Updates on the care and genetics of children with CHARGE Syndrome

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Objectives

• Recognize the features of CHARGE syndrome

• Identify the medical concerns in CHARGE syndrome
CHARGE syndrome

Coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities, and ear anomalies/deafness

Occurs in one in 10,000 births
How does a parent describe CHARGE syndrome?
Imagine for a moment, a baseball cap on your head pulled all the way over your eyes, so that your only vision is your side vision. Imagine for a minute hearing the sounds around you at a whisper so that you have to strain to hear every word. Imagine every morsel you ingest being declared a feat because it requires the concentration of every brain cell. Now imagine living like this for the rest of your life. If that does not define a hero then what does?
Clinical features of children with CHARGE syndrome
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Manifestations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular coloboma</strong></td>
<td>Coloboma of the iris, retina, choroid, disc; microphthalmos</td>
<td>80 – 90%</td>
</tr>
<tr>
<td><strong>Choanal atresia or stenosis</strong></td>
<td>Unilateral/bilateral: bony/membranous, atresia/stenosis</td>
<td>50 – 60%</td>
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<tr>
<td><strong>Cranial nerve dysfunction or anomaly</strong></td>
<td>I: Hyposmia or anosmia</td>
<td>Frequent</td>
</tr>
<tr>
<td></td>
<td>VII: Facial palsy (unilateral or bilateral)</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>VIII: Hypoplasia of auditory nerve</td>
<td>Frequent</td>
</tr>
<tr>
<td></td>
<td>IX/X: Swallowing problems with aspiration</td>
<td>70 - 90%</td>
</tr>
<tr>
<td><strong>Characteristic CHARGE syndrome ear</strong></td>
<td>Outer ear: Short, wide ear with little or no lobe, often protrude, usually asymmetric</td>
<td>90-100%</td>
</tr>
<tr>
<td></td>
<td>Middle ear: Ossicular malformations</td>
<td></td>
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<tr>
<td></td>
<td>Mondini defect of the cochlea</td>
<td></td>
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<tr>
<td></td>
<td>Temporal bone abnormalities; absent or hypoplastic semicircular canals</td>
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</table>
# Blake’s Minor Diagnostic Criteria

<table>
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<tr>
<th>Characteristics</th>
<th>Manifestations</th>
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</thead>
<tbody>
<tr>
<td>Genital hypoplasia</td>
<td>Males: Micropenis, cryptorchidism; Females: Hypoplastic labia; Both: Delayed puberty</td>
<td>50-60%</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>Delayed milestones, hypotonia</td>
<td>≤100%</td>
</tr>
<tr>
<td>Cardiovascular malformation</td>
<td>Including conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies</td>
<td>75-85%</td>
</tr>
<tr>
<td>Growth deficiency</td>
<td>Short stature, usually postnatal with or without growth hormone deficiency</td>
<td>70-80%</td>
</tr>
<tr>
<td>Orofacial cleft</td>
<td>Cleft lip and/or palate</td>
<td>15-20%</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>TE defects of all types</td>
<td>15-20%</td>
</tr>
<tr>
<td>Distinctive facial features</td>
<td>Square face with broad prominent forehead, prominent nasal bridge and columella, flat midface</td>
<td>70-80%</td>
</tr>
</tbody>
</table>
Diagnosis

• **Definite CHARGE syndrome.** Individuals with all four major characteristics or three major and three minor characteristics.

• **Probable/Possible CHARGE syndrome.** Individuals with one or two major characteristics and several minor characteristics.
• We have about 20,000 plus genes
• Human genome has about 3 billion letters
• Only 1.5% of that are functional players
CHD7 gene

- Vissers et al. (2004) reported mutations in CHD7 gene in individuals with CHARGE syndrome

- CHD genes play an important role in regulating early embryonic development and cell cycle control by affecting chromatin structure and gene expression
CHD7 mutation (Misspelling)

• The majority of children with CHARGE syndrome have a mutation in the CHD7 gene

• In the majority of individuals, the mutation is not inherited from a parent

• The empiric risk of having another child with CHARGE syndrome is about 1%-2% when parents are unaffected

• If a parent is affected, then the risk of having another child with CHARGE syndrome is 50%
What does it mean when \textit{CHD7} sequencing is normal in \textit{CHARGE} diagnosis?
There can be DELETION of the CHD7 gene rather than misspelling!
The entire \textit{CHD7} gene is missing, along with other genes
Chromosomal microarray analysis in a 2-week old infant

Deletion of CHD7 on chromosome 8

Heart defect
Cleft palate
Small right kidney
Hearing loss
Inner ear abnormalities
No colobomas
Familial cases?

• There are rare familial cases in which a parent or a sibling may also be affected

• There is significant intrafamilial variability associated with CHD7 mutations
CHA 19

VSD, ASD, PDA
Coloboma
Choanal atresia
TE fistula

TOF
Coloboma
Cleft lip/palate

R1069X R1069X
Management of children with CHARGE syndrome

• **Airway** can be compromised due to many reasons:
  – Choanal atresia, TE fistula, aspiration pneumonias, and tracheomalacia (about 15%-60% of individuals with CHARGE syndrome require tracheostomy)

• **Heart defects**: managed as in any individual with a congenital heart defect

• **Choanal atresia**: Multiple surgeries for often required for correction
Management of children with CHARGE syndrome

- **Colobomas:** Visual field defects can result from retinal coloboma and central visual defects resulting from optic nerve involvement. Sign language may need to be presented in child's lower visual field.

- **Hearing loss** should be assumed until proven otherwise. Hearing aids and hearing habilitation (which may include sign language) should be started as soon as hearing loss is documented. Cochlear implants have been successful in a subset of children.

- **Deaf-blind service referral**

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Management of children with CHARGE syndrome

• **Feeding/swallowing dysfunction.** A multidisciplinary approach is needed with specialists in speech-language pathology, occupational therapy, and nutrition

• For children with G-tube, oral stimulation needs to be maintained to reduce future oral sensitivity/aversion
Management of children with CHARGE syndrome

• **Renal:** Kidney evaluation is recommended in all children with CHARGE syndrome

• **Endocrinology:** Referral for decelerating linear growth; GH treatment may be needed; hypogonadotrophic hypogonadism
Conclusions

• CHARGE syndrome is a recognizable genetic condition characterized by a specific combination of congenital anomalies

• The majority of children with CHARGE syndrome have a \textit{de novo} mutation in the \textit{CHD7} gene

• A multidisciplinary team is required for management of complex problems in children with CHARGE syndrome
We are now approaching ONE MILLION DOLLARS of Foundation-supported research since the inception of our Pilot Research Grant Program in 2012.

A better world for people with CHARGE syndrome.
The CHARGE Syndrome Foundation champions the lifelong potential of people with CHARGE syndrome through outreach, education and research.