

# Facial features and skeletal abnormalities in Larsen syndrome – a study of three generations of a Tunisian family

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## Summary

We report on a 3 generation study of a Tunisian family, in which eight subjects had or have features of Larsen syndrome: three siblings, two females and one male are affected with flattened facies, multiple congenital joint dislocations, and club foot deformities. Five other family members were recognised as being variably affected with the syndrome. Over the three generations,

despite the characteristic facial features being the most constant clinical signs of the syndrome, none of those still living had palatal clefts, the multiple infantile deaths in this family, however, were characterised by an association with cleft palate.

*Key words: Larsen syndrome; facial features; multiple joint dislocations*

## Introduction

A number of publications have stressed the importance of the facial features as a key factor in recognising individuals with Larsen syndrome [9], Latta (1971). The syndrome, first recognised as a distinct entity by Larsen in 1950, includes flattened facies, multiple congenital joint dislocations, clubfoot deformities, and frequently cleft palate. The vast majority of papers on the syndrome, however, have focussed on other clinical and radiological features. The variability of clinical presentations in this disorder can be very misleading for physicians and orthopaedic surgeons. We have encountered an association which emphasises the necessity for identifying the facial features as a crucial step in recognising the syndrome [1].

Generally the vast majority of these children are categorised under the diagnosis of arthrogyposis multiplex. When orthopaedic surgeons, paediatricians or other medical practitioners apply such *labelling*, the consequence is an accelerated rate of diagnosis of such deformities, which renders the process of management difficult if not frankly inadequate.

We report eight distantly related family members of a Tunisian family, who over three generations had variable clinical manifestations, ranging from full clinical diagnostic criteria for Larsen syndrome in four subjects, to less apparent skeletal, oral, and mental manifestations in the rest of the family members. Though, the most constant clinical criterion in this family was the facial anomaly, which was typical in all eight subjects, the rest of the clinical criteria were extremely variable.

The family pedigree reported here suggests that in three generations of one family eight cases of Larsen syndrome arose. We propose a distinct mode of inheritance consistent with single-gene autosomal dominance. There is also evidence that the multiple neonatal deaths in the family might represent the extreme of expression of the syndrome.

The purpose of this study is to highlight the importance of the facial changes of this heterogeneous syndrome in aiding the correct diagnosis of Larsen syndrome and its distinction from other congenital skeletal disorders.

### Case reports

The index case (III 3) (figure 1A) was referred because of congenital hip dislocation associated with clubfoot by another orthopaedic centre at the age of six months, accompanied by X-ray plates done at the age of two months. The accompanying referral letter described the case as arthrogyriposis multiplex (familial type), and pointed to the presence of the same deformities in the other older female siblings. The child, born at full term, had a birth-weight, length, and head circumference, which were all around the 10<sup>th</sup> Percentile. The mother was aged 31 years, gravida 6, mortality 3, married to 36 year old distantly related man. The pregnancy of the index case was characterised by feeble foetal uterine movements associated with bouts, of uterine bleeding particularly in the first trimester.

#### Examination of the child aged 5 years (when seen by the author for the first time)

*Developmental:* marked retardation in acquiring the skills of gross motor development secondary to the multiple joint dislocations and the apparent ligamentous hyperlaxity, speech was also delayed because of recurrent bouts of middle ear infections.

*Growth:* at the 50<sup>th</sup> percentile.

*Craniofacial:* marked frontal bossing, typically flattened face, depressed nasal bridge; eyes widely set, small mouth, and micrognathia.

*Musculo-skeletal:* Generalised ligamentous hyperlaxity.

*Joints:* The child presented with multiple joint dislocations, bilateral hip dislocation, bilateral anterior dislocation of the radial head, bilateral anterior dislocation of the tibia on the femur (Genu recurvatum), and bilateral talipes equinovarus, the patellae are bilaterally and laterally dislocated.

*Spinal column:* Thoracic scoliosis secondary to congenital flattening of the thoracic vertebrae, and cervical vertebral flattening particularly of the 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>.

*Hands:* Long fingers, cylindrical (pseudoclubbing), spatulate thumb, multiple subluxations of the interphalangeal joints of fingers and toes.

*Oral manifestations:* microdontia, with clefting of the uvula.

*Genitalia:* Normal.

*Neurological examination:* normal.

*Performance:* Normal intelligence.

*Abdominal ultrasound* revealed nothing of significance.

**Figure 1**

A: the index case (III 3) – note the characteristic facial features of Larsen syndrome, also the severe ligamentous hyperlaxity, with genu recurvatum, and the multiple joint dislocations. B: the mother (II 2) – note the typical facies of Larsen syndrome, very much like her offspring, also note the female siblings both have the characteristic facial appearance of Larsen syndrome. Published with the informed consent of the described family.



**Figure 2**

Radiological examination: bilateral dislocation of the hip, anterior dislocation of the knee, dislocation of the radial head, of the patellae, the shoulders, and the carpo-metacarpal joint of the thumb, severe talipes equinovarus were encountered in the three siblings, thoracic scoliosis secondary to congenital flattening of the thoracic vertebrae, and cervical vertebral flattening particularly of the 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup> vertebrae. Advanced bone age in the carpals, and subluxation of the carpo-metacarpal joint. A: X rays of the index case (III 3) note the multiple dislocations; bilateral hip dislocation, bilateral anterior dislocation of the tibia on the femur, the fibulae are hypoplastic bilaterally, the patellae are dislocated laterally, and bilateral talipes equinovarus. B: X ray hand at age two months note: advanced bone age in the carpals and subluxation of the carpo-metacarpal joint of the thumb. C: X ray of the upper limb: note anterior dislocation of the of the radial head, with total disruption of both the radio-capitellar and humero-ulnar joints, this may be partly due to dysplasia of the distal humerus and condylar underdevelopment.



**Table 1**  
Family pedigree.

Subject	Age	Facial features	Orthopaedic abnormalities	Other abnormalities	Performance
I 1	62 years	Typical	Kyphoscoliosis	–	Normal
II 1	46 years	Typical	Joint stiffness	Sterility	Normal
II 2 (mother)	31 years	Typical	Joint stiffness with waddling gait (hips)	–	Mentally subnormal
II 3	36 years	Typical	–	–	–
II 4	38 years	Typical	Cervical vertebral kyphosis	Bouts of severe pain over the shoulders with crises of paresis.	–
III 1 & 2	10 & 8 years respectively	Typical facies	Both have bilateral anterior radial head dislocations, bilateral hip dislocation, and bilateral talipes equinovarus	Subject III 1 has a ventricular septal defect	Normal

*Echo-Cardio-Doppler:* done systematically in most of children with skeletal abnormalities, showed no associated cardiac abnormalities.

*Investigations:* Routine vigorous investigations are carried out in all skeletally affected children, siblings and

parents, particularly the chromosomal studies and in this family the results were normal, simultaneously metabolic tests were done and no accompanying metabolic disturbances were encountered.

## Discussion

This syndrome is characterised by joint hypermobility, multiple joint dislocations, especially of the knees, and talipes equinovarus. The mid-face is hypoplastic with a depressed nasal bridge. Cleft palate may be present. Radiographs reveal under-mineralisation and over-tubulation of the long bones, a bifid calcaneus and advanced bone age in the carpal, or extra carpal bones. Scoliosis, coronal clefts of the vertebrae and subluxation of the vertebrae may be found.

Larsen and co-workers [9], described the association of multiple congenital dislocations with a characteristic facial abnormality. This disorder has since come to be known as Larsen's syndrome.

The varying family histories had raised the question of whether this syndrome was hereditary, until Harris [5] described the syndrome as being autosomal-dominant in its inheritance. Larsen and associates had originally concluded that it was not.

The syndrome has been described in siblings whose parents were apparently normal, Steel et al. [13], Block [2], Fryns [4] described the disorder in a mother and her daughter, both presenting with bilateral clubfoot. In our family, the constellations of the clinical features over three generations with the constant facial features in eight subjects, and the low mental performance of the mother, gives a more apparent picture of the nature of this disorder.

The misidentification of such cases, given the diagnosis of arthrogyriposis multiplex, is absolutely misleading, since the resultant management can be very deficient and short sighted. The accumulation of three siblings with talipes equinovarus, gives an idea to any observer, of the devastating consequences of such mistaken diagnoses. Houston et al. [6], emphasised the importance of differentiating Larsen syndrome from other conditions in which

arthrogryposis is the presumed diagnosis. The latter is, however, a symptom complex and not a diagnosis. Physicians and Orthopaedic surgeons must not throw these clinical entities into the basket of arthrogyriposis, otherwise underestimations can be expected. Similarly, the spinal malalignment is another clinical feature that can lead to under-estimations of this syndromic entity, in which congenital scoliosis and vertebral dys-segmentation in connection to the facial abnormality can occur, as in a family with Larsen syndrome [1].

Stanley [12], described the syndrome in nine patients from one family, making particular reference towards the recognition of the syndrome through the foot complex deformities, however, he paid little attention to the facial abnormalities in his patients.

Topley et al. [14] described two siblings with Larsen syndrome in a consanguineous parents, he emphasised shortness of stature and joint dislocations, but made little reference to the facial abnormality as a means of recognising the syndrome.

Orthopaedic management of multiple dislocations often proves difficult with a tendency to recurrence. The older female siblings and the index case underwent many operations without achieving proper correction. The other problems are with knees, which are difficult to stabilise. In our case, in spite of prolonged splinting, they still remain unstable.

In our family we encountered a combination of clinical features in eight family subjects, of which three siblings presented with the full clinical criteria in association with catastrophic skeletal malformations. The consistent clinical feature in all the affected family members over three generations was the facial abnormality. The latter finding, if missed, can lead to apparent misman-

agement for the whole family. We insist, in our practice at the department of paediatric orthopaedics, on the necessity of being able to make the link between the diversity of readable clinical signs and the dreadful congenital orthopaedic abnormalities of this syndrome.

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