2nd Annual
CHARGE Syndrome
Professional Day

July 28, 2011
Rosen Shingle Creek
Orlando, Florida

PROFESSIONAL DAY PROGRAM AND HANDOUTS

The CHARGE Syndrome Foundation, Inc.
www.chargesyndrome.org
<table>
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<tr>
<th>Time</th>
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<tr>
<td>8:00 - 9:00</td>
<td>Professional Day Registration at registration desk in Transportation Lobby (between hotel lobby and conference center)</td>
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<tr>
<td>8:00 - 9:00</td>
<td>Continental Breakfast in Wekiwa # 6</td>
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<tr>
<td>8:00 - 9:00</td>
<td>Poster Set up in Wekiwa # 5</td>
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<tr>
<td>9:00 - 9:15</td>
<td>Welcome and Opening Remarks in Wekiwa 3&amp;4</td>
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<tr>
<td>9:15 - 9:40</td>
<td>Molecular Studies to uncover the Cellular Functions of CHD7 – Peter Scacheri</td>
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<td>9:40 - 10:05</td>
<td>Phenotypes in Drosophila Model of CHARGE Syndrome – Daniel Marenda</td>
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<td>10:05 - 10:30</td>
<td>Advances in Understanding CHD7 through Use of Genetically Engineered Mice – Donna Martin, E. Hurd, W. Layman, Y. Raphael</td>
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<td>10:30 - 11:00</td>
<td>Break</td>
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<td>11:00 – 11:25</td>
<td>CHD7 Mutations &amp; CHARGE Syndrome: Clinical &amp; Diagnostic Implications of an Expanding Phenotype – Conny van Ravenswaaij-Arts, J. Bergman, N. Janssen, L. Hoesfroot, M. Jongmans, R. Hofstra</td>
</tr>
<tr>
<td>11:25 – 11:50</td>
<td>National Cochlear Implantation Studies with Children Who Experience Deafblindness: Results For Participants With CHARGE Syndrome – Susan Bashinsky</td>
</tr>
<tr>
<td>11:50 – 12:15</td>
<td>The Child’s Voice (Case Study: Interview with a 9 Year old) – Eva Seljestad, Wenche Anderson</td>
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<tr>
<td>12:15 – 1:15</td>
<td>Lunch in Wekiwa #6</td>
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<tr>
<td>1:15 – 2:30</td>
<td>Poster Presentations in Wekiwa # 5</td>
</tr>
<tr>
<td>2:30 – 2:55</td>
<td>Problems with Self-Regulation &amp; Behavior in CHARGE Syndrome – Tim Hartshorne</td>
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<tr>
<td>3:20 – 3:45</td>
<td>Navigating the NIH – Tiina Urv</td>
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<tr>
<td>3:45 – 4:10</td>
<td>Break</td>
</tr>
<tr>
<td>4:10 – 4:35</td>
<td>CHARGE Syndrome: Quality of Life in Adolescence &amp; Adulthood (study) – Nancy Salem Hartshorne, Kim Blake, J MacCuspie, T Nacarato</td>
</tr>
<tr>
<td>4:35 – 5:00</td>
<td>So Many Ways to Have a Conversation – Martha Majors</td>
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<tr>
<td>5:00 – 5:25</td>
<td>The Potential of Diversity – Andrea Scheele, Ursula Horsch</td>
</tr>
<tr>
<td>5:25 – 5:30</td>
<td>Concluding Remarks</td>
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</table>
Molecular Studies to Uncover the Cellular Functions of CHD7.

Thursday, 07/28/11
Platform #1: 9:15-9:40
Wekiwa 3 & 4

Peter C. Scacheri, PhD
Assistant Professor
Department of Genetics
Case Western Reserve University

Presenter Information:

Peter Scacheri graduated with a BS in Biology from Gettysburg College and earned his Ph.D. in Biochemistry and Molecular Genetics from the University of Pittsburgh. His graduate work was focused on the genetics of muscular dystrophy. His postdoctoral fellowship was at the National Human Genome Research Institute at the National Institutes of Health, where he studied a type of cancer that affects the endocrine organs. Dr. Scacheri is currently an Assistant Professor in the Department of Genetics at Case Western Reserve University School of Medicine. The Scacheri lab uses cutting edge genomics to investigate the function of the CHD7 protein and its role in CHARGE syndrome. Dr. Scacheri's research on CHARGE syndrome is supported by an R01 grant awarded from the National Institute of Child Health and Human Development.

Presentation Abstract:

It is known that DNA mutations in the CHD7 gene cause CHARGE syndrome, but how? My lab has been addressing this question by investigating the function of CHD7 in both normal and CHD7 mutant cells from humans, mice, and zebrafish. Our research indicates that CHD7 functions in the cell nucleus to fine-tune the expression of genes that control the development of organs that are affected in CHARGE syndrome. In addition CHD7 activates genes that encode components of the protein manufacturing machinery of all living cells. These findings suggest that the multiple anomalies in CHARGE syndrome are due to the combined effects of altered gene expression and reduced protein synthesis.
Molecular studies to uncover the cellular functions of CHD7.

Peter C. Scacheri, PhD
Department of Genetics
Case Western Reserve University
Cleveland, OH

Outline
• Overview of the cellular functions of CHD7
  – Regulator of genes that orchestrate development
  – Regulator of protein synthesis.
• Zebrafish model of CHARGE syndrome
• Overview of high-throughput sequencing of CHD7 to identify mutations in patient cohorts
• Where we are headed

Mutations in CHD7 (chromodomain helicase DNA-binding protein 7) cause CHARGE syndrome

- Mutations in 58-71% of patients
- Arise spontaneously
- Mostly protein truncation mutations (loss-of-function)
- Haploinsufficiency (one-half the amount of CHD7 protein is made, but half isn't enough for normal development)

What does CHD7 do?

Model Systems for studying CHD7 function

ChIP-seq – A method to find the sites on DNA where CHD7 binds
**CHD7 ChIP-seq (embryonic stem (ES) cells)**

> 20,000 CHD7 binding sites across the genome

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**CHD7 Mutations Cause Changes in Gene Expression**

- CHD7 binds to thousands of genes
- Only about 10% have altered expression in ES cells
- We think most CHD7 target genes probably change later in development in the eyes, ears, heart, and other tissues affected in CHARGE syndrome

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**CHD7 as a regulator of tissue-specific genes**

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**Working Model**

Misexpression of lineage specific genes during embryonic development, due to haploinsufficiency of CHD7, leads to CHARGE syndrome.
The Nucleolus and Ribosomal RNA

CHD7 is also located in the cell nucleolus

Ribosomal RNA (rRNA)

- rRNA accounts for 60-80% of all RNA in the cell
- rRNA makes proteins and helps cells grow and divide
- Problems with rRNA synthesis kills cells or slows their growth
- Human diseases due to problems with rRNA:
  - Treacher Collins syndrome
  - Diamond-Blackfan anemia
  - Cancer

CHD7 binds to ribosomal RNA genes

CHD7 Helps Make Ribosomal RNA

Mutations in the \textit{Chd7} gene in CHARGE mouse models reduce rRNA levels
Problems with rRNA production can cause genetic diseases

- Diamond-Blackfan anemia
  - Mutations in RPS19, and other ribosomal genes
  - Mostly sporadic dominant
  - Likely haploinsufficiency
  - Red blood cell aplasia, craniofacial, thumb, cardiac and urogenital abnormalities

- Treacher Collins syndrome
  - Mutations in TCOF1, encoding nucleolar treacle
  - Autosomal Dominant
  - Haploinsufficiency
  - Craniofacial abnormalities, including coloboma of the lid, micrognathia, microtia and other ear deformities, conductive hearing loss, cleft palate

CHARGE Syndrome

Summary: Two functions for CHD7

- Nucleolus
- Cytoplasm

Outline

- Overview of the cellular functions of CHD7
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Zebrafish: A powerful model system

- Zebrafish is a vertebrate that shares the majority of genes with mammals, including CHD7
- Developmental processes are highly conserved between zebrafish and mammals
- Transparent embryogenesis that is also very rapid
  - Eggs to embryo within 24 hours
- Targeted gene knockdown is feasible and straightforward (Morpholino (MO) technology)
- Low cost

Chd7-MO phenotypes

(Highly Dose Dependent)

- Pectoral Fin Defects
- Jawless
- Osseous Edema, Lens Defects
- Cardiac edema, Weak heartbeat
- Deformed otoliths

Effects on rRNA biogenesis in zebrafish

- JHDM18/FBXL10 is a nuclear protein that represses transcription of ribosomal RNA genes

**Stephanie Balow**

**Chd7-MO phenotypes**

**Effects on rRNA biogenesis in zebrafish**
Rescue of CHARGE phenotype

Outline

• Overview of the cellular functions of CHD7
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• Zebrafish model of CHARGE syndrome
• Overview of high-throughput sequencing of CHD7 to identify mutations in patient cohorts
• Where we are headed

CHD7 gene sequence analysis that is fast and cheap

• CHD7 gene is big, mutation analysis is expensive through commercial labs.
• CHARGE syndrome shares clinical overlap with Kallmann syndrome, T-cell immunodeficiency, idiopathic scoliosis, and DiGeorge syndrome.
• Allows for testing in large patient cohorts

Strategy

It works!
• We pooled ~50 patients with known mutations in CHD7 and ran them through our analysis. We were "blinded" to the location of the CHD7 mutation in all patients. Virtually all CHD7 mutations were detected!
• Also tested 80 patients with isolated coloboma.
• Major reduction in costs.

Summary

• CHD7 binds to thousands of gene enhancer elements
  – These enhancers regulate the genes that specify the tissues & organs that are affected in CHARGE syndrome.
• CHD7 controls the genes that are responsible for synthesizing proteins.
• The gene targets of CHD7 are dysregulated in other congenital disorders that show clinical overlap with CHARGE syndrome.
• CHD7 mutations can be identified in large patient cohorts relatively quickly and at low cost
Outline

• Overview of the cellular functions of CHD7
  – Regulator of genes that orchestrate development
  – Regulator of protein synthesis.
• Zebrafish model of CHARGE syndrome
• Overview of high-throughput sequencing of CHD7 to identify mutations in patient cohorts
• Where we are headed

Where we are headed & what we need

• Clinical Samples (blood and skin biopsies)
  – CHD7 mutation screening
  – Generation of induced pluripotent stem cells (iPS cells).
  • Further molecular understanding of human CHD7.
• Additional Government funding for research

Acknowledgments

Scacheri Lab
Cindy Bartels, MS
Batool Akhtar-Zaidi
Michael Schnetz*
Gabe Zentner
Stephanie Balos
Olivia Corradin
Deb Schelling
Alina Saiakhova
Pavel Manaenkov*
Dheepa Balasubramanian, PhD
Lain Paceo, PhD*
*former member
CWRU
Paul Tesar, PhD
Tom LaFramboise, PhD
John Wang, PhD
Xiaodong Zhang, PhD
Maria Hatzoglou, PhD
Peter Harte, PhD

University of Michigan
Donna Martin, MD, PhD

Funding:
NICHD & NHGRI

Publications/Resources

• Review Article on CHARGE syndrome
• CHD7 as an enhancer binding protein
• CHD7 as a regulator of ribosomal genes
Phenotypes in a Drosophila model of CHARGE syndrome

Thursday, 07/28/11
Platform #2: 9:40-10:05
Wekiwa 3 & 4

Daniel R. Marenda
Ph.D., Assistant Professor, Drexel University, Philadelphia PA

Presenter Information:
Dr. Marenda is an Assistant Professor in the department of Biology at Drexel University in Philadelphia.

Presentation Abstract:
In the study of human disease, animal models (called model organisms) often act as surrogates for patients when (as if often the case) experimentation on humans is unfeasible or unethical. One of these model organisms, the fruit fly Drosophila melanogaster, has been a powerhouse in the understanding of human disease. Using this powerful system, my lab inactivated the Drosophila equivalent of the Chd7 gene in the fly (a gene called kismet), and discovered that kismet was required in the muscle cells of the fly for posture and coordinated movement, and in the fly brain for memory. We also found that kismet is required for the maintenance and growth of axons (structures in brain cells that function similarly to telephone wires, bringing information from one part of the brain to another). By better understanding some of the basic functions of kismet, our hope is that we can shed light on similar functions of CHD7 in humans, and eventually help give all of the researchers working on CHARGE syndrome the information they need to develop a therapeutic intervention for patients with CHARGE."
Phenotypes in a Drosophila Model of CHARGE Syndrome

Daniel R. Marenda, Ph.D.
Assistant Professor

First things First:

$\$\$\$ Average 2000-2009

2.149 Trillion income
National Debt (2010): ~12.4 trillion
371.4 billion in interest (~17.3%)
~26.2 billion to NIH (~1.2%)
~4.9 billion to NSF (.22%)
~446.3 billion to DOD (~20.8%)
~109.9 MILLION to NEA (.005%)

Model Organisms:

• Because models are JUST LIKE everybody else.....
• Right???

Model Organisms:

• Model organisms are widely used to explore potential causes and treatments for human disease when experimentation on humans would be unfeasible or unethical.

Why use model systems?
Model Organisms:

• The expectation that discoveries made in the organism model will provide insight into the workings of other organisms.

• Why?

Model Organisms:

• This strategy is made possible by the common descent of all living organisms, and the conservation of metabolic and developmental pathways and genetic material over the course of evolution.

Indeed, flies are like little people with wings.

What about the Public Good?

The laws of Heredity.
Gregor Mendel

The common garden pea

Mendel did his pioneering work from 1856 to 1865 and his results were published in one paper (reports) in 1866.

X-linked inheritance
Gene linkage

Thomas Hunt Morgan: Nobel Prize in Medicine or Physiology 1933

Drosophila

- At the time it was generally assumed that chromosomes could not be the carriers of the genetic information.
- Showed chromosomes carried Genetic information
- Showed a difference between the chromosomes in male and female (XY vs. XX) and sex linked inheritance (with a white eyed fly)
- Showed that genes were arranged linearly along chromosomes and that this length could be measured genetically (centiMorgans)

"for his discoveries concerning the role played by the chromosome in heredity"

Most common form of inherited mental retardation
Most common form of autism

Researchers used mice to decrease glutamate receptor expression in Fragile X mice, and “cured” the disease

Pharmacological Rescue of Synaptic Plasticity, Courtship Behavior, and Mushroom Body Defects in a Drosophila Model of Fragile X Syndrome

PS: They did it in flies first.
Developing a model of CHARGE Syndrome in Flies.

**PROTEIN DOMAINS**
- Chromo-domain: chromatin remodeling and manipulation
- SNF2/ATPase domain: similar to chromatin remodeling proteins
- BRK domain: found only in metazoans. Function is unclear

**CELLULAR FUNCTIONS**
- Member of the trithorax group of transcriptional activators
- Proposed to facilitate an early step in transcriptional elongation
- Regulator of circadian rhythm
- Involved in hedgehog pathway, Ras, Notch (eyes, wings)

## KISMET: Fate; Fortune
Homolog of CHD7

**Motor function: Climbing Assay**
- Negative Geotaxis behavior of flies
- Ability to climb predetermined length in a given time.
- Predicts:
  - Functioning of nervous system
  - Reflex behavior
  - Spatial awareness

Kismet Knockdown flies have abnormal posture

Kismet Knockdown flies have defective motor reflex function.

Kismet knockdown flies have defective immediate recall memory
Kismet knockdown flies have defective axon pruning in learning and memory neurons.

<table>
<thead>
<tr>
<th>Neuron</th>
<th>Gold-line</th>
<th>e</th>
<th>Defect observed</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>y neuron, MAIR</td>
<td>0%</td>
<td>—</td>
<td>—</td>
<td>0%</td>
</tr>
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<td>—</td>
<td>—</td>
<td>0.05</td>
</tr>
<tr>
<td>y neuron, MAIR</td>
<td>56%</td>
<td>—</td>
<td>—</td>
<td>0.05</td>
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By better understanding some of the basic functions of kismet, our hope is that we can shed light on similar functions of CHD7 in humans, and eventually help give all of the researchers working on CHARGE syndrome the information they need to develop a therapeutic intervention for patients with CHARGE.
Advances in Understanding CHD7 through Use of Genetically Engineered Mice

Thursday, 07/28/11
Platform #3: 10:05-10:30
Wekiwas 3 & 4

Donna Martin, MD, PhD,
Elizabeth A. Hurd, PhD,
Wanda S. Layman, PhD,
Yehoash Raphael, PhD
The University of Michigan

Presenter Information:
Donna M. Martin is a Physician-Scientist and Associate Professor at The University of Michigan Medical School in the Departments of Pediatrics and Human Genetics. Her expertise is in Medical Genetics of developmental disorders including CHARGE syndrome.
Elizabeth A. Hurd is a Senior Research Associate working in Dr. Martin’s laboratory. Dr. Hurd generated Chd7 mutant mice and is analyzing them for inner ear defects and hearing abilities.
Wanda S. Layman is a recent PhD graduate of the Department of Human Genetics at The University of Michigan. She worked in Dr. Martin’s laboratory and generated all of the data on endocrine and olfactory systems in Chd7 mutant mice.
Yehoash Raphael is Professor of Otolaryngology at The University of Michigan. He specializes in studies of the inner ear, with a special focus on CHARGE syndrome.

Presentation Abstract:

CHD7, the gene mutated in human CHARGE Syndrome, encodes a chromodomain DNA-binding protein that is highly expressed in specific tissues of the developing embryo. Our laboratory has generated and analyzed several different strains of mice with mutations in the mouse Chd7 gene, with the goal of exploring the underlying mechanisms by which CHD7 regulates organ growth and development. We will discuss recent findings and roles for CHD7 in the development of several organs and tissues, including neurons that influence hearing, balance, and olfaction.
Advances in Understanding CHD7 through Use of Genetically Engineered Mice

CHARGE Syndrome Conference
July 28-31, 2011

Donna M. Martin, MD, PhD
Elizabeth A. Hurd, PhD
Wanda S. Layman, PhD
Yehoash Raphael, PhD

Departments of Pediatrics, Human Genetics, and Otolaryngology
The University of Michigan

Outline

- Chd7 deficient mice
  - ENU mutants
  - Gene trapped allele
  - Conditional (flox) allele
- Organ system-specific defects
  - Olfactory
  - Endocrine
  - Inner ear

Mouse models of CHARGE Syndrome

- ENU-derived mutants (10 alleles) with single base pair heterozygous loss of function mutations in Chd7
- Chd7Gt/+ gene trapped loss of function allele
- Phenotypes of Chd7 heterozygous mutant mice are consistent with those observed in CHARGE patients

Hurd et al., Mammalian Genome, 2007; Bosman et al., Human Mol Gen 2005

First report of Chd7 mutant mice

Hurd et al., Mammalian Genome, 2007

Generation of a Chd7flox allele

Hurd et al., Development 2011

Chd7Gt/+ mice are a model for CHARGE

Hurd et al., Mammalian Genome, 2007

Multiple mutations in mouse Chd7 provide models for CHARGE syndrome

Erika A. Bosman1, Andrew C. Pero1, John C. Ambrose2, Ross Kettleborough, Derek L. Stample and Karen P. Steel1

Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK

Table 1. Mutations identified in mouse Chd7 mutant mouse lines

<table>
<thead>
<tr>
<th>Mutant</th>
<th>DNA mutation</th>
<th>Exon</th>
<th>Protein consequence</th>
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<tr>
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<td>4</td>
<td>ئ (p.R349Q)</td>
</tr>
<tr>
<td>Thy</td>
<td>1045C&gt;T</td>
<td>4</td>
<td>ئ (p.R349Q)</td>
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<tr>
<td>Br</td>
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<tr>
<td>P1a</td>
<td>1045C&gt;T</td>
<td>4</td>
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</tr>
</tbody>
</table>
Chd7Gt/+ mutants have postnatal growth delays and circling

Hurd et al., Mammalian Genome, 2007

Outline

- Chd7 deficient mice
  - ENU mutants
  - Gene trapped allele
  - Conditional (flox) allele
- Organ system-specific defects
  - Olfactory
  - Endocrine
  - Inner ear

Olfaction and CHARGE syndrome

- Olfactory bulb defects (33/33) and olfactory impairment (18/19) are common features of CHARGE
- Chd7 is expressed in olfactory epithelium and olfactory bulb in humans and mice

Layman et al., Human Molecular Genetics 2009

Olfactory sensory neurons are reduced in Chd7Gt/+ mice

Chd7+/+ Chd7Gt/+ Layman et al., Human Molecular Genetics 2009

Conclusions (olfactory)

- Chd7Gt/+ mice have olfactory defects similar to human CHARGE individuals
- Olfactory sensory neurons are reduced in Chd7Gt/+ mice
- Cellular proliferation is reduced in Chd7Gt/+ olfactory epithelium

Chd7Gt/+ mice have olfactory bulb hypoplasia

Layman et al., Human Molecular Genetics 2009
Outline

• Chd7 deficient mice
  – ENU mutants
  – Gene trapped allele
  – Conditional (flox) allele

• Organ system-specific defects
  – Olfactory
  – Endocrine
  – Inner ear

Endocrine dysfunction and CHARGE

• 81% of males and 93% of females with CHARGE have LH and FSH are deficient

• Genital hypoplasia including cryptorchidism and micropenis occurs in 62% of CHARGE individuals with confirmed CHD7 mutations
  – Females often have hypoplastic labia

• Anosmia and hyposmia can predict idiopathic hypogonadotropic hypogonadism in CHARGE individuals (Bergman et al., 2010)

Chd7Gt/+ female mice have delayed puberty

Chd7Gt/+ mice have decreased levels of LH and FSH

GnRH neurons are reduced in Chd7Gt/+ mice

Conclusions part II (endocrine)

• Chd7Gt/+ mice have pubertal defects and decreased LH, FSH similar to human CHARGE individuals

• GnRH neurons are reduced in Chd7Gt/+ embryos and adults

• Cellular proliferation is reduced in the olfactory epithelium of Chd7Gt/+ embryos

• Reduced CHD7 dosage lowers expression of Bmp4, Fgfr1, Otx2, GnRH1, and GnRHR
Outline

• Chromatin remodeling proteins
  – Classification and roles in human disease
  – CHD7 and CHARGE Syndrome
• Organ system-specific defects
  – Olfactory
  – Endocrine
  – Inner ear

Outline

Chd7Gt/+ mice have defects in inner ear morphogenesis

Layman et al., Clin Gen 2010; Hurd et al, Mamm Gen 2007;
Bosman et al, HMG, 2005; Adams et al, JCN 2008

Elizabeth Hurd

FoxG1cre-Chd7 conditional mutants have severe semicircular canal and cochlear defects

Hurd et al., Development, 2010

Chd7 mutants have reduced proliferation in the neurogenic domain

Hurd et al., Development, 2010

Model for CHD7 Developmental Gene Regulation in Inner Ear

Hurd et al., Development, 2010

Conclusions part III (inner ear)

• Chd7Gt/+ mice have inner ear defects and hearing loss similar to human CHARGE individuals
• Inner ear neuroblast proliferation is sensitive to CHD7 dosage
• CHD7 likely acts upstream of proneural genes to regulate inner ear neurogenesis
Take-home points

- CHD7 deficiency affects development of multiple similar tissues in humans and mice
- Neurogenesis in the olfactory epithelium and inner ear requires appropriate CHD7 dosage
- Mouse mutants are a powerful tool for exploring CHD7 function during development and beyond

Acknowledgements

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NIH-NINDS
NOHR

Transgenic Animal Model
Core
Thom Saunders
Sally Camper
CHD7 Mutations and CHARGE Syndrome: Clinical and Diagnostic Implications of an Expanding Phenotype

Thursday, 07/28/11
Platform #4: 11:00-11:25
Wekiwa 3 & 4

Prof. Conny van Ravenswaaij-Arts
Dept. of Genetics, University Medical Centre Groningen, Groningen,
The Netherlands

Presenter Information:

Conny van Ravenswaaij studied medicine at the University of Leiden. In 1997 she was registered as a clinical geneticist. Her main interest has always been children with multiple congenital anomalies. Her group discovered the CHD7 gene as major cause of CHARGE syndrome in 2004. In 2006 she changed affiliation to the University Medical Centre Groningen, where she continued her multi-disciplinary outpatient clinic for CHARGE syndrome. She supervises studies in CHARGE syndrome, focusing on clinical variability and phenotype-genotype correlations, puberty development and smell, the role of CHD7 in heart development, Cochlear Implants and other aspects of CHARGE syndrome.

Presentation Abstract:

CHARGE syndrome is a highly variable syndrome of which the phenotypic spectrum could only be revealed after the identification of the CHD7-gene. We evaluated the clinical features in our cohort of 280 CHD7-positive patients and compared these with previously reported patients with CHARGE syndrome but unknown CHD7 status. Interestingly, 14% of the CHD7 positive patients could not be clinically diagnosed as having CHARGE syndrome based on the Blake criteria. This was most obvious in familial CHARGE syndrome; only 62% of familial cases could be diagnosed as CHARGE syndrome on clinical features alone.

The expanding phenotype has several clinical implications and updated recommendations for surveillance based on the phenotypic spectrum and on our experience in a multidisciplinary clinic for CHARGE syndrome will be given. Finally, guidelines for CHD7 analysis will be proposed.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011
CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype

J E H Bergman,¹ N Janssen,¹ L H Hoefsloot,² M C J Jongmans,² R M W Hofstra,¹ C M A van Ravenswaaij-Arts¹

ABSTRACT

Background CHARGE syndrome is a highly variable, multiple congenital anomaly syndrome, of which the complete phenotypic spectrum was only revealed after identification of the causative gene in 2004. CHARGE is an acronym for ocular coloboma, congenital heart defects, choanal atresia, retardation of growth and development, genital hypoplasia, and ear anomalies associated with deafness. This typical combination of clinical features is caused by autosomal dominant mutations in the CHD7 gene.

Objective To explore the emerging phenotypic spectrum of CHD7 mutations, with a special focus on the mild end of the spectrum.

Methods We evaluated the clinical characteristics in our own cohort of 280 CHD7 positive patients and in previously reported patients with CHD7 mutations and compared these with previously reported patients with CHARGE syndrome but an unknown CHD7 status. We then further explored the mild end of the phenotypic spectrum of CHD7 mutations.

Results We discuss that CHARGE syndrome is primarily a clinical diagnosis. In addition, we propose guidelines for CHD7 analysis and indicate when evaluation of the semicircular canals is helpful in the diagnostic process. Finally, we give updated recommendations for clinical surveillance of patients with a CHD7 mutation, based on our exploration of the phenotypic spectrum and on our experience in a multidisciplinary outpatient clinic for CHARGE syndrome.

Conclusion CHARGE syndrome is an extremely variable clinical syndrome. CHD7 analysis can be helpful in the diagnostic process, but the phenotype cannot be predicted from the genotype.

INTRODUCTION

The first patients with what later became known as CHARGE syndrome (OMIM 214800) were described in 1961.¹ ² In 1979, two independent clinicians recognised that coloboma, choanal atresia, and congenital heart defects clustered together in several patients.³ ⁴ The acronym CHARGE dates from 1981 and summarises some of the cardinal features: ocular coloboma, congenital heart defects, choanal atresia, retardation of growth and/or development, genital anomalies, and ear anomalies associated with deafness.³ In 2004, mutations in the CHD7 gene were identified as the major cause and ‘CHARGE association’ was changed to ‘CHARGE syndrome’.⁶ CHARGE syndrome occurs in approximately 1 in 10 000 newborns.⁷ The inheritance pattern is autosomal dominant with variable expressivity. Almost all mutations occur de novo, but parent-to-child transmission has occasionally been reported.⁸ In this review, we explore the phenotypic spectrum of CHD7 mutations with special focus on the mild end of the spectrum. In the light of this expanding phenotype, we discuss whether CHARGE syndrome is a clinical or a molecular diagnosis, we propose guidelines for CHD7 analysis, and give updated recommendations for the clinical surveillance of CHD7 positive patients.

BACKGROUND

Clinical diagnosis

Before discovery of the causative gene, CHARGE syndrome was a clinical diagnosis (clinical features summarised in figure 1). Pagon was the first to introduce diagnostic criteria for CHARGE syndrome in 1981,⁹ but these criteria are no longer in use. At present, the clinical criteria by Blake et al and Verloes are used in conjunction (table 1).⁹ ¹⁰

The Blake criteria⁹ were slightly adjusted by a consortium and last updated in 2009.¹¹ These criteria encompass four major and seven minor criteria. The four major criteria are coloboma, choanal atresia, cranial nerve dysfunction, and abnormalities of the inner, middle, or external ear. At least four major, or three major and three minor, criteria must be present in order to diagnose CHARGE syndrome. In 2005, Verloes proposed renewed criteria.¹⁰ He included semicircular canal defects as a major criterion, as these defects were shown to be a very specific and consistent feature in CHARGE syndrome.¹² Verloes also anticipated broadening of the phenotypic spectrum and reduced the number of features necessary for a diagnosis of CHARGE (to only three major, or two major and two minor, criteria) and he made his criteria less age and sex dependent. A common feature of both sets of criteria is that either coloboma or choanal atresia (which can sometimes be replaced by cleft palate, table 1)¹³ must be present in order to diagnose CHARGE syndrome.

Molecular diagnosis

Nowadays, CHARGE syndrome can also be diagnosed by a molecular genetic test. The CHD7 gene, mutated in the majority of patients with CHARGE syndrome, consists of 57 coding exons and one non-coding exon.⁶ The gene encodes for a 2997 amino acid long protein that belongs to the Chromodomain Helicase DNA binding (CHD) family.¹⁴ CHD7 can form complexes with different proteins,
thereby ensuring specific binding to different enhancer regions leading to time and tissue specific regulation of gene expression. One example is the association of CHD7 with PBAF (polybromo- and BRG1-associated factor containing complex) that is essential for neural crest gene expression and cell migration. This is in line with previous assumptions that many of the congenital defects seen in CHARGE syndrome may be neural crest related.

CHD7 was also shown to associate with rDNA and was therefore suggested to play a role as positive regulator of rRNA synthesis. Haploinsufficiency of the CHD7 gene leads to CHARGE syndrome and, as expected, most patients are found to have truncating CHD7 mutations. Missense mutations occur in a minority of patients and partial or full deletions of the CHD7 gene are rare events. There are no mutational hotspots and recurrent mutations are rare. Most CHD7 mutations occur de novo. There are no mutational hotspots and recurrent mutations are rare. No clear genotype-phenotype correlation exists, although it seems that missense mutations in general are associated with a milder phenotype.

CHD7 analysis detects mutations in more than 90% of patients fulfilling the clinical criteria for CHARGE syndrome. The lack of mutation detection in the remaining 5–10% of patients suggests genetic heterogeneity. The SEMA3E gene was proposed as

Table 1 Clinical criteria for CHARGE syndrome

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Inclusion rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blake*</td>
<td>1. Coloboma, microphthalmia</td>
<td>Typical CHARGE: 4 major or 3 major + 3 minor</td>
</tr>
<tr>
<td></td>
<td>2. Choanal atresia or stenosis†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Characteristic external ear anomaly, middle/inner ear malformations, mixed deafness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Cranial nerve dysfunction</td>
<td></td>
</tr>
<tr>
<td>Verloes10</td>
<td>1. Ocular coloboma</td>
<td>Typical CHARGE: 3 major or 2 major + 2 minor</td>
</tr>
<tr>
<td></td>
<td>2. Choanal atresia</td>
<td>Partial CHARGE: 2 major + 1 minor</td>
</tr>
<tr>
<td></td>
<td>3. Hypoplastic semicircular canals</td>
<td>Atypical CHARGE: 2 major + 0 minor or 1 major + 3 minor</td>
</tr>
</tbody>
</table>

*Updated by a consortium in 2006 and 2009.†Cleft palate can be substituted for choanal atresia, since these anomalies rarely occur together.
a candidate gene, but it seems to play a minor role as only two
SEMA3E alterations have been described in patients with
CHARGE syndrome.\textsuperscript{32} Besides genetic heterogeneity, it is also
possible that mutations in intronic regions, \(S\) or \(S\) untranslated
regions, or in regulatory elements of \(CHD7\) underlie the \(CHD7\)
negative cases. Phenocopies of CHARGE or CHARGE-like
syndrome can be due to teratogen exposure (eg, thalidomide,
retinoic acid, maternal diabetes) or chromosomal aberrations.\textsuperscript{8}

PHENOTYPIC SPECTRUM OF PATIENTS WITH A MUTATION
IN THE CHD7 GENE

Phenotypic spectrum in our \(CHD7\) positive cohort compared
to two other cohorts

Our \(CHD7\) positive cohort consists of patients who had \(CHD7\)
analysis done in Nijmegen in the Netherlands. In Nijmegen,
\(CHD7\) analysis was performed in 863 patients suspected of
CHARGE syndrome and 560 \(CHD7\) mutations were found (360/
863=42\%). The mutations were scattered throughout the entire
coding region and splice sites of the \(CHD7\) gene. One third of
the mutations were found in exons 2, 3, 30, and 31 (34\% of
mutations, 35\% of genomic size). However, exons 8, 12, 26, 30, and 36
showed a remarkably high number of mutations relative to their
genomic size (19\% of mutations, 9\% genomic size). No mutations
were found in exons 6, 7, 20, and 28, but these comprise only 5\%
of the coding genome of \(CHD7\). Apart from the high number of
mutations in exon 2 (the largest exon), our results do not agree
with a previous report (\(n=91\)).\textsuperscript{33} Most mutations were nonsense
(58\%) or frameshift mutations (32\%). Missense mutations and
splice site mutations occurred in 13\% and 17\%, respectively,
and deletions were rarely present (<1\%). The phenotypic spec-
trum of the missense mutations was more variable and on
average milder when compared to the truncating mutations.

In table 2 we present an overview of the clinical features of
280 of our \(CHD7\) positive patients, the \(CHD7\) positive
cohort reported in the literature (reviewed by Zentner et al,
\(n=254\)),\textsuperscript{24} and a cohort of patients clinically diagnosed with
CHARGE syndrome, but of whom the \(CHD7\) status is unknown
\((n=124)\). We only included 280 of our 360 \(CHD7\) positive
patients, because clinical data were lacking in the other 80
patients. The phenotypes of 64 of the 280 patients have been
published previously (table 2).\textsuperscript{20} 26 35–40

The clinical features of the \(CHD7\) positive patients, previously
reported or presented here, are rarely completely known. When
calculating the percentage of patients who exhibit a certain
feature, the incompleteness of the clinical data will have a major
effect on the accuracy of the percentage. In order to compensate
for this inaccuracy, we also calculated the frequency range. The
minimum frequency is defined as the number of patients with

Table 2 Clinical features of patients with a \(CHD7\) mutation compared to clinically diagnosed patients with CHARGE syndrome

| Feature | Our \(CHD7\) positive cohort (\(n=280\)) | \(CHD7\) positive cohort from the literature (\(n=254\)* | \(CHD7\) patients before \(CHD7\) discovery (\(n=124\)†)
| --- | --- | --- | ---
| External ear anomaly | 224/231 | 214/235 | 74/77
| | 97% (80–98%)§ | 91% | 96%
| Cranial nerve dysfunction (VII, VIII and others) | 173/174 | ? | 107/124
| | 99% (62–100%) | ? | 86%
| Semicircular canal anomaly | 110/117 | 94/96 | 12/12
| | 94% (39–98%) | 98% | 100%
| Coloboma | 189/234 | 190/253 | 96/124
| | 81% (68–84%) | 75% | 77%
| Choanal atresia | 98/179 | 95/247 | 76/124
| | 55% (35–71%) | 38% | 61%
| Cleft lip and/or palate | 78/163 | 79/242 | 22/124
| | 48% (28–70%) | 33% | 18%¶
| Feeding difficulties necessitating tube feeding | 90/110 | ? | 40/47
| | 82% (32–93%) | ? | 85%
| Facial palsy | 80/121 | 72/187 | 17/47
| | 66% (29–85%) | 39% | 36%
| Anosmia on formal smell testing | 24/30 | ? | ?
| | 80% | ? | ?
| Genital hypoplasia | 118/145 | 116/187 | 45/124
| | 81% (42–90%) | 62% | 36%¶
| Congenital heart defect | 191/252 | 193/250 | 105/124
| | 76% (68–78%) | 77% | 85%¶
| Tracheo-oesophageal anomaly | 42/146 | 35/185 | 22/124
| | 29% (15–63%) | 19% | 18%
| Developmental delay | | | |
| Delayed motor milestones | | | |
| Delayed milestones | | | |
| 147/149 | 107/141 | 47/47
| | 99% (53–99%) | 76% | 100%
| Intellectual disability | | | |
| 108/134 | | | |
| 74% (39–91%) | | | |
| Growth retardation | 35/94 | 101/141 | 80/124
| | 37% (13–79%) | 72% | 65%

*\(CHD7\) positive cohort from the literature as reviewed by Zentner et al in 2010.\textsuperscript{34} This cohort partially overlaps with our \(CHD7\) positive cohort because the phenotypes of 64 of our patients were published previously.\textsuperscript{20} 26 35–40
†Cohort of patients with clinically diagnosed CHARGE syndrome reported by Tellier et al in 1998 and Issekutz et al in 2005, before \(CHD7\) analysis was possible.\textsuperscript{7} 34
§Frequency are represented as the number of patients with a particular feature/the total number of patients that were tested for that particular feature.
¶The range of percentages presented between brackets was calculated as: (positive/total)×100%−(positive+unknown/total)×100% (for further explanation see text).
¶Outside the frequency range of patients with a \(CHD7\) mutation.
a particular feature divided by the total number of patients in the cohort. The maximum frequency is defined as the number of patients with a particular feature plus patients for whom it is unknown whether they have the feature, divided by the total number of patients in the cohort.

Four features are almost always present in patients with a CHD7 mutation: external ear anomalies, cranial nerve dysfunction, semicircular canal hypoplasia, and delayed attainment of motor milestones (table 2). The characteristic external ear anomaly consists of triangular conchae or cup shaped ears (figure 1) and occurs in more than 90% of patients with a CHD7 mutation. The second feature, cranial nerve dysfunction, is present in more than 95% of patients. The seventh and eighth cranial nerves are most often affected, leading to facial palsy and sensorineural hearing loss, respectively. Dysfunction of other cranial nerves can also occur. The third feature, semicircular canal hypoplasia, is not always assessed, but when investigated it is found to be present in over 90% of patients. The high frequency of semicircular canal hypoplasia is reflected in the delayed attainment of motor milestones (often scored as developmental delay in previous papers), that is almost universally present in patients with CHARGE syndrome. A delay in speech development is also common in these patients who suffer from multiple sensory impairment (eg, blindness and/or deafness). In our cohort, approximately 75% of patients had intellectual disability, indicating that one quarter had a normal intelligence.

Two features seem to occur more frequently since CHD7 analysis has become available as a diagnostic tool in CHARGE syndrome (table 2). These are cleft lip and/or palate and genital hypoplasia; in the study by Tellier et al,40 the percentages of these two features were below our frequency range. The most likely explanation is that in the past, patients with cleft palate, children without a heart defect were more likely to be missed, as the mild end of the CHARGE spectrum is only recently starting to emerge. Several studies have shown that an increasing number of patients with a CHD7 mutation do not fulfill the clinical criteria, as they do not have coloboma or choanal atresia or cleft palate. Exploration of the mild end of the CHARGE spectrum can be undertaken in four ways: by studying familial CHARGE syndrome; by evaluating very mildly affected patients who are picked up with CHD7 analysis; by performing CHD7 analysis in cohorts of patients with only one CHARGE feature; and finally by studying syndromes that show clinical overlap with CHARGE syndrome (eg, 22q11 deletion syndrome and Kallmann syndrome).

### Exploration of the mild end of the phenotypic spectrum of CHD7 mutations

Patients with a typical presentation of CHARGE syndrome are easily clinically recognised, but those who are mildly affected can be missed, as the mild end of the CHARGE spectrum is only recently starting to emerge. Several studies have shown that an increasing number of patients with a CHD7 mutation do not fulfill the clinical criteria, as they do not have coloboma or choanal atresia or cleft palate. Exploration of the mild end of the CHARGE spectrum can be undertaken in four ways: by studying familial CHARGE syndrome; by evaluating very mildly affected patients who are picked up with CHD7 analysis; by performing CHD7 analysis in cohorts of patients with only one CHARGE feature; and finally by studying syndromes that show clinical overlap with CHARGE syndrome (eg, 22q11 deletion syndrome and Kallmann syndrome).

### Familial CHARGE syndrome

Very mildly affected patients with CHARGE syndrome can be identified by studying familial CHARGE syndrome. In the literature, only 16 families have been described with recurrence of molecularly confirmed CHARGE syndrome. These families include seven sib-pairs, three monozygotic twin-pairs, and six two-generation families. In this review, we describe another two-generation family from our CHD7 positive cohort, making a total of 17 families (table 3).

### Table 3 Familial CHARGE syndrome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Fulfilling clinical criteria</th>
<th>Segregation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sib-pairs</strong></td>
<td>CHD7 mutation</td>
<td>Sib 1</td>
</tr>
<tr>
<td>1. Wincent24</td>
<td>c.4015C→T; p.R1339X</td>
<td>+ (case 11a)</td>
</tr>
<tr>
<td>2. Pauli24</td>
<td>c.7302dupA</td>
<td>+ (girl)</td>
</tr>
<tr>
<td>4. Jongmans37</td>
<td>c.2442+5G→C</td>
<td>– (case 1)</td>
</tr>
<tr>
<td>5. Jongmans37</td>
<td>c.2520G→A; p.W840X</td>
<td>+ (case 3)</td>
</tr>
<tr>
<td>6. Jongmans37</td>
<td>c.1610G→A; p.W537X</td>
<td>+ (case 5)</td>
</tr>
<tr>
<td><strong>Monozygotic twins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Wincent24</td>
<td>c.5428C→T; p.R1810X</td>
<td>+ (case 13a)</td>
</tr>
<tr>
<td>2. Jongmans21</td>
<td>p.E1271X</td>
<td>+ (case A)</td>
</tr>
<tr>
<td>3. Jongmans20</td>
<td>c.5752_5753dupA; p.T1918fs</td>
<td>+ (case 26)</td>
</tr>
<tr>
<td><strong>Parent—child</strong></td>
<td></td>
<td>Child 1</td>
</tr>
<tr>
<td>1. Vuorela46</td>
<td>c.4795C→T; p.Q1599X</td>
<td>+ (case 1)</td>
</tr>
<tr>
<td>2. Delahaye43</td>
<td>c.2501C→T; p.S834F</td>
<td>+ (case A III-2)</td>
</tr>
<tr>
<td>3. Delahaye43</td>
<td>c.4696C→T; p.R1571X</td>
<td>+ (B III-1)</td>
</tr>
<tr>
<td>5. Jongmans37</td>
<td>c.6322G→A; p.G2108R</td>
<td>– (case 7)</td>
</tr>
<tr>
<td>7. This study</td>
<td>c.7763del</td>
<td>–</td>
</tr>
</tbody>
</table>

Total clinical criteria positive: Children 24/32 Parents 0/7

+ *, fulfilling the criteria; –, not fulfilling the clinical criteria of Blake et al and/or Verloes.* Somatic mosaicism was excluded (the CHD7 mutation was present in both peripheral blood lymphocytes and buccal cells).

---

Of the 39 CHD7 positive individuals, only 24 (62%) fulfilled the clinical criteria for CHARGE syndrome as defined by either Blake et al® or Verloes. Atypical CHARGE patients are most frequently seen in the two-generation families. Often, the mildly affected individuals were recognised only after a CHD7 mutation was found in a more severely affected family member. The most mildly affected patients described in the literature had dysmorphic ears and balance disturbance as the only manifestations of CHARGE syndrome. Somatic mosaicism was considered unlikely in two of the very mildly affected parents, because the CHD7 mutation was found in different tissues. The monozygotic twin pairs showed strikingly discordant features and underscore the great intra-familial variability seen in CHARGE syndrome.

Mildly affected patients from our CHD7 positive cohort

The most widely used criteria are those of Blake et al and Lalani et al. Interestingly, 18 out of the 131 (14%) CHD7 positive patients that could be scored for these criteria had only one or two major Blake features and thus could not be clinically diagnosed as having CHARGE syndrome. Based on the presence of none, or only one major Verloes feature, as many as 17% (22/124 patients) could not be clinically diagnosed with CHARGE syndrome using the Verloes criteria. The phenotypes of the three most mildly affected (previously unpublished) patients are presented below.

The first patient had abnormal external ears and a congenital heart defect, but no other features of CHARGE syndrome. She had normal semicircular canals, no cranial nerve dysfunction, and a normal pubertal development. She had a de novo pathogenic missense mutation in the CHD7 gene that had not been described before (c.4406A→G, p.Y1469C in exon 19).

The second patient had mild semicircular canal anomalies and a mild hearing loss. His external ears were normal. He was only recognised as having CHARGE syndrome after a CHD7 splice site mutation was found in his more severely affected children (table 3, two-generation family from this study).

The third patient was diagnosed with Kallmann syndrome and had sensorineural hearing loss. After a de novo pathogenic missense mutation in the CHD7 gene (c.6522G→A, p.G2108R in exon 31) was identified, a CT scan of his temporal bone was re-evaluated and semicircular canal hypoplasia was seen. He had normal external ears.

CHD7 analysis in cohorts of patients with only one CHARGE feature

Some authors have undertaken CHD7 screening in patients with only one CHARGE syndrome feature—for example, cleft lip and/or palate, congenital heart disease, or scoliosis. These studies did not identify pathogenic CHD7 mutations. The general impression is that in the absence of other CHARGE features, the chance of finding a CHD7 mutation is very low.

Studies in syndromes that overlap with CHARGE syndrome

Thus far, two clinically overlapping syndromes have been studied in relation to CHD7 mutations: velocardiofacial syndrome (VCFS), and Kallmann syndrome.

Velocardiofacial or 22q11 deletion syndrome shares many features with CHARGE syndrome, including congenital heart defects, cleft palate, developmental delay, renal anomalies, growth retardation, ear anomalies, hearing loss, hypoglycaemia, and lymphopenia. In particular, thymus aplasia and hypoparathyroidism are increasingly recognised in CHARGE syndrome and mark the clinical overlap with the DiGeorge phenotype of 22q11 deletions. In approximately 85% of VCFS patients, a common 3 Mb heterozygous deletion of 22q11.2 is present, resulting in TBX1 haploinsufficiency. Mutations in the TBX1 gene are present in a minority of VCFS patients. Array comparative genomic hybridisation (CGH) in a cohort of VCFS patients without 22q11 deletion or TBX1 mutation revealed one heterozygous deletion encompassing the CHD7 gene in a patient with features typical of VCFS. This patient had a learning difficulty with speech delay, severe feeding difficulties, a congenital heart defect (interruption of the aortic arch, coarctation of the aorta, bicuspid aortic valve, ventricular and atrial septal defect), long slender fingers, and low set, over-folded ear helices. The patient did not have coloboma, choanal atresia or cleft palate, but did have typical CHARGE ears with triangular conchae. To our knowledge, CHD7 sequence analysis has not yet been performed in a cohort of VCFS patients without deletion or mutation of TBX1. In figure 2 we illustrate how difficult it can be to distinguish between CHARGE syndrome and 22q11 deletion syndrome. The phenotypic similarity between VCFS and

Figure 2 Patient with typical CHARGE syndrome and a 22q11 deletion. This 3½-year-old girl presented with retinal and iris coloboma, unilateral choanal stenosis, abnormal semicircular canals, mixed hearing loss, pulmonary valve stenosis, and simple ears. Clinically she has typical CHARGE syndrome, but neither a CHD7 mutation nor a deletion could be detected by sequence analysis and multiplex ligation dependent probe amplification (MLPA). Subsequently, array comparative genomic hybridisation (CGH) was performed (Agilent 180 K custom HD-DGH microarray) and revealed a de novo 3 Mb 22q11.2 loss, suggestive for the typical DiGeorge/velocardiofacial syndrome deletion. Informed consent was obtained for publication of the photographs.
CHARGE syndrome is also apparent in mice with haploinsufficiency of *Tbx1* and *Chd7*. Both genes are required in pharyngeal ectoderm for fourth pharyngeal artery development. In addition, both genes are important in development of the thymus and semicircular canals. The *Tbx1* and *Chd7* genes were shown to interact in mice, but a direct regulatory effect of Chd7 on *Tbx1* expression could not be demonstrated.

Kallmann syndrome usually presents as the combination of hypogonadotropic hypogonadism (HH) and anosmia. Both features also occur in the majority of patients with CHARGE syndrome. Other features that can be present in both syndromes are hearing loss, cleft lip/palate, and renal malformations. Two studies have been performed in which patients with normosmic HH or Kallmann syndrome were screened for *CHD7* mutations. *CHD7* mutations were reported in seven out of 197 patients with normosomic HH or Kallmann syndrome, and in three out of 36 patients with Kallmann syndrome (confirmed by a smell test), but in none of 20 patients with normosmic HH. The second study showed that after thorough clinical examination of the *CHD7* positive Kallmann patients, other CHARGE features were universally present. The authors concluded that these patients represent the mild end of the CHARGE phenotypic spectrum, as we also demonstrated in our patient who was referred with Kallmann syndrome (see the section ‘Mildly affected patients from our *CHD7* positive cohort’).

**CHD7 AND CHARGE SYNDROME: THE CLINICAL IMPLICATIONS**

Based on the studies conducted after the identification of *CHD7* and summarised above, we discuss whether CHARGE syndrome is a clinical or molecular diagnosis, propose a new guideline for *CHD7* analysis, and give recommendations for clinical surveillance of *CHD7* positive patients.

**CHARGE syndrome, a clinical or molecular diagnosis?**

In our opinion, CHARGE syndrome is primarily a clinical diagnosis. If patients fulfil the clinical criteria of Blake or Verloes, and chromosomal aberrations and teratogenic exposure effects fully explaining the clinical features have been ruled out, then they have CHARGE syndrome, irrespective of the results of *CHD7* analysis. On the other hand, patients who do not completely fulfil the clinical criteria should not be excluded from *CHD7* analysis. If a mutation is found in these patients, clinical follow-up and genetic counselling should be performed as in clinically diagnosed patients with CHARGE syndrome.

**Guideline for *CHD7* analysis**

Considering the broad phenotypic spectrum, it is evident that *CHD7* analysis should not be restricted to patients fulfilling the clinical criteria for CHARGE syndrome. Coloboma and choanal atresia (or cleft palate) are not always present in CHARGE syndrome. Therefore patients with other CHARGE features, but without those cardinal features, should not be excluded from *CHD7* analysis. When a patient is suspected of CHARGE syndrome, the external ears, cranial nerve function, and semicircular canals should be thoroughly examined, as these features occur in the great majority of patients with a *CHD7* mutation (table 2).

We propose a guideline for *CHD7* analysis in figure 3. In our experience, imaging of the semicircular canals is not an easy
Phenotypes

routine in daily clinical practice, especially in children in whom sedation can be complicated (see ‘Clinical surveillance’ and table 4). Therefore, in our guideline we have indicated when imaging of the semicircular canals is needed to support the decision for CHD7 analysis. We based our guideline on the clinical features that were present in our CHD7 positive patients (n=280). When applying our guideline, CHD7 analysis would not have been recommended in one of our patients. This patient is the first one described in the section ‘Mildly affected patients from our CHD7 positive cohort’ and is extremely mildly affected. A prospective study is needed to evaluate the usefulness of this guideline in clinical practice.

Clinical surveillance of patients with a CHD7 mutation or typical CHARGE syndrome

Ideally, follow-up of patients with a CHD7 mutation or typical CHARGE syndrome should be done by an expert multidisciplinary team, because this approach will ensure optimal treatment of this very complex patient group. In the Netherlands, several specialities are involved in the CHARGE outpatient clinic of the University Medical Centre Groningen: clinical genetics, paediatric endocrinology, ear nose throat (ENT), speech and occupational therapy, ophthalmology, child and youth psychiatry, social paediatrics, gynaecology, endocrinology, paediatric cardiology, neuroradiology, and dentistry. In table 4, we show updated recommendations for clinical surveillance of patients with a CHD7 mutation based on the experiences of our CHARGE outpatient clinic, on the clinical features in our CHD7 positive cohort (table 2), and on a literature review.

An ultrasound of the heart and kidneys should be done in all patients, because mild congenital anomalies can remain undetected until adulthood, but may have therapeutic consequences (eg, early treatment of urinary tract infections in case of renal anomalies).

Table 4 Clinical surveillance of patients with a CHD7 mutation

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Tests</th>
<th>Treatment/advice</th>
<th>Be aware of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmology</td>
<td>Full ophthalmological examination including funduscopy</td>
<td>Tinted spectacles for photophobia (iris coloboma) Artificial tears in case of facial palsy Correction of refraction errors</td>
<td>Retinal detachment (in case of retinal coloboma)</td>
</tr>
<tr>
<td>ENT, audiology, occupational/speech therapy, gastroenterology</td>
<td>Multidisciplinary evaluation: Assess patency of choanae (CT scan or nasal endoscopy) Evaluation for cleft palate and tracheo-oesophageal anomalies Audiometry (BAER), tympanometry Temporal bone CT scan (pathology of middle ear, inner ear, cranial nerves, semicircular canals, aberrant course of blood vessels or cranial nerves) Cranial nerve function tests Swallowing studies, pH monitoring, reflux scan in case of feeding/swallowing difficulties University of Pennsylvania Smell Identification Test</td>
<td>Early treatment of bladder infections (especially in case of unilateral renal agenesis or vesico-urethral reflux) Growth hormone treatment if growth hormone deficiency is present</td>
<td>Respiratory aspiration (recurrent pneumonias) Aberrant course of blood vessels or cranial nerves when surgery for cochlear implants Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Paediatrics/endocrinology</td>
<td>Renal ultrasound, voiding cysto-urethrogram in case of urinary infections Immunological studies in case of recurrent infections or suspected hypocalcaemia Follow-up of growth and development (growth hormone stimulation test if indicated) Monitor cryptorchidism Gonadotropin levels (age 6–8 weeks) and follow-up of pubertal development DEXA scan (when suspected for osteoporosis)</td>
<td>Monitor for scoliosis Cardiac evaluation including ultrasound</td>
<td>Cardiac surgery and/or antibiotic prophylaxis Postoperative complications (due to aspiration/cranial nerve dysfunction)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Extensive preoperative assessment</td>
<td>Cardiac surgery including ultrasound</td>
<td>Long-term surveillance after surgery</td>
</tr>
<tr>
<td>Anaesthesiology</td>
<td></td>
<td>Cardiac surgery including ultrasound</td>
<td>Cardiac surgery and/or antibiotic prophylaxis Postoperative complications (due to aspiration/cranial nerve dysfunction)</td>
</tr>
<tr>
<td>Neurology</td>
<td>Cerebral MRI scan (including visualisation of olfactory bulbs, and inner ear if no temporal bone CT scan has been performed) EEG (only when clinically seizures are observed)</td>
<td>Anticonvulsants if overt epilepsy seen</td>
<td>Problems with intubation</td>
</tr>
<tr>
<td>Behavioural and educational services</td>
<td>Extensive multidisciplinary evaluation of developmental and sensory impairments and behavioural problems Use formal tests in order to screen for autism spectrum, obsessive compulsive disorders and ADHD Perform IQ tests regularly</td>
<td>Integrated individualised therapy with special attention for optimising communication</td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>Assessment of balance problems, motor delay, visuospatial coordination, and hypotonia</td>
<td>Therapy for hypotonia and devices to overcome balance impairment</td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td>CHD7 analysis (when no CHD7 mutation or deletion is found, perform array CGH)</td>
<td>Genetic counselling, options for prenatal diagnosis Intra-familial variability in CHARGE syndrome</td>
<td></td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; BAER, brain stem auditory evoked response; CGH, comparative genomic hybridisation; DEXA, dual energy x-ray absorptiometry; EEG, electroencephalogram; ENT, ear nose throat; GORD, gastro-oesophageal reflux disease.
Cranial nerve investigation is important. Dysfunction of the seventh, ninth, and 10th cranial nerve can lead to severe feeding and swallowing problems, can result in respiratory aspiration and postoperative complications, and might be involved in sudden death.59–62

HH should be diagnosed at an early stage, because patients are at risk for osteoporosis if hormone replacement therapy is not started in time. We recently demonstrated that anosmia and HH are 100% correlated in CHARGE syndrome and we proposed smelling test as a predictive test for HH.63

Last, but not least, an individualised educational programme is needed in order to stimulate fully the intellectual potential of a child with CHARGE syndrome and to manage behavioural problems.64–66 Clinicians should be aware that semicircular canal hypoplasia, a very frequent feature in CHARGE syndrome, causes balance problems and therefore a delay in motor development. This motor retardation may erroneously lead to the suspicion of intellectual disability, although approximately 25% of patients have a normal intelligence.

In addition, identifying a CHD7 mutation gives further tools for genetic counselling of both the parents and the patients themselves. When the CHD7 mutation has occurred de novo in the index patient, the recurrence risk for the parents is 2–5% because both germline and somatic mosaicism have been described in CHARGE syndrome.20 37–44 Patients themselves, when fertile with or without appropriate hormone replacement therapy, have a 50% chance of transmitting the CHD7 mutation to their offspring. The severity of CHARGE syndrome in offspring cannot be predicted, because intra-familial variability is large. Prenatal diagnosis, either by molecular analysis or ultrasound, and pre-implantation genetic diagnosis, when appropriate, should be discussed with parents and patients.

CONCLUSIONS

CHARGE syndrome is extremely variable, an observation that has been strongly underscored since the discovery of the CHD7 gene. The phenotype cannot be predicted from the genotype, as exemplified by intra-familial variability. CHARGE syndrome remains primarily a clinical diagnosis, but molecular testing can confirm the diagnosis in mildly affected patients. Guidelines for CHD7 analysis in individuals suspected of having CHARGE syndrome are proposed in figure 3. In addition, updated guidelines for the surveillance of patients with a CHD7 mutation or typical CHARGE syndrome are presented in table 4.

Acknowledgements

We are indebted to the patients for cooperating in this study. We thank the Netherlands Organisation for Health Research (ZonMW 92030460 to JEH) and Fund NutsOhra [project 0901-80 to NJ] for financial support and thank Jackie Senor for editing the manuscript.

Funding

Netherlands Organisation for Health Research and Fund NutsOhra.

Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

Ethics committee approval not necessary. Clinical information was collected with informed consent and subsequently used strictly anonymously according to local ethical regulations, except for some individual patients who might be identifiable in the paper, but who all gave their consent.

Contributors

All authors have substantially contributed to the manuscript and will take public responsibility. There is no one else who fulfils the authorship criteria who has not been included as an author.

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES


CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype


J Med Genet 2011 48: 334-342 originally published online March 4, 2011
doi: 10.1136/jmg.2010.087106
National Cochlear Implantation Studies with Children Who Experience Deaf-Blindness: Results for Participants with CHARGE Syndrome

Thursday, 07/28/11
Platform #5: 11:25-11:50
Wekiwa 3 & 4

Susan M. Bashinski, Ed.D.
East Carolina University

Presenters Information:
Dr. Susan M. Bashinski has been working in the field of special education for more than 35 years, teaching in public school Pre-K through high school programs, as well as at the university level. She has been recognized with several teaching awards. She is the author/co-author of numerous published research articles, chapters, and manuals associated with topics relevant to learners who experience low-incidence disabilities and/or deaf-blindness (DB). For the past six years, Dr. Bashinski has served as a Site Principal Investigator for two national research projects conducted on learners who experience DB and have received a cochlear implant. Dr. Bashinski has extensive experience providing professional development and technical assistance across the US and internationally, particularly in the areas of communication development, AAC, and nonsymbolic communication intervention strategies for learners with low-incidence disabilities, including CHARGE syndrome.

Presentation Abstract:
Since October 2005, back-to-back national research studies have been underway with children who experience deaf-blindness and have received a cochlear implant. The second largest participant subgroup in these studies, by etiology, is children with CHARGE syndrome. This session will highlight results obtained with this subgroup of participants. Data for the entire subgroup of participants with CHARGE, as well as a comparison of skill gains and communication development for the CHARGE participant subgroup and the overall study group will be presented. Specific data regarding any relationship of age at implant, as well as duration of time in sound since implantation, to communication development for children with CHARGE will be discussed. Finally, the session will introduce the Language Environmental Analysis (LENA)—an emerging technology that measures a child’s auditory environment (i.e., meaningful talk, distant talk, television, general noise, and silence) across a 16-hour period. LENA software, used to analyze the frequency of adult words spoken to a child, a child’s vocalizations, and conversational turns will be described. One case study with a participant with CHARGE Syndrome, including LENA data, will be presented.
National Cochlear Implant Studies with Children with Deaf-Blindness: Results for Participants with CHARGE Syndrome

10th International CHARGE Syndrome Conference
July 2011
Susan M. Bashinski, Ed.D.

Funded by the U.S. Department of Education, Office of Special Education Technology and Media Services for Individuals with Disabilities (CFDA 84.327A).
Grant #H327A080045
Project Officer, Maryann McDermott

Opinions expressed within are those of the project / authors and do not represent the position of the U.S. Department of Education.

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East Carolina University
Susan M. Bashinski, Ed.D.

Cincinnati Children’s Hospital Medical Center
Susan Wiley, MD & Charlotte Ruder

Acknowledgements

• We wish to extend a special “thank you” to all of the children and their parents who are participating in the study.
• We also wish to thank the many state Deaf-Blind projects and private consultants who have assisted with the research.
• We couldn’t have accomplished these tasks without you!

States Represented (26 + DC)
(States in blue include children with CHARGE)

<table>
<thead>
<tr>
<th>Arizona</th>
<th>Maryland</th>
<th>Oklahoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>Massachusetts Perkins</td>
<td>Oregon</td>
</tr>
<tr>
<td>Delaware</td>
<td>Mississippi</td>
<td>Pennsylvania</td>
</tr>
<tr>
<td>Florida</td>
<td>Missouri</td>
<td>South Carolina</td>
</tr>
<tr>
<td>Georgia</td>
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<td>Tennessee</td>
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<tr>
<td>Illinois</td>
<td>New Jersey</td>
<td>Texas</td>
</tr>
<tr>
<td>Indiana</td>
<td>New York</td>
<td>Virginia</td>
</tr>
<tr>
<td>Kansas</td>
<td>North Carolina</td>
<td>Washington</td>
</tr>
<tr>
<td>Kentucky</td>
<td>Ohio (CCHMC)</td>
<td>Washington DC</td>
</tr>
</tbody>
</table>
Three Major Project Phases

- Research - Today’s focus
- Research to Practice - Intervention Strategies
- Practice to Technical Assistance & Training – Methods used to teach care providers

Outcomes Participants will:

- learn aspects of cochlear implantation that appear to be positively correlated with communication skill gains by children with CHARGE
- gain knowledge regarding the range of outcomes achieved by children who have CHARGE Syndrome, following CI surgery
- learn about LENA technology and ways in which this data collection system can be used to guide intervention and language stimulation in the home

2009 National Child Count for Children Who Are Deaf-Blind

- Overall 4,313 children have a moderate-severe, severe, or profound sensori-neural hearing loss
- States increased their identification of children with implants from 251 in 2005, to 581 in 2009
- An increased number of children are receiving bilateral implants
- 747 children have been identified as having CHARGE Syndrome, of which 72 have confirmed implants

Outcomes of Project

- To collect data on the outcomes and related factors for children so parents / guardians can make more informed decisions about implantation, services, types of therapy for their children
- To identify factors correlated with more positive child outcomes, with the long-term objective of improved intervention and access to opportunities for language growth

Research Studies

- Study A – What effect does age at implant and “time in sound” (hearing age) have on child outcomes?
- Study B – What are the differences in the care provider’s verbal interactions before and after implant?
- Study C – What are the effects of individualized interventions carried out by care providers, post-implant, in natural environments? (In Progress)

Research: Children Who Are Deaf-Blind With Cochlear Implants

- Participants’ Status: How many children are participating?
- Demographics: Who are these children?
### Participant Demographics: Children with CHARGE

#### Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Number of Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Post CI Only</td>
<td>1</td>
</tr>
<tr>
<td>Pre CI Only</td>
<td>6</td>
</tr>
<tr>
<td>Pre-Post CI</td>
<td>--</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1</td>
</tr>
</tbody>
</table>

* 3 children with bilateral implants

### Vision Impairment  
(n = 29)

<table>
<thead>
<tr>
<th>Vision Impairment</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Vision (&lt;20/200)</td>
<td>38%</td>
</tr>
<tr>
<td>Legally Blind</td>
<td>28%</td>
</tr>
<tr>
<td>Light perception only</td>
<td>3%</td>
</tr>
<tr>
<td>Totally Blind</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>13%</td>
</tr>
</tbody>
</table>

### Additional Challenges

- 58.6% have physical challenges
- 58.6% have cognitive challenges
- 20.7% have behavior challenges
- 93.1% have complex health care needs

### Race/Ethnicity  
(n = 29)

- Black (6.9%)
- Latino (6.9%)
- White (82.8%)
- Mixed Race (3.4%)

### Participants’ Age at Implant  
(n = 23)

- 12 months or younger = 6
- 13 - 24 months = 7
- 25 – 36 months = 8
- 37 – 48 months = 1
- over 48 months = 1

### Participants’ “Time in Sound” / Hearing Age  
(as of most recent assessment)  
(n = 22)

- 12 months or less = 8
- 13 - 24 months = 4
- 25 – 36 months = 2
- 37 – 48 months = 1
- over 48 months = 7

* A large number of young participants have little “time in sound.”
Participant Demographics: Children with CHARGE

Participants’ Age (as of most recent assessment) (n = 22) (Range = 19 month to 8 years 3 months)

- 12 months or less = 0
- 13 - 24 months = 4
- 25 – 36 months = 4
- 37 – 48 months = 2
- over 48 months = 12

Research Studies

- **Study A:** What effect does age at implant and “time in sound” (hearing age) have on outcomes for children with CHARGE Syndrome?
  - n = 22
  - Longitudinal design
  - **Outcomes:** Taken from a battery of assessments

Assessments

- A battery of assessments was selected that examined child behaviors across a variety of domains (birth to 60 months) & included small increments across items
- The Reynell-Zinkin Scales have been validated for children with low vision and blindness
- Assessments were repeated across time (depending on post-implant or pre-implant status; at least annually for post)

Assessments Used In the Research/Intervention Project

- Communication & Symbolic Behavior Scales Developmental Profile
- MacArthur-Bates Communicative Developmental Inventory (W&G or W&S)
- Reynell-Zinkin Scales - 7 sub-scales
- Infant-Toddler Meaningful Auditory Integration Scale or Meaningful Auditory Integration Scale
- Speech Intelligibility Measures

STUDY A: Example Data Analyses

- **Reynell – Zinkin Scales:**
  - Response to Sound
  - Vocalization and Expressive Language
- **Other:**
  - Age at Implant
  - “Time in Sound”
  - Age at Assessment

Data Analysis
Data Analysis

Most Recent Post CI Reynell-Zinkin Response to Sound by Time in Sound

(r = .693, p = .0001)

Time in Sound (Months)

Data Analysis

Most Recent Post CI Reynell-Zinkin Response to Sound by Age Assessment

(r = .542, p = .009)

Age at Assessment (Months)

Data Analysis

Response to Sound: Implanted at 24 Months or Earlier

1st Assessment Score
2nd Assessment Score
3rd Assessment Score

Data Analysis

Response to Sound: Implanted After 24 Months of Age

1st Assessment Score
2nd Assessment Score
3rd Assessment Score
4th Assessment Score

Data Analysis

Pre-Post CI: Response to Sound

Pre CI Post CI 1 Post CI 2

Reynell-Zinkin Response to Sound

- Weak relationship between age at implant and receptive language
- Significant and relationships between “time in sound” (hearing age) and age at assessment and receptive language
- Receptive language of children with CHARGE DOES improve significantly over time, post-implant
- Receptive language DOES improve significantly from pre- to post-implant
Data Analysis

Most Recent Post CI Reynell-Zinkin Vocalization and Expressive Language by Age at Implant
\( r = -0.117, p = .603 \)

Age at Implant (Months)

Data Analysis

Most Recent Post CI Reynell-Zinkin Vocalization and Expressive Language by Time in Sound
\( r = 0.792, p = .0001 \)

Time in Sound (Months)

Data Analysis

Most Recent Post CI Reynell-Zinkin Vocalization and Expressive Language by Age at Assessment
\( r = 0.616, p = .002 \)

Age at Assessment (Months)

Data Analysis

Vocalization and Expressive Language: Implanted at 24 Months or Earlier

Age at Implant

Data Analysis

Vocalization and Expressive Language: Implanted After 24 Months of Age

Age at Implant

Data Analysis

Pre-Post CI: Vocalization and Expressive Language

Age at Implant (Months)
**Reynell-Zinkin Vocalization and Expressive Language**

- Little relationship between age at implant and expressive language
- Significant and strong relationships between “time in sound” (hearing age) and age at assessment and expressive language
- Expressive language of children with CHARGE does improve significantly over time, post-implant
- Expressive language does improve significantly from pre- to post-implant for some but not all children (to date)

**Data for Post-Implant Children**

<table>
<thead>
<tr>
<th></th>
<th>RECEPTIVE LANGUAGE</th>
<th>EXPRESSIVE LANGUAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to sound</td>
<td>94.4%</td>
<td>Sound production 100%</td>
</tr>
<tr>
<td>Response to words and phrases</td>
<td>53.5%</td>
<td>One-word production/jargon 45.4%</td>
</tr>
<tr>
<td>Word identification (out of context)</td>
<td>45.4%</td>
<td>Meaningful words 45.4%</td>
</tr>
<tr>
<td>Simple directives</td>
<td>36.3%</td>
<td>Simple sentences 31.8%</td>
</tr>
<tr>
<td>Complex directives</td>
<td>31.8%</td>
<td>Complex sentences 18.2%</td>
</tr>
</tbody>
</table>

**Data for Pre-Post Implant Children**

<table>
<thead>
<tr>
<th></th>
<th>RECEPTIVE LANGUAGE</th>
<th>EXPRESSIVE LANGUAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to sound</td>
<td>Pre- 60% Post- 100%</td>
<td>Sound production Pre- 11% Post- 100%</td>
</tr>
<tr>
<td>Response to words and phrases</td>
<td>20% 60%</td>
<td>One-word production/jargon 0% 40%</td>
</tr>
<tr>
<td>Word identification (out of context)</td>
<td>0% 20%</td>
<td>Meaningful words 0% 40%</td>
</tr>
<tr>
<td>Simple directives</td>
<td>0% 20%</td>
<td>Simple sentences 0% 20%</td>
</tr>
<tr>
<td>Complex directives</td>
<td>0% 20%</td>
<td>Complex sentences 0% 0%</td>
</tr>
</tbody>
</table>

**Overall Findings to Date: Study A**

- Participants in the study are a very diverse group
- With this diversity come complex relationships (rather than simple relationships between such variables as age and outcomes)

**Study B – Care providers’ talk to the child, after implantation (i.e., compared to pre-implant)**

Use of the Language Environmental Analysis (LENA) to record:
- the auditory environment
- the adult’s verbalizations
- the child’s vocalizations
- the turns taken in conversation
LENA Data

- Auditory Environment:
  - meaningful talk
  - distant talk
  - TV
  - noise
  - silence
- Adult Words
- Child Vocalizations

LENA Data

- Conversational Turns
- Estimated Mean Length of Utterance
- Estimated Developmental Age (in months)
- Standard Score
- Percentile

LENA Data

LENA Data

LENA Data

LENA Data

LENA Data

- Mean Counts Per Hour: Child A
- Adult Word Count
- Child Vocalizations
- Conversational Turns

LENA Data

- Mean Counts Per Hour: Child A
- Adult Word Count
- Child Vocalizations
- Conversational Turns
Overall Findings to Date: Study B

- Small numbers of pre-/ post-implant children and their parents have participated [to date]
- Significant variability seen in parents’ interactions with their children
- Some initial increase in verbal interactions, by both parents, has been observed after CI surgery
- Parents’ verbal interactions vary considerably over time

Study C –Effects of individualized interventions, implemented by the care providers in natural environments, after CI surgery (In Progress)

[One participant with CHARGE]

Overall Findings to Date: Study C

- Multiple child behaviors and care provider strategies are targeted in 12-16 sessions
- Repeated sessions, across time, are necessary for parent implementation [implications for TA]
- Three participants & their care providers have completed the intervention; four others are in progress
- Observed parent and child outcomes in maintenance and generalization conditions are encouraging

Limitations To Progress

- Many participants did not have prelinguistic communication skills
- Many participants did not have skills of functional object use
- Auditory - Verbal programs were not individualized
- Many participants did not wear their implants consistently
- Many participants were not mapped frequently (and, possibly, accurately)
Limitations To Progress

- Many children were “dropped” from Auditory - Verbal programs, due to lack of progress
- Parents reported not being taught effective strategies that could be used at home
- Frequent use (in therapy and in-home interactions) of toys / objects with “high” tactile and visual properties—but not sound
- Many children do not have the opportunity to frequently hear speech directed to them in close proximity

Variability in Outcomes Indicates ....

- the need for individualized and adaptive approaches (Moeller, 2006)
- the need to integrate perception / receptive and production / expressive outcomes
- the need to incorporate more cognitive skills into intervention (Pisoni, et al., 2010)
- the need to do a better job of teaching parents how to implement strategies and embed them in caregiving, play, and family activities

PLEASE visit our website: www.kidsdbci.org

Family stories
Resources
Links

Thanks so much for your attention!

Susan M. Bashinski
bashinkis@ecu.edu
252.737.1705
The Child`s voice

Thursday, 07/28/11
Platform #6: 11:50AM-12:15PM
Wekiwa 3 & 4

Wenche Andersen and Eva Seljestad
Skaadalen Resource Centre for
the Deafblind

Presenter Information:
Wenche Andersen, Senior Adviser, Skaadalen Resource Centre for the Deafblind, Oslo, Norway
Eva Seljestad, Senior Adviser, Skaadalen Resource Centre for the Deafblind, Oslo, Norway

Presentation Abstract:
Comments on a conversation with a 9 year old girl with CHARGE syndrome. The combined hearing and vision loss makes it exhausting for the child to follow and participate in dynamic dialogues between hearing children. It is easy to underestimate this fact when a child in general, fulfills adequate demands for her age. She is talking, signing, reading and writing. Her cognitive capacity is good, but might not be properly evaluated because she often becomes overwhelmed with impressions from the environment. We focus upon challenges in social activities and communication. We also discuss how our counseling is influenced and enriched when we stop talking and start to listen.

(Case Study. Video)

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011
Problems with Self-Regulation and Behavior in CHARGE

Thursday, 07/28/11
Platform #7: 2:30-2:55
Wekiwa 3 & 4

Tim Hartshorne, Ph.D.
Central Michigan University

Presenter Information:

Tim Hartshorne is a professor of psychology, specialized in school psychology, at Central Michigan University. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. His particular interest is in understanding the challenging behavior exhibited by many individuals with CHARGE. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project.

Presentation Abstract:

The proposed CHARGE behavioral phenotype includes problems with self-regulation. This presentation explores the nature of self-regulation, its role in the behavioral challenges found with CHARGE, problems with the regulation of learning, behavior, emotions, and sensations, and how parents and teachers might use scaffolding to assist individuals with CHARGE to learn to self-regulate.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011
Problems of self-regulation in the behavior of individuals with CHARGE syndrome
Tim Hartshorne
Central Michigan University

Two ends of the spectrum
• Totally regulated
• Completely dysregulated

Self-regulation Scale
I have a hard time paying attention and my mind tends to wander.
When I really need to pay attention I can focus my mind.
I can readily prioritize the things I need to get done in a day.
I become overwhelmed when faced with too many things to take care of.
I get upset a lot and cannot find any way to get rid of those feelings.
When I really need to control my feelings I can do it.
When there is nothing going on I have to create it.
When I am in a noisy crowd I have to find a way to leave.

Self-Regulation
• Managing the threshold of arousal
• Processes of self-control
• Both suppresses and encourages; inhibits and promotes
• Supports homeostasis of the system
• Critical to development

Dunn Conceptual Model

Jude Nicholas and Tim Hartshorne, 2009
The extremes

- If a system cannot self-regulate, we have to provide external systems of regulation
- Too much regulation can stifle innovation
- Too little regulation can lead to chaos and abuse

Diagnoses in CHARGE

- OCD – a way to reduce stimulation and exercise control
- ADHD – a problem with regulating sensory stimulation and focusing on a problem
- Tic disorder – a stress response to lack of control over environment
- Autistic-like behavior – the failure of regulation strategies

Scaffolding

- The process of planning and organizing the activity of children so that they can execute a task that is beyond their current level of ability.

Scaffolding for self-regulation

- Because self-regulation skills are hard for children with significant disabilities to develop
- We have to provide the external support for what will become an internal self-regulatory process

Components of Scaffolding

1. Identification of the problem to be solved
2. Focus activities on outcomes and goals
3. Frustration control
4. Reducing the complexity of the task
5. Marking critical relevant features
6. Modeling

The Shape Sorter

1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling
The four areas of self-regulation

- Define each area of self-regulation
- What is involved?
- Describe scaffolding strategies

Cognitive Regulation

- Motivated to think about a problem
- Being precise and accurate
- Comparing alternative choices
- Adapting prior learning to the problem

How learning changes

- Concrete reasoning
  - Objects and events available to the senses
- Rote learning and memorization
  - Alphabet
  - Multiplication table
  - Names of things
- Abstract reasoning
  - Ideas or concepts with no physical referents

Executive Function

- Initiate – goal, planning, getting started
- Sustain – staying on task, moving toward goal
- Inhibit – avoiding getting side tracked
- Shift – changing directions when needed

These functions continue to develop into early adulthood and can be improved.

Cognitive Scaffolding

- Mediated Learning Experience

  1. Problem identification
  2. Focus on outcomes
  3. Frustration control
  4. Reducing complexity
  5. Marking features
  6. Modeling

Example

- Motivated to think about a problem
- Being precise and accurate
- Comparing alternative choices
- Adapting prior learning to the problem

Figure 2: Raven’s progressive matrices
Behavior Regulation

- What is the purpose of the behavior?
- Is it consciously planned and intentional?
- Well regulated behavior is both intentional and goal directed.

The Self-Regulation of Behavior

- Too often we tell children what we do not want them to do, and not what we very much do want them to do.

- Strategies for building self-regulation
  - Offering choices (shared control)
  - Rehearsing behavior options
  - Building communication
  - Delay of reinforcement
  - Embedding a positive context

Behavior Scaffolding

- Supporting what we want the child to do
- Positive Behavioral Supports
  - How does the social environment support positive behavior?
  - How does the physical environment support positive behavior?
  - What skills does the child possess for positive behavior?

Social Environment

- Social embeddedness
- Social skills
- Negative relational schemas
- Circle of Friends

Physical Environment

- Supporting what we want the child to do
- Responsive to sensory needs of the child
- Responsive to physical limitations
- Reducing complexity

Child’s Behavior

- Supporting what we want the child to do
- Reading behavior as communication
- Understanding the purpose of behavior
- Functional Communication Training

1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling
Emotion Regulation

- What a person does to manage his or her emotional states
  - Regulate both negative and positive emotions
  - Decrease emotions or increase emotions
  - May be conscious or unconscious
  - May be internal or external
  - Are generally goal directed

Learning to regulate emotions

- “She didn’t know what to do with her emotions”
  - Emotional expression
    (What does it look like to be angry, sad, etc.?)
  - Emotional intensity
    (How worried, sad or mad would you feel in this situation?)
  - Emotional self-efficacy
    (How could you make yourself feel better in this situation?)

Emotion Scaffolding

- Social referencing
- Attachment
- Talking about how you feel
- Soothing
- Positive face to face play
- Distraction
- Problem-solving
- Altering interpretations
- Suggesting better ways to respond
- Creating daily routines that make emotional demands predictable and manageable

Physiological Regulation

- Sensory
- Pain
- Fatigue
- Eating
- Sleeping
- Respiratory/Digestive/Temperature/Other systems

The Self-Regulation of Physical States

- Relaxation
- Tuning in to our bodies
- Bio-feedback – being aware of control
- Management of arousal
  - Timeout
  - Sensory room

Physiological Scaffolding

- Developmental Care
- Sensory Integration
- Physical responses
  - Hug
  - Squeeze
  - Touch
  - Rock
  - Tickle
Fun Chi
• Reduced stress
• Reduced anxiety
• Reduced depression
• Increased self-esteem
• Increased energy/focus/concentration
• Increased positive mood
• Better balance
• Improved sleep
• Improved immune system

1. Problem Identification
2. Focus on outcomes
3. Frustration control
4. Reducing complexity
5. Marking features
6. Modeling

Summary
• Children with CHARGE often have poorly regulated systems
• They will do better socially and academically if they can learn to self-regulate
• They can only develop self-regulation skills slowly unless they experience a lot of scaffolding from the adults in their lives

Thanks to my Lab
— Tasha Nacarato
— Maria Ramirez
— Rachel Vert
— Stephanie Budde
— Valerie Webber
— Kasee Stratton

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Identifying the ‘P’ in CHARGE: Pain & the Relationship of Pain to Challenging Behavior

Thursday, 07/28/11
Platform #8: 2:55-3:20
Wekiwa 3 & 4

Kasee Stratton, M.A.
Kennedy Krieger Institute: Pediatric Developmental Disorders Clinic at John Hopkins University School of Medicine
Central Michigan University

Presenter Information:

Kasee Stratton is a doctoral student at Central Michigan University. She received her Master of Arts in School Psychology in December of 2010. Currently she is completing her pre-doctoral internship in the Pediatric Developmental Disorders Clinic at the Kennedy Krieger Institute, a part of the John Hopkins University School of Medicine. She has been researching CHARGE syndrome, pain, and challenging behaviors for six years and has presented previously in Australia, New Zealand, Denmark, and at the 9th International CHARGE Syndrome Conference.

Presentation Abstract:

The research on pain in children with developmental disabilities is limited, including individuals with CHARGE. It has long been suspected that individuals with CHARGE have a high-threshold for pain. Our research, however, found that individuals with CHARGE experience considerable pain, including long term (chronic) pain. A relationship was found between challenging behavior (e.g. self injury) and an increase in pain intensity. A non-vocal pain measure will be discussed that was designed specifically for individuals with CHARGE to identify pain. Further, the relationship between pain and challenging behaviors will be described and intervention strategies will be suggested.
Identifying the ‘P’ in CHARGE:
Pain and the Relationship of Pain to Challenging Behavior

Kasee K. Stratton, M.A.
Kennedy Krieger Institute at John Hopkins University School of Medicine
Central Michigan University

CHARGE FAST PASS

- Pain in developmental disabilities
- CHARGE syndrome and pain
- Are we identifying pain?
- Challenging behaviors in CHARGE
- How pain is related to challenging behavior
- Reducing the pain experience

Pain in Developmental Disabilities

- “Higher” threshold for pain
  - Has been suggested in CHARGE (Davenport, 2002)
- No evidence
- Higher risk for experiencing more frequent pain
- Identifying Pain in CHARGE
  - Poor communication strategies

Common Pain Experiences

<table>
<thead>
<tr>
<th>Pain Experience</th>
<th>N=58*</th>
<th>n= Percentage of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear Infections</td>
<td>39</td>
<td>67.2</td>
</tr>
<tr>
<td>Sinus Infections</td>
<td>24</td>
<td>41.4</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>24</td>
<td>41.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>41.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>23</td>
<td>39.7</td>
</tr>
<tr>
<td>Tactile Defensiveness</td>
<td>20</td>
<td>34.5</td>
</tr>
<tr>
<td>Migraine</td>
<td>14</td>
<td>24.1</td>
</tr>
<tr>
<td>Stoma Pain</td>
<td>12</td>
<td>20.7</td>
</tr>
<tr>
<td>Abdominal Migraine</td>
<td>11</td>
<td>19.0</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>11</td>
<td>19.0</td>
</tr>
<tr>
<td>Back Pain</td>
<td>8</td>
<td>13.8</td>
</tr>
<tr>
<td>Hip Pain</td>
<td>6</td>
<td>10.3</td>
</tr>
<tr>
<td>Jaw Pain</td>
<td>5</td>
<td>8.6</td>
</tr>
<tr>
<td>Pain During Sleep</td>
<td>5</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Most Intense Pain and Average Duration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>2.67 (.87)</td>
<td>2-4 (13.50 ± 13.51)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.38 (.80)</td>
<td>1-4 (52.25 ± 58.38)</td>
</tr>
<tr>
<td>Surgery</td>
<td>2.34 (.97)</td>
<td>1-4 (9.52 ± 9.40)</td>
</tr>
<tr>
<td>Chronic Recurrent Oral Ulcers</td>
<td>2.24 (.99)</td>
<td>0-4 (22.88 ± 32.18)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.17 (.82)</td>
<td>1-4 (35.13 ± 41.51)</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>2.06 (.14)</td>
<td>0-4 (149.0 ± 149.0)</td>
</tr>
<tr>
<td>Breathing</td>
<td>2.09 (.83)</td>
<td>1-4 (108.67 ± 131.82)</td>
</tr>
<tr>
<td>Hip/Back Pain</td>
<td>1.86 (.95)</td>
<td>1-4 (90.90 ± 144.14)</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>1.82 (.87)</td>
<td>1-3 (95.70 ± 156.97)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.61 (.80)</td>
<td>1-3 (66.48 ± 99.42)</td>
</tr>
<tr>
<td>Jaw Discomfort</td>
<td>1.56 (.88)</td>
<td>1-3 (13.22 ± 11.17)</td>
</tr>
<tr>
<td>Difficulty Swallowing</td>
<td>1.59 (.83)</td>
<td>1-4 (129.00 ± 154.64)</td>
</tr>
</tbody>
</table>
Migraines

• Trigeminal nerve (CN V)
  — Sensation and function to your jaws, face, tongue, sinus, palate, eyes, teeth, and lips.
  — Also has a role with chewing and swallowing
  — CN dysfunction in CHARGE

Abdominal Migraine

• Typically children ages 5 to 9
• Linked to adult migraines
• Lasts 1 to 72 hours
• Acute stomach pain with
  — Nausea
  — Vomiting
  — Light sensitivity
  — Diarrhea
  — Loss of appetite

Constipation

• Painful bowel movements
• Dry or hard stool
• Nausea
• Cramps, abdominal pain
• Fecal impaction
  — Abdominal cramping
  — Rectum discomfort

Gastroesophageal Reflux

• Average of 170 days a year
• Heartburn
  — Involves a burning pain in the chest (under the breastbone)
  — Increased by bending, stooping, lying down, or eating
  — More frequent or worse at night
  — Relieved by antacids
• Nausea and vomiting
• Regurgitation of food
• Sore throat

Tactile Defensiveness

• textured materials or items
• “messy” things
• vibrating toys
• a hug or kiss
• certain clothing textures
• rough or bumpy bed sheets
• seams on socks
• tags on shirts
• light touch
• hands or face being dirty
• shoes and/or sandals
• wind blowing on bare skin
• bare feet touching grass or sand

Are we identifying pain?

• Are you able to determine when your child is experiencing pain?
  — 75% -Yes
  — Did not vary significantly by age of child

• Zero parents could identify chronic pain and no child could indicate chronic pain
Behaviors that Indicate Pain

- Vocal
  - Crying, moaning
- Social
  - Withdrawn, obstinate, difficult to distract, hard to console
- Facial
  - Frowns, mouth turned down, grinding teeth
- Activity
  - Less active, restless, disturbed sleep
- Body and Limb Movement
  - Rubbing area of pain, stiffness/spasms/seizures
- Physiological
  - Change in color, sharp intake of breath

Challenging Behaviors Indicate Pain

- Behavioral Challenges
- Self-Injurious Behavior (SIB)
- Dangerous Behaviors
  - Aggressive, bites, hits head, throws objects, punches, pulls out g-tube

Why is it difficult to identify and measure pain in CHARGE?

- Limited or no communication strategies
  - Cannot use the gold-standard
- Possible social-communicative deficits
  - (Craig, 2006)
- Possible social referencing deficit
  - (Recchia 1997)

Measuring Pain

- Facial Reactions to Pain
  - Limited research
  - Facial palsy in CHARGE
- Rating Pain
  - Numerical ratings with pictures
  - Multidimensional pain tools

Measuring Pain

- Created a non-vocal, multidimensional pain scale
  - CHARGE Non-Vocal Pain Assessment (CNVPA)
- Developed from:
  - NCCPC-R (Breau et al., 1998)
  - PPP (Hunt, 2003)
  - Parent/caregiver input
What do we know about the CNVPA?

- Mean differences between no-pain and pain assessments were significantly different.

Do parents find this pain assessment to be relevant to identify their child’s pain (non-vocally)?

<table>
<thead>
<tr>
<th>Relevance</th>
<th>n</th>
<th>Percentage of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely Relevant</td>
<td>14</td>
<td>24.6</td>
</tr>
<tr>
<td>Relevant</td>
<td>17</td>
<td>29.8</td>
</tr>
<tr>
<td>Somewhat Relevant</td>
<td>18</td>
<td>31.6</td>
</tr>
<tr>
<td>Not Relevant</td>
<td>8</td>
<td>14.0</td>
</tr>
</tbody>
</table>

Instrument may not be relevant because:

- Child can verbalize pain vocally (12)
- Never complains of pain and seems to tolerate it well
- I’ve already developed ways to identify pain for my child (3)
  - “After 24 years, I am in tune to my child’s health”

PAIN AND BEHAVIOR

Does Pain Impact Behavior?

- Evidence that pain is associated with behavior problems in typical-developing children
  - De Lissovoy (1962) head banging and otitis media
  - Hart, Box, & Jenkins (1984) tantrums and upper respiratory infection
- Evidence that pain is associated with behavior problems in children with disabilities
  - O’Reilly (1997) self-injury and otitis media
  - Carr & Owen-DeSchryver (2007) sick days
  - Lekkas & Lento (1978) constipation
  - Kennedy & Meyer (1996) allergies

Does Pain Impact Behavior?

- Aggressive behavior, destructive behavior, and self-injury (Kennedy & O’Reilly, 2006)
- Elevated pain → elevated self-injury (Symons & Danov, 2005)
- Attachment
- Adaptive Functioning
- Quality of life may be compromised (Oberlander & Symons, 2006)
Understanding Pain

- Unknown what children with CHARGE know about pain
  - How to predict when and how it will be resolved
  - Increase the intensity of the experience and also increase challenging behaviors
  - Individuals with CHARGE may need to be explicitly taught coping strategies to help identify pain and how to control these events in their lives

All Behavior is Communication!

Reducing the pain experience

- Mitigation
  - Analgesics
  - Bed rest
  - Dietary change
- Redesigning the environment
  - Reducing the demands
- Teaching coping skills
  - Self advocacy
  - Functional communication alternatives

Caution with Medications

Analgesic failure may be due to ...
- Inappropriate drug or dose selection for type of pain
- Genetic factors inherent to capacity to metabolize medications
- Impact of use of multiple drugs with competition for metabolic and excretory pathways
- Neurological substrate underlying CHARGE

Presenter Information:

Kasee Stratton, M.A.
Central Michigan University
Doctoral Student in School Psychology

Kennedy Krieger Institute at John Hopkins University School of Medicine
Behavioral Psychology Intern

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strat1kk@cmich.edu
Navigating the NIH

Thursday, 07/28/11
Platform #9: 3:20-3:45
Wekiwa 3 & 4

Tiina K. Urv, Ph.D.
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institutes of Health (NIH)

Presenter Information:

Tiina Urv, Ph.D., joined the Intellectual and Developmental Disabilities (IDD) Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH) as a program director in October 2006. Dr. Urv is a developmental disabilities specialist with a Ph.D. from Columbia University and over 25 years of experience working with individuals with intellectual disabilities in both clinical and research settings. Prior to joining the Branch, she was an assistant professor at University of Massachusetts Medical School's Eunice Kennedy Shriver Center and a research scientist at the New York State Institute for Basic Research in Developmental Disabilities. The focus of her work has been the behavioral aspect of aging and Alzheimer disease in adults with Down syndrome and developmental disabilities. Dr. Urv's work in the IDD Branch has focused on Newborn Screening of Rare Diseases and Fragile X syndrome (FXS).

Presentation Abstract:

Discussion of funding opportunities at the NIH for grants related to CHARGE syndrome.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011
CHARGE Syndrome: Quality of Life in Adolescence and Adulthood

Thursday, 07/28/11
Platform #10: 4:10-4:35
Wekiva 3 & 4

Nancy Salem-Hartshorne, Ph.D., Delta College
Kim Blake, M.D., Dalhousie University/IWK Health Center
Jillian McCuspie, Medical Student, Dalhousie University
Tasha Nacarato, Graduate Student, Central Michigan University

Presenter Information:
Dr. Salem-Hartshorne is an instructor at Delta College in Central Michigan. Her research has focused on developmental outcomes for individuals with CHARGE syndrome. She has a son, Jacob, aged 22, who has CHARGE syndrome.

Dr. Blake is a Pediatrician at IWK Health Center and Director of Undergraduate Education in Pediatrics at Dalhousie University in Nova Scotia. Her research focus is CHARGE syndrome, with a particular focus on adolescent and adult issues.

Jillian MacCuspie is a medical student at Dalhousie University. She has been research assistant to Dr. Blake for 3 years and her main interest is in pediatrics and disability.

Tasha Nacarato is a graduate student in School Psychology at Central Michigan University. She has been a research assistant to Dr. Hartshorne during the past two years in the area of CHARGE syndrome.

Presentation Abstract:
Very little is known about the quality of life of individuals with CHARGE syndrome during their adolescent and early adult years. Data was gathered both during the the previous CHARGE syndrome conference in Illinois, and over the phone and via mail. There were more than fifty respondents, most from the United States. Participants consisted of individuals aged 13 and up. Participants and their parents or guardians gave details, through interview and checklist, about their CHARGE features, developmental histories, medical and behavioral concerns, and independent abilities. They also completed measures of general quality of life and health-related quality of life. Results will be presented and implications about findings will be discussed so that parents and professionals may have awareness of this information when working with individuals with CHARGE syndrome. Handouts will be available at the poster session.
So Many Ways to Have a Conversation

Thursday, 07/28/11
Platform #11: 4:35-5:00
Wekiwa 3 & 4

Martha Majors
Assistant Education Director
Deafblind Program
Perkins School for the Blind

Presenter Information:

Perkins School for the Blind developed a series of 3 webcasts related to CHARGE syndrome; Martha participated in these webcasts focusing on the educational implications for a child with CHARGE syndrome.

Presentation Abstract:

The development of communication for children with CHARGE syndrome can be challenging for both the child and their team (families and educators). For most students receptive language is the area of strength; the use of expressive communication can be delayed and as a result there is a level of frustration that builds within the child. Current thinking includes the consistent use of total communication as well as assistive technology as a support. The best solutions come from a team approach where several disciplines come together to consider the strengths of the child that not only includes communication but use of vision, hearing, and physical presentation. In this way, the whole child is taken into consideration and outcomes can be more child specific and focused.

2nd Professional Day at the 10th International CHARGE Syndrome Conference
Rosen Shingle Creek Resort, Orlando, FL, July 28-31, 2011
Many Ways to Have a Conversation

Martha M. Majors
Assistant Education Director
Deafblind Program
Perkins School for the Blind

Conversation Format

**Case Study**
- Description of Sensory Loss
- Developmental Level
- Communication Matrix
  - Receptive
  - Expressive
- Description of Total Communication
  - Receptive
  - Expressive

Conversation Conclusion

- Each child is an individual learner
- Each child develops a way to communicate
- Each child uses total communication in their own unique way
- Each child makes progress over time with consistent access to appropriate communication modes
The Potentials of Diversity. Results of a doctoral thesis referring early dialogues between children with CHARGE Syndrome and their parents

Thursday, 07/28/11
Platform #12: 5:00-5:25
Wekiwa 3 & 4

Andrea Scheele, Prof.
Dr. Ursula Horsch
University of Education Heidelberg, Germany

Presenter Information:
Ursula Horsch is Professor for the education of hard of hearing and deaf children and for Early Education at the University of Education in Heidelberg/Germany (since 1991). She is general and special education teacher and is working at the institute for special education since 1974. She finished her PhD at the University in Cologne in 1981. Her main areas are education of the hard of hearing under a dialogical point of view, research on the early and very early education with concentration on early dialogues between parents and their impaired and not impaired infants with a focus on “Bildung” within international and interdisciplinary research projects with partner Universities in Turku/Finland, Olsztyn/Poland and Listen and Talk Seattle/USA. She develops didactic dvds for computer based analysis of early dialogical interactions and has numerous publications referring early education and supports more than 20 doctoral studies, she has publications in research, book contributions as well as presentations in research at national and international conferences. Contact: ursulahorsch@aol.com, website: www.ursula-horsch.de; Andrea Scheele became teacher and early educationer for the deaf and the blind at the University of Education Heidelberg in Germany and is concentrating on pedagogic for the deafblind since 2002. In 2006 she became member of the research team of Prof. Dr. Horsch at the University of Education Heidelberg and started her PhD study on early interactions between infants and toddlers with CHARGE Syndrome and their parents, which will be finished 2011. During that time she participated in many conferences on Deafblindness and had the chance to exchange and network with lots of people about Deafblindness and CHARGE Syndrome. In Germany she cooperates intensively with the CHARGE foundation of parents. Contact: as@andrea-scheele.de, website: www.andrea-scheele.de

Presentation Abstract:
The study “Early dialogues of children with CHARGE Syndrome and their parents” is introduced and the most striking results are presented. Next to scientific results of early dialogues between children with CHARGE Syndrome and their parents in contrast to early dialogues of children without disabilities and their parents' selected screenshots from eminenty interesting video sequences with different topics like gentle gestures are shown and discussed in the context of potentials of diversity and inclusion. In the presentation a short introduction into the methodology of the study is given and explained how more than 200 videos of children with CHARGE Syndrome and their parents were evaluated since 2006 and what they show. After that the scientific results which accentuate important elements in early dialogues like Motherese/Fatherese but also signs and gestures or touch, their correlations to each other and transition probabilities from one to the other and the effect of time are presented and discussed.
The Potentials of Diversity
Results of a doctoral thesis referring early dialogues between children with CHARGE Syndrome and their parents

2nd Professional Day
10th International CHARGE Syndrome Conference
July 28th 2011, 5 - 5.25
Orlando/FL

Andrea Scheele, Prof. Dr. Ursula Horsch
University of Education Heidelberg

Agenda

1. A short insight into the PhD study
2. Let’s have a look at a dialogue
3. Most striking outcomes
4. Outlook and questions

A short insight into the PhD study

Aims

- Widespread collection, documentation and qualitative analysis of observable dialogic elements (Motherese/Fatherese, Dialogic Echo, vocalisation, eye and body contact),
- statements referring the development of the dialogical structure,
- reference to data and outcomes of children without disabilities and with different ones,
- evaluation of meaningful data and consequential impulses for early education,
- toehold for further research,
- calling attention to the topic of Deafblindness and CHARGE Syndrome.

Method

- 25 Child-Parent-Pairs
- Congenitally Deafblind, 14 have CHARGE
- Monthly video recording (15 min./analysis: 4 min.)
  - „Natural setting“
  - Twelve months (+ more, some over 5 years)
- n=325 video recordings (February 2011)
- Analysis with software „Interact“ (Mangold) and statistical research instrument SAS
  - Macro: mean values, correlations, variance
  - Micro: transition probabilities, time series analysis, image recognition

Analysis process
Agenda

1. A short insight into the PhD study
2. Let's have a look at a dialogue
3. Most striking outcomes
4. Outlook and questions

Let's have a look at a dialogue

Video

Let's briefly talk about what you have just seen!

Most striking outcomes

Mean values

Most striking outcomes (mean values)

Variables: Frequency referring number

- Dialogic Editing
- Eye contact
- Body contact
- Vocalization
- Motherese, Fatherese

Mean values

n=168 videos, n=28 participants
**Most striking outcomes**

- **Mean values**
  - Similarities over the groups in the tendency of the frequencies
  - Varieties in the particular form, especially referring Motherese/Fatherese (more rare used!)

  More rare use of spoken language in the dialogues with a child with CHARGE?

- **Mean values**
  - Similarities over the groups in the tendency of the duration
  - Varieties in the particular form, especially referring body contact and Motherese/Fatherese (longer used!)

  Duration makes the difference!

- **Mean values**
  - Not just a differing development over the two groups, but actually a contrary development referring the vocalisation of the child.

  (This is also true for eye contact.)

  Increasing diversity with time

**Selected summarized outcomes**

- **Graphs**
  - Frequency vocalisation control group
  - Frequency vocalisation group CHARGE Syndrome
  - Duration vocalisation control group
  - Duration vocalisation group CHARGE Syndrome

- **Table**
  - n=168 videos, n=28 participants

- **Bar charts**
  - Chart showing the number of vocalisations over different dates of testing with control and group CHARGE Syndrome.
Most striking outcomes

- Same elements!
- CHARGE:
  - eye & body contact: Dialogic echo
  - Children try to keep the dialogue going by the use of body contact and vocalisations, but parents especially answer on eye contact and the child offering non of the examined variables
  - Less correlations for Motherese/Fatherese and the variables of the child (and lower frequency)

Outlook and questions

- We could just highlight some of the outcomes of the study, but if you are interested in more (like the results of some of the other analysed areas), please feel free to contact us.
- We hope the research on CHARGE Syndrome goes on and we hope a connection between the outcomes and the practical work can be drawn, because we think that it’s most important to improve the current support system for families.

Agenda

1. A short insight into the PhD study
2. Let’s have a look at a dialogue
3. Most striking outcomes
4. Outlook and questions

Thank you for your attendance!
We are looking forward to questions, comments, suggestions and an inspiring discussion.

Contact: ursulahorsch@aol.com and Andrea.Scheele@gmx.de or www.ursula-horsch.de and www.andrea-scheele.de
Transcripts of the videos

Father (F) and son (S): 2 years and 6 months

F: Did you notice Mom? What are you doing now? Are you distracted? Yes? Are you distracted because Mom turned on the camera? Yes? Shall we put the picture away again? Yes? Well, let’s put the picture up. Of Mom and Dad. Look. Let’s put it there, the picture. Okay? Can you still see it? Yes? There is the picture. Well, up there. What is over there? Can you show me? That, over there. Hey! Is that the light over there? The picture? That’s what you want? Yes? Okay! Look out, I get it again. I get it again. Have a look, There it is. What do you see at the picture? A nose? Hey. And you see Mom, too. And an eye. Aha, aha. Hmm. Und now? Shall I put it back again? Look out, Dad puts it up once more. Look out. Do you still see it? There it is again. What? You want to have it again? But you just said, I shall put it up. Shall I get it again? Shall I show it once more to Jonas? Okay, look out. Let’s get it again. Is it a nice picture? Yes? Dad sees it, too. Dad. And Mom. And who else is on the picture? Mom, exactly. And Jonas? Is Jonas also at the picture? Can you show him to me? You are kidding around. Are you all done with… There it shall be put? Shall I put it up again? Yes? Okay. Okay. Let’s put it up. It’s away. What is over there? There? What is there? Tell it Dad. The light, exactly. And again the picture. But above, there above, there is the light. Did you see it? The light, exactly. Can you, can you also show your Dad’s nose? That’s the nose of Dad, yes. Super, you are doing so well, you are doing well.

Vater (V) und Sohn (S): 2 Jahre und 6 Monate

Father (F) and son (S): 5 years and 5 months
(cursive = addressed to another person)

F: Look. Now. Look at me.
S: Yes.
F: Now it’s your turn to turn a card around.
S: Yes.
F: One.
S: Yes.
F: Your turn. Turn around a card.
S: Yes.
F: Okay. Who is that? Put it back again.
S: Dora.
F: That is Dora. Now you have to find a second Dora. Where is the other Dora? There, you think?
S: Yes.
F: Oh. Who’s that? Put it down.
S: A Boots.
F: A Boots! Mmh. That doesn’t fit.
S: Yes.
F: Look. A Dora. And…
S: A Boots.
F: Okay. Let’s turn them around again. One for you.
S: Yes.
F: Okay. Turning around again. Now it’s daddys turn.
S: Yes.
F: Okay. Here was the Dora, there was the Boots.
S: Yes.
F: Okay, now it’s daddys turn.
S: Swiper.
F: A Swiper. Oh. Now we have had each of them. Super. And Backpack.
S: And backpack.
F: Doesn’t fit.
S: Yes.
F: Do you still remember? Dora.
S: Dora.
F: Boots.
S: Boots.
F: Swiper.
S: Swiper.
F: Backpack.
S: Backpack.
F: Now it’s Jonas turn again. That’s clever. I would have done the same.
S: Swiper.
F: Put down.
S: Swiper.
F: Blimey! Jonas found it!
S: Yes.
F: Yes, super!
S: Yes.
F: Okay, now you may put them right here and then it’s your turn again. Because you found a pair.
S: Yes.
F: Now it’s Jonas turn again. How clever!
S: Dora.
F: A Dora. Where is the other Dora?
S: Dora!
F: Unbelievable! You found it again?
S: Yes.
S: Yes.
F: Then it’s your turn again. You’ve again got a pair.
S: Yes.
F: Now look at me. It’s your turn again. You again.
S: Yes.
F: Boots.
S: Boots.
F: And where is the other Boots? That one? Mmh. Well, at least not that one.
S: There!
F: There or there?
S: There. Ohhh!!!
F: Laughing. Unbelievable. You found it?
S: Yes.
F: Oh. He was sure that it is not this one. Mmh. And now?
S: Backpack?
F: Backpack.
S: Yes.
F: And where is the other Backback?
S: Ahaaaaaa!
F: Yes great! Super. Fantastic. You’ve all of them and I have nothing. Look, how many did you find? Please count them.
S: One. Two. Three. Four.
F: And how many has daddy?
S: Naught.
F: I have nothing. You found all of them on your own!
S: Yes.
F: Super!
S: Yes.
V: That was really great.
Vater (V) und Sohn (S): 5 Jahre und 5 Monate
(kursiv = richtet sich an eine andere Person)

S: Ja.
V: Jetzt darfst Du eine Karte umdrehen.
S: Ja.
V: Eine.
S: Ja.
V: Mach mal. Dreh mal eine Karte um.
S: Ja.
V: Okay. Wer ist das? Leg sie wieder hin.
S: Dora.
V: Das ist die Dora. Und jetzt musst Du noch eine zweite Dora finden. Wo ist die andere Dora? Da, denkst Du?
S: Ja.
V: Oh. Wer ist das? Leg es hin.
S: Ein Boots.
S: Ja.
V: Schau. Eine Dora. Und...
S: Ein Boots.
S: Ja.
S: Ja.
V:Okay. Hier war die Dora. Da war der Boots.
S: Ja.
V: Okay, jetzt ist der Papa dran.
S: Swiper.
S: Und Backpack.
V: Passt auch nicht.
S: Ja.
V: Weißt Du noch? Dora.
S: Dora.
V: Boots.
S: Boots.
V: Swiper.
S: Swiper.
V: Backpack.
S: Backpack.
S: Swiper.
V: Leg hin.
S: Swiper.
V: Ich werd` verrückt! Der Jonas hat´s gefunden!
S: Ja.
V: Ja super!
S: Ja!
The potentials of diversity
2nd Professional Day; 10th International CHARGE Syndrome Conference: Orlando
Andrea Scheele, Ursula Horsch July 28th, 2011

V: So, dann darfst Du die hier herlegen und dann darfst Du auch nochmal. Du hast ja ein Paar gefunden.
S: Ja.
V: Jetzt darf der Jonas noch einmal. Clever.
S: Dora.
V: Eine Dora. Wo ist die andere Dora?
S: Dora!
V: Das gibt´s doch nicht! Du hast es schon wieder gefunden?
S: Ja.
S: Ja.
S: Ja.
S: Ja.
V: Boots.
S: Boots.
S: Da!
V: Da oder da?
S: Da. Ohhh!!
V: Lachen. Das gibt´s doch nicht! Du hast ihn gefunden?
S: Ja.
V: Ach. Er war sich sicher, dass es die nicht ist. Mmh. Und nun?
S: Backpack?
V: Backpack.
S: Ja.
V: Und wo ist der andere Backpack?
S: Ahaaaaaaa!
V: Und wie viel hat der Papa?
S: Null.
V: Ich hab gar nichts. Du hast alle allein gefunden!
S: Ja.
V: Super!
S: Ja.
V: Das war ja mal klasse.