Medical management and surveillance in 22q11.2DS

Kathy Angkustsiri, M.D., M.A.S.
Developmental Behavioral Pediatrics
Medical Director, 22q Healthy Minds Clinic
UC Davis MIND Institute
Outline

• What is chromosome 22q11.2 deletion syndrome (22q11.2DS)?
• Clinical features
  – Medical issues and surveillance
  – Behavioral and educational concerns
• Summary and recommendations
All the names....

• Velo-cardio-facial syndrome (VCSF)
• Conotruncal anomaly face syndrome (CAFS)
• DiGeorge syndrome (DGS)
• Autosomal dominant Opitz G/BBB syndrome
• Cayler Cardiofacial syndrome
• 22q11.2DS
22q11.2 deletion
22q11.2 deletion

- Estimated incidence 1:2000-4000 live births
- Most are “de novo” (new) deletion
  - Affected individuals have a 50% chance of passing the deletion to offspring (autosomal dominant)
- Large spectrum of involvement
  - Heart
  - Face/Palate
  - Immune
  - Developmental
  - Others

http://pharyngula.org/index/weblog/comments/deep_homologies_in_the_pharyngeal_arches/
Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome

Anne S. Bassett, MD,* Donna M. McDonald-McGinn, MS, CGC,* Koen Devriendt, MD, Maria Cristina Digilio, MD, Paula Goldenberg, MD, MSW, Alex Habel, MD, Bruno Marino, MD, Solveig Oskarsdottir, MD, PhD, Nicole Philip, MD, Kathleen Sullivan, MD, PhD, Ann Swillen, PhD, Jacob Vorstman, MD, PhD, and The International 22q11.2 Deletion Syndrome Consortium**

Table II. Recommended assessments for 22q11.2 deletion syndrome*

<table>
<thead>
<tr>
<th>Assessment</th>
<th>At diagnosis</th>
<th>Infancy (0-12 months)</th>
<th>Preschool age (1-5 years)</th>
<th>School age (6-11 years)</th>
<th>Adolescence (12-18 years)</th>
<th>Adulthood (&gt;18 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized calcium, parathyroid hormone†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyrotropin (thyroid-stimulating hormone)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood cell count and differential (annual)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunologic evaluation‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluate palate†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical spine (&gt;age 4 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Development‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socialization/functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric/emotional/behavioral‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systems review</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deletion studies of parents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic counseling‡‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecologic and contraceptive services</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Heart / Cardiac Problems (75%)

- Tetralogy of Fallot
- Ventricular Septal Defect
- Pulmonary Stenosis
- Vessel anomalies
  - Interrupted aortic arch
  - Vascular ring
  - Aberrant carotid vessels
- Echocardiogram, EKG

Ear, Nose, Throat

- Cleft Palate or Velopharyngeal Incompetence (VPI) (75%)
  - Feeding difficulties
  - Nasal regurgitation
  - Cleft Palate (full, submucous)
  - Hypernasal Speech, Articulation disorders
- Chronic ear infections, may need PE tubes
  - SNHL (10%), CHL (45%)
- Vocal cord paralysis
- Laryngeal web
- Nasendoscopy
- Routine hearing screens
- Neck MRI if surgical procedures

http://homepage.mac.com/changcy/endo.htm
Immunologic Problems (25-30%)

- Low T cells (usually mild with normal function) due to thymus involvement
- Antibody production usually intact
- Usually improves with age
- Recurrent infections: ear infections, sinusitis, bronchitis, pneumonia

- Flow cytometry (T and B cell counts), antibody levels, other immune function tests
- Important to know immune status before giving live vaccines or blood transfusions
- May want to check for adequate vaccine response

Endocrine

- Hypoparathyroidism (25%)
- Low calcium levels (hypocalcemia)
  - Seizures
- Hypothyroid
- Short stature

- Ionized calcium levels, thyroid levels
- Endocrinology referral if abnormal labs or <3<sup>rd</sup> percentile on growth curves
Gastrointestinal

- Feeding/Failure to Thrive
- Constipation
- GERD (gastroesophageal reflux disease)
- Hernia
- Malrotation
Musculoskeletal

- Cervical spine anomalies
- Flat feet
- Chronic leg pain (hypotonia and flat feet)
- Hypotonia
- Polydactyly
- Craniosynostosis

- 5 view c-spine x-rays after age 4
Eye

- Strabismus (lazy eye)
- Ptosis
- Retinal vessels
- Hooded eyelids

- Yearly eye exams, including dilation
Other Systems

• Autoimmune disorders (10%)
  - Blood: platelets (ITP, vWD, Bernard-Soulier), white blood cells
  - Juvenile Rheumatoid Arthritis (JRA)
  - IgA deficiency
  - Raynaud’s phenomenon
  - Celiac disease
  - ? cancer

• Kidney abnormalities (33%)
  - Small kidneys
  - Duplicated kidneys or renal system

• Renal ultrasound
Developmental-Behavioral Concerns

• Developmental Delays
  – Motor delays
  – Speech and language delays
  – Learning disabilities
    • FSIQ low-average to borderline range
    • Sometimes misleading b/c usually verbal IQ better than performance IQ
    • Difficulties with planning, math, and visuospatial tasks
  – Social immaturity
Developmental-Behavioral Concerns

- **Attention Deficit/Hyperactivity Disorder (ADHD) 30-50%**
  - Impulsivity
  - Inattentive, easily distracted

- **Anxiety Disorders: 40-60%**
  - Specific phobias
  - Obsessive Compulsive Disorder
  - General Anxiety
  - Separation Anxiety Disorder

- **Mood disorders**
Treatments/Recommendations

• Varies based on individual needs

• Behavioral

• Educational

• Medical
  – Labs/procedures
    • Thyroid, calcium, complete blood count, etc.
  – Medications
ADHD treatment

- Behavioral intervention
- Classroom modifications
- Parent training
- Medications
  - Stimulants
  - Alpha agonists (use with caution if cardiac hx)
  - Atomoxetine (Strattera)
  - Others
Stimulants for ADHD

• Why the concern?
  – Cardiac side-effects
  – Growth
  – Psychotic symptoms?
  – Altered dopamine levels in 22q11.2DS due to COMT?
Stimulants in 22q11.2DS

• Gothelf 2004 (4 weeks)
  – 12 children with ADHD
  – Low dose methylphenidate (0.3 mg/kg)
• Gothelf 2011 (6 months) – 0.5 mg/kg
  – 22 children treated
  – No psychotic/manic symptoms
  – Mild elevations in blood pressure

• Conclusion:
  – methylphenidate is effective and usually well-tolerated
  – be aware of side effects and potential risks
  – must weigh risks/benefits with your provider
Anxiety treatment

- Cognitive behavioral therapy
- Social skills group
- Medications
  - SSRI
    - Side effects
      - Sleep, headaches, appetite
      - Suicidal thinking
Resources

• Early intervention
  – Speech therapy
  – Occupational therapy
  – Physical therapy
  – Social skills

• School
  – IEP classifications
    • Other Health Impaired (OHI)
    • Specific Learning Disability (SLD)
    • Speech/Language impairment (SLI)
  – 504 plan
    • Computer assisted learning
    • Classroom accommodations
Recommedations

• At diagnosis or at least once
  – Echocardiogram
  – Immune function
  – ENT-nasendoscopy
  – Cervical spine films
  – Renal ultrasound
  – Genetic counseling

• Yearly
  – Eye exam
  – Hearing exam
  – CBC, calcium, thyroid
  – Dental

• As needed
  – Craniofacial/cleft palate team
  – Chest MRI to assess vasculature if surgical procedure in neck area
  – Endocrinology
  – Immunology
  – Hematology
  – Rheumatology
  – Orthopedics
  – Gastroenterology
  – Neurology
  – Developmental pediatrician or child psychiatry
  – School involvement
Websites

- MIND Institute Cognitive Analysis and Brain Imaging Laboratory (CABIL) [http://cabil.mindinstitute.org](http://cabil.mindinstitute.org)
- International 22q11.2 Foundation [http://www.22q.org/](http://www.22q.org/)
- CHOP The 22q and You Center [http://www.chop.edu/consumer/jsp/division/generic.jsp?id=74654](http://www.chop.edu/consumer/jsp/division/generic.jsp?id=74654)
- Chromosome 22 Central [www.c22c.org](http://www.c22c.org)

Books:
- [Educating Children with Velo-Cardio-Facial Syndrome](http://example.com) by Donna Cutler-Landsman
- [Missing Genetic Pieces. Strategies for Living With VCSF](http://example.com) by Sherry Baker-Gomez
References


Thank you!

– To all of the families who have participated in research

– Cognitive Analysis and Brain Imaging Laboratory (CABIL) Funded by:
  • National Institutes of Health
    – 2R01HD42974, 1R01HD46159, 1RL1NS62412 (Simon)
  • Center for Excellence in Developmental Disabilities (CEDD)
    – Administration on Developmental Disabilities 90DD0596 (Hansen)
  • UC Davis
    – M.I.N.D. Institute
    – Clinical and Translational Science Center UL1 RR024146