Medical Care and Genetic Mechanisms
Objectives

• Increase identification of children with the disorder
• Describe the associated medical symptoms and differences in presentation with age
• Review guidelines for medical work-up & surveillance
What organ systems are affected?

• Audience participation
Variable phenotype

- Presenting symptom leading to diagnosis varies by age (Oskarsdottir *et al.* 2005)
  - Infancy: cardiac issues
  - 2-20 years: learning and behavioral issues

<table>
<thead>
<tr>
<th>Infants</th>
<th>Preschool</th>
<th>Childhood-adolescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiac defect (TF, IAA, TA, PA + VSD, VSD + arch anomaly)(^a)</td>
<td>→ Infection problems (respiratory tract infections, middle ear infections)</td>
<td>→ Infection problems</td>
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<tr>
<td>2. Non-visible/hypoplastic thymus</td>
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<tr>
<td>Immunodeficiency</td>
<td>Hypoparathyroidism</td>
<td>Autoimmune phenomena</td>
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<tr>
<td>Infection problems</td>
<td>Speech-language impairment</td>
<td>Hypoparathyroidism</td>
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<td>3. Hypocalcaemia</td>
<td>Velopharyngeal insufficiency</td>
<td>Velopharyngeal insufficiency</td>
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<td>4. Feeding problems</td>
<td>Developmental delay</td>
<td>Learning difficulties</td>
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<tr>
<td>5. Cleft palate</td>
<td>Behavioural abnormalities</td>
<td>Behavioural abnormalities</td>
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<td>6.</td>
<td>→</td>
<td>→ (+ scoliosis)</td>
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<tr>
<td>7. Other malformations and deformities (e.g. skeletal, urinary tract, clubfoot, anal atresia, polymicrogyria, inguinal or abdominal hemia, retentio testis)</td>
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<tr>
<td>8. Characteristic pattern of subtle dysmorphic features (this feature may be an aid in making a diagnosis in a child with at least one of the other domains)</td>
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</tbody>
</table>

\(^a\)If a typical cardiac defect is found in an infant, this is sufficient for genetic testing for a 22q11 deletion
Case 1: video
Case 1: Early diagnosis

- Pregnancy—mother with vWD and borderline hyperglycemia
- Born with small, overfolded ears
- Laryngeal web—4 weeks in NICU
- 2 weeks old: right sided aortic arch discovered
- Hypocalcemia
- Feeding difficulty, aspiration, and nasal regurgitation
- GE reflux treated with Prevacid

- Dx at 4 weeks with 22q11.2DS
Diagnosis: FISH
Genetics

• Estimated incidence
  – 1:4000 live births (underestimate)
• Most (85-90%) are “de novo” (new) deletion
  – 10-15% inherited
  – Affected individuals have a 50% chance of passing the deletion to offspring (autosomal dominant)
Characteristic Features

- Asymmetric (crying) facies
- Puffy eyelids
- Wide spaced eyes (hypertelorism)
- Narrow palpebral fissures
- Broad nasal bridge
- Long nose with bulbous tip
- Short philtrum
- Small ears
- Overfolded Helix
- Long, tapered fingers

Heart / Cardiac Problems (75%)

- Tetralogy of Fallot
- Ventricular Septal Defect
- Pulmonary Stenosis
- Truncus arteriosus
- Vessel anomalies
  - Aortic arch abnormalities
  - Vascular ring
  - Aberrant carotid vessels
- Echocardiogram, EKG
- Neck MRI if surgical Procedures (aberrant vessels)

Velopharyngeal Insufficiency (VPI)

• aka VPD (velopharyngeal dysfunction)
  – Hypernasal voice
  – Nasal regurgitation

http://homepage.mac.com/changcy/endo.htm
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
- Nasopharyngoscopy
- Routine hearing screens

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Back to the case...other history

- Gastrointestinal
  - Poor feeding and hypotonia
  - G-tube placed
  - GERD (gastroesophageal reflux disease)

- Frequent infections
  - Bronchitis, croup, sinus infections
  - Recurrent ear infections (9x's/year)
    - PE tubes
Immune (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

- 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 titers for adequate vaccine response

Endocrine

• Endocrine
  – Hypoparathyroidism (25%)
    • Low calcium levels (hypocalcemia)
      – Seizures
    – Hypothyroid
    – Short stature

• Ionized calcium levels, thyroid levels
• Endocrinology referral if <3rd percentile on growth curves
Recommendations

• Routine medical surveillance (see summary slide at end)
• Classroom accommodations and medication for
  – ADHD: stimulant (*cardiac SE)
  – ADHD and anxiety: Strattera
• Occupational therapy evaluation
• Social skills group
Case 2: Late Diagnosis

• Concerning constellation of ongoing medical problems in the first 4 years of life
  – Difficulty Breastfeeding
  – Bottle fed with regular nipple, no nasal regurgitation
  – Dysphagia, poor weight gain, GERD
  – Speech delay-ST at 27 months of age
  – Hypotonia- ongoing PT
  – Eczema-severe in infancy, morphea
Hospitalization, Age 3

- Leg pain followed by adenopathy, epistaxis, bruising, gingival bleeding, hepatomegaly, fever
- Anemia, thrombocytopenia (10k)
- Admitted and leukemia ruled out but….
  - Significant thrombocytopenia, required transfusion
  - Bone marrow normal, but megakaryocytosis
- Positive CMV titers
- Consistent with CMV, but healthy 3 year olds……
- HIV, Immunoglobulin normal, no further work-up
Platelet Problems in 22q11.2 DS

- ITP: incidence about 4%
  - 200 times more common than GP
- Other cytopenias, Evan’s syndrome
- Bernard Soulier Syndrome
  - Macrothrombocytopenia
  - Functional problem: binding site for VWF
  - Platelet count usually normal
  - The GPIBB gene is in the typically deleted region of 22q11, haplo-insufficiency of GPIBB

Lawrence, 2003
Autoimmunity in 22q11.2 DS

- Autoimmune disease in about 10%
  - Idiopathic Thrombocytopenic Purpura
  - Juvenile Rheumatoid Arthritis
  - Celiac disease
  - Raynaud’s phenomenon
  - Autoimmune thyroiditis

(Gennery, 2002)
Mechanism of Autoimmunity

- Autoimmunity occurs when self, non-self recognition is impaired and immune mediated damage to self occurs.
- Self-antigen recognition develops in the thymus during “thymic education”
- Strongly self-reactive cells undergo negative selection and are deleted in the thymus
- Abnormal thymus results in escape of self-reactive T-cells which would normally be deleted.  
  (Tooke, 2007)
By age 10

- Constipation, weight loss and hematochezia: requiring EGD, colonoscopy
- GI and Hematology consults
  - Work up for bleeding disorder again unremarkable
    - CBC, Coags, VWf, hemophillia w/u all negative
  - Dental problems, caries, crowding
  - Pes planus: requiring orthotics
  - 3 urinary tract infections: no imaging
  - Allergic rhinitis and recurrent ear infections
Something a bit more familiar

- Sensory difficulties, especially auditory
- Looses track of time
- Anxious, nervous when kids are mean and stays in class at recess, recently asked to see counselor
- Sleep problems became more significant, daytime somnolence more obvious
- Hard worker, “good girl”
Case 2: Final clue

- Obstructive sleep apnea confirmed by multiple sleep studies, requiring surgery at age 10
- New onset hypernasal speech after T&A
- Genetics consult for VPI
- FISH for 22q11.2 DS
Lovely Girl

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Other surveillance

- **Musculoskeletal**
  - Cervical spine series (5-view) after 4 years
  - Monitoring for scoliosis
- **Ophthalmologic**
  - Yearly exams with dilation
- **Renal**
  - Abdominal ultrasound for structural abnormalities
- **Dental**
  - Yearly exams
Other surveillance

- Developmental Delays
  - Motor delays
  - Speech and language delays
  - Learning disabilities
  - Social immaturity
Summary of Recommendations

- 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

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Summary

• There is a characteristic physical phenotype
• 22q11.2DS affects many organ systems (heart, immune, endocrine, ENT, GI)
• Infants are usually identified because of heart or feeding/palate problems
• Older children often present with learning or mental health issues
References