In 1950, Larsen et al. described a condition characterized by multiple large joint dislocations and flat face. The condition occurs in approximately 1 in 100,000 births.

GENETICS/BASIC DEFECTS
1. Subtypes
   a. Sporadic form
   b. Autosomal dominant form
   c. Autosomal recessive form: clinical phenotype more debilitating with higher mortality than the autosomal dominant form
   d. Possible lethal form
2. The first known gene mutated in Larsen syndrome, \textit{LARI}, for autosomal dominant form: mapped to 3p21.1-14.1 in the proximity of, but distinct from, the \textit{COL7A1} locus
3. Unilateral manifestation of typical skeletal defects in some patients indicates that this condition might represent unilateral somatic cell-line mosaicism

CLINICAL FEATURES
1. Broad inter- and intrafamilial clinical variability
2. Characteristic flat facial appearance (“dish face”)
   a. Prominent forehead (frontal bossing)
   b. Hypertelorism
   c. Hypoplastic midface
   d. Depressed nasal bridge
   e. Micrognathia
   f. Occasional cleft palate, lip or uvula
3. Bilateral multiple joint dislocations
   a. Shoulders
   b. Elbows
   c. Wrists
   d. Hips
   e. Patella
   f. Ankles
   g. Knees
4. Variable handicap due to joint luxations
5. Hand abnormalities
   a. Long, cylindrical, and tapering fingers (pseudoclubbing)
   b. Spatulate/bifid thumbs
   c. Dislocation of distal radioulnar joint
   d. Delayed carpal ossification
   e. Supernumerary ossification centers
   f. Brachymetacarpia
   g. Brachytelephalangia
   h. Hyperextension of distal interphalangeal joints
6. Feet abnormalities
   a. Spatulate hallux
   b. Equinovarus or valgus deformities of the feet
7. Respiratory distress due to tracheolaryngomalacia
   a. Stridor
      i. Inspiratory reflecting laryngomalacia or extrathoracic cervical tracheomalacia
      ii. Expiratory reflecting intrathoracic tracheomalacia
   b. Cyanosis
   c. Obstructive apnea
   d. Possibly life-threatening
8. Bronchomalacia
   a. Lobar atelectasis
   b. Hyperinflation
   c. Pneumonias
9. Respiratory embarrassment in infancy due to soft tracheolaryngeal cartilage
10. Soft/collapsing thorax
11. Cardiovascular abnormalities
    a. Congenital defects
       i. Bicuspid aortic valve
       ii. Subaortic stenosis
       iii. Atrial septal defect
       iv. Ventricular septal defect
       v. Patent ductus arteriosus
       vi. Pulmonary stenosis
       vii. Endocardial fibroelastosis
    b. Acquired lesions
       i. Dilated aortic root
       ii. Elongated aorta
       iii. Mitral valve prolapse
       iv. Aneurysm of ductus arteriosus
       v. Arterial tortuosity and dilatation
12. Associated spinal anomalies
    a. Cervical spine involvement
       i. More often affected than thoracic or lumbar spine
       ii. Results in:
          a) Midcervical kyphosis, usually at the C4–C5 region
          b) Cervicothoracic lordosis
          c) Spinal instability
    iii. Flattened, hypoplastic, and often bifid cervical vertebrae
    b. Atlantoaxial instability
       i. A rare finding
       ii. May be associated with other abnormalities of the upper cervical spine
          a) Occipitalization of the atlas
          b) Basilar impression
    c. Lumbar or sacral dysraphism: may lead to neurological impairment
    d. Thoracic scoliosis
    e. Hypoplasia of the vertebral bodies or posterior elements
    f. Quadriplegia secondary to segmentation abnormalities of the vertebrae

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13. Mixed hearing loss due to ossicular abnormality
14. CNS anomalies
   a. Hydrocephalus (rare)
   b. Glial proliferation in the brain
15. Short stature
16. Normal intelligence
17. Possible lethal form
   a. Tracheomalacia
   b. Pulmonary hypoplasia
   c. Collagen fiber dysmaturity
18. Prognosis
   a. Generally good after aggressive orthopedic management, except some lethal cases due to tracheolaryngomalacia and/or lung hypoplasia
   b. Compatible with successful pregnancy if the maternal and fetal safety issues are properly considered

DIAGNOSTIC INVESTIGATIONS
1. Radiography
   a. Bilateral dislocations of shoulders, elbows, wrists, hips, patella, ankles, and knees (anterior dislocation of the tibia on the femur, most characteristic)
   b. Genu recurvata
   c. Talipes deformities (club feet)
   d. Spatulate thumbs
   e. Shortened metacarpals
   f. Multiple supernumerary carpal ossification centers (short, small, and increased in number)
   g. Poor ossification of phalanges
   h. Delayed coalescence (duplication) of calcaneal ossification centers
   i. Occasional abnormal segmentation of vertebrae (± fusion defects of cervical spine)
   j. Cervical kyphosis
   k. Spina bifida occulta
   l. Scoliosis
   m. Craniofacial disproportion
2. Polysomnography for assessing the severity of airway obstruction
3. Echocardiography for cardiovascular lesions
4. MRI of the brain for cerebral malformations

GENETIC COUNSELING
1. Recurrence risk
   a. Patient’s sib
      i. Sporadic form (consider germ-line mosaicism when neither parent appears to be affected)
      ii. Autosomal dominant inheritance: risk not increased unless a parent is affected
      iii. Autosomal recessive inheritance: 25% risk of having sibs affected
   b. Patient’s offspring
      i. Sporadic form: risk not increased unless the patient has germ-line mosaicism
      ii. Autosomal dominant inheritance: 50% risk of having offspring affected
      iii. Autosomal recessive inheritance: risk not increased unless the spouse is also a carrier
2. Prenatal diagnosis accomplished in rare cases by ultrasonography in pregnancies at risk
   a. Multiple joint dislocations
      i. Elbow
      ii. Knees
      iii. Hips
   b. Flat facial profile
      i. Prominent forehead
      ii. Hypertelorism
      iii. A depressed nasal bridge
      iv. Micrognathia
   c. Genu recurvatum
   d. Club feet
3. Management
   a. Supporting therapy for airway difficulty
      i. Antibiotics as needed
      ii. Supplemental oxygen
      iii. Chest physiotherapy to augment mucus clearance
      iv. Require intubation for severe respiratory distress with positive end-expiratory pressure (PEEP) to maintain a patent airway
   b. Cleft palate repair
   c. Closed or open reduction and stabilization of dislocated joints
      i. Securing stability of the knee joints for weight-bearing: primary importance
      ii. Correction of foot deformities through operative and nonoperative measures
   d. Stabilization of the cervical spine
      i. Early bracing and stabilization
      ii. Stabilization of the neck may be required before surgical correction of joint abnormalities to prevent possible complications associated with the induction of anesthesia
   e. Care for possible poor wound healing
   f. Obstetrical care of an affected mother and fetus
      i. Regional anesthesia for possible difficulty in intubation and the cervical spine may be subluxated during extension of the neck for intubation
      ii. Cesarean section if the patient is unable to abduct the hips, making vaginal delivery potentially traumatic for both mother and infant
      iii. Risk of fetal injury includes cervical spine instability

REFERENCES