22q11 Deletion: Knowing What to Look For
Laurie S. Sadler, MD
October 21, 2011

Overview
- Most common deletion syndrome
  - Occurs in 1/2000 – 1/4000 live births
- Broad phenotypic spectrum affecting multiple systems
- Embryology: abnormal development of pharyngeal arch system resulting in craniofacial, cardiac, thymic and parathyroid abnormalities

History of 22q11 deletion: “multiple syndromes”
- Sedlackova syndrome (1955)
  - Velopharyngeal insufficiency and dysmorphic facies
- DiGeorge syndrome (1965)
  - Absent thymus and parathyroid glands
- Conotruncal anomalies face syndrome (1976)
  - Cardiac defects and dysmorphic facies
- Velocardiofacial syndrome (Shrintzen, 1978)
  - Palatal clefts (overt or submucous), cardiac defects, dysmorphic facies and learning disabilities
- CATCH 22
  - Acronym: Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate and Hypocalcemia

Velocardiofacial syndrome phenotype
Craniofacial
- Narrow palpebral fissures
- Prominent nasal bridge
- Narrowed alar base and/or pinched alae nasae
- Palatal defects
- Mild auricular anomalies
Limbs
- Slender, hyperextensible hands and fingers

Cardiac Manifestations
- Cardiac defects in ~75% of cases
  - Tetralogy of fallot in 20%
  - Ventricular septal defects in 21%
  - Interrupted aortic arch in 12%
  - Truncus arteriosus in 6%
  - Vascular ring in 6%
  - Other in 10%
**Immunologic Manifestations**
- Immunologic deficits in ~75% of cases secondary to thymic hypoplasia
  - Mild to moderate decrease in T cell count in peripheral blood
  - Prolonged viral infections with or without secondary bacterial infection
  - Increased risk of autoimmune disorders (~10%)
- Normal B cell numbers
- Little or no increased risk of opportunistic infections

**Palatal Manifestations**
- Hypernasal speech in ~75%
  - Velopharyngeal insufficiency in 42%
  - Inability of the velopharyngeal mechanism to adequately separate the nasal cavity from the oral cavity during speech
  - Submucous cleft palate in 16%
  - Overt cleft palate in 11%

**Submucous Cleft Palate**
- Incidence: 1/1200 live births
- Definition: deficiency or lack of muscular tissue on the superior surface of the palate with intact oral mucosa
- Clinical symptoms
  - Nasal regurgitation
  - Otitis media with effusion
  - Hypernasal speech

**Submucous Cleft Palate**
- Physical Findings
  - Bifid uvula
  - Zona pellucida
  - Notching between hard and soft palate
- Occult submucous cleft palate
  - Normal intraoral examination
- Diagnosis
  - Physical examination
  - Videofluoroscopy
    - Barium study visualizing the velopharyngeal mechanism in multiple planes during speech
  - Videonasoendoscopy
    - Direct visualization of the velopharyngeal mechanism during speech

**Submucous cleft palate**

[Image of a submucous cleft palate]
**Neurodevelopmental Findings**

- Feeding difficulties common
- Hypotonia with delayed motor milestones
- Delayed speech acquisition in addition to hypernasality
- Mild learning problems common
  - Mean FSIQ ~70 (borderline intelligence)
  - Verbal IQ better than performance IQ
  - Rote memory a specific strength
  - Math skills a specific weakness

**Psychiatric Manifestations**

- Adult psychiatric disease in 25–30% of cases
  - Greatest risk for schizophrenia and schizoaffective disorders (20 times population risk)
  - ~1% of schizophrenics in the general population are found to have 22q11 deletion
- Behavioral findings in childhood
  - Increased incidence of ADD, ODD, OCD, GAD and autistic spectrum disorder
- 22q11 deletion considered one of the main schizophrenia susceptibility loci in humans

**Other Findings**

- Malpositioned carotid arteries: must evaluate with MRA prior to surgical intervention for VPI
- Hypocalcemia secondary to hypoparathyroidism; usually transient in the neonatal period
- Renal anomalies

**Molecular Findings**

- 22q11 deletion
  - Identical 3Mb deletion in 90% of patients
  - Smaller deletions in 10%
  - Common deletion includes 35–40 genes
- Mechanism
  - Misalignment of series of low copy repeats during meiosis with unequal crossing over
  - 90% of cases de novo
  - 10% of cases familial (autosomal dominant); familial cases increasing due to improved cardiac outcomes

**Laboratory Diagnosis**

- FISH study
  - Diagnostic technique routinely used since 1992
  - Use of chromosome specific probe and second probe that hybridizes to the deleted region in question
  - If second probe is absent, diagnosis is confirmed
  - FISH only detects common 22q11 deletion

**FISH study for 22q11 deletion**
**“FISHable Disorders”**

- Angelman syndrome  
  - FISH only after abnormal methylation study  
  - Deletion 15q11-13 on maternal chromosome  
- Prader-Willi syndrome  
  - FISH only after abnormal methylation study  
  - Deletion 15q11-13 on paternal chromosome  
- Williams syndrome  
  - Deletion 7q11.23  
- Miller-Dieker syndrome  
  - Lissencephaly  
  - Deletion 17p13.3  
- Smith-Magenis syndrome  
  - Specific behavioral phenotype characterized by self-injurious behaviors and polymicrogiolamania  
  - Deletion 17p11.2

**Putative Genes**

- **TBX1**  
  - T-box genes encode for transcription factors involved in regulation of gene expression  
  - T-box 1 gene important for normal embrylogic development of craniofacial region, cardiac outflow tracts, thymus and parathyroids  
  - Susceptibility gene but not sufficient for 22q11deletion cardiac phenotype

- **COMT**  
  - Catechol-O-methyltransferase is an enzyme that degrades dopamine and norepinephrine  
  - Expressed at high levels in prefrontal cortex  
  - Haploinsufficiency increases levels of neurotransmitters during embryologic development as well as postnatally  
  - Susceptibility gene for schizophrenia

**Case Report: Patient 1**

- Referred by pediatrician for evaluation of cleft palate and developmental delays  
- Family history  
  - Craniosynostosis syndrome in the mother and maternal grandmother  
  - Submucous cleft palate and learning problems in the father (adopted)  
- Pregnancy and delivery  
  - First born infant to 23-year-old woman and her 29-year-old nonconsanguineous husband  
  - No prenatal or perinatal complications  
  - Term infant; Caesarean section for breech presentation  
  - Birthweight of 10 lb 10 oz; cleft palate recognized in newborn period

- Referred by otolaryngologist for evaluation of cardiac defect, hypernasal speech and dysmorphic features (consider Kabuki syndrome)
- Medical history  
  - Short stature in mother (4’9”), maternal uncle and both maternal grandparents  
  - Distant maternal cousin with a congenital cardiac defect  
- Pregnancy and delivery  
  - Second born infant to 21–year-old woman and her nonconsanguineous 23-year-old husband  
  - Pregnancy complicated by bleeding requiring bedrest beginning at 7 weeks  
  - Term infant; vaginal vertex delivery  
  - Birth weight of 4 lbs 6 oz; remained in NICU in Puerto Rico for 11 days; initially required tube feedings

**Physical Examination: Patient 1 (age 4 years)**

- Growth  
  - Normal height, weight and head circumference
- Craniofacial  
  - Periorbital puffiness  
  - Notched alae nase  
  - Minor auricular abnormalities  
  - Repaired posterior palatal cleft  
- Limbs  
  - Tapered, hyperextensible fingers  
- Other  
  - Hypernasal speech

- Medical History  
  - Normal motor milestones, e.g., walked at age 14 months  
  - Speech delays, e.g., first word at age 2 years  
  - Began therapeutic intervention at age 2 years  
  - Attending BOCES preschool program  
- Surgical History  
  - Cleft palate repair at age 9 months (Rochester)  
  - Two sets of tympanostomy tubes

**Case Report: Patient 2**

- Referred by pediatrician for evaluation of cleft palate and developmental delays  
- Family history  
  - Craniosynostosis syndrome in the mother and maternal grandmother  
  - Submucous cleft palate and learning problems in the father (adopted)  
- Pregnancy and delivery  
  - First born infant to 23-year-old woman and her 29-year-old nonconsanguineous husband  
  - No prenatal or perinatal complications  
  - Term infant; Caesarean section for breech presentation  
  - Birthweight of 10 lb 10 oz; cleft palate recognized in newborn period

- Referred by otolaryngologist for evaluation of cardiac defect, hypernasal speech and dysmorphic features (consider Kabuki syndrome)  
- Family history  
  - Short stature in mother (4’9”), maternal uncle and both maternal grandparents  
  - Distant maternal cousin with a congenital cardiac defect  
- Pregnancy and delivery  
  - Second born infant to 21–year-old woman and her nonconsanguineous 23-year-old husband  
  - Pregnancy complicated by bleeding requiring bedrest beginning at 7 weeks  
  - Term infant; vaginal vertex delivery  
  - Birth weight of 4 lbs 6 oz; remained in NICU in Puerto Rico for 11 days; initially required tube feedings
Case Report: Patient 2

- Developmental History
  - Motor delays, e.g., walked at age 18 months
  - Speech delays, e.g., first words at age 2 years
  - Began therapeutic intervention at age 2 years
  - Doing well academically in a regular classroom setting

- Medical History
  - Ventricular septal defect diagnosed shortly after birth
  - Hospitalized for pneumonia as infant
  - Growth hormone injections for GH deficiency
  - Gastroesophageal reflux (prevacid)
  - Asthma (albuterol as needed)

- Surgical History
  - Repair of VSD, age 6 months
  - Tonsillectomy/adenoidectomy, age 3 years
  - Surgical correction of dacrotension

Physical Examination: Patient 2 (age 6 years)

- Growth
  - Short stature
  - Normal weight relative to height
  - Normal head size

- Craniofacial
  - Canthal folds with periorbital puffiness
  - Limbs
    - Slender fingers
  - Other
    - Grade II/VI blowing systolic murmur
    - Severe hypernasality of speech

Multidisciplinary Approach

- Cardiology
- Developmental pediatrics
- Endocrinology
- Gastroenterology
- Immunology
- Otolaryngology
- Plastic surgery
- Psychiatry
- Speech/language pathology

Think 22q11 Deletion

- Two or more of the following:
  - Velopharyngeal insufficiency with hypernasal speech
  - Cardiac defects
  - Developmental delay/learning disabilities
  - Behavior problems/psychiatric illness