Dual sensory impairment and deafblindness in a life perspective

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50% of all hearing impairment requiring treatment is hereditary
List of relevant literature at your disposal
Causes of hearing impairment

- Congenital hearing impairment
  - Unknown etiology
  - Environmental
    - CMV-infections
    - Congenital rubella
    - Ototoxicity
    - Prematurity
    - Neonatal asphyxia
    - Others
  - Genetic
    - Syndromic
      - 80%
        - Autosomal recessive
        - DFNB1-67
        - DFNB1-85
    - Nonsyndromic
      - 67%
        - Autosomal dominant
        - DFNA1-54
        - DFNA1-60
        - X-linked
        - DFN2-4+6
        - Mitochondrial
          - mt+mutation type and position
  - Other
    - Other ways of classifying HI
      - >450 conditions with HI as prominent manifestation

Other ways of classifying HI

Only connexin 26 (GJB2) is so frequent that we do routine sequencing of this small gene
Implications of a diagnosis

• Distinguish between genetic/non-genetic cause (CRS vs CHARGE, chromosomal abnormality)
• Be tuned for early assessment of associated medical problems (WFS1 related disease/Usher syndrome)
• Be prepared for progressive/stable condition, and guide choice of treatment (CI or not) and method of communication (CHARGE/Usher)
• The parents always will ask: WHY OUR CHILD??
Rubella
Congenital Rubella syndrome (CRS)

- Coined the awareness towards congenital deafblindness in general
- Has almost disappeared as etiology
- Miscarriage, hearing impairment, cataract, heart malformations, mental delay
- Late -manifestations: diabetes mellitus, hypertension, neurological and psycho-social problems, endocrine abnormalities, early menopause, osteoporosis, progressive rubella panencephalitis(learning disability, ataxia, cerebral palsy, psychosis)
CRS-Dammeyer, 2010

<table>
<thead>
<tr>
<th>Condition</th>
<th>CRS [n (%)]</th>
<th>Not CRS [n (%)]</th>
<th>Difference (Fisher’s test) [P (2-tailed)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2 (6)</td>
<td>1 (1)</td>
<td>0.224</td>
</tr>
<tr>
<td>Thyroid diseases</td>
<td>0 (0)</td>
<td>6 (7)</td>
<td>0.182</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>6 (17)</td>
<td>31 (38)</td>
<td>0.135</td>
</tr>
<tr>
<td>Vascular diseases</td>
<td>3 (9)</td>
<td>4 (5)</td>
<td>0.675</td>
</tr>
<tr>
<td>Cardiac problems</td>
<td>6 (17)</td>
<td>6 (7)</td>
<td>0.195</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>0 (0)</td>
<td>12 (15)</td>
<td>0.036</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>6 (17)</td>
<td>27 (33)</td>
<td>0.196</td>
</tr>
<tr>
<td>Ataxia</td>
<td>3 (9)</td>
<td>3 (4)</td>
<td>0.372</td>
</tr>
<tr>
<td>Psychosis</td>
<td>5 (14)</td>
<td>8 (10)</td>
<td>0.753</td>
</tr>
<tr>
<td>OCD (obsessive compulsive disorder)</td>
<td>3 (9)</td>
<td>3 (4)</td>
<td>0.372</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (17)</td>
<td>5 (6)</td>
<td>0.172</td>
</tr>
<tr>
<td>Attacks of anger, crying and anxiety more than one time per week</td>
<td>6 (17)</td>
<td>17 (21)</td>
<td>0.906</td>
</tr>
</tbody>
</table>

Late manifestations of congenital rubella syndrome (CRS) ?
Are they real?

• 123 congenital deafblind adult individuals (evaluated in 2003)
• N= 35 with CRS – average age 41 years
• No evidence for more frequent occurrence of the postulated late-manifestations cp with a group of 82 non-CRS cong deafblind individuals (etiology other or unknown)
• (Dammeyer J et al, 2010)
Rubella? CHARGE?

• Female LC141258:
• Twin sister GC141258 døde 1993
• LC born by a 18-year old woman, serologically verified rubella during early pregnancy. Termination of pregnancy was refused
• Female twins born with severe malformations
• CHD7-sequencing and MLPA analysis of CDH7 were normal.
• Conclusion: Congenital Rubella Syndrome.
Wolfram syndrome and \textit{WFS1} related disorders

- \textbf{Wolfram syndrome (WS)}: Diabetes mellitus and Optic atrophy- age of onset < age 14 years and autosomal recessive.
- 1998: \textit{WFS1} mutations cause WS
- But: \textit{WFS1} mutations may cause autosomal dominantly inherited OA+HI, AR inherited OA+HI without diabetes, and AD inherited OA+HI? Neurological + psychiatric disease
**WFS1-p.A684V- frequent cause of AD OA+SNHL**

15 unrelated families with AD OA+SNHL: **WFS1** and **OPA1**:
8 with **WFS1** and 2 with **OPA1**

*Samuelson, 1940*

**WFS1** p.A684V in six AD families with OA+SNHL

*Rendtorff ND et al, under review, 2010*
OA+ auditory neuropathy+ gait abn associated with de novo OPA1- mutation: p.G439V/N

MR700228: 40-year-old Swedish female
De-novo OPA1 mutation associated with OA+auditory neuropathy

• At 7 y: SNHI 40-60 dB HL at all frequencies, progressive auditory neuropathy
• At 8 y: OA- now legally blind
• At 28 y: polyneuropathy, ataxia, liver dysfunction
• Cerebral MRI: N
• Muscle biopsy not analyzed
• 4-year-old daughter not examined

OPA1: exon 14: c.1316G>T: p.G439V/N
Exon 14: c.1443+23G>A: IVS14+23G>A

Similar to: Liguori M et al, 2008/ Amati-Bonneau P et al, 2008:
p.G439V/N in father/daughter: OA, SNHL, ataxia, cerebellar atrophy, abnormal mitochondria, RRFs, elevated se-lactate-R445H and S545R also associated with auditory neuropathy
Multidisciplinary 360º evaluation of pts with dual sensory impairment in DK
# Overview of Usher genes—extreme genetic heterogeneity and very large genes

Table 1. Overview of known Usher syndrome genes and loci

<table>
<thead>
<tr>
<th>USH type</th>
<th>Locus</th>
<th>Protein</th>
<th>Gene</th>
<th>Exons</th>
<th>Proportion</th>
<th>Clinical</th>
<th>APEX vs 5.0</th>
<th>APEX vs 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1B</td>
<td>11q13.5</td>
<td>Myosin VIIa</td>
<td>MYO7A</td>
<td>49</td>
<td>30-50%</td>
<td>DFNB2;DFNA11</td>
<td>136</td>
<td>179</td>
</tr>
<tr>
<td>1C</td>
<td>11p15.1</td>
<td>Harmonin</td>
<td>USH1C</td>
<td>28</td>
<td>7-12%</td>
<td>DFNB18</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>1D</td>
<td>10q22.1</td>
<td>Cadherin 23</td>
<td>CDH23</td>
<td>69</td>
<td>10-35%</td>
<td>DFNB12</td>
<td>58</td>
<td>91</td>
</tr>
<tr>
<td>1E</td>
<td>21q21</td>
<td>Unknown</td>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1F</td>
<td>10q21.1</td>
<td>Protocadherin 15</td>
<td>PCDH15</td>
<td>35</td>
<td>11%?</td>
<td>DFNB23</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>1G</td>
<td>17q25.1</td>
<td>SANS</td>
<td>USH1G</td>
<td>3</td>
<td>7%?</td>
<td>-</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>1H</td>
<td>15q22</td>
<td>Unknown</td>
<td>Unknown</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2A</td>
<td>1q41</td>
<td>Usherin</td>
<td>USH2A</td>
<td>72</td>
<td>85%</td>
<td>arRP</td>
<td>191</td>
<td>265</td>
</tr>
<tr>
<td>2C</td>
<td>5q14.3</td>
<td>VLGR1</td>
<td>GRP98 (VLGR1)</td>
<td>90</td>
<td>?</td>
<td>-</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>2D</td>
<td>9q32</td>
<td>Whirlin</td>
<td>WHRN</td>
<td>12</td>
<td>&lt;1%</td>
<td>DFNB31</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>3A</td>
<td>3q25.1</td>
<td>Clarin-1</td>
<td>USH3A</td>
<td>4</td>
<td>1-6%</td>
<td>-</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>429</td>
<td>612</td>
</tr>
</tbody>
</table>
Usher syndrome- clinical diagnosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Hearing impairment</th>
<th>Vestibular function</th>
<th>Loss of night vision</th>
<th>Loss of visual field</th>
<th>Relative frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>USH1 (5 large genes)</td>
<td>Stable profound congenital</td>
<td>Absent</td>
<td>&lt; age 10</td>
<td>&lt; Puberty (age 10)</td>
<td>33-44 %</td>
</tr>
<tr>
<td>USH2 (3 large genes)</td>
<td>Stable or slowly progressive- mild-severe-affects high frequencies</td>
<td>Normal</td>
<td>at puberty (In general)</td>
<td>Variable (age 25)</td>
<td>56-67 %</td>
</tr>
<tr>
<td>USH3 (1 gene)</td>
<td>Progressive</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>2-42 %</td>
</tr>
</tbody>
</table>

Concern that CI treated patients will not be strictly followed up with ophthalmological examinations to discover RP- They ”disappear in mainstream school- and spread around in many schools

Regular eye exams by Usher competent ophthalmologists!!!!!
CDH23 mutations: Usher or "only" cong. deafness

Iranian family living in DK/Norway
C-H-A-R-G-E Association

- C: Coloboma
- H: Heart malformation
- A: Atresia Choanae
- R: Retarded growth and development
- G: Genital-urinvejsabnормитeter
- E: Ear anomaly and/or hearing impairment

(Pagon et al, 1981)
CHARGE: from clinical description to so much more

- 1979/81: Hall/Pagon - Diagnostic criteria are coined and revised
- 2004: one patient: with chrom 8 abn: the CHD7 gene is identified
- 2005-2006: > 200 pts mutations analysed

- The unusual presentations are found: familial cases, Kallman’s syndrome associated, demonstration of de-novo mutations, verification of germ-line mosaicism.

- % of pts with identified CHD7 mutations is very high (65-70%).
- This rate decreases along with atypical clinical patients are investigated.
- More CHARGE genes (type 1- type 2 etc)? How many?
- Frequency: 1: 10.000
- Second most frequent etiology among Danish deafblind children
- 20% 20 out of 67 children

(Dammeyer J, Int J Audiol, 2010;49: 76-82)
Clinical characteristics

Meta-analysis from 25 reports: 254 pts with CDH7 mutations, and 125 were negative

<table>
<thead>
<tr>
<th>Syndrome feature</th>
<th>CHD7 Mutation Positive</th>
<th>CHD7 Mutation Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloboma</td>
<td>190/253 (75%)</td>
<td>74/114 (65%)</td>
</tr>
<tr>
<td>Heart malformations</td>
<td>193/250 (77%)</td>
<td>86/120 (72%)</td>
</tr>
<tr>
<td>Cheanal atresia</td>
<td>95/247 (38%)</td>
<td>52/110 (47%)</td>
</tr>
<tr>
<td>Retarded growth</td>
<td>101/141 (72%)</td>
<td>31/33 (94%)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>107/141 (76%)</td>
<td>44/47 (94%)</td>
</tr>
<tr>
<td>Genital hypoplasia</td>
<td>116/187 (62%)</td>
<td>46/66 (70%)</td>
</tr>
<tr>
<td>Ear abnormalities including deafness</td>
<td>198/223 (89%)</td>
<td>83/103 (86%)</td>
</tr>
<tr>
<td>Temporal bone anomalies</td>
<td>94/96 (98%)</td>
<td>21/28 (75%)</td>
</tr>
<tr>
<td>External ear malformations</td>
<td>214/235 (91%)</td>
<td>46/51 (90%)</td>
</tr>
<tr>
<td>Facial nerve palsy</td>
<td>72/187 (39%)</td>
<td>19/102 (19%)</td>
</tr>
<tr>
<td>Cleft lip and/or Cleft palate</td>
<td>79/242 (33%)</td>
<td>34/119 (29%)</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>35/185 (19%)</td>
<td>8/45 (18%)</td>
</tr>
<tr>
<td>Urogenital abnormalities</td>
<td>86/142 (61%)</td>
<td>38/55 (69%)</td>
</tr>
</tbody>
</table>

Significant features as identified by Chi-square test are in bold.

CHARGE-familial case-Fam A

Diagnostic criteria:

Major: 1/3 1/3 2/3
Minor: 2/5 5/5 3/5

CHARGE-Familiær

Fam A:
• III:2: læbe-ganespalte, øsophagus atresi+ fistel, complex hjertefeil, og ribbensanomalier, lærevansker, ingen anosmi, kortvokst

• III:3: retina colobom, ingen hjertefeil, gik 21 mdr gl,

• II:2: asymptomatisk vestibulær abnormiteter, retina colobom-diagnosticeret efter børnenes diagnose, balanceproblemer som barn, normal mentalt. (Mosaik i kønseller for mutationen?)

• CHD7 mutation: c.2501C>T; p.S834F
  *(Delahaye A et al, 2007)*
Rubella? CHARGE?

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- Twin sister GC141258 døde 1993
- LC born by a 18-year old woman, serologically verified rubella during early pregnancy. Termination of pregnancy was refused
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CHARGE syndrome- old pt

- 56-year old cong.deaf-blind female- protected living conditions-
- An older brother died perinatally with similar malformations
- Clinically: HA from age 17 years: conductive/sensorineural HI, right ear deaf
- Eyes: left blind, glassesbriller from age 42 years, incipient cataract, scars in retina, no colobomas
- Never mentruated, hyperthyroidism, adipose
- Broadbased gait, poor balance
- Heart malformation
- Unilateral facial paresis
- Emotionally fragile
- Peculiar behaviour
- CHD7-sequencing: c.7252C>T: p.R2418X/N
- CT scan of temporal bones: Mondini dysplasia, complete agenesis of semicircular canals, small orbital coloboma
Atypical CHARGE- late diagnosis

- MH 090801, 1. child- born to Turkish consanguineous parents
- In 2002: severe HI diagnosed- sign language
- Agenesis of acoustic nerve unilaterally, bilat agenesis of semicircular canals
- CI operation had to be refused
- No coloboma, or choanal atresia
- Major problems with coordination of vision due to paresis of the abducens nerve
- Hardly any feeding problems, good olfactory sense
- Short stature (6,5 år gl: 103 cm)
- Aud afd, neuropaediatrician, dept for growth and reproduction, eye dept: none raised the CHARGE suspicion
- CHARGE diagnosis obtained by deafblind coordinator and geneticist in 2007
CHARGE: prototype of congenital deafblindness

- Relative frequent (1: 8,000?)
- Serious neonatal course in some children
- Highly variable degree of visual/hearing and other impairments
- Partially invisible malformations (coloboma, agenesis of semicircular canals)
- Usually minor recurrence risk
- Multidisciplinary /functional/psychological thorough follow up: Motivates advanced examinations (CT scan, eye exam etc)
Diagnostisk algoritme for CHARGE

Clinical diagnosis of CHARGE Syndrome

CHD7 mutations analysis by direct sequencing

Pathogenic mutation identified

Yes

No

Chromosome analysis

Chromosome anomaly

Yes

No

FISH on CHD7 locus (deletion)*

Yes

No

CHD7 Exonic deletion*

Molecular diagnosis of CHARGE syndrome

Diagnosis rests on clinical features only

Chromosomal phenocopy

Array CGH

Ankesi af semicirkulære kanaler: 9/15 havde CHARGE syndrom

Anbefaling: us af begge forældre
N fund udelukker ikke mosaiktilstand i æg/sædceller.
Derfor:
Prænatal us af senere børn

EJHG 2007; 15: 389-399
Chromosome 13q deletion

- EM081099: del13(q32.3-q34)
- 7-year-old, severe MR, low FV, corpus callosum agenesis, microcephaly, trigonocephaly, Developmental anomaly of brain cortex, deep set eyes, hypertelorism, epicanthal fold, cortical visual problems(?), strabismus, dysplastic auricles, hearing impairment, vaulted palate, proximally misplaced thumbs
Kromosom 13q deletion

Dysmorphic face

Size and localization of the deletion via array CGH

Multidisciplinarity in hereditary hearing impairment—examining the patient

- Family history
- Clinical photos
- CT scan, Eye exam, Renal US, Array CGH
- Geography and ethnicity
- Audiological profile
- GJB2 and other genes
- Bioinformatics
- Genetic counselling
- Hearing impairment
Multiple approaches - in order to identify disease mutations

- Histology
- Micro arrays
- Functional genomics
- Audiology
- Genetic epidemiology
- Linkage analyses