Updates on the Care for Children with 22q11.2 Deletion Syndrome

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Objectives

1. Define genetic/genomic basis.
2. Clinical features by age group.
3. Outline medical management.
4. Identify resources for families and professionals.
What is deletion 22q11.2 Syndrome?

- Microdeletion of chromosome 22q11.2
- Medical problems spanning all organ systems
- Extremely variable clinical presentation
~20,000 genes packaged on 23 pairs of chromosomes
Geography of a Chromosome

p = short arm
q = long arm

Bands = the *bar code*
       (light and dark stripes)
Microdeletion is **NOT** visible on G-banded chromosome analysis.
Laboratory Diagnosis
Karyotype vs FISH vs Microarray

Chromosomal microarray (also known as CMA or aCGH) is greatly improving the rate of diagnoses. CMA is the appropriate test in 2018.
Before I talk about the clinical features of deletion 22q11.2 syndrome, I have to discuss the history. This syndrome was described based solely on clinical features long before the genetic basis was discovered.
del 22q11.2: What’s in a Name?

- DiGeorge syndrome
- Cayler asymmetric crying face
- Takao syndrome
- Shprintzen syndrome
- Velo-Cardio-Facial syndrome
- Sedlac’kova´ syndrome
- Conotruncal anomalies face syndrome
History: What’s in a Name?

Angelo DiGeorge, M.D.
Pediatric Endocrinologist

Robert Shprintzen, Ph.D.
Speech Pathologist
1965 Dr. DiGeorge describes children with low calcium, seizures, infections, and heart defects.

1976 Dr. Kinouchi reports a typical facial appearance seen in patients with heart problems and calls it conotruncal anomaly facial syndrome (CTAF).

1978 Dr. Shprintzen describes a condition running in families. Patients have cleft palate or velopharyngeal incompetence, heart defects, learning disabilities and a characteristic facial appearance. He calls it velocardiofacial syndrome.

1981/1982 Some patients with DiGeorge syndrome noted to have a rearrangement of chromosome 22 that caused them to be missing a very small piece of chromosomal material on the long arm (q11.2).

1990 Some parents of DiGeorge patients noted to have features of VCFS.

1992 DGS and VCFS found to be due to deletion 22q11.2.

1994 Diagnostic test (FISH) becomes available in clinical laboratories.

2004-present Better diagnostic test (Chromosomal DNA “Chip” or Microarray) is widely used.
A single genomic abnormality explains many syndromes

22q11.2DS

DiGeorge syndrome

Shprintzen syndrome

Velo-Cardio-Facial syndrome

Conotruncal anomalies face syndrome
Deletion 22q11.2

DiGeorge
- Presenting in infancy
- Severe heart defects
- Severe infections
- Seizures

Velocardiofacial
- Childhood/adulthood
- Minor heart defects
- Weak palate; cleft palate
- Long face and fingers
Deletion 22q11.2

Fetal Demise — Severe Neonatal — Early Childhood — School Years — Teen — Adult

IUFD — CHD/Seizures — Feeding/DD — LDs — Behavior — Psych — Incidental

CATASTROPHIC to ASYMPTOMATIC
Deletion 22q11.2

Incidence of ~1 in 2000

Diagnosis is dependent on:
Experience and Awareness of Providers
Severity of Phenotype
Objectives Redefined

1. Recognize 22qDS in your patients.
2. Confirm diagnosis by laboratory testing.
3. Discuss recurrence risk for family members.
4. Provide recommendations for medical intervention and surveillance.
5. Provide information regarding support/advocacy groups.
Case Presentation

• 10 month old girl
• History of atrial septal defect
• Developmental delay
  - Hypotonia
  - Poor feeding
  - Delayed milestones
• Observation in clinic
  - Nasopharyngeal reflux

What type of Genetic Test would you recommend?

- Chromosome analysis
  NO

- FISH for 22q
  NO

- Chromosome microarray
  YEAH

Intrauterine Fetal Demise/Miscarriage

Young and healthy couple
No family history of genetic diagnoses or “birth defects”
No maternal illnesses or exposures
Normal ultrasounds
Normal prenatal screening tests
Lack of fetal movement at 25 weeks
Consent for autopsy
  Small parathyroid glands
  Absent thymus
  Severe heart defect
Newborn Period

BabyBoy-low weight and small for age
Poor circulation-severe heart defect
Seizures due to low calcium
Severe infection due to low T cells
Diagnostic Approach

Chromosomal microarray

deletion 22q11.2

Should we stop there?

family history

parental studies

mother with deletion 22q
Recurrence Risk

95% deletions—“de novo”

5% are inherited from a parent.
Recurrence Risk

For someone who HAS the deletion
Recurrence risk is 50%
Always test the parents
Case Presentation

17yo girl
ADHD noted in childhood
Learning disabilities identified in H.S.
Recently diagnosed with ODD
Physical examination
CMA revealed 22q11.2 deletion
Indications for Genetic Evaluation

1. Establish diagnosis
2. Anticipatory guidance
3. Medical management
4. Developmental intervention
5. Behavioral intervention
6. Psychological management
7. Recurrence risk
Clinical Features of Deletion 22q11.2

Over 180—involving many organs and systems

BRAIN
- INTERUPTED AORTIC ARCH
- HYPERNASAL SPEECH
- GROWTH
- SPEECH DELAY
- BIPOLAR DISORDER

PARATHYROID

THYMUS
- DISMOTILITY

HEART
- ANXIETY
- SEIZURES

IMMUNE SYSTEM
- CALCIUM REGULATION

KIDNEYS

GASTROINTESTINAL TRACK
- NASOPHARYNGEAL REGURGITATION
- AUTISM

VISION

GASTROESOPHAGEAL REFLUX

INFECTIONS

FEEDING DIFFICULTIES

SWALLOWING PROBLEMS

SPEECH DELAY

INFECTIONS

Low Muscle Tone

Learning

Hearing Loss

Dismotility

Schizophrenia

Submucous Cleft

Hypernasal Speech

Anxiety

Seizures

Calcium Regulation

Autism

Interrupted Aortic Arch

Attention Deficit
Diagnosis of Deletion 22q11.2
1 in 2,000

Birth 30%
By age 5 years 70%
By age 18 years 95%

Some people with deletion 22q11.2 are diagnosed following the birth of affected child.
Clinical Features of Deletion 22q11.2
Facial features can be very subtle.
Clinical Features of Deletion 22q11.2

No feature occurs in ALL patients.

NO patient has all features.

Extremely variable.

Current laboratory techniques allow earlier diagnosis.

Early diagnosis leads to better clinical and educational outcome.
## Anticipatory Care—Medical

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Follow Up</th>
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</thead>
<tbody>
<tr>
<td>Heart defects</td>
<td>Cardiac surgery; Cardiology</td>
</tr>
<tr>
<td>Feeding and swallowing difficulties</td>
<td>Feeding team; Occupational Rx</td>
</tr>
<tr>
<td>VPI; Nasal speech</td>
<td>Otolaryngology</td>
</tr>
<tr>
<td>Infections</td>
<td>Immunology</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Endocrinology</td>
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<tr>
<td>Gastro-esophageal reflux</td>
<td>Gastroenterology</td>
</tr>
<tr>
<td>Vision; strabismus</td>
<td>Ophthalmology</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Audiology</td>
</tr>
<tr>
<td>Poor growth (40%)</td>
<td>Endocrinology</td>
</tr>
<tr>
<td>Seizures (10%)</td>
<td>Neurology; Endocrinology</td>
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</tbody>
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## Anticipatory Care—Developmental and Psychiatric

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Follow Up</th>
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</thead>
<tbody>
<tr>
<td>Developmental Delay (70-90%)</td>
<td>Early Childhood Intervention Occupational/Physical Therapy</td>
</tr>
<tr>
<td>Speech delay (70-90%) Articulation difficulty</td>
<td>ECI; Speech therapy Augmentative communication</td>
</tr>
<tr>
<td>Learning disability (70-90%)</td>
<td>Developmental specialist</td>
</tr>
<tr>
<td>Attention deficit</td>
<td>Developmental specialist Psychiatrist</td>
</tr>
<tr>
<td>Autistic spectrum disorder</td>
<td>Developmental specialist Psychiatrist</td>
</tr>
<tr>
<td>Schizophrenia; Bipolar; Psychosis Depression; Anxiety disorder</td>
<td>Psychiatrist</td>
</tr>
</tbody>
</table>
ADHD—most frequent in children: 37% (M>F)

Disruptive disorders—(ODD/Conduct): 7-14% (M>F)

Anxiety disorders—↑children and adolescents (F>M)

Panic disorder—increased with age

Mood disorders—increased with age (F>M)

Autism Spectrum—(M=F)

Psychotic disorders—41% of adults >25 years
CONCLUSIONS: Individuals with 22q11DS share overarching similarities with non-deleted individuals in psychosis symptoms and age of onset for psychosis proneness; this continues to support the 22q11DS model as a valuable window into mechanisms contributing to psychosis.
Living With a Child at Risk for Psychotic Illness: The Experience of Parents Coping With 22q11 Deletion Syndrome: An Exploratory Study
Laura Hercher¹* and Georgette Bruenner²

Survey of 41 caretakers of individuals with deletion 22q11.2.

Information about the association between deletion 22q11.2 and psychiatric disease was omitted at diagnosis most of the time and rarely addressed by medical specialists.

Families frequently received their information only from non-medical sources, principally the internet.
Which problems are cause for parental concern?

22q11.2 DS Resources

Your local geneticist.

Internet:

GeneReviews
Genetic Home Reference
22q and You (CHOP)
VCFS Texas
PubMed, Amazon, Google

https://www.dshs.texas.gov/genetics/provider.shtm
References:

- 22q and You Website: Children’s Hospital of Philadelphia. http://www.chop.edu/consumer/jsp/division/service.jsp?id=74652
  Also see 22q and You Newsletter AND Faces of Sunshine—A Handbook for Parents and Professionals
- GeneClinics GeneReviews : www.genetests.org