndrome is caused by mutations in FLNB gene which code for filamin B. Filamin B binds to actin which forms branching network of filaments as a part of cell’s cytoskeleton4.

Other conditions labeled as Larsen syndrome or Larsen-like entities have been described (OMIM 245650), many of them with a more severe phenotype including additional extraskeletal features. Associated malformations include cardiac defects, laryngotracheomalacia, brain abnormalities (microcephaly, pachygyria, corpus callosum agenesis),5 6 7 8 9. Some of these phenotypes segregated in a fashion consistent with autosomal recessive inheritance, prompting some to recognize a recessive form of Larsen syndrome10 11. Many have noted more severe skeletal and extraskeletal phenotypic features including perinatal lethality in presumptive recessively inherited cases. However, clear criteria that definitively delineate recessively inherited locus of Larsen syndrome from the dominantly inherited entity have not been established.

Clinical similarities between Larsen syndrome and a group of lethal osteochondrodysplasias including atelosteogenesis types I (AOI) and III (AOIII), and boomerang dysplasia suggested that they represent an allelic series of conditions12. These more severe dysplasias are characterized by underossification of skeletal elements, hypoplastic or absent limb bones, joint dislocations and craniofacial abnormalities. These observations, led to description of mutations in the filamin B gene (FLNB) underlying Larsen syndrome, AOI, AOIII and boomerang dysplasia13 14 15. Differential diagnosis also includes otopalatodigital syndrome type I (OPD1), an X-linked
skeletal disorder caused by mutations in filamin A gene (FLNA).

Mutations that lead to Larsen syndrome are either missense or small in-frame deletions, thus predicted to encode full-length filamin B protein. They are clustered in exons 2-5 and 27-33 of the FLNB gene\(^3\). Three recurrent mutations have been reported, the most common of which is p.Gly1691Ser\(^3\).

Intrafamilial variation in Larsen syndrome is a prominent feature of the disorder\(^16\). Here we present a family with Larsen syndrome, comprising 3 affected individuals: father, son and daughter. We noted the clinical features of the disease associated with the presence of a FLNB mutation. The daughter is having significant intellectual and motor developmental delay and more severe clinical presentation compared with mildly delayed brother; the father presented with dysmorphic facial features and deformities of hands and foot only.

**Patient 1**

A four-year-old female was born at term, with cesarean section. Her birth weight was 3700g and Apgar score 10 after 5 minutes. The parents were young and unrelated couple. We saw the patient for the first time at the age of 6 months because of epileptic seizures. Physical examination revealed hypertelorism, flattened nasal bridge, cleft palate, spatulate distal phalanges of the fingers, dislocations at hip, knee, and elbow joints, and the foot deformities, talipes equinovarus (club feet).

Neurological examination revealed mild generalized hypotonia, reduced motor activity and hyperactive deep tendon reflexes. She had epileptic focal seizures and electroencephalographic (EEG) recording showed mild bilateral epileptiform discharges with anterior maximum. Antiepileptic therapy was given (carbamazepine 20 mg per kg) and a good control of seizures was achieved. Magnetic resonance imaging (MRI) done at this age showed atrophy of the brain with ventriculomegaly and delayed myelinisation/dysmielinisation. Dislocations of hip, knee and elbow joints were seen by long bone radiograms. Apart from secondary abnormalities attributable to chronic joint dislocations, the metaphyses and diaphyses of the long bone were normal.

She had been treated on three times because of hyperextension of hips by orthopedic surgeons after she was diagnosed as Larsen syndrome. Immediately after birth, percutaneous extension of hips was done and correction of the orthopedic deformities of knee joints. At the age of six months she was treated by orthopedic interventions because of dislocation of the right hip.

Her psychomotor development showed delay in achievement of gross motor milestones. She started to sit unsupported from two and one-half years of age with kyphosis and scoliosis of the back, and crawl from three and one-half years of age. Antero-posterior and lateral cervical X-rays revealed both kyphosis and scoliosis of the cervical and thoracic spine. At the age of three years, the cervical magnetic resonance imaging (MRI) showed vertebral bodies' hypoplasia in the region between C3 and C6 and the kyphosis to 126 degrees occurred in this region (Figure 1). MRI of the brain showed hypoplastic corpus callosum, ventriculomegaly of lateral ventricles and brain atrophy. White matter signal was showing incomplete mielinisation/dysmielinisation in frontal and temporal region bilaterally. There was no progression in atrophy of the brain comparing with previous MRI (Figure 2).

In the control examination at the age of 4 years, she was not able to walk independently; she had partial control of urination and has put on weight. Valgus of both feet was prominent and she was wearing orthotic for knee on daily basis and orthopedic shoes, too. (Figure 3)

She had a prominent speech delay and her developmental...
quotient (RQ) was 24. Physical and speech rehabilitation was performed every day. Antiepileptic treatment (carbamazepine) was given regularly and complete control of seizures had been achieved.

At her family history, her four years older brother and father were affected by the syndrome. The brother was diagnosed with Larsen syndrome at the age of 6 years. The father showed facial features and mild skeletal changes from the spectrum of Larsen syndrome (mild deformities of hand and foot with no other physical abnormalities).

An analysis of the FLNB gene was performed in patient’s brother, mother, father and both paternal grandparents in Department of Women’s and Children Health Clinical Genetic Research Group in University of Otago in New Zealand. A previously unpublished heterozygous mutation c.5706C>A, which leads to p.S1902R amino acid substitution, was disclosed in our patient, the brother and the father, but not in the paternal grandparents and the mother. Thus, de novo origin of the mutation in the father (less probably gonadal mosaicism) and it’s vertical transmission consistent with autosomal-dominant inheritance was confirmed. Classical chromosomal analysis showed normal karyotype in all affected family members.

Patient 2

A brother of the patient 1 was born at term, as a first child from uncomplicated pregnancy. Delivery was with cesarean section. His birth weight was 4100g and Apgar score was 8 in the 5. minute of life. Immediately after birth distinctive deformities of the arms and feet were diagnosed. He had bilateral elbow dislocations, pes equinovarus and hip dysplasia. X-ray of the hands revealed absence of os capitatum and os hamatum. His neurological examination revealed generalized mild hypotonia, poor control of the head, as well as characteristic flattened facies with frontal bossing, depressed nasal bridge and hypertelorism. Ultrasound of the brain showed bilateral non-progressive ventriculomegaly. Foot deformities were treated by orthopedic interventions at the age of fifteen days of life and bilateral hip dysplasia with Pavlik harness.
He was slightly delayed in terms of psychomotor development, partially due to hypotonia and orthopedic problems. He started to sit unsupported from the age of 9 months and started to walk independently from the age of 19 months. MRI of the brain performed at the age of two years showed multiple ischemic changes in cortical and subcortical regions, and the MRI of the lumbo-sacral spine spina bifida occulta.

Multiple joint operations on his right foot by an orthopaedic surgeon were done because of metatarsus varus deformities, as a sequelae of clubfoot deformities, at the age of five years.

A control examination at the age of eight years showed normal mental development and normal walking pattern. He has no epilepsy like his sister and EEG was normal.

**DISCUSSION**

The clinical manifestation of a patient with Larsen syndrome are easily recognized because of the multiple congenital dislocations of the joints (hips, knees, and elbows), distinctive deformities of the hands and feet (equinovarus or equinovalgus), dysmorphic facies (described as “dish face” with a saddle nose and hypertelorism), kyphoscoliosis and segmentation anomalies of the vertebral spines. Many patients who have Larsen syndrome are described as being hypotonic, a feature that contributes to a delay in the achievement of motor skills, such as the ability to walk. Hyperlaxity and dislocations of joints are cardinal features and delay in walking and delay in other developmental milestones are mainly due to both hypotonia and orthopaedic problems.

Larsen syndrome is a rare inherited defect of connective tissue that is transmitted in autosomal dominant and rarely, autosomal-recessive fashion. There have been no reports describing epilepsy with this syndrome.

In the study of Bicknell et al, including 20 individuals diagnosed with Larsen syndrome that were heterozygous for mutation in *FLNB* mutation, all cases had dislocations or subluxation of the large joints (65% with elbow, 80% with hip and 80% knee dislocations). Clubfoot was present in 75%. Anterior thoracic wall deformities (pectus excavatum or pectus carinatum) were present in 55% of patients. Short stature was common. The majority of individuals had the characteristic prominent forehead, hypertelorism, midface hypoplasia and depressed nasal bridge, although exceptions were observed in one case. All but one individual had spatulate fingers, most specifically in the thumb. Cervical kyphosis was noted in 50% of cases, usually on the basis of subluxation or fusion of the C2-C3-C4 vertebral bodies. Clinical myelopathy, complicated by secondary encephalopathy, was observed in 3 of 20 individuals.

Cervical spine anomalies, leading to cervical kyphosis were not emphasized in the original description of Larsen syndrome. Although these orthopedic manifestations have been previously identified, there are only few published cases of cervical kyphosis associated with Larsen syndrome like in our patient. It is therefore possible that cervical deformity has been under diagnosed in patients with this syndrome. The potential morbidity and mortality due to cervical deformity is obvious.

At literature, a few lethal forms of Larsen syndrome were described which inherits autosomal-recessively. One case with diaphragmatic hernia and a few cases with laryngomalacia and apnea were described. Chen et al. reported two cases with multiple joint dislocations, tracheomalacia and lung hypoplasia led to death by pulmonary failure in a short time. For our case, no such complications were found.

Clinical and radiological analysis can distinguish Larsen syndrome from other joint dislocation syndromes, like other osteochondrodysplasias, pseudodystrophic dysplasia (similar to Larsen syndrome with midface hypoplasia and clubfoot, but patients have rhizomelia, prominent dislocations of the interphalangeal joints and most often perinatal lethality) and Ehlers-Danlos syndromes (large joint dislocations, hyperelastic skin, a feature not found in Larsen syndrome).

Central nervous system is not commonly affected in patients with Larsen syndrome. Mental retardation has been reported in 15% and deafness, including sensorineural, in 20% of patients. In this study we present the family with Larsen syndrome and draw attention to the member (patient 1) with severe developmental delay and pronounced skeletal changes. Such severe disturbances of the central nervous system have not been described in the literature to date. Comprehensive clinical evaluation did not reveal any other explanation for neurological manifestation.

**CONCLUSION**

This study has described a family case of Larsen syndrome as a clinically and radiographically characteristic condition with pronounced intrafamiliar variability. The identification of the basis of its aetiopathogenesis as clustered missense mutation in the cytoskeletal protein *FLNB* in our family provides a valuable adjunct to the diagnosis of the clinically highly variable disorder. Further reports and investigations are needed to better understand mechanisms and clinical spectrum of central nervous system involvement in patients with Larsen syndrome.

**SUMMARY**

Uvod. Larsenov sindrom je retko, autozomno-dominantno oboljenje koje se karakteriše zaravnjenim licem sa hipertelorizmom, brojnim dislokacijama zglobova, kifoskoliozom i ekvinovarus ili ekvinovalgus deformitetima stopala. Prikaz bolesnika. Prikazali smo četverogodišnju devojčicu sa Larsenovim sindromom, a u porodičnoj anamnези otac i stariji brat imaju istu dijagnostiku. Uočili smo kliničke karakteristike bolesti povezane sa prisustvom *FLNB* mutacije. Devojčica ima značajno kašnjenje u psihomotornom razvoju i težu kliničku sliku u odnosu na brata; otac ima samo dizmorfičan facies i blage deformitete šaka i stopala. Zaključak. Prikazali smo porodicu sa Larsenovim...
sindrom i skrenuli pažnju na člana sa teškim kašnjenjem u psihomotornom razvoju i značajnim skeletnim deformitetima. Dalja ispitivanja su potrebna za bolje razumevanje mehanizama i kliničkog spektra zahvaćenosti centralnog nervnog sistema kod pacijenata sa Larsenovim sindromom.

Ključne reči: Larsenov sindrom, zahvaćenost nervnog sistema, cervicalna krifoza

REFERENCES:


