De Lange Syndrome

In 1933, Cornelia de Lange reported two nonfamilial infant girls with severe mental retardation and multiple abnormalities of the skull, face, and extremities. Earlier in 1916, Brachmann had described a child with similar features. The syndrome is also called Brachmann-de Lange syndrome or Cornelia de Lange syndrome. The prevalence is estimated to be 1 in 10,000 births.

GENETICS/BASIC DEFECTS

1. A heterogeneous clinical entity
   a. Sporadic in vast majority of cases (99%)
   b. Striking concordance in MZ twins
   c. Rare familial occurrences
      i. Autosomal dominant inheritance
      ii. Autosomal recessive inheritance: unlikely
2. Both missense and protein-truncating mutations in NIPBL, the human homolog of the Drosophila melanogaster Nipped-B gene, have recently been reported to cause de Lange syndrome
3. Inconsistent chromosome abnormalities occasionally associated with de Lange phenotype

CLINICAL FEATURES

1. Marked clinical variability
2. General history
   a. Prenatal and/or postnatal growth deficiency
   b. Prematurity
   c. Diminished sucking and swallowing ability
   d. Low pitched cry (74%) in the newborn period and in the early infancy but may disappear in the late infancy
   e. Global developmental delay
   f. Initial hypertonicity
   g. Recurrent respiratory tract infections
   h. Gastroesophageal reflux
   i. Failure to thrive
3. Growth
   a. Prenatal onset growth retardation
   b. Short stature
4. Skin
   a. Hypertrichosis (hirsutism) (78%): often with hairy whorls over the shoulders, lower back, and extremities
   b. Cutis marmorata (60%)
   c. Periorbital “cyanosis”
5. Characteristic craniofacial appearance
   a. Microcephaly (98%)
   b. Brachycephaly
   c. Hairy (low hairline) forehead
   d. Mask like (grim, devoid of expression) facies
   e. Hypertelorism
   f. Antimongoloid slant of palpebral fissures
   g. Synophrys (prominent bushy, confluent eyebrows joining at the nose) (99%)
   h. Long and curly eyelashes (99%)
6. Eye abnormalities (57%)
   a. Strabismus
   b. Nystagmus (37%)
   c. Myopia (60%)
   d. Ptosis (45%)
   e. Microcornea
   f. Astigmatism
   g. Optic atrophy
   h. Coloboma of the optic nerve
   i. Eccentric pupils
   j. Microphthalmia
   k. Blue sclerae
7. Limb abnormalities
   a. Upper extremities
      i. Micromelia (shortened limbs) (93%)
      ii. Ectrodactyly/oligodactyly/phocomelia (27%)
      iii. Clinodactyly of the 5th fingers (74%)
      iv. Small hands
      v. Proximally placed thumbs
      vi. Camptodactyly
      vii. Webbings of fingers
      viii. Brachydactyly
      ix. Flexion contractures of the elbows common (64%)
      x. Restriction of supination and pronations
      xi. Subluxation or dislocation of the radial head
   b. Lower extremities
      i. Small feet
      ii. Cutaneous syndactyly of the second and third toes (86%)
      iii. Tight Achilles tendon (equines deformity)
      iv. Pes planus
      v. Valgus heel
      vi. Flexion contractures of the knees
8. CNS anomalies
   a. Variable mental retardation to near-normal intellect
   b. Seizures (23%)
   c. Abnormal speech development
   d. Hearing deficits (60–100%)
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9. Behavior disorder
   a. Sleep disturbance (55%)
   b. Aggression (49%)
   c. Self-destructive tendencies (44%)
   d. Hyperactivity (40%)
   e. Low-pitched growling sound rather than cry
   f. Infrequent facial expressions of emotion
   g. Severe language delay
   h. Autistic-like behavior
      i. Repetitive stereotypic movement
   j. Eliciting pleasurable responses by vestibular stimulation or vigorous movement

10. Other anomalies
   a. Small hypoplastic nipples (55%)
   b. Small hypoplastic umbilicus (53%)
   c. Cardiovascular anomalies (15–20%)
      i. Ventricular septal defect
      ii. Atrial septal defect
      iii. Patent ductus arteriosus
      iv. Aortic valve anomaly
      v. Hypoplasia of the aorta
      vi. Persistent left superior vena cava
      vii. Pulmonary stenosis
      viii. Endocardial cushion defect
      ix. Tetralogy of Fallot
   d. Gastrointestinal anomalies
      i. Inguinal hernia
      ii. Hiatus hernia
      iii. Congenital diaphragmatic hernia
      iv. Gut duplication
      v. Malrotation of colon
      vi. Pyloric stenosis
   e. Genitourinary anomalies
      i. Hypoplastic, dysplastic, or cystic kidneys
      ii. Hypoplastic external genitalia, cryptorchidism or hypospadias in males
      iii. Small labia majora, bicornuate or septate uterus in females
   f. Abnormal dermatoglyphics
      i. Transverse palmar creases (51%)
      ii. Increased atd angle
      iii. Hypoplastic finger ridge patterns

DIAGNOSTIC INVESTIGATIONS

1. Radiography
   a. Skull
      i. Microcephaly: frequent
      ii. Brachycephaly: frequent
      iii. Trigonocephaly with orbital hypotelorism
      iv. Parietal foramina
      v. Micronathia
      vi. High-arched palate
      vii. Cleft palate
   b. Spine
      i. Kyphoscoliosis
      ii. Platyspondyly
      iii. Scheuermann disease
   c. Chest
      i. Aspiration pneumonia: frequent
      ii. Thin ribs
      iii. Short clavicles
      iv. Short hypoplastic sternum with reduced number of ossification centers
      v. Abnormal sternal angle
      vi. Cervical ribs
      vii. Hypoplasia of the first rib
      viii. Chronic pneumonia
      ix. Bronchiolitis
   d. Congenital heart diseases
   e. Gastrointestinal tract
      i. Swallowing dysfunction: frequent
      ii. Bowel rotation anomalies with bands: frequent
      iii. Hiatal hernia
      iv. Hypertrophic pyloric stenosis
      v. Duodenal stenosis
      vi. Colon duplication
      vii. Inguinal hernia
   f. Genitourinary tract
      i. Incomplete rotation of the kidneys
      ii. Renal duplication
      iii. Polycystic kidneys
      iv. Chronic pyelonephritis
      v. Abnormal renal function with poor visualization on excretory urography
      vi. Vesicoureteral reflux
      vii. Divided uterine canal with septate vagina
   g. Limbs
      i. Micromelia: frequent
      ii. Short humerus and/or forearm bones: frequent
      iii. Elongated humeral neck (similar to femoral neck): frequent
      iv. Subluxation or dislocation of malformed radius and/or ulna at elbow with fixation in flexion
      v. Absent or hypoplastic ulna: frequent
      vi. Retarded bone maturation with abnormal sequence of appearance of ossification centers: frequent
      vii. Absent carpals, metacarpals, and fingers (ectrodactyly/oligodactyly): frequent
      viii. Short, broad metacarpals, particularly 1 and 5: frequent
      ix. Hypoplastic phalanges particularly middle 5th (curved) and middle second fingers: frequent
      x. Cutaneous syndactyly of second and third toes or other toes and fingers: frequent
      xi. Cutis valgus
      xii. Absent or hypoplastic radius
      xiii. Lunate and triquetral fusion
      xiv. Aplastic or hypoplastic ulnar styloid
      xv. Double distal phalanges of thumbs and/or great toes
      xvi. Congenital dislocated hips
      xvii. Aseptic necrosis of femoral head
xviii. Broad ischial bones  
xix. Large obturator foramina  
xx. Short broad femoral necks  
xxi. Absent tibia with deformed fibula  
xxii. Fusion of phalanges of fifth toe  
xxiii. Rocker-bottom foot  
xxiv. Metatarsus adductus  
xxv. Planovalgoid foot  
xxvi. Talipes equinovarus  
xxvii. Shortening of femur and/or leg bones  
xxviii. Wide gap between first and second toes  
xxix. Osteoporosis  

2. Endocrinologic studies in patients with severe growth retardation  
3. Echocardiography for evaluation of congenital heart defects  
4. Abdominal ultrasonography for GU anomalies  
5. EEG for seizures  
6. High resolution chromosome analysis for associated chromosome anomaly  
7. DNA mutation analysis of NIPBL (positive in 47%)  

GENETIC COUNSELING  
1. Recurrence risk  
a. Patient's sib: an empiric risk of about 1–4%  
b. Patient's offspring: 50% in case of an autosomal dominant inheritance  
2. Prenatal diagnosis by ultrasonography  
a. Intrauterine growth retardation  
b. Characteristic facies  
i. A small bulging nose  
ii. Long bulging philtrum  
iii. Protruding and overhanging upper lip  
iv. Micrognathia  
c. Limb defects  
i. Micromelia  
ii. Monodactyly  
iii. Ulnar agenesis  
d. Diaphragmatic hernia  
3. Management  
a. Adequate caloric intake  
b. Treat gastroesophageal reflux with thickened feeds in an upright position and pharmacotherapy  
c. Fitting of hearing aids and early consistent training for hearing impaired children  
d. Early intervention and special education programs for psychomotor delay  
e. Behavioral modification  
f. Correction of refractory errors with glasses  
g. Anticonvulsants for seizures  
h. Surgical repairs  
i. Fundoplication and gastrostomy feedings necessary in patients with severe esophagitis and progressive failure to thrive despite conservative intervention  
ii. Diaphragmatic hernia  
iii. Cardiac defect  
iv. Severe skeletal deformities  
v. Renal malformations  
vi. Ptosis obstructing the visual axis  
vii. Orchiplexy  

REFERENCES  

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Fig. 1. A neonate and a child with de Lange syndrome showing characteristic facies, oligodactyly, and severe hirsutism.
Fig 2. Four patients with classic De Lange syndrome of different ages showing typical facial appearance (synophrys, coarse eyebrows, long curly eyelashes, depressed nasal bridge with anteverted nares, long thin upper lip, down-turned angles of the mouth, and widely spaced teeth) and ectrodactyly/oligodactyly in the first two cases.

Fig 3. A 46,XX male with de Lange phenotype.

Fig 4. Two adults with de Lange syndrome showing hirsutism and mental retardation.