Tiny Pieces Matter: Caring for Children and Adolescents with DiGeorge Syndrome

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Speaker Introduction

- Dr. Teresa Whited is a certified pediatric primary care nurse practitioner who has practiced for more than 15 years in primary care, pediatric cardiology and complex health care settings. Dr. Whited completed her BSN and MS at the University of Oklahoma and her DNP at Texas Christian University. She is interim associate dean of academic programs and director of the MNSc program for UAMS College of Nursing. She has a strong passion for educating future and current nurse practitioners, legislative issues and caring for all children but especially the most vulnerable like those with complex healthcare needs.

Disclosures

Teresa Whited receives speaker compensation for the Pediatric Primary Care Review Course from NAPNAP.

No off label drugs will be discussed during this presentation.

Learning Objectives

- Integrate the key components in caring for children with DiGeorge Syndrome and ways to maximize their potential.
- Identify the latest recommendations related to DiGeorge Syndrome.
- Incorporate the nurse practitioner’s role in caring for children and adolescents with DiGeorge Syndrome.

What is 22q11.2 deletion syndrome (22q11.2DS)?

- Also known as:
  - DiGeorge Syndrome
  - Velocardiofacial Syndrome
  - Conotruncal anomaly faces syndrome
  - A compilation of disorders associated with a specific microdeletion on 22q11.2

History:

- First identified by Angelo DiGeorge-1965
  - Endocrinologist-studying patients with thymic aplasia and congenital hypoparathyroidism
- Microdeletion syndrome
  - Affects neural crest cell migration in the 3rd and 4th pharyngeal pouches
  - Leading to thymic hypoplasia
  - Hypoplasia of the parathyroid glands
  - Outflow tract anomalies of the cono-truncal region of the heart
  - Facial abnormalities
  - Many others.
Epidemiology

- The most common microdeletion syndrome
- Affects 1-2,000 births
- Affects 1-1,000 unselected fetuses
- ~150,000 Americans
  - ~35,000 children and Adolescents
  - Increased number of children advancing to adulthood

Epidemiology

- Affects all sexes, races and ethnic groups
- Slightly more often maternal in origin
- Non-white patients may be diagnosed less often or later
- Average Cost: $727,178
- Prenatal diagnosis: $2,599,955
- Cardiac or low T cell diagnosis: $1,382,222
- Less than 5% mortality in childhood
- Manage as chronic medical condition
- Premature mortality in adulthood
- Median age of death 40-50 years of age

Genetics

- Most deletions are De-NoVo (90-95%)
- Risk factors:
  - Maternal Diabetes
  - Retinoic Acid Exposure
  - First degree relative
    - 10% inherit from affected parent
    - 50% risk of transmitting to offspring

Genetics

- Deletions related to:
  - Underlying architecture of the 22q11 region
  - Multiple repetitive sequences
  - Mediate misalignment and non-allelic homologous recombination
  - Susceptible to translocations, inversions, deletions, and duplications
- Most patients (75-80%) have the same large deletion
  - 50 genes and 7 micro-RNAs affected
  - Remainder smaller deletions but does not equate to milder symptoms

Genetics

- Not captured on karyotype-
  Normal Karyotype

Genetics-FISH

- Fish for microdeletion (Fluorescent probes for specific chromosomal regions)
- Fluorescence in situ hybridization
- Limits:
  - Must have clinical suspicion to identify the correct region to FISH
  - May miss deletions and duplications
Genetics-Microarrays

- Chromosomal microarrays with dense genome wide coverage
- Allows identification of smaller chromosomal deletions and duplications
- Can capture submicroscopic deletions/duplications

Diagnosis

- Can be diagnosed in-utero
  - 1st trimester-Chorionic villus sampling
  - 2nd trimester-Amniocentesis
- Most diagnosed infancy with clinical suspicion in-utero:
  - Cardiac defects
  - Cleft lip/palate
  - Polyhydramnios
  - Clubfoot
  - Renal anomalies
  - Diaphragmatic hernia
  - Spina bifida
  - Cleidocranial dysostosis
- Some detected secondary to abnormal newborn screening
  - SCID-low T cell

Variable Phenotype

- While the micro-deletion is typically the same-> phenotype may be very different
- Phenotype expression varies widely in individuals
- High clinical suspicion:
  - Palatal anomalies
  - Dysmorphic craniofacial features
  - Laryngotracheoesophageal abnormalities
  - Speech, language and cognitive delays
  - Cardiac defects-conotruncal
  - Poor development of thymus
  - Hypoparathyroidism

Core Clinical Phenotype

- Conotruncal cardiac anomaly
  - Truncus arteriosus, TOF, Interrupted aortic arch (Type B)
  - Aplasia/hypoplasia of the thymus and parathyroid glands
  - Functional T cell abnormalities
  - Hypocalcemia

Core Clinical Phenotype

<table>
<thead>
<tr>
<th>Dysmorphic Facial Features:</th>
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<tbody>
<tr>
<td>Long Face</td>
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<tr>
<td>Malar Flattening</td>
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<tr>
<td>Hypertelorism</td>
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<tr>
<td>Short Palpebral Fissures</td>
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<tr>
<td>Wide and Prominent nasal root</td>
</tr>
<tr>
<td>Wide Nasal Bridge</td>
</tr>
<tr>
<td>Bulbous Nasal Tip</td>
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<tr>
<td>Micrognathia</td>
</tr>
<tr>
<td>Small nose</td>
</tr>
<tr>
<td>Small low-set ears</td>
</tr>
<tr>
<td>Hooded Eyelids</td>
</tr>
<tr>
<td>Asymmetric crying faces</td>
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<tr>
<td>Thick overfolded helices</td>
</tr>
</tbody>
</table>

Other features:

- Palate defects
- Vascular rings
- Feeding and swallowing dysfunction
- GERD
- Renal agenesis
- Hypospadias
- Clubfoot
- Thyroid dysfunction
- FTT
- Growth Hormone deficiency
- Hypotonia
- Etc.
Guidelines for Managing Patients with 22q11.2DS

- Bassett et al. (2011). Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome
- Fung et al. (2015). Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome

At Diagnosis:

- Work up:
  - Ionized calcium
  - Parathyroid hormone
  - TSH
  - CBC with Diff
  - Immunologic Evaluation
  - Ophthalmology
  - Palate evaluation
  - Spinal Evaluation
  - Audiology
  - Renal Ultrasound
  - EKG
  - Echocardiogram
  - Deletion studies of parents with genetic counseling, family history evaluation

Infancy Workup

- Ionized Calcium
- Parathyroid hormone
- Immunologic Evaluation
- Ophthalmology
- Palate Evaluation
- Audiometry
- Development
- Socialization/functioning of family

Preschool Work up

- Same as infant +
  - Spinal evaluation
  - Dental evaluation
  - School Performance
  - Behavioral/Psychiatric Evaluation

School age Work up

- Ionized Calcium
- Parathyroid hormone
- TSH
- Dental Evaluation
- School performance
- Socialization/Functioning
- Psychiatric/Behavioral

Adolescence Workup

- Same as school age +
  - Scoliosis exam
  - Genetic counseling
  - Gynecologic/Contraceptive Services
Infancy Primary Issues

• Feeding difficulties
• Frequent infections
• Cardiac issues
• Motor and Speech problems

Pre-School/School-Age Child Primary Issues

• Global developmental delays
• Frequent monitoring of IQ and learning disabilities
• May begin to have psychiatric/behavioral issues
• Can have hearing and vision issues

Care of the Infant to Child-Multidisciplinary Care

Component: Management/Evaluation:

Genetics
Fish/Microarray, Diagnosis with genetic counseling

Cardiovascular
Echocardiogram, 40% requiring surgical correction (rarely blood products), increased risk for vascular ring, dilated aortic root, arrhythmias.

Pala/tar related issues
Surgical correction of clefts, TE fistula, esophageal atresia, sensorineural/conductive hearing loss.

Immune related
Recurent infections, T-cells low or impaired function, increased risk for autoimmune disease, poor response to vaccines, high risk for recurrent respiratory infections.

Influenza vacines, Immunology, ENT, Allergist, Rheumatology, Thymus transplant

Endocrine
Hypoparathyroidism (60%+), Thyroxin (hypothyroidism), obesity, growth hormone deficiency. Vitamin D and Calcium supplementation, growth hormone, dietary counseling, Endocrine follow up

GI
GERD, Diaphragm, Constipation, Cholelithiasis, Herxheimer: Less common: Infantile anemia, malnutrition, Henchsprung’s, diaphragmatic hernia
GI follow up, speech therapy, May need G-tube and Nissen

GU
Multiple kidney anomalies, urinary tract anomalies
Need ultrasound/VCGU, may need kidney transplant Follow-up by Nephrology, Urology, Gynecology

Growth and Development
FTT, motor/speech delays (90%+), Learning disabilities (80%+), 90% of cases IQ low to normal (IQ 70-75 average), IQ can decrease over time, Early intervention
IEP, frequent cognitive re-evaluation

Neuropsychiatric Disorders
ADHD, Autism Spectrum Disorders, Anxiety/Depressive disorders, Schizophrenia/psychotic disorders
Evaluation by Developmental pediatrics and Psychiatry/Therapist

Dental
Enamel Hypoplasia/chronic caries, Regular dental evaluation

Dermatology
Atopic, seborrhea, severe acne/Dermatologist

Care of the Infant to Child-Multidisciplinary Care

Component: Management/Evaluation:

Ophthalmology
Strabismus, refractive errors, tortuosity retinal vessels, colobomas, ptosis, sclerocornea. Needs regular eye exams by Ophthalmology

MSK
Scoliosis, spinal cord anomalies, thoracic butterfly vertebrae, sphenioptosis, metyosynostosis, polydactyly
Orthopedics, neurology, OT

Neu/CNS
Thrombocytopenia, splenomegaly, increased risk for leukemia, lymphoma, hepatoblastoma

Neurology
Seizures/Epilepsy (5-40%), neural tube defects, encephalab abnormalities. Follow up by neurology

Neuropsychiatric Disorders
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Dermatology
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Adolescents/Adult Primary Issues

- Ongoing care of anomalies—Cardiac, Palatal, Immunology, Hypoparathyroidism
  - Increased risk for psychiatric disorders
  - Anxiety and Depression
  - Cognitive functioning
  - Borderline/mild intellectual disability
  - Accommodations in school and workplace

- Most common group of later onset conditions—Neuropsychiatric
  - Increased risk for psychiatric disorders
  - 20 fold increased risk for schizophrenia
  - Anxiety and Depression

- Cognitive functioning
  - Borderline/mild intellectual disability
  - Accommodations in school and workplace

- Financial/Competency concerns
  - May need additional assistance from families into adulthood
  - Special education on money management and other ADLs

Long term issues:

- Need follow up by multi-disciplinary team
  - Adult providers not always equipped to deal with ongoing issues of congenital nature
  - Aging parents/caregivers
  - Transition should begin early and often
    - AAP recommends at least by 12-13 years of age for children with chronic illness
    - Unknown long term issues
      - Oldest patients are in their 60s so still identifying premature mortality reasons
      - More patients living into adulthood
  - Un-identified patients
  - Coping of families and patients with multi-system disorder
    - Quality of Life Issues

New research:

- Ongoing Genetic research:
  - Genetic drivers of kidney defects
  - Prevalence of microdeletions and microduplications
- Management Research:
  - Best practices for management of disorder
  - Psychiatric disorders
  - Autism spectrum disorders
- Family/Coping Research
  -Sibling, family functioning

References:

References


