Functions for CHD7, the Gene Altered in CHARGE, in Developing Cells and Tissues

Donna Martin, Joseph Micucci, and Ethan Sperry
The University of Michigan Medical School

Presenter Information:
Mutations in the CHD7 gene are a common cause of CHARGE. Our laboratory has been studying mice with mutations in the Chd7 gene. We will discuss recent data indicating roles for CHD7 in development of skeletal structures and in stem cells of the ear, nose, and brain.

Presentation Abstract:
CHD7, the gene for chromodomain DNA-binding protein 7, is a common genetic cause of CHARGE Syndrome. CHD7 is highly expressed in developing human and mouse embryos, especially in stem cells and tissues that are affected in CHARGE. In order to identify the underlying mechanisms by which CHD7 regulates organ growth and development, our laboratory has generated and analyzed mice with mutations in the mouse Chd7 gene. Mice with reduced Chd7 function have many of the same structural and functional deficits as those observed in CHARGE; thus, detailed understanding of Chd7 function in mice can provide critical information for designing effective therapies. We will present recent data show CHD7 functions in the development of stem cells of the ear, nose, and brain and in development of craniofacial structures. We will also discuss progress using induced pluripotent stem cells generated from skin cells of children with CHARGE and CHD7 mutations. Together, these studies are helping to pave the way for novel, innovative strategies to develop regenerative therapies for individuals with CHARGE.
CHARGE Syndrome: Advances in Research

Donna M. Martin
MD, PhD
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Ethan Sperry, BS

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Exploring Genetic Mechanisms in CHARGE

Identification of Genetic Disease
Gene Discovery
Generation of Animal Models
Drug Development and Treatment
Underlying Mechanisms

Chromodomain Helicase DNA-binding (CHD) Family

Layman et al. Clin Genetics 2010

Gene Structure and Chromatin Modifications


Chd7 alleles

Hurd et al., 2007
Hurd et al., 2010

Chd7 expression is tissue-restricted during development

Layman et al., Clin Genetics, 2010
CHARGE is associated with semicircular canal hypoplasia

- Semicircular canal hypoplasia with vestibular dysfunction is common (temporal bone CT scan)
- Lateral SCC is always involved, while the superior or posterior may be normal
- Patients display abnormal canal vestibulo-ocular responses (>90%)

Inner Ear Development

Conditional Mutant Mice

Inner ear formation requires Chd7

Chd7 mutants have reduced proliferation in the neurogenic domain
Model for CHD7 Developmental Gene Regulation in Inner Ear

\[ \text{Wild type} \quad \text{Chd7 Mutant} \]

\[ \text{EYA1} \quad \text{CHD7} \quad \text{LFNG} \quad \text{NGN1} \quad \text{TUJ1} \]

\[ \text{OTX2} \quad \text{~ITB~} \quad \text{~FGF10~} \quad \text{\textit{NeuroD/ISL1}} \]

\[ \text{natural development} \quad \text{development} \quad \text{development} \quad \text{development} \]

Hurd et al., Development, 2010

Chd7\textsuperscript{Gt/+} mice have mild hearing loss

\[ \begin{array}{c}
\text{Wild type} \\
\text{Chd7\textsuperscript{Gt/+}}
\end{array} \]

\[ \begin{array}{c}
4 \text{kHz} \\
16 \text{kHz} \\
32 \text{kHz}
\end{array} \]

Hurd et al., Hearing Research, 2011

\[ \text{Chd7 is expressed in the mature cochlea} \]

\[ \text{X-gal:Neurofilament} \]

Hurd et al., Hearing Research, 2011

Cochlear innervation is abnormal with complete loss of Chd7

\[ \begin{array}{c}
\text{Neurofilament} \\
\text{Provodin} \\
\text{Merge}
\end{array} \]

Hurd, unpublished

Cochlear hair cells are disorganized with loss of Chd7

Hurd, unpublished

Lessons Learned

- CHARGE is a genetic disorder caused by CHD7 mutations
- Mice are an excellent model of CHARGE
- The mouse Chd7 gene is required for proper inner ear development and for hearing
Electro-olfactograms show severely impaired olfaction in \textit{Chd7} mutant mice.

\textbf{Olfactory sensory neurons are reduced in \textit{Chd7}^Gr/+ mice}

Cellular proliferation is reduced in the \textit{Chd7} mutant olfactory epithelium.

\textbf{\textit{Chd7}^Gr/+ female mice have delayed puberty}

\textbf{\textit{Chd7}^Gr/+ mice have decreased levels of LH and FSH}
GnRH is reduced in the median eminence of Chd7Gt/+ mice

Layman et al., Hum Mol Gen 2011

Wanda Layman

Normal

NORMAL MICE

Stem Cells in the Subventricular Zone (SVZ) Give Rise to All Olfactory Bulb Interneurons

LV: Lateral Ventricle
E: Ependymal Cell
B: Type B stem cell
C: Type C transit amplifying cell
A: Type A neuroblast
BV: Blood Vessel

Haish J. Genes and Development 2012.

Olfactory bulb defects in CHARGE

Pinto et al., J. Clin. Endocrinol. Metab. 2005

Chd7Gt/+ mice have olfactory bulb hypoplasia

Layman et al., Human Molecular Genetics 2009

* p < 0.05
** p < 0.01

Stem Cells in the Subventricular Zone (SVZ) Give Rise to All Olfactory Bulb Interneurons

Many Cell Types are Present in the SVZ

Adapted from Haish J. Genes and Development 2012.

Olfactory bulb anatomy

Rostral Migratory Stream (RMS)
Granule Cell Layer (GCL)
External Plexiform Layer (EPL)
Glomerular Layer (GL)

Layman et al., Hum Mol Gen 2011

Wanda Layman

7/4/2013
Neurosphere Assay

Pastrana, E. et al.
Cell Stem Cell. 2011.

Self Renewal: Dissociation and replating of cells within a sphere to generate secondary neurospheres

Individuals with CHARGE syndrome have skeletal abnormalities

- 30%-50% of patients present with skeletal abnormalities (Brock et al., 2003; Tellier et al., 1998)
- Isolated cases
  - Neck and shoulder abnormalities (Issekutz et al., 2005)
  - Spine anomalies (Stromland et al., 2005)
  - Hypoplastic vertebrae (Jongmans et al., 2006)
  - Tracheoesophageal fistula (Lee et al., 2008)
  - Other hand and foot deformities (various authors)

Hartshorne et al., 2011

Craniofacial features in CHARGE

- External ear abnormalities
- Micrognathia, glossoptosis (>95%)
- Cleft lip and/or palate (20%)
- Cranial nerve dysfunction (VII, VIII, IX, X)
- Dental abnormalities
- Tracheomalacia and/or laryngomalacia

Hartshorne et al., 2011; Hall and Hefner, 1999; CHARGE Syndrome Foundation

Chd7 is necessary for proper bone development

Adapted from Takada et al., 2007; Nature Publishing Group; Dennis Discher; Science Photo Library (Paul Gunning); University of Michigan Medical School (Michael Hortsch, Ph.D.)

Skeleton Preparations

- Isolation of bone and cartilage from post-natal mice
- Stain with Alizarin red (for bone) and Alcian blue (for cartilage)
- De-stain using gradient mixtures of glycerol and potassium hydroxide

Lessons Learned

- Mice with heterozygous Chd7 mutations have anosmia, fewer olfactory sensory neurons, and fewer GnRH neurons
- Chd7 is required for normal proliferation and neurogenesis in the olfactory epithelium
- Chd7 appears to be necessary for subventricular zone neural stem cell function and for skeletal development

Hartshorne et al., 2011

Ethan Sperry
Current Research Goals

- Identify critical target genes and interacting partners that mediate CHD7 function
- Characterize roles for CHD7 in adult cells and tissues using induced pluripotent stem cells
- Design regenerative strategies for treating CHARGE-related disorders
- Determine the cause of the remaining 15-25% of CHARGE cases not due to CHD7 mutations

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Jennifer Sindone
Joe Micucci
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Mark Durham
Sophia Frank

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Elizabeth Hurd
Wonda Loyman
Elyse Reamer
Heather Poucher

UM Collaborators
Yehoash Raphael
Jeff Martens

Other Collaborators
Peter Scacheri (CWRU)
Bob Hevner (U Washington)

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- NIH-NIDCD
- National Organization for Hearing Research (NOHR)
- Hearing Health Foundation
- The CHARGE Syndrome Foundation

NOHA and NIDCD logos
Phenotypes in a Drosophila model of CHARGE Syndrome

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

Presenter Information:
Dr. Marenda is an Assistant Professor in the Department of Biology at Drexel University with a joint appointment in the Department of Neurobiology and Anatomy at the Drexel University College of Medicine. He has been working in the field of developmental neurobiology using the fruit fly Drosophila melanogaster for more than a decade.

Presentation Abstract:
In human disease, animal models (called model organisms) often act as surrogates for patients when experimentation on humans is unfeasible or unethical. The fruit fly, Drosophila melanogaster, has been a powerhouse model organism in studying human disease. Using Drosophila, my lab inactivated the fly equivalent of the Chd7 gene (called kismet). In this presentation, I will discuss the work my lab has accomplished in understanding the function of the kismet gene in the development of the fly nervous system, and how this relates to normal fly behavior in the context of further understanding CHARGE syndrome by using this animal. I will show data on kismet dependent regulation of steroid hormone signaling, and how this affects the proper development of neural circuits in the brain that control learning and memory behavior. Steroid hormones are critical regulators of normal development, and kismet-mediated regulation of steroid hormone function is an important observation that may have significant and broad reaching impact.
**Presenter Information:**
CHARGE syndrome, which includes congenital defects in the cardiac outflow tract, is caused by CHD7 mutation. Our studies of Brg1, a chromatin-remodeling factor, demonstrate a molecular interaction between Chd7 and Brg1 to control mammalian fetal heart development. Brg1 and Chd7 are chromatin-regulating factors that structure the epigenome to program gene expression. Within neural crest cells, Brg1 partners with Chd7 on the promoter of PlexinA2 to program its expression, which is essential for guiding neural crest cells to the heart to control the development of cardiac outflow tract. In addition, Brg1 is necessary for maintaining neural crest cell pool for heart development. These studies thus uncover a new layer of regulation related to the pathogenesis of CHARGE syndrome.

**Presentation Abstract:**
Development of the cerebral vessels, pharyngeal arch arteries (PAAs) and cardiac outflow tract (OFT) requires multipotent neural crest cells (NCCs) that migrate from the neural tube to tissue destinations. However, little is known about how mammalian NCC development is orchestrated by gene programming at the chromatin level. Here we show that Brg1, an ATPase subunit of the BAF chromatin-remodeling complex, is required in NCCs to direct cardiovascular development. Mouse embryos lacking Brg1 in NCCs display immature cerebral vessels, aberrant PAA patterning, and shortened OFT. Brg1 suppresses an apoptosis factor Ask1 and a cell cycle inhibitor p21^{cip1} to inhibit apoptosis and promote proliferation of NCCs, thereby maintaining a multipotent cell reservoir at the neural crest.
Also, Brg1 supports *Myh11* expression for NCCs to develop into mature vascular smooth muscle cells of cerebral vessels. Within NCCs, Brg1 partners with a chromatin remodeler Chd7 on the *PlexinA2* promoter to activate *PlexinA2*, which encodes a receptor for semaphorin to guide NCCs into the OFT. Our studies thus reveal a new role of Brg1 and its downstream pathways in the survival, differentiation, and migration of the multipotent NCCs, critical for mammalian cardiovascular development.
CHD7-mutation positive CHARGE patients display a range of clinical abnormalities including temporal bone defects, hearing defects, heart defects, craniofacial defects and choanal atresia. Although CHARGE Syndrome results in a seemingly diverse spectrum of congenital abnormalities, one unifying explanation is that the phenotypic traits result from abnormal neural crest cell (NCC)-mediated differentiation and/or migration. Cardiac NCCs (CNCCs) are a NCC population that migrate to the heart and great vessels where they are important for the development of the aorta and pulmonary artery from the pharyngeal arch arteries (PAAs) as well as the septation of the conotruncus into the ventricular outflow tract. We hypothesized that the absence of Chd7 in murine cardiac neural crest cells could recapitulate the congenital abnormalities seen in patients with CHARGE Syndrome. Using a Wnt1-Cre mouse model and a floxed Chd7 allele, Chd7 was conditionally deleted from neural crest cells (Wnt1-Cre) in vivo. We observed that a lack of Chd7 in Wnt1-Cre expressing neural crest cells does not compromise the ability of these cells to migrate and differentiate into normal cardiac structures. Thus, we conclude that Chd7 is not necessary for the development of neural crest-derived cardiac structures in our murine model.
People with CHARGE Syndrome often have congenital cardiovascular defects. Mutations in \( CHD7 \), the gene encoding chromodomain helicase DNA binding protein 7, have been identified in CHARGE Syndrome in a majority of cases. In an effort to understand more about this syndrome, scientists have created mice that have only one functioning copy of the \( Chd7 \) gene. Mice with a loss of \( Chd7 \) function display CHARGE-like phenotypes and are an excellent model of human CHARGE Syndrome. Several of the murine models with one functioning \( Chd7 \) gene display congenital cardiac abnormalities. In patients with CHARGE Syndrome, observed congenital heart problems are likely a result of abnormal development of the conotruncal region (outflow tract- i.e. where the pumping chambers of the heart give rise to pulmonary artery and the aorta) and the great vessels (aorta and pulmonary artery).

During development, the conotruncal region and the great vessels are derived from several different populations of early progenitor cells. Neural crest cells (NCCs) are one developmental cell population that is necessary for the proper development of these cardiac structures. NCCs are an interesting cell type that originates near the neural tube. NCCs migrate to many different parts of the developing embryo where they differentiate into a diverse array of tissues. Thus, it is plausible that many of the clinical features of CHARGE Syndrome may be a result of an inability of NCCs to migrate and differentiate into various tissues. Interestingly, it has been shown that one
group of NCCs, namely cardiac NCCs, migrate from the neural tube to the heart where they are important for the normal development of the heart and the great vessels. The objective of our study was to determine whether Chd7 is important for NCCs to migrate to the heart region and successfully participate in the development of the outflow tract and the great vessels.

We created a unique mouse model in which we could breed mice to selectively delete Chd7 (Chd7\textsuperscript{flox}) from NCCs (Wnt1-Cre). We found that we were not able to generate viable pups that have Chd7 deleted from the NCC population (Wnt1-Cre:Chd7\textsuperscript{flox/flox}). The pups died shortly after birth, and our observations revealed that the pups likely died due to abnormal brain development and oral palate defects that prevented them from feeding properly. In order to determine if mice without Chd7 in the NCC population have abnormalities in the development of the conotruncal region and the great vessels, we studied at embryonic mice just before birth (e16 and later). As shown in figure 1, at embryonic day 18, we observed normal development of the outflow tract and normal septation of the aorta and pulmonary trunk. In order to further visualize the structure of the outflow tract, pulmonary trunk and aorta of these structures, we fixed and cut tissues from mice with and without Chd7 in the NCCs. As shown in figure 2, staining revealed that the aorta and the pulmonary trunk were septated.

Thus far, our results suggest that Chd7 deletion in NCCs using a Wnt1-Cre driver is not critical for the development of the outflow tracts and the septation of the pulmonary trunk and the aorta. We are currently looking at earlier time points to see if the development of the pharyngeal arch arteries is impacted by the deletion of Chd7 in NCCs. We are also using other murine models to delete Chd7 from a variety of early cell populations that participate in the development of the cardiac structures that are often impacted in patients with CHARGE Syndrome.
Presenter Information:
Currently, I am a junior at the University of Michigan studying Cellular and Molecular Biology. For the past two and a half years I have worked with Dr. Donna Martin studying the molecular mechanisms causing CHARGE Syndrome. My research interests include Neurodevelopmental disorders, Biochemistry, Genetics, and Genomics. After my undergraduate education I plan to attend an M.D. PhD. program and pursue a career as a physician-scientist in the field of medical genetics.

Presentation Abstract:
Recent studies have linked CHARGE Syndrome to developmental defects of the midbrain, hindbrain, and cerebellum. To investigate this further, our lab is studying the inner ear and central nervous system of mice with Chd7 mutations. We will present our results showing that reduced Chd7 leads to central nervous system abnormalities.
**Presenter Information:**
*Kelvin Kwan* is an Assistant Professor in the Department of Cell Biology and Neuroscience at Rutgers University. His lab is located in the Rutgers University Stem Cell Center. Dr. Kwan’s lab is interested in regenerating the sensory and nerve cells of the inner ear. He is working closely with the Rutgers University Cell and DNA Repository, the largest university based cell and DNA biobank, to generate induced pluripotent stem cells from archived cells.

**Presentation Abstract:**
Encased in a bony labyrinth, the cochlea residing within the inner ear allows us to discriminate and hear complex sounds. Hair cells in the cochlea are the sensory cells that convert sound into neural signals, which are then relayed to the brain by auditory neurons. Patients with CHARGE are frequently affected by sensorineural hearing loss resulting from hair cells or auditory neuron dysfunction. Currently, the only treatment for hearing loss is the use a cochlear implant or a hearing aid. A major factor for auditory prosthesis candidacy is a functional auditory nerve. Since auditory neuron impairment can vary dramatically in CHARGE, it would be ideal to determine functional activity of neurons from individuals. However, direct recording from the auditory nerve is invasive and difficult because the inner ear is small, encased in bone and difficult to access. Instead, we have established a progenitor cell line that continually proliferates and can differentiate into auditory neurons. I propose to use progenitor-derived auditory neurons as a platform for identifying a panel of genes that correlates to auditory neuron function. In the future, when samples from patients with become available, induced pluripotent stem cells (iPSCs) can be made. Auditory neurons generated from iPSCs from patients with CHARGE can be used to determine their candidacy for auditory prosthesis.
Presenter Information:
Laurie S. Denno, Ph.D., is a behavior analyst at the Perkins School for the Blind, Deafblind Program, and also in private practice serving adults with developmental disabilities in residential and day programs. She has worked with children and young adults with CHARGE syndrome and behavior challenges for 20 years.

Poster Abstract:
This poster outlines Laurie’s dissertation research that taught parents who were considering a psychiatric consultation how to present their child’s challenging behavior to a psychiatrist in a specific and organized manner. A self-directed teaching program was used. Data for all six participants is presented. This is an educational presentation.
**Presenter Information:**

**Gail** has a B.Ed in Special Education, is a qualified teacher of the deaf and also has a M.Ed. in Multi-sensory Impairment. Gail works in the UK and has over twenty-five years experience in the field of special education, working initially in schools for children with severe learning difficulties and then a school for the deaf before moving into peripatetic work focusing on learners who are deafblind. Joined Sense in December 2001 and is working in the Children’s Specialist Services as a Principal MSI Consultant. Gail has a particular interest in CHARGE and is on the committee for the CHARGE Family Support Group in the UK. She is currently undertaking a PhD, focusing on the educational environment for children with CHARGE Syndrome.

**Presentation Abstract:**

This pack of information arose from parental request for information to share with professionals who become involved with their child following diagnosis. The aim is to have a web-based package of information that parents of children with CHARGE, or other interested parties, can pass to the varied professionals that work with their children. It will be possible to download the pack either by section or in its entirety. Each topic is essentially a summary of immediately relevant information for each professional area with suggestions for further reading and where additional information and advice can be found. The topics were chosen following consultation with a range of professionals who work with children with CHARGE and as a result of a questionnaire returned by approximately 70 families.

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3rd Professional Day & 11th International CHARGE Syndrome Conference  
Poster Session

Thursday
1:15-2:30

Category: Family Support

CHARGE syndrome in German speaking countries

CHARGE Syndrom e.V.
(German CHARGE Family Support Group)
Claudia Junghans, Dr. Julia Benstz,
Dr. Phil. Andrea Wanka

Presenter Information:
Claudia Junghans, President of the German CHARGE Family Support Group and mother of a 9 year old son with CHARGE syndrome (non-attendant).

Dr. Julia Benstz is Vice President of the German CHARGE Family Support Group and mother of a 14 year old daughter with CHARGE syndrome.

Co-presenter Dr. Phil. Andrea Wanka is representative for deaf blindness and hearing impairment at the foundation St. Franziskus Heiligenbronn and educational consultant of the German CHARGE Family Support Group. She works with affected families above all in the area of communication and the behaviour of children with CHARGE syndrome.

Presentation Abstract:
The poster is about the foundation “CHARGE Syndrom e.V.”, the Family Support Group for German speaking countries and exposes the most important information on the formation.

Focus of attention will be the possibilities of support for affected families, which shall help to cope with the CHARGE Syndrome. These include for example the offer of topic based weekends for a smaller number of families up till about 5 (weekends on communication and behavior, for siblings, for mothers, for CHARGE youngsters, on music and animals).

3rd Professional Day & 11th International CHARGE Syndrome Conference
Category: Behavior

Thursday
1:15-2:30
Poster Session

Understanding Behavioral Self-Regulation in CHARGE

Sarah Haney and
Dr. Tim Hartshorne
Central Michigan University, Psychology Department

Presenter Information:
Sarah Haney is a senior at Central Michigan University studying Psychology and Child Development. She plans on attending graduate school to pursue a degree in Applied Behavior Analysis. She has been researching CHARGE for one year now and has presented a poster of her research at the Australian CHARGE Syndrome conference in 2012.

Tim Hartshorne is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book CHARGE Syndrome.

Presentation Abstract:
Nicholas and Hartshorne have proposed four areas of functioning that are impacted by problems with self-regulation. This poster focuses on one of these, the area of behavior. It will describe the difficulty, and offer parents, educators, and others insight into how to help these individuals learn to self-regulate their behavior. This is one of four companion posters illustrating areas of self-regulation.

3rd Professional Day & 11th International CHARGE Syndrome Conference
Category: Behavior, Family Support

Thursday
1:15-2:30
Poster Session

Physiological Self-Regulation in CHARGE

Tim Hartshorne, Ph.D.
Central Michigan University
and
Andrea Larson

Presenter Information:
Tim Hartshorne is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book CHARGE Syndrome.

Andrea Larson is a graduate of Central Michigan University with a major in psychology. She is taking a year off before pursuing a medical education.

Presentation Abstract:
Nicholas and Hartshorne have proposed four areas of functioning that are impacted by problems with self-regulation. This poster focuses on one of these, the area of physiological experience. It will describe the difficulty, and offer parents, educators, and others insight into how to help these individuals learn to self-regulate their behavior. This is one of four companion posters illustrating areas of self-regulation.

3rd Professional Day & 11th International CHARGE Syndrome Conference
Presenter Information:

**Tate Jenkins** is a psychology student at Central Michigan University. She is a senior and studying for Medical School.

**Tim Hartshorne** is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book *CHARGE Syndrome*.

Presentation Abstract:

There is little information about the experience of individuals with CHARGE Syndrome and headaches. Headaches may be the result of cranial nerve anomalies, dental complications, and migraines. Classification of headaches, possible sources of headaches due to CHARGE, data collection strategies, and estimation of incidence will be addressed.
Fathers and CHARGE: Work and Friendships

Shantell Johnson, Kirsten Hissong (with Timothy Hartshorne)
Central Michigan University

Presenter Information:
Shantell and Kirsten are both students at Central Michigan University.

Tim Hartshorne is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book CHARGE Syndrome.
Presentation Abstract:
Familial research traditionally is centered around the maternal viewpoint; paternal research is extremely underrepresented across subject fields. Commonly, their viewpoints are synonymously linked to the views, thoughts, stresses of the mother. It is known that fathers and mothers have very different thoughts regarding parenthood and their children. Further, fathers differ significantly in the prioritizing of work over family. Women are more likely to put their family above any work related events. The work more, play less language of the father often translates into fewer friendships. Male-male friendships often exhibit weaker, fewer intimate and superficial relationships. This has been found for fathers of developmentally on-track and fully able children, but does the same idea hold true for fathers of children with disabilities? More specifically, does this hold true for fathers of children with CHARGE? CHARGE is a rare, genetic disorder in which the child has pronounced birth and developmental deficits. This study aims to examine whether fathers with CHARGE parallel the work practice and male-male friendship patterns of fathers with non-disabled children.
Chromatin remodeling by the CHD7 protein is impaired by mutations that cause human developmental disorders

Karim Bouazoune, Ph.D.
Massachusetts General Hospital/
Harvard Medical School

Presenter Information:
Karim Bouazoune, Ph.D.
Post-doctoral fellow in Prof. Robert E. Kington’s lab
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Presentation Abstract:

Background
Mutations in the CHD7 gene cause CHARGE syndrome. To understand how the CHD7 protein achieves its function and how mutation of CHD7 leads to developmental disorders, it is critical to characterize wild-type and mutant CHD7 proteins biochemically. However to date, CHD7 has not been characterized for activity, as it is extremely large and has resisted purification.

Approach
We used the baculovirus system and a dual-tag strategy to purify intact recombinant WT and mutant CHD7 proteins. We subjected these polypeptides to nucleosome remodeling and ATPase assays to characterize the CHD7 basic properties, perform a structure-function analysis of CHD7 and examine point mutants reported in human patients.

Results
We show that CHD7 is an ATP-dependent nucleosome remodeling factor with distinct characteristics. Further investigations show that CHD7 patient mutations have consequences that range from subtle to complete inactivation of remodeling activity, raising the possibility that even partial impairment of remodeling function has a significant impact on human biology. In addition, we find that patient mutations leading to protein truncations upstream of amino acid 1899 of CHD7 are likely to cause a hypomorphic phenotype for remodeling.

Conclusions
We propose that nucleosome remodeling is a key function for CHD7 during developmental processes and provide a molecular basis for predicting the impact of disease mutations on that function.
**Presenter Information:**

**Benjamin Kennert** is a first year graduate student in the School Psychology Ph.D. program at Central Michigan University. He has been working with Dr. Tim Hartshorne on research involving self-regulation and CHARGE Syndrome.

**Tim Hartshorne** is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book *CHARGE Syndrome*.

**Presentation Abstract:**

Nicholas and Hartshorne have proposed four areas of functioning that are impacted by problems with self-regulation. This poster focuses on one of these, the area of cognition. It will describe the difficulty, and offer parents, educators, and others insight into how to help these individuals learn to self-regulate their behavior. This is one of four companion posters illustrating areas of self-regulation.
**Presenter Information:**

**Benjamin Kennert** is a first year graduate student in the School Psychology Ph.D. program at Central Michigan University. He has been working with Dr. Tim Hartshorne on research involving self-regulation and CHARGE Syndrome.

**Tim Hartshorne** is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book *CHARGE Syndrome*.

**Maria Ramirez** is a Doctoral student in the School Psychology program at Central Michigan University. For the past three and a half years she has been working with Dr. Tim Hartshorne exploring self-regulation in children with CHARGE. Her current research focuses on the assessment and validation of a Fun Chi video to be used in future research to assess the effects of Fun Chi on sleep, balance, and self-regulation in children with CHARGE.

**Presentation Abstract:**

Nicholas and Hartshorne have proposed four areas of functioning that are impacted by problems with self-regulation. This poster focuses on one of these, the area of emotion. It will describe the difficulty, and offer parents, educators, and others insight into how to help these individuals learn to self-regulate their behavior. This is one of four companion posters illustrating areas of self-regulation.
Microenterprises – Building on Strengths and Promoting Self-Sufficiency: Factors to Consider with Individuals with CHARGE syndrome

Seraphim Mork, doctoral student
Maria Ramirez, doctoral student
Tim Hartshorne, Ph.D.
Central Michigan University

Presenter Information:
Seraphim Mork is a Doctoral student in the School Psychology program at Central Michigan University. She is currently examining the concurrent validity of the Bayley Scales of Infant and Toddler Development, Third Edition; the most commonly used measure of cognitive development with the Cognitive Abilities Scale-Second Edition; a test that has considerable support for its validity. Her research interests are in early literacy especially for individuals with developmental impairments.

Maria Ramirez is a Doctoral student in the School Psychology program at Central Michigan University. For the past three and a half years she has been working with Dr. Tim Hartshorne exploring self-regulation in children with CHARGE. Her current research focuses on the assessment and validation of a Fun Chi video to be used in future research to assess the effects of Fun Chi on sleep, balance, and self-regulation in children with CHARGE.

Tim Hartshorne is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book CHARGE Syndrome.
Presentation Abstract:
Currently there is a movement towards promoting more choices and self-sufficiency among people with disabilities using microenterprises. This is an area that has not yet been explored in individuals with CHARGE syndrome. Microenterprises offer a viable opportunity for self-determination and self-sufficiency. This poster provides a brief overview of things the processes, benefits and barrier in starting microenterprises.

3rd Professional Day & 11th International CHARGE Syndrome Conference
**Models of Conceptualizing Self-Regulation in CHARGE syndrome**

Maria Ramirez, doctoral student
Tim Hartshorne, Ph.D.
Central Michigan University

**Presenter Information:**

**Maria Ramirez** is a Doctoral student in the School Psychology program at Central Michigan University. For the past three and a half years she has been working with Dr. Tim Hartshorne exploring self-regulation in children with CHARGE. Her current research focuses on the assessment and validation of a Fun Chi video to be used in future research to assess the effects of Fun Chi on sleep, balance, and self-regulation in children with CHARGE.

**Tim Hartshorne** is a professor of psychology, specialized in school psychology, at Central Michigan University. He is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book *CHARGE Syndrome*.

**Presentation Abstract:**

Individuals with CHARGE syndrome have difficulties with self-regulation, or the voluntary management of goal directed behavior. This poster provides an overview of what self-regulation is and why it can be problematic for individuals with CHARGE. Four areas of self-regulation are described: cognitive, behavior, emotion, and physiological. This poster serves to introduce four other posters which focus on each one of these areas.
The Cerebral Cortex in CHARGE Syndrome

Robert F. Hevner, MD, PhD
Professor, University of Washington and
Seattle Children’s Research Institute

Presenter Information:
Dr. Hevner is a pediatric neuropathologist at Seattle Children’s Hospital. His lab studies development and malformations of the cerebral cortex, using mice as a model system. Dr. Hevner obtained his B.S. in Cellular and Molecular Biology (with High Honors) from the University of Michigan, and M.D. and Ph.D. degrees from the Medical College of Wisconsin. He completed residency in Anatomic Pathology at Brigham and Women’s Hospital, and fellowship in Neuropathology at Stanford University. He then performed postdoctoral research at UCSF. He has been at the University of Washington since 2000, and at Seattle Children’s Research Institute since 2008.

Presentation Abstract:
CHARGE syndrome is caused in most cases by mutations in CHD7, a gene that is highly expressed in many areas of the developing brain, including the cerebral cortex. The cerebral cortex may develop abnormally in CHARGE syndrome, contributing to cognitive and behavioral problems in some affected individuals. To investigate this possibility, we have studied mice with Chd7 gene mutations to evaluate cortical development. The cortex in these mice indeed shows multiple anomalies of cortical gene expression during development, including defects of neuronal differentiation and cell migration. Both projection neurons (excitatory neurons with long axons) and interneurons (inhibitory neurons with short axons) are affected. Our findings suggest that cortical development may be perturbed in CHARGE syndrome and contribute to disease symptoms.
Gene therapy induces nerve fiber regeneration in the inner ear of deaf mutant mice

Yehoash Raphael, Hideto Fukui, Yohei Takada, Donna M. Martin
The University of Michigan, Ann Arbor

Presenter Information:
Yehoash Raphael is Professor of Otolaryngology, Head & Neck Surgery, working in Kresge Hearing Research Institute at The University of Michigan. He specializes in inner ear biology, with a special focus on ear trauma, repair and regeneration. The lab personnel study both hereditary and environmental ear disease and design therapies for prevention and for hearing restoration.

Drs. Hideto Fukui and Yohei Takada have performed the laboratory work presented at the meeting. They are Otolaryngology specialists originally from Kansai Medical University in the Osaka area, Japan.

Dr. Donna Martin is a colleague who works with Dr. Raphael on characterizing ears of a mouse model for CHARGE. Dr. Martin is also a spouse, and together, Donna and Yehoash are parents of a 19 year-old son, Noam Raphael, with CHARGE, and a 17-year old daughter, Maya Raphael. Both Noam and Maya are also attending the meeting.

Presentation Abstract:
The outcome of cochlear implant therapy depends on a healthy auditory nerve. We tested whether BDNF gene transfer into the cochleae of deaf mice can influence the fate of neurons. We determined that the diameter and number of nerve fibers in the auditory epithelium were increased compared to non-treated ears, and that spiral ganglion cell density in Rosenthal’s canal was also increased. The data suggest that nerve fiber regeneration treatment may augment cochlear implant therapy.
Study of CHARGE syndrome clinical studies: UK Survey & the Clinical Database Project

Gail Deuce, M.Ed
Steve Rose M.Ed
Simon Howard
Meg Hefner, MS
Emily Fassi

**Presenter Information:**

**Gail** is a qualified teacher of the deaf with expertise in multi-sensory impairment with 25 years experience in the field of special education in the UK. She is on the committee for the CHARGE Family Support Group in the UK. She is currently undertaking a PhD, focusing on education of children with CHARGE Syndrome.

**Steve** is a speech and language therapist specialising in deafblindness. He has worked as an intervenor family support groups for Sense. Steve has particular interest in the development of eating and drinking skills and early interventions, including parent-child interaction therapy.

**Simon** has a daughter, Jessica (now 12), with CHARGE. He is the point of contact and newsletter organizer for the CHARGE Family Support Group. He has worked closely with Sense in the UK regarding CHARGE including organising a UK conference in 2011.

**Meg** is a genetic counselor with 30 years experience with CHARGE and started the CHARGE Syndrome Foundation. She started the first CHARGE Syndrome Clinic in the US in 2011.

**Emily** is about to start formal training as a genetic counselor. She became interested in CHARGE working with Meg and has been instrumental in the development of the Clinical Database Project.
**Presentation Abstract:**

UK study: This presentation will briefly report a few findings of a paper questionnaire completed by families living in the UK with a child (aged 15 years or younger) with a medical diagnosis of CHARGE syndrome. The questionnaire contained three sections: Diagnosis & medical issues, child development; and educational provision (including identification of educational need in relation to multi-sensory impairment/deafblindness, support from specialist teachers and other professionals, and parental satisfaction.

Clinical Database Project: an Internet-based survey of a very broad spectrum of CHARGE features launched in May, 2013. The presentation will show the features collected in the survey, current status of data entry, and intended uses of the database. The intent of this project is to provide as much information on CHARGE as possible to as broad an audience as possible: families, medical and educational professionals and other doing research on CHARGE syndrome.

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3rd Professional Day & 11th International CHARGE Syndrome Conference
We have developed a comprehensive database of clinical information on CHARGE syndrome (CS). If you or your child has been diagnosed with CS, you may be eligible to participate.

**What is this for?** The purpose of this study is to create a comprehensive clinical database and registry of individuals with CS of all ages from all over the world. Information from this database will provide meaningful contributions to CS knowledge and research.

**Who can do this?** Any adult with CS or parent/guardian of an individual with CS is eligible.

**How would I do it?** Participation in this project involves entering data (mostly medical information) into a web-based questionnaire. There are opportunities to directly upload photographs and certain medical records in some sections.

**How long will it take?** Completing the entire questionnaire will take several hours. It can be done in multiple sittings over several weeks. We may ask for yearly updates.

**What do I need?** You must have email and Internet access to participate in this project. You will need access to your/your child’s medical history. The study is in English only.

**Will I get paid?** No. Your participation is strictly voluntary.

**I want more information. What do I do now?** If you are interested in learning more about this project, or if you have questions, you can go to the Clinical Database Project link at chargeysndrome.org, or contact Meg Hefner directly at hefnerma@slu.edu. Thank you for your interest in this study.

This project is endorsed by the CHARGE Syndrome Foundation and Saint Louis University.
A study of CHARGE syndrome in the UK by Deuce, Howard, Rose & Fuggle

Steve Rose (Head of Service) and Gail Deuce (Principal MSI Consultant)
Children’s Specialist Services, Sense

Purpose of study:
- Build upon existing knowledge of CHARGE syndrome
- Help recognize areas of need
- Improve the support we can give to children, young people and their families and to the professionals working with them

Survey:
- Designed following an earlier pilot (Deuce 2009)
- A questionnaire sent out by post or email
- Families with a family member with CHARGE under the age of 16

The questionnaire was divided into three parts:
1. Diagnosis:
   - Presence of major and minor characteristics (according to Sanlaville & Verloes 2007)
   - Prevalence of other conditions
   - Provision of aids for vision and hearing
   - Genetic testing and prevalence of CHD7 genetic defect
   - Medication

2. Child development
   - Hospitalisation following birth
   - Early developmental milestones
   - Eating and drinking

3. Educational provision
   - Types of provision
   - Range of professionals involved and levels of support
   - Statutory assessment
   - Parental satisfaction

Collation and analysis
- A framework set up using Microsoft Excel to record quantitative and qualitative information
- Structured to code the responses so that the outcomes could be identified and cross reference analysis undertaken
- Data was collated by an external company on a pro bono basis
- Analysed by the authors
Issues for consideration:

- How to gain information from a wider cohort or allows for easy comparison
- Over 15’s– real need to develop knowledge of late teens and adulthood
- Need for empirical research to support anecdotal evidence
- Time! Very few have clear dedicated time for research that is not impinged upon by other work commitments

Part 1 is reported in:

A Study of CHARGE syndrome in the UK
The British Journal of Visual Impairment 30(2) 91–100
Behavior as self-regulatory adaptation, or “I can’t believe my child just did that!

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 is the grant holder for DeafBlind Central: Michigan’s Training and Resource Project, which provides support to children who are deafblind in Michigan. He has been researching and presenting about CHARGE syndrome since 1993, motivated by the birth of his son with CHARGE in 1989. He has been awarded the Star in CHARGE by the CHARGE Syndrome Foundation. He is first editor of the book CHARGE Syndrome.

Presentation Abstract:
Individuals with CHARGE often show odd, sometimes challenging, behaviors. These can lead to various psychiatric diagnoses. However, behavior is rarely random, and in fact humans actively attempt to adapt to their experience. The concept of self-regulation is a way to view “CHARGE behavior” as adaptation, and leads to avenues for intervention. This is the first of three presentations on self-regulation and intervention for behavioral challenges.
Behavior as self-regulatory adaptation, or “I can’t believe my child just did that!”

Tim Hartshorne
Central Michigan University

Typical Deafblind Behavior

- Eye pressing
- Finger flicking
- Rocking
- Tapping body/objects
- Self-injurious behavior
- Mouthing objects
- Tactile defensiveness
- Clinging
- Spinning
- Vocal tics
- Feces smearing
- Lining things up
- Extreme preferences
- Darting/running off
- Learned helplessness
- Submissive
- Stare at lights
- Inappropriate vocalization

How to make sense of it

- The kid has a syndrome!
- It’s pathological and should be eliminated
- It’s due to frustration and pain
- It’s communication
- It works for the kid

Not because they guarantee success, but because they serve a purpose

Self-regulation problems in CHARGE

- Rapid changes in arousal levels
- Melt downs
- Unfocused behavior
- Diagnoses
  - OCD – a way to reduce stimulation and exercise control
  - ADHD – a problem with regulating sensory and behavioral stimulation and focusing on a goal
  - Tic disorder – a stress response to lack of control over environment
  - Autistic-like behavior – the failure of regulation strategies, and the adoption of dysregulated behavior

Definition

The primarily voluntary regulation of cognition, behavior, emotion, and physiological states for the purpose of goal-directed actions
Adversity

- Fragile health
  - Breathing problems
  - Multiple hospitalizations
  - Multiple surgeries with anesthesia
  - Multi-sensory impairment
  - Defects in major organs
- Nervous parents
- Sources of stress
  - Social relationships
  - School
  - Family
  - Abuse

Quality of Services and Support

- Lack of medical or specialist knowledge
- Needs multi-disciplinary medical and educational teams
- Parent-Professional relationships
- Lack of social support
- Parent and family resilience

CHD7 Gene

- Regulatory gene
  - Neural crest
  - Placode cells
- Multisensory impairment
- Major organs may be affected
- Vestibular functioning impaired

Stress

- Endocrine regulatory system
- Perception of adversity
- Availability of resources
- Response of professionals
- Response of family

Neural Connectivity

- Prefrontal cortex and executive function
  - Reactive forms of learning and behavior
  - Reflective forms of learning and behavior
- Neuropsychological control over behavioural schemas
  - Routine control
  - Supervisory attentional system

Jude Nicholas and Tim Hartshorne, 2009
Dunn Conceptual Model

<table>
<thead>
<tr>
<th>Arousal of thoughts, behavior, feelings, sensations</th>
<th>PASSIVE Self-regulation Strategies</th>
<th>ACTIVE Self-regulation Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitation</td>
<td>Non-reactive Tuning it out</td>
<td>Sensation Seeking</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Reactive to Stimuli</td>
<td>Sensation Avoiding</td>
</tr>
</tbody>
</table>

Self-regulation begins with a goal
- What do you want to have happen?
- What must you do to make it happen?

Supporting 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

Study for an exam
- Cognitive
- Behavioral
- Emotion
- Physiological

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.
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

Examples

- Cognitive self-regulation
  - Break down larger goals into shorter (pie)
- Behavioral self-regulation
  - Feedback on reactions from others (consequences)
- Emotional self-regulation
  - Creating an environment for self-soothing
- Physiological self-regulation
  - Squeeze technique; hand on arm or leg

Summary

- Children with disabilities often have poorly regulated systems
- This is centrally related to stress, deriving from adversity, quality of supports, and genetics
- The child’s attempts to self-regulate manifest as peculiar behavior, often labeled as challenging
- They will do better socially and academically if they can learn to self-regulate
- They can only develop self-regulation skills slowly while they experience a lot of scaffolding from the adults in their lives

Thanks to my Lab

- Maria Ramirez
- Andrea Larson
- Sarah Haney
- Kayla Hilyard
- Ben Kennert

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  Central Michigan University
  Mount Pleasant, MI 48859
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  tim.hartshorne@cmich.edu
  www.chsbs.cmich.edu/timothy_hartshorne
Presentation Abstract:
As the most multi sensory impaired of syndromes, people with CHARGE are challenged to explore a range of apparently unusual behaviors in order to function effectively to satisfy their own needs. Many of these unusual behaviors seen in people with CHARGE are attempts to compensate for sensory losses and obtain the best and most reliable information possible, both from the environment and also from their own bodies. Other of these behaviors originate as attempts to modulate arousal levels – what we would call self-regulation. All these behaviors can be characterised as ‘self stimulation’, which is a normal part of human behavior but often occasions extreme and persistent opposition when seen in people with CHARGE. Indeed, in the field of special education self-stimulation, or ‘stimming’, is often regarded as a cardinal sin to be opposed and removed at all costs. This presentation will try to clarify the role of unusual postures and self stimulation behaviors, and will encourage more careful and informed observation as the essential prelude to any intervention.
Self-regulatory strategies for children with CHARGE syndrome

Maria A Ramirez
Doctoral Student
Central Michigan University

Presenter Information:
Maria Ramirez is a Doctoral student in the School Psychology program at Central Michigan University. For the past three and a half years she has been working with Dr. Tim Hartshorne exploring self-regulation in children with CHARGE. Her current research focuses on the assessment and validation of a Fun Chi video to be used in future research to assess the effects of Fun Chi on sleep, balance, and self-regulation in children with CHARGE.

Presentation Abstract:
The four windows of self-regulation (physiological, behavioral, cognitive, and emotional) provide the perfect areas for intervention in children with CHARGE. Although individuals with CHARGE may often use compensatory behaviors to aid in regulating their behavior, because of the presence of multisensory impairments and maladaptive patterns of behavior, positive self-regulatory strategies may at times be compromised. Using the four windows of self-regulation may prove to be an invaluable tool in understanding the function of the child’s behavior, identifying the child’s behavioral strengths that we can build up on, and in identifying specific self-regulatory areas to target for intervention. Strategies to enhance self-regulation in both the school and home will be presented. This presentation will be the third, preceded by Tim Hartshorne and David Brown.

3rd Professional Day & 11th International CHARGE Syndrome Conference
FOSTERING SELF-REGULATORY STRATEGIES IN CHILDREN WITH CHARGE SYNDROME

Maria Alejandra Ramirez
School Psychology Doctoral Student
Central Michigan University

Agenda
1. Overview of 4 areas/windows of Self-Regulation
2. Example of Self-Regulation
3. What we know about Self-Regulation in children with CHARGE syndrome
4. Using the Windows of Self-Regulation to identify strengths and identify difficulties
5. Using the window of self-regulation to prioritize areas to target
6. In Detail: Specific strategies to foster each window of self-regulation

What is Self-Regulation?
- Adaptive and flexible management of four domains:
  - Physiological, behavioral, cognitive, and emotion
- In order to describe regulation as “self-regulation” two components are necessary:
  - 1) self-awareness of the process
  - 2) a subsequent goal-directed action.
- Self-regulation must begin with a goal, and that goal describes what you want to have happen and what you must do to make that goal happen.
- Self-regulation involves gauging internal and external stimuli and responding appropriately under environmental expectations.

Self-Regulation:

Goal

What are the 4 Windows of Self-Regulation?

- Physiological
- Behavior
- Cognitive
- Emotion

Discussion Goal 1:
Quick Overview Self-Regulation and the 4 Windows of Self-Regulation
What is Physiological Self-Regulation?

- Self’s ability to react and alter its own states and responses to meet the needs of the body.
- In great part under the control of the somatic, endocrine and autonomic nervous systems.

What is Behavioral Self-Regulation?

- Awareness of a behavior
- And choosing those behaviors most adaptive toward achieving a goal.

- Goal directed and purposeful behavioral patterns consisting of:
  - one’s ability to inhibit, regulate, pace, and delay gratification
  - Jahromi and Stifter (2008)

What is Cognitive Self-Regulation?

- Voluntarily regulating thoughts and mental processes by balancing inhibition and initiation of behavior in order to achieve a goal
- Involves:
  - Attention
  - Memory
  - Learning (as well as using prior learning)
  - Reasoning
  - Problem-solving
  - Decision-making
  - Metacognition

What is Emotion Self-Regulation?

- Using emotion regulation, the individual analyzes, controls, alters, or prevents behaviors related to the adaptive expression of emotions
- Lam & Lewis, 2010
- May occur at different points in time during the emotional response

Example: Dentist Appointment

- Physiological: You make sure to brush and floss your teeth really well a couple days before the appointment
- Behavioral: You make sure to put the appointment time/day in your planner, you get a babysitter
- Cognitive: You mentally prepare yourself for the procedure
- Emotion: You tell yourself the pain will be over soon, you ask for a lot of pain medicine to make sure you feel no pain

Discussion Goal 2: Example of Self-Regulation

- Physiological: You make sure to brush and floss your teeth really well a couple days before the appointment
- Behavioral: You make sure to put the appointment time/day in your planner, you get a babysitter
- Cognitive: You mentally prepare yourself for the procedure
- Emotion: You tell yourself the pain will be over soon, you ask for a lot of pain medicine to make sure you feel no pain
Discussion Goal 3:
What we know about Self-Regulation in children with CHARGE syndrome

What do we know about Self-Regulation in CHARGE?

- Multi-sensory difficulties may limit exposure to environmental stimuli, their exposure to interactions and reactions to the environment.
- As DeGangi (2000) states, early deficiencies in self-regulation may lead to challenging behavior, and deficits in attention and inhibition.

What do we know about Self-Regulation in CHARGE?

- Physiological:
  - Brown (2005) notes that individuals with CHARGE syndrome are truly multi-sensory impaired, often having challenges with vision, hearing, balance, touch, temperature, pain, pressure, smell, breathing, swallowing, eating, drinking, digestion, and temperature control

- Behavior:
  - May display behaviors typical of individuals with: Autism Spectrum Disorder, ADHD, OCD, Tourette’s syndrome, and Deaf Blindness (Hartshorne & Cypher, 2004).
  - These may include: restricted range of interest, stereotyped movements, fidgeting with objects, preference for certain objects or people, tactile defensiveness, staring at lights, vocal stimulation.

What do we know about Self-Regulation in CHARGE?

- Cognitive:
  - Children with CHARGE may present with executive dysfunction.
  - Specifically in the areas of shifting, monitoring, and inhibiting.
    - Hartshorne, Nicholas, Grialou, and Russ (2007)

- Emotion:
  - This area is much less explored than the other areas of self-regulation
  - Given that children with CHARGE have difficulty in the other areas of self-regulation and all the areas are related…it is possible that this may also be an area of difficulty.
Discussion Goal 4:
Using the Windows of Self-Regulation to:
1. identify strengths
2. identify difficulties

Identifying Regulatory Strengths/Difficulties in YOURSELF
- Physiological
- Behavior
- Cognitive
- Emotion

Identifying Regulatory Strengths/Difficulties in YOUR CHILD
- Physiological
- Behavior
- Cognitive
- Emotion

Complete handouts for yourself and child

Prioritizing Areas to Target
Things to consider:
- What would increase the most function?
- What would increase quality of life?
- What would save time?
- What would save resources?
- Do I have time to target this area?
- Do I have the resources to target this area?
- Are the final outcomes worth it?
Discussion Goal 6: Specific Regulatory Strategies to Foster Each Window

Factors to consider:
- ID problematic behavior
- What preceded the behavior?
- What follows the behavior?
- Who is present when the behavior occurs?
- Where does the behavior take place?

Strategies: Behavior
- Modeling, role-playing, and reinforcement
- Predictable routines
- Visual Schedule
- Increasing choices
- Pre-correction
- Red Dot Timer
- First-Then Statements
- Scaffolding
- Requesting breaks with visuals
- Pressure vests and deep tissue massages

Strategies: Cognitive
- Modeling thinking, planning, and inhibitory strategies
- Modification of stressful environments
- Preparation to enter stressful environments
- Use of mind-body and technology practices to foster concentration and inhibition
- Take advantage of the child’s favorite activities to imbed teaching of waiting and engaging.

Strategies: Physiological
- Sensory stimulation
- Environmental modifications
- Relaxation Therapies
- Diet
- Feeding
- Toileting
- Sleep issues
Strategies: Emotion

- To develop awareness of emotion: teaching feeling vocabulary (modeling, scaffolding, and reinforcement)
- Mirroring feeling and modeling appropriate emotional responses
  - "I am happy, this is what happy looks like"
  - "You look upset, like this"
- Repetition and rehearsal of skills
- Use of visuals: colors, faces, traffic lights – to represent feeling or state
- Recognizing triggers that produce emotional response
- Teaching strategies to deal with emotions (deep breathing, location to calm down, attachment objects, etc.)
- Using all daily events to teach feelings, reactions, and modeling appropriate ways of coping

Remember to:

- Teach in different environments (home, school, grocery store)
- Teach with different people (peers, parents, siblings, etc.)
- Reinforce all appropriate behaviors in new environments

Thank you for your time!!!

If you have questions, please contact me at:
ramir1ma@cmich.edu
Identifying Regulatory Strengths and Difficulties in ME
Identifying Regulatory Strengths and Difficulties in MY CHILD
More clinical overlap between 22q11.2 deletion syndrome and CHARGE syndrome than often anticipated

Nicole Corsten-Janssen, MD
Dept. of Genetics, University Medical Center Groningen, Groningen, The Netherlands

Presenter Information:
Nicole Corsten-Janssen studied medicine at the University of Groningen in the Netherlands. She has been working in clinical genetics in the University Medical Center Groningen since 2008 and is currently in training to become a clinical geneticist. In 2009 she started her PhD project that focuses on CHARGE syndrome, CHD7 and heart defects for which she has studied among other heart defects in patients with CHD7 mutation, the overlap between CHARGE syndrome and 22q11.2 deletion syndrome and made an online database for CHD7 mutations (www.CH7D.org). She also participates in the Dutch multidisciplinary CHARGE outpatient clinic and is actively involved in the Dutch CHARGE parent support group.

Presentation Abstract:
CHARGE and 22q11.2 deletion syndrome are both variable, multiple congenital malformation syndromes that show considerable phenotypic overlap. In our presentation we’ll demonstrate this overlap and show that it may hamper their differential diagnosis: patients with clinical CHARGE syndrome may have a 22q11.2 deletion and patients with clinically 22q11.2 syndrome may have a CHD7 mutation. This overlap also has consequences for the clinical follow-up of thus far not well recognized clinical features in CHARGE syndrome, like T-cell dysfunction and hypocalcaemia.
The clinical overlap between CHARGE syndrome and 22q11.2 deletion syndrome

Nicole Corsten-Janssen
Clinical geneticist in training
University Medical Center Groningen
The Netherlands

It started with a patient...

- 3 years old
  - Coloboma of iris and retina
  - Pulmonary stenosis
  - Unilateral choanal stenosis
  - IQ 91
  - Height -1.3 SD
  - Simple ears
  - Mixed hearing loss
  - Abnormal semicircular canals

CHARGE syndrome

Birth incidence 6-7:100,000

- Coloboma
- Heart malformation
- Atresia of choanae
- Retardation (growth and development)
- Genital hypoplasia
- Ear abnormality (including deafness)
- Other features

Diagnosis of CHARGE syndrome

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Verloes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloboma</td>
<td>Major criteria</td>
</tr>
<tr>
<td>Choanal atresia</td>
<td>Coloboma</td>
</tr>
<tr>
<td>Hypoplastic semicircular canals</td>
<td>Choanal atresia</td>
</tr>
</tbody>
</table>

Blake:

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coloboma</td>
</tr>
<tr>
<td>Choanal atresia</td>
</tr>
<tr>
<td>Cranial nerve dysfunction</td>
</tr>
<tr>
<td>Characteristic ear abnormalities</td>
</tr>
</tbody>
</table>

(3 major or 2 major + 2 minor)

DNA analysis

CHD7 gene

Verloes AJMG 2005

CHD7 mutation?

- Sequencing and MLPA of CHD7: no mutations or deletion
- 180 k oligo whole genome array

22q11.2 deletion syndrome

Birth incidence 10-50:100,000

- Congenital heart defect
- Velar insufficiency, cleft palate
- Hypocalcaemia
- Learning difficulty, speech delay
- Behavioural problems
- Hypoplastic alae nasi, simple ears
- Thymic abnormalities, T-cell dysfunction
- Problem with TBX1 gene

Classical 3 Mb 22q11.2 deletion
### 22q11.2 features in CHARGE patients

- **Database**
- **802 patients with CHD7 mutations**
- **Clinical features**
  - Hypocalcaemia
  - T-cell dysfunction
  - Severe immunological problems
  - Thymus anomalies
  - "DiGeorge phenotype"
  - "22q11.2 deletion syndrome phenotype"

- 30 patients (3.7%) CHD7 positive patients with 22q11.2 deletion features

### CHARGE patients with 22q11.2 deletions

- > 4 other patients from literature and our own patients

### CHARGE association, no further information

### Digilio

### Devriendt

### Pt1

### Pt2

### 22q11.2 features in CHARGE patients

- Database
- 802 patients with CHD7 mutations
- Clinical features
  - Hypocalcaemia
  - T-cell dysfunction
  - Severe immunological problems
  - Thymus anomalies
  - "DiGeorge phenotype"
  - "22q11.2 deletion syndrome phenotype"

- 30 patients (3.7%) CHD7 positive patients with 22q11.2 deletion features

### CHD7 mutations in patients with clinical 22q11.2 deletion syndrome

- > 20 patients with clinical 22q11.2 deletion syndrome
- > No problems with TBX1
- > 5 with CHD7 mutations

### Explanation clinical overlap?

- **TBX1** is a transcription factor
- **CHD7** influences gene expression by binding chromatin

- > Randal et al (2009): great vessel development

- Shared molecular pathway
- Overlap in target genes

### Are CHD7 and TBX1 the only genes with overlapping clinical features?

- "CHARGE association, no further information"
Conclusions

> 22q11.2 deletion syndrome and CHARGE syndrome are more alike than often anticipated

> Challenging differential diagnosis
  - CHD7 analysis in clinical 22q11.2 deletion patients
  - Whole genome array in CHD7 negative CHARGE patients

> Immunological investigation in CHARGE patients

> Further research on the molecular link

Acknowledgement

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Questions??

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**Presenter Information:**
Dr. Kasee Stratton has been researching and working with children and young adults who have CHARGE for the past 7 years. She is a previous student of Dr. Timothy Hartshorne. Dr. Stratton’s primary research and clinical interests include: reducing challenging behaviors, teaching appropriate adaptive skills, identifying non-vocal pain behaviors, and reducing the pain experience for individuals with CHARGE. Kasee is currently finishing her Post-Doctoral Fellowship at the Johns Hopkins University School of Medicine and the Kennedy Krieger Institute. She plans to continue her work with CHARGE following completion of her fellowship and hopes to open a CHARGE clinic in the near future.

**Presentation Abstract:**
This presentation is designed to highlight the importance of pain for individuals with CHARGE and how to identify pain non-vocally. The presentation will emphasize results from two pain studies that are the first of their kind for individuals with CHARGE. Results are presented in a manner appropriate for parents, caregivers, educators, and physicians.
Specific highlights include: the variety of pain experiences (both acute and chronic), how to identify and track pain for your child, how pain impacts behavior, and strategies for reducing the pain experience.
HOW TO IDENTIFY PAIN AND THE RELATIONSHIP OF PAIN TO CHALLENGING BEHAVIOR

11th International CHARGE Syndrome Conference
Kasee Stratton, Ph.D.

THANK YOU!

- CHARGE Syndrome Foundation
  - Research funding support
  - Supporting our participant lists

- Families of children with CHARGE

- Central Michigan University
  - Funding support

CHARGE and Pain Overview

◆ Pain in developmental disabilities
◆ CHARGE syndrome and pain
◆ Are we identifying pain?
◆ How pain is related to challenging behavior
◆ Areas of future research

A Parent’s Story...

“Since my son was born almost 29 years ago, every aspect of his care has been a challenge. Being a single parent has been hard, but never harder than when my son is in pain and I can’t help him. As a parent, it is my job to make sure his needs are met and that he is loved. I feel like I have let him down when he is having pain and I can’t make it better. Unless it is something obvious, I have to play the guessing game of what hurts and why.

...continued

...My son is non-vocal and cannot tell me what is wrong. One of the biggest barriers to our children is others (e.g. doctors) understanding children with disabilities can have chronic pain too. And they don’t understand that pain contributes to behavior issues, such as SIB, that can be life-threatening. My son has had two subdural hematomas from SIB. It took me 6 months to get a CT scan of his head. In that 6 months he was in such excruciating pain. There is a fight everyday to get him what he needs.”

Pain and Developmental Disabilities

- “Higher” threshold for pain
  - Has been suggested in CHARGE (Davenport, 2002)
  - Limitations with Communication: Changes expression of pain

- No evidence
- Higher risk for experiencing more frequent pain
- High Pain Threshold vs. High Pain Tolerance
Sources of pain related to CHARGE

- Surgery
  - 1 to 63 procedures
  - Average 13
- Procedures
- Doctor visits
- CHARGE Characteristics

<table>
<thead>
<tr>
<th>Pain Experience</th>
<th>(N=61)</th>
<th>Percentage of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear Infections</td>
<td>41</td>
<td>67.2</td>
</tr>
<tr>
<td>Sinus Infections</td>
<td>27</td>
<td>44.3</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>26</td>
<td>42.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>42.6</td>
</tr>
<tr>
<td>Surgery</td>
<td>23</td>
<td>37.7</td>
</tr>
<tr>
<td>Tactile Defensiveness</td>
<td>21</td>
<td>34.4</td>
</tr>
<tr>
<td>Migraine</td>
<td>15</td>
<td>24.6</td>
</tr>
<tr>
<td>Stoma Pain</td>
<td>12</td>
<td>19.7</td>
</tr>
<tr>
<td>Abdominal Migraine</td>
<td>12</td>
<td>19.7</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>12</td>
<td>19.7</td>
</tr>
<tr>
<td>Back Pain</td>
<td>8</td>
<td>13.1</td>
</tr>
<tr>
<td>Hip Pain</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Jaw Pain</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
<td>Pain During Sleep</td>
<td>5</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Does your child experience pain from?

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


Migraines

- Most intense pain for children with CHARGE
- Range of 2-40 days/year
  - M = 14
  - Average Rating: 2.67 (Range: 2-4)

Abdominal Migraine

- Range from 2-365 days/year (M = 97)
- Average Rating: 2.45 (Range 1-4)
**Constipation**

- Painful bowel movements
- Dry or hard stool
- Nausea
- Cramps, abdominal pain
- Average pain for 52 days/year (1-203)
- Hurts more rating (2.38) (1-4)
- Fecal impaction
  - Abdominal cramping
  - Rectum discomfort

**Otitis Media**

- Range from 1 to 160 days a year; $M=26$ days
- Average rating 2.24 (Range 0-4)

**Gastroesophageal reflux disease**

- 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
- 10-365 days/year ($M=169$)
  - Average rating 2 (hurts more)

**Tactile Defensiveness**

- texted materials/items
- "messy" things
- vibrating toys
- a hug or kiss
- certain clothing textures
- rough or bumpy bed sheets
- seams on bumpy things
- tags 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

**Most Intense Pain and Average Duration**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pain Intensity</th>
<th>Days per Year in Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>Migraine</td>
<td>2.67</td>
<td>.87</td>
</tr>
<tr>
<td>Abdominal Migraine</td>
<td>2.45</td>
<td>1.10</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.38</td>
<td>.80</td>
</tr>
<tr>
<td>Surgery Pain</td>
<td>2.34</td>
<td>.97</td>
</tr>
<tr>
<td>Chronic Recurrent Otitis Media</td>
<td>2.24</td>
<td>.99</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.17</td>
<td>.82</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>2.06</td>
<td>1.14</td>
</tr>
<tr>
<td>Breathing</td>
<td>2.00</td>
<td>1.03</td>
</tr>
<tr>
<td>Hip/Back Pain</td>
<td>1.86</td>
<td>.95</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>1.82</td>
<td>.87</td>
</tr>
<tr>
<td>Coughing</td>
<td>1.61</td>
<td>.80</td>
</tr>
<tr>
<td>Jaw Discomfort</td>
<td>1.56</td>
<td>.88</td>
</tr>
<tr>
<td>Difficulty Swallowing</td>
<td>1.50</td>
<td>.83</td>
</tr>
</tbody>
</table>

**Identifying Pain in CHARGE**

- Are you able to determine when your child is experiencing pain?
  - 75% - Yes
  - Did not vary significantly by age of child
- What about educators, therapists, & doctors?
- Zero parents could identify chronic pain and no child could indicate chronic pain
What behaviors indicate pain?

• Vocal
  • Crying, screaming, moaning

• Social
  • Irritable, withdrawn, doesn't follow directions

• Facial
  • Grinds teeth, changes in eyes (glassy), furrowed brow

• Activity
  • Lethargic, inconsiderable, decreased movement/activity

• Body and Limb Movement
  • Rubbing area of pain, holding body in unusual posture

• Physiological
  • Fever, splotchy appearance, bowel movements, congestion

• Eating/Sleeping
  • Tired, changes in sleep

What behaviors indicate pain?

• Behavioral Challenges

• Self-Injurious Behavior (SIB)

• Dangerous Behaviors

• Aggressive, bites, hits head, throws objects, punches, pulls out g-tube

Amount of Pain

Why is it difficult to 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

SCALES

• Non-Communicating Children’s Pain Checklist-Revised (NCCPC-R)
  • 30 items; 7 subscales
    • vocal, social, facial, activity, body and limbs, physiological, and eating/sleeping

II. Social
Not cooperating, cranky, irritable, unhappy…………………………………….. 0 1 2 3 NA
Less interaction with others, withdrawn…………………………………….. 0 1 2 3 NA
PPP
• Pediatric Pain Profile (PPP)
• 20 items
• Rate: 0-3
  • Not at all, a little, quite a lot, and a great deal

Examples:
• Grinds teeth or makes mouthing movements
• Is restless/agitated or distressed
• Tenses/stiffens or spasms

Measuring Pain
• Baseline:
  • Complete NCCPC-R and PPP on a good day
  • NCCPC-R and PPP day of pain
  • A significant difference was found

Common Pain Behaviors

<table>
<thead>
<tr>
<th>NCCPC-R</th>
<th>PPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>not moving, less active, quiet</td>
<td>not cheerful</td>
</tr>
<tr>
<td>tears</td>
<td>crying, moaning</td>
</tr>
<tr>
<td>not cooperating, cranky, irritable, unhappy</td>
<td>not socially responsive</td>
</tr>
<tr>
<td>crying</td>
<td>grimaces, screws up eyes and face</td>
</tr>
<tr>
<td>moaning, whining, whimpering</td>
<td>frowns/furrowed brow</td>
</tr>
<tr>
<td>less interaction w/others, withdrawn</td>
<td>hard to console/comfort</td>
</tr>
<tr>
<td>not smiling</td>
<td></td>
</tr>
<tr>
<td>being difficult to distract, unable to satisfy</td>
<td></td>
</tr>
<tr>
<td>furrowed brow</td>
<td></td>
</tr>
</tbody>
</table>

Not entirely useful for CHARGE

• Did not display a meaningful difference:
  • Flexing inward/drawing legs up (PPP #15)
  • Stereotypical movements/jumping/seizures (PPP #20)
  • Flopping (NCCPC-R #16)
  • Shivering (NCCPC-R #22)
  • Jumping around/agitation/fidgety (NCCPC-R #15)

CNVPA
• Items from parental input and previous study
• Significant difference between no pain and pain ratings; strong reliability
• For 36% of our sample, physicians were able to confirm a diagnosis that is known to produce pain (e.g. sinus infection)
**CNVPA**

At least 1 point difference:
- Not Cheerful
- Aggressive
- Not Sociable
- Frowns/furrowed brow/looks worried
- Less active/quiet

.9 difference
- Restless/Agitated
- Change in Eating
- Specific movement to indicate pain
- Not cooperative
- Change in color

**Differ by age?**

- 1 month to 5 years
  - Fewer challenging behaviors
  - Change in eating
  - Less active/quiet
  - Change in color
- 11 to 15 years
  - Lower mean difference
    - More aggressive behaviors
    - Grinding teeth/clenching teeth

**Differ by Age?**

- Age 26 and +
  - Squinting eyes/eyes wide open/eyes frowning
  - Mouth turned down
  - SIB
  - Disturbed sleep
  - Resist being moved
  - Specific body part held

**CNVPA: Is it helpful?**

Do parents find the CNVPA to be relevant to identify their child’s pain (non-vocally)?
- Approximately 85% endorsed the CNVPA to be a relevant assessment to identify pain

**CNVPA helpful?**

- Why might this instrument not be relevant?
  - 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”

**Functions of Behaviors**

- Attention
- To gain access to preferred items/activities
- To escape/avoid demands or less preferred items/activities
- Stimulatory
All Behavior is...

Challenging Behavior in CHARGE

- Common challenging behaviors
  - Preference for certain items
  - Restricted range of interests
  - Difficulty with social relationships
  - Repetitive behaviors; increase under stress
  - High levels of sensation seeking; may include self injurious behavior
  - Executive Dysfunction
  - Regulatory Disorder

Does pain affect behavior?

- Evidence that pain is associated with behavior problems in typical-developing children
  - DeLissovoy (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-injur and otitis media
  - Carr & Owen-DeSchryver (2007) sick days
  - Lekkas & Lentino (1978) constipation
  - Kennedy & Meyer (1996) allergies

Does pain affect behavior?

- Aggressive behavior, destructive behavior, and self-injury
  (Kennedy and O’Reilly, 2006)
- Elevated pain → elevated self-injury (Symons and Danov, 2005)
  - We found similar results
- Attachment and Adaptive Functioning
  - Withdrawing and decreased communication
- 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

Challenging behavior as...
Reducing the pain experience
• Use CNVPA to track progress over time
• Mitigation
  • Analgesics
  • Dietary change
• Redesigning the environment
  • Reducing the demands
• Teaching coping skills
  • Self advocacy
  • Functional communication alternatives
• Parental Interaction with Physicians

Conclusion
• Children with CHARGE experience considerable amounts of pain and often exhibit problem behavior
• Problem behavior may have many causes, but one of them can be pain
• Pain can be managed when we know the child is experiencing pain, but not all children with CHARGE can easily communicate this
  • CNVPA may be a useful alternative

Future Pain Research
• Relationship between behavior and duration of pain
  • Impact adaptive, academic, and overall functioning
• Relationship between challenging behavior, pain, and communication (adaptive behaviors)
• Analgesics, neurological development, and the treatment of pain
• Controlled validity studies (e.g. surgery)
• Further investigation of age and sex differences

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Soon to be joining Mississippi State University