1st CHARGE Syndrome Conference for Professionals

Conference Evaluation

Who are you? _____Professional _____ Parent _____ Other: _____*:*

Did you get what you wanted from the Conference? _____

_____

What did you want from the Conference? _____

_____

What were the notable positive factors? _____

_____

Things that could be improved? _____

_____

Would you want to attend the Professional Conference in 2011? _____

Presenters or presentations with information that was of particular value to you:

PLATFORM PRESENTATIONS

___van Ravensvaaij-Arts & Bergman: Genetic testing in CHARGE syndrome

___Brown: Vision issues for people with CHARGE syndrome

___Kirk: The "R" and "G" in CHARGE

___Hall: Non-CHARGE syndrome with choanal atresia/stenosis

___Denno: Behavior analysis and CHARGE syndrome

___T. Hartshorne: Update on the CHARGE behavioral phenotype

___Blake & MacCuspie: Anesthetic management in CHARGE

___Bergman & van Ravenswaaij-Arts: Smell & puberty in CHARGE

___Scacheri: Insights into the function of CHD7 through genomics

___Bashinski & Stremel Thomas: Impact of cochlear implants in CHARGE

___Purvis: The NICU experience: its impact & implications

___Bergman et al: Cause of death in the post-natal period in CHARGE

POSTER PRESENTATIONS

___Nikki Anderson et al: Parental attitudes toward NMES

___Zambone et al: Preparation and certification in deafblindness

___Blake & Macuspie: Boxtox for dysphagia in CHARGE (case study)

___Consacro, Balderson & Brandrup: Cued speech

___Girardi: CHARGE feet: fact or fiction (Part II)

___N. Salem Hartshorne: Person-centered planning & evaluation

___Haynes: Constructing meaningful conversations

___King Miller et al: Communicative rate, forms, & function

___Krivenki & Thelin: Vestibulo- & cervico-ocular reflexes in CHARGE

___Majors & Stelzer: Multi-media tour of classrooms for CHARGE

___Swanson & Herrick: Manual signs to promote speech (case study)

___Stratton & T. Hartshorne: Identification of pain in CHARGE

___T. Hartshorne & Stratton: Prevalence of genetic testing in CHARGE

___Howard: The CHARGE Family Support Group in the UK

___Deuce: "Sense for deaf-blind people"- organization (Europe & UK)

___Kennedy, Purvis & Bruce: Person-centered planning & transition

1st CHARGE Syndrome Conference
For Professionals

July 23, 2009
Indian Lakes Resort
Bloomingdale, IL

PROFESSIONAL CONFERENCE PROGRAM AND HANDOUTS

The CHARGE Syndrome Foundation, Inc.
www.chargesyndrome.org

1st CHARGE Syndrome Conference for Professionals

Thursday, July 23, 2009, Bloomingdale, IL

Conference Schedule

ED – education, development & behavior | GI – general interest | SE – sensory

FS – family support | MG – medical, genetic | TX – therapy, treatment

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8:00- 9:00 **REGISTRATION & COFFEE & *POSTER SET-UP***

9:00- 9:15 **WELCOME** Foundation President Neal Stanger, Conference Chair Brownie Shott, Research Committee Chair Meg Hefner, and Program Chair James Thelin

9:15-12:00 **MORNING PLATFORM PRESENTATIONS**

9:15- 9:40 #1 Conny van Ravenswaaij-Arts & Jorieke Bergman *[University Medical Center, Groningen, NL]*
MG ***DNA diagnostics in CHARGE syndrome***

9:40-10:05 #2 David Brown *[California Deaf-Blind Project]*
SE ***Vision issues for people with CHARGE syndrome***

10:05-10:30 #3 Jeremy Kirk *[Diana, Princess of Wales Hospital, Birmingham, UK]*
MG ***CHARGE syndrome: the "R" and the "G"***

10:30-11:00 **BREAK (Beverages, pastries, & fruit)**

11:00-11:25 #4 Bryan Hall *[University of Kentucky School of Medicine]*
MG ***Non-CHARGE multiple congenital anomaly (MCA) syndromes associated with choanal atresia/stenosis (CAS)***

11:25-11:50 #5 Laurie Denno *[Perkins School for the Blind]*
ED ***Behavior analysis and CHARGE syndrome***

11:50-12:15 #6 Timothy Hartshorne *[Central Michigan University]*
ED ***Update on the CHARGE behavioral phenotype***

12:15- 1:15 **BUFFET LUNCH**

1:15- 2:30 **POSTER PRESENTATIONS**

TX Nikki Anderson, Shawn Herrick, Mikal, Folstaedt, Jaymie Barker & Amber Hamilton *[Spalding University]*
Parental attitudes toward the use of neuromuscular electrical stimulation (NMES) for the treatment of dysphagia in children with CHARGE syndrome: a pilot study

ED Alana Zambone, Susan Bashinski & Melissa Darrow Englemann *[East Carolina University]*
Preparation/certification of professionals in the area of deaf-blindness

TX Kim Blake & Jill MacCuspie *[Dalhousie University]*
Botox for dysphagia in CHARGE syndrome: a case study

ED Donna Consacro, Linda Balderson & Julie Brandrup *[TREDS – Tennessee Deaf-Blind Project]*
Cued speech: What is it? Would it be useful to our family?

MG Maryann Girardi *[Perkins School for the Blind]*
CHARGE feet: fact or fiction (Part II)

(Poster presentations continued on the next page)

1:15- 2:30 **POSTER PRESENTATIONS *(continued)***

ED Nancy Salem-Hartshorne *[Central Michigan University]*
Person centered planning as an adjunct to psychoeducational evaluation for individuals with CHARGE

ED Diane Haynes *[Kentucky Deaf-Blind Project]*
Constructing meaningful conversations

ED Emily King Miller[1], Lori Swanson[2], Nancy Steele[3], Ilsa Schwarz[1], Sara Thelin & James Thelin[1]
[1 University of Tennessee;2 University of Wisconsin-River Falls, 3 National Consortium forDeaf-Blindness]
Communicative rate, forms, and functions in CHARGE syndrome

SE Sarah Krivenki & James Thelin *[University of Tennessee]*
Vestibulo- and cervico-ocular reflexes in CHARGE syndrome

ED Martha Majors & Sharon Stelzer *[Perkins School for the Blind]*
A multi-media tour of classrooms with students with CHARGE syndrome

ED Lori Swanson *[University of Wisconsin- River Falls]* & *Shawn Herrick {Spalding University]*
Use of manual signs promotes speech: a case study

MG Kasee K. Stratton and Timothy S. Hartshorne *[Central Michigan University]*
Identification of pain in CHARGE syndrome

MG Timothy S. Hartshorne & Kasee K. Stratton *[Central Michigan University]*
Prevalence of genetic testing in CHARGE syndrome

GI Simon Howard *[CHARGE Family Support Group, UK]*
The CHARGE Family Support Group in the United Kingdom

GI Gail Deuce *[Sense, UK]*
"Sense for deaf-blind people" – an organization in the UK and Europe

ED Beth Marie Shaver Kennedy *[Deafblind Central]*, Barbara Purvis *[National Consortium for Deaf-Blindness*], & Nicole Bruce *[Deafblind Central]*
Using person-centered planning for students with low-incidence disabilities who are transitioning from school

2:30- 5:30 **AFTERNOON PLATFORM PRESENTATIONS**

2:30- 2:55 # 7 Kim Blake & Jill MacCuspie *[Dalhousie University, Halifax, Nova Scotia, Canada]*
MG ***Anesthesia complications in CHARGE syndrome***

2:55- 3:20 # 8 Jorieke Bergman & Conny van Ravenswaaij-Arts *[University Medical Center, Groningen, NL]*
MG-SE ***Smell and puberty in CHARGE syndrome***

3:20- 3:45 # 9 Peter Scacheri *[Case Western Reserve University, School of Medicine]*
MG ***Insights into the function of CHD7 revealed through genomics***

3:45- 4:10 **BREAK *(Beverages and snacks)***

4:10- 4:35 #10 Susan Bashinski *[University of North Carolina-Greensboro]* & Kathleen Stremel Thomas *[National Consortium for Deaf-Blindness]*
ED-SE ***Impact of cochlear implants for children with CHARGE syndrome – preliminary findings***

4:35- 5:00 #11 Barbara Purvis *[National Consortium for Deaf-Blindness]*
ED-MG ***The NICU experience: its impact and implications***

5:00- 5:25 #12 Jorieke Bergman[1], Kim Blake[2], Rolien Free[1], & Conny van Ravenswaaij-Arts[1] *[1 University Medical Center, Groningen, NL; 2 Dalhousie University, Halifax, Nova Scotia, Canada]*
MG ***Cause of death in CHARGE syndrome after the neonatal period: a report of six cases***

5:25- 5:30 **CONCLUDING REMARKS** Meg Hefner and James Thelin

1st CHARGE Syndrome Conference for Professionals

POSTER

ABSTRACTS

1st CHARGE Syndrome Conference for Professionals

Thursday, July 23, 2009, Bloomingdale, IL

POSTER ABSTRACTS

TX Nikki Anderson, Shawn Herrick, Mikal, Folstaedt, Jaymie Barker & Amber Hamilton *[Spalding University]*

Parental attitudes toward the use of neuromuscular electrical stimulation (NMES) for the treatment of dysphagia In children with CHARGE syndrome: a pilot study

Poster Abstract: The purpose of this pilot study is to determine the attitudes of parents toward Neuromuscular Electrical Stimulation (NMES), trade name VitalStim, as an intervention to treat swallowing difficulties (dysphagia) in children who have CHARGE Syndrome. A questionnaire has been completed by parents and an unstructured phone interview will be conducted if additional information is needed. The results of this study are currently being analyzed and will be completed by June of 2009.

ED Alana Zambone, Susan Bashinski & Melissa Darrow Englemann *[East Carolina University]*

Preparation/certification of professionals in the area of deaf-blindness

Poster Abstract: East Carolina University's (ECU) new Graduate Certificate in Deafblindness and Intervener Certificate effectively prepare personnel to meet the new national standards and attain national accreditation through distance education. The research and development process for the national teacher and intervener standards, accreditation, and ECU's courses and practica through distance education will be shared. The ways in which ECU's certificate programs apply principles of Universal Design to accommodate participants' diverse knowledge, experience, and learning styles are described.

TX Kim Blake & Jill MacCuspie *[Dalhousie University]*

Botox for dysphagia in CHARGE syndrome: a case study

Poster Abstract: Our patient's neonatal surgeries included Tracheooesophageal fistula repair, PDA and vascular ring ligation. He remained ventilation dependent because of excessive oral secretions and was awaiting tracheostomy. At 2 months of age, botox was injected into two pairs of his salivary glands and within 24 hours he was extubated. Five months later increasing oral secretions and aspiration pneumonia resulted in our patient requiring mechanical ventilation. Botox was successfully used again to reduce oral secretions.

ED Donna Consacro, Linda Balderson & Julie Brandrup *[TREDS – Tennessee Deaf-Blind Project]*

Cued speech: What is it? Would it be useful to our family?

Poster Abstract: This presentation will explore Cued Speech's effectiveness as a tool for receptive and expressive language development for children. Participants will gain an understanding of what Cued Speech is, how it might be used alone or to supplement sign language, the speed with which it can be acquired by parents and the subsequent breadth of language exposure it offers to their children. Possible physical reasons that might prevent the use of Cued Speech will also be explored.

MG Maryann Girardi *[Perkins School for the Blind]*

CHARGE feet: fact or fiction (Part II)

Poster Abstract: This poster will present the results from the study of foot anomalies at the 2007 conference

ED Nancy Salem-Hartshorne *[Central Michigan University]*

Person centered planning as an adjunct to psychoeducational evaluation for individuals with CHARGE

Poster Abstract: This poster will describe useful Person-Centered Planning techniques the presenter has used to assist families and professionals to come together to meet the needs of students with CHARGE syndrome. In both situations, the family members and professionals were at odds prior to the evaluation and Person-Centered Plan. The presentation will be highlighted with photographs and descriptions of the specific plans created, the stories behind the plans, and the positive outcomes for the students. The families of these students may be available to answer questions as well.

ED Diane Haynes *[Kentucky Deaf-Blind Project]*

Constructing meaningful conversations

Poster Abstract: The basic premise of this presentation is that any interaction between human beings is the basis for a conversation. Successful interactions / conversations depend on our ability as communication partners to perform the steps necessary to complete a basic dyadic interaction. Steps encompass accurate identification of receptive functions and receptive forms that reflect knowledge of a partner's functioning within all seven sensory systems. The presenter will share strategies for developing an intervention plan.

ED Emily King Miller[1], Lori Swanson[2], Nancy Steele[3], Ilsa Schwarz[1], Sara Thelin & James Thelin[1]
[1 University of Tennessee;2 University of Wisconsin-River Falls, 3 National Consortium forDeaf-Blindness]

Communicative rate, forms, and functions in CHARGE syndrome

Poster Abstract: A method of analyzing communicative rate, forms (pre-symbolic or symbolic), and functions (purposes) was developed to describe communication development in individuals with CHARGE. Video-taped communication samples were analyzed of 21 individuals with CHARGE syndrome (1:8 to 20:5 years: months). The analyses provide a means for describing specific communication abilities for an individual and for planning therapy to develop communication abilities. The results of the analyses were also used to describe the communication of the participants as a group.

SE Sarah Krivenki & James Thelin *[University of Tennessee]*

Vestibulo- and cervico-ocular reflexes in CHARGE syndrome

Poster Abstract In CHARGE syndrome, critical structures of the VOR and COR (which stabilize visual images with head motion) are often abnormal: incomplete or missing semicircular canals and ocular colobomas. A VNG procedure was used to measure the VOR and COR in subjects who could only provide minimal cooperation for brief periods. In subjects with CHARGE syndrome, horizontal VOR was absent for 29 of 29 subjects and horizontal COR was absent for 12 of 13 subjects.

ED Martha Majors & Sharon Stelzer *[Perkins School for the Blind]*

A multi-media tour of classrooms with students with CHARGE syndrome

Poster Abstract: This session will include a photo board of the key educaetional components of the Deafblind Program at Perkins School for the Blind; this will be a visual presentation to support discussion related to families questions about the Program; Martha Majors and Sharon Stelzer will be at the Poster Session.

ED Lori Swanson *[University of Wisconsin- River Falls]* & *Shawn Herrick {Spalding University]*

Use of manual signs promotes speech: a case study

Poster Abstract: This case study describes the development of oral language skills in a boy with CHARGE syndrome. Fluent manual sign and speech input were provided to this child at an early age. He relied on manual signs for language production while his tracheostomy was in place. When his trach was removed, he made any easy transition to speech. The importance of early intervention to facilitate language development will be discussed.

ED-MG Kasee K. Stratton and Timothy S. Hartshorne *[Central Michigan University]*

Identification of pain in CHARGE syndrome

Poster Abstract: Parents and professionals working with children with CHARGE have long suspected that these children experience considerable pain that is related to some of their behavioral difficulties. Pain may result from some of the physical anomalies of CHARGE and from multiple, extensive surgeries, as well as on-going health issues such as ear infections and headaches. To better understand the relationship between pain and behavior, we have proposed a method for measuring pain in CHARGE

MG Timothy S. Hartshorne & Kasee K. Stratton *[Central Michigan University]*

Prevalence of Genetic Testing in CHARGE Syndrome

GI Simon Howard *[CHARGE Family Support Group, UK]*

The CHARGE Family Support Group in the United Kingdom

GI Gail Deuce *[Sense, UK]*

"Sense for deaf-blind people" – an organization in the UK and Europe

ED Beth Marie Shaver Kennedy *[Deafblind Central],* Barbara Purvis *[National Consortium for Deaf-Blindness*], & Nicole Bruce *[Deafblind Central]*

Using person-centered planning for students with low-incidence disabilities who are transitioning from school

Poster Abstract: DB Central and the National Consortium on Deaf-Blindness are working in collaboration with Michigan School for the Deaf on an initiative to improve post-secondary outcomes for students with low incidence disabilities. Participants involved in the initiative are trained in the philosophy of person-centered planning (PCP) and the many ways in which the PCP can be used to enhance post-secondary transition planning. Participants are also encouraged, throughout the process, to function as a team, sharing common goals and desired outcomes. To increase local capacity, efforts are also made to train local person-centered planning facilitators and to initiate a person-centered planning community of practice.

1st CHARGE Syndrome Conference for Professionals

PLATFORM PRESENTATION ABSTRACTS & HANDOUTS

Medical & Genetic Information

Platform Presentation #1
9:15 – 9:40
Trillium Ballroom II, Conference Center

DNA DIAGNOSTICS IN CHARGE SYNDROME

Conny M. A. van Ravenswaaij-Arts, M.D., Ph.D.
Associate Professor in Clinical Genetics
and
Jorieke Bergman
Clinical Geneticist in Training and Ph.D. Student
Department of Genetics
University Medical Center Gronigen
The Netherlands

Primary Presenter Information: Conny van Ravenswaaij studied medicine at the University of Leiden, Netherlands. A PhD study was completed in 1993 at the Radboud University Nijmegen. In 2002 she was registered as a clinical geneticist. Her main interest has always been children with multiple congenital anomalies and chromosome disorders. 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 two multi-disciplinary outpatient clinics (for rare chromosome disorders and for CHARGE syndrome) and her studies in these syndromes. Amongst many other activities, she initiated a European project on rare chromosome disorders (www.ECARUCA.net). Beside her work as a clinical geneticist she is involved in a number of parent support groups (CHARGE, Wolf-Hirschhorn syndrome, European 11q, Rare chromosome disorders).

For the studies in CHARGE syndrome she collaborates with many other researchers in Groningen as well as abroad. At this moment the studies focus on clinical variability and phenotype-genotype correlations, puberty development and smell, the role of CHD7 in heart development, and other aspects of CHARGE syndrome.

ADDRESS: University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands; TEL: 0031(0)503617229, FAX: 0031(0)503617231,EMAIL: c.m.a.van.ravenswaaij@medgen.umcg.nl

Presentation Abstract: The gene involved in CHARGE syndrome was identified in 2004. Mutations in this gene, the CHD7 gene, are found in the majority of CHARGE syndrome patients. Different techniques are used to analyze this large gene. Sequence analysis is the method of first choice and will identify mutations in the CHD7 gene. Two other techniques, MLPA and array CGH, can be used to find deletions or duplications of the CHD7 gene.

University Medical Center Groningen

DNA diagnostics in CHARGE syndrome

the Dutch experience

Conny van Ravenswaaij-Arts
Department of Genetics,
University Medical Center Groningen
The Netherlands

Outline of the presentation

- ✓ **The clinical diagnosis of CHARGE syndrome**
- ✓ **the *CHD7* gene**
- ✓ **DNA-diagnostics in CHARGE syndrome**
- ✓ **Future studies**

Clinical criteria

	Major criteria	*Minor criteria*	*Inclusion rule*
Pagon	1. Choanal atresia 2. Ocular coloboma	1. Heart defects of any type 2. Retardation (of growth and/or of development), 3. Genital anomalies 4. Ear anomalies (abnormal pinnae or hearing loss)	Four criteria out of six, and at least one major
Blake	1. Coloboma – of iris, retina, choroid, disc; microphthalmia 2. Choanal atresia – unilateral/bilateral, membranous/bony, stenosis/atresia 3. Characteristic ear abnormalities – external ear (lop or cup-shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects 4. Cranial nerve dysfunction – facial palsy (unilateral or bilateral), sensorineural deafness and/or swallowing problems	1. Genital hypoplasia – males: micropenis, cryptorchidism; females: hypoplastic labia; both males and females: delayed, incomplete pubertal development 2. Developmental delay – delayed motor milestones, language delay, mental retardation 3. Cardiovascular malformations – all types, especially conotruncal defects (eg, tetralogy of Fallot), AV canal defects, and aortic arch anomalies 4. Growth deficiencies – short stature, growth hormone deficiency 5. Orofacial cleft – cleft lip and/or palate 6. Tracheoesophageal-fistula – tracheoesophageal defects of all types 7. Characteristic face – sloping forehead, flattened tip of nose	Four majors OR three majors +three minors
Verloes	1. Ocular coloboma 2. Choanal atresia 3. Hypoplasia of semicircular canals	1. Rhombecephalic dysfunction (brainstem and cranial nerve III to XII anomalies, including sensorineural deafness) 2. Hypothalamo-hypophyseal dysfunction (including GH and gonadotropin defects) 3. Malformation of the ear (internal or external) 4. Malformation of mediastinal organs (heart, esophagus,) 5. Mental retardation	Typical CHARGE: three majors OR two majors + two minors Partial CHARGE : two majors +one minor Atypical CHARGE: two majors but no minors OR one major + two minors

Sanlaville & Verloes
EJHG 2007;15:389-399

Clinical criteria

Blake:
(4 major or 3 major + 3 minor)

Major criteria

- Coloboma
- Choanal atresia
- Cranial nerve dysfunction
- Characteristic ear abnormalities

Verloes:
(3 major or 2 major + 2 minor)

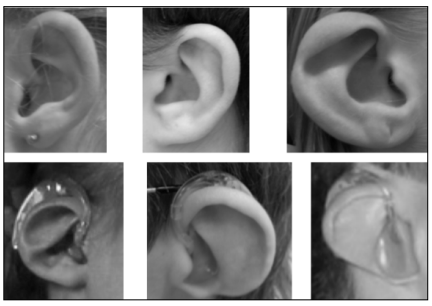
Major criteria

- Coloboma
- Choanal atresia
- Hypoplastic semicircular canals

Blake *et al* Clin Pediatrics 1998

Verloes AJMG 2005

Clinical variability in CHARGE syndrome



Aspecific CHARGE syndrome

- Feeding problems / tracheomalacia
- Heart defect: vascular ring
- Mild MR
- Height P3
- Dysmorphic ears
- Bilateral severe hearing loss
- Aplasia of semicircular canals

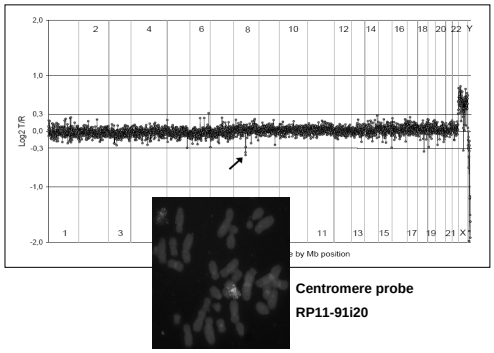
- No coloboma
- No choanal atresia
- No cleft lip/palate

- 5833C>T (R1945X)

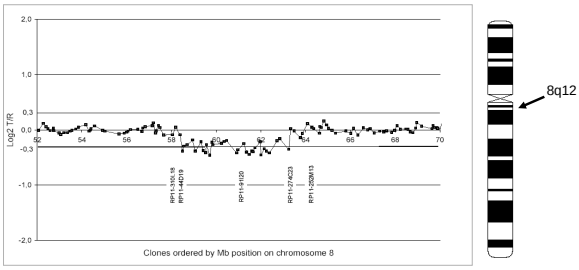
Outline of the presentation

- ✓ **the clinical diagnosis of CHARGE syndrome**
- ✓ **the *CHD7* gene**
- ✓ **DNA-diagnostics in CHARGE syndrome**
- ✓ **Future studies**

Array CGH: deletion 8q12



Array CGH: deletion 8q12



31 clones deleted spanning 4.8Mb

CHD7 and CHARGE syndrome

Patient	Sex	Coloboma	Heart malformation	Atresia of Choanae	Retardation of growth and development	Genital hypoplasia	Ear abnormality including deafness	DNA mutation	Exon	Protein consequence	De novo
1	F	+	+	-	+	-	+	del 8q12 region			yes
2[b]	F	+	+	-	+	-	+	del 8q12 region			U
3	F	+	+	-	+	-	+	469 C>T	2	Arg157stop	U
4	F	-	+	+	+	-	+	1078 G>T	2	Gly360stop	U
5	M	-	-	-	+	+	+	1714 C>T	3	Gln572stop	yes
6	F	+	-	-	+	-	+	3082 A>G	12	Ile1028Val	yes
7	F	+	-	-	+	+	+	3770 T>G	15	Leu1257Arg	yes
8	F	-	+	+	+	+	+	5418 C>G	26	Tyr1806stop	yes
9	M	+	-	-	+	+	+	6051 T>A	30	Cys2017stop	U
10	F	+	+	-	+	-	+	6070 C>T	30	Arg2024stop	U
11	F	-	+	+	+	-	+	7824 T>A	35	Tyr2608stop	yes
12	M	+	+	-	+	+	+	IVS26-7G>A	26	Splice site	yes
13	F	+	+	+	+	+	+				
14	F	+	-	+	+	-	+				
15	M	+	-	-	+	-	+				
16	F	+	+	-	+	+	+				
17	F	-	+	-	+	+	+				
18	M	+	+	-	+	+	+				
19	M	+	+	+	+	+	+				

Haploinsufficiency of *CHD7* in 12/19 patients

18/19

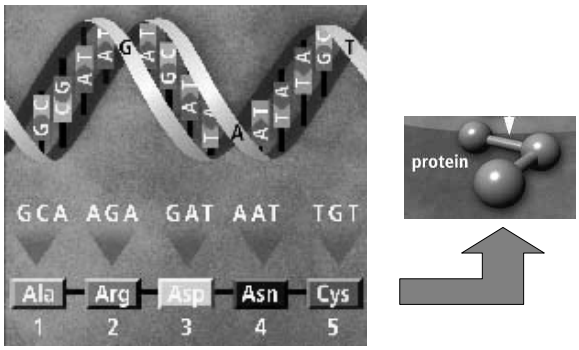
nature genetics

2004

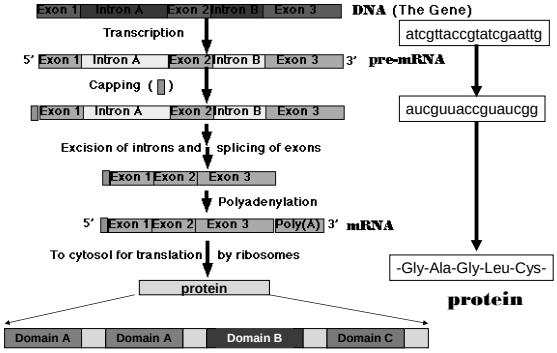
Mutations in a new member of the chromodomain gene family cause CHARGE syndrome

Lisenka E L M Vissers[1], Conny M A van Ravenswaaij[1,2]

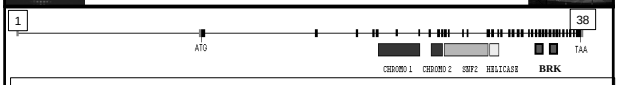
Genotype



DNA – genes - protein

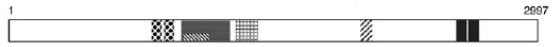


CHD7



CHD proteins play a role in embryonic development by affecting chromatin structure/ remodelling and gene expression

Cavalli *et al* Curr Opon Cell Biol 10, 354-360 (1998)

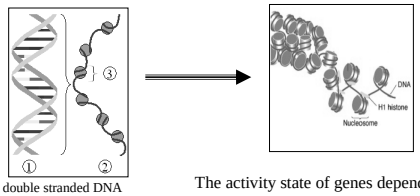


CHD7 functions in enhancer mediated transcription, the congenital anomalies in CHARGE syndrome are due to alterations in transcription of tissue-specific genes normally regulated by CHD7 during development.

Schnetz, Genome Research 2009

Function *CHD7*

The activity state of chromosomal loci is determined by:
- rigidity & compactness of the folded chromatin fibre
- subnuclear localisation of chromatin



1 double stranded DNA
2 chromatin: DNA + histons
3 histon complex, nucleosoom

The activity state of genes depends on:
- the association of non-histone proteins
- enzymes that modify the basic nucleosomal fibre

Function *CHD7*

Deletion = mutation

↓

Loss-of-function / haplo-insufficiency

CHD7 enhances transcription

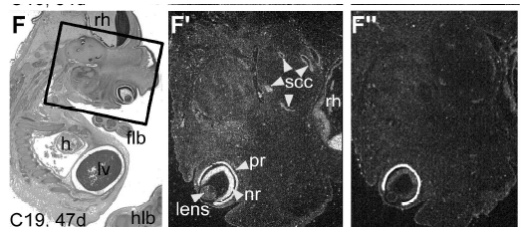
↓

Mutation

↓

tissue-specific diminished transcription of genes

CHD7 expression



Expression of CHD7 in the inner ear and eye

Sanlaville JMG 2005

Outline of the presentation

- ✓ **The clinical diagnosis of CHARGE syndrome**
- ✓ **the *CHD7* gene**
- ✓ **DNA-diagnostics in CHARGE syndrome**
- ✓ **Future studies**

***CHD7* diagnostics: methods**

***CHD7* sequencing:**

Mutation frequency: 65-75%

In typical CHARGE: > 90%

atcgtt**a**ccgtatcgaattg

↓

aucg**u**uaccguaucgg

↓

-Gly-Leu-**Stop**

CHD7 diagnostics: methods

***CHD7* sequencing:**

Mutation frequency: 65-75%

In typical CHARGE: > 90%

***CHD7* MLPA:**

Whole gene deletions are extremely rare

Whole exon deletions in a few patients

CHD7 diagnostics: methods

***CHD7* sequencing:**

Mutation frequency: 65-75%

In typical CHARGE: > 90%

***CHD7* MLPA:**

Whole gene deletions are extremely rare

Whole exon deletions in a few patients

Cytogenetics:

translocations involving 8q12, extremely rare

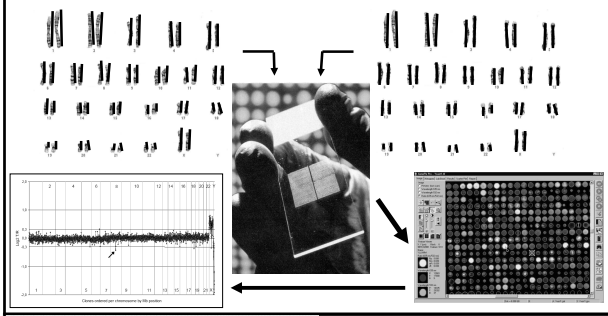
The Dutch experience

450 patients suspected for CHARGE syndrome:

1 whole gene deletion	**(array CGH)**
1 intragenic deletion	**(MLPA)**
302 mutations	**(sequencing)**

Comparative Genomic Hybridisation

patient controle

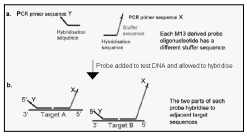


The Dutch experience

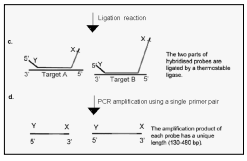
450 patients suspected for CHARGE syndrome:

1 whole gene deletion	**(array CGH)**
1 intragenic deletion	**(MLPA)**
302 mutations	**(sequencing)**

MLPA



(partial) deletions of *CHD7* (MLPA)



Deletions of *CHD7*

Methods:

MLPA of 54 CHARGE patients without *CHD7* mutation

Clinical information of patients was obtained through a written questionnaire

Deletions of *CHD7*

Patients:	Diagnostic criteria	
	Blake	Verloes
6	+	+
5	+	atypical
7	-	+
30	-	atypical
6	-	-
54	**18 typical** **30 atypical** **6 suspected**	

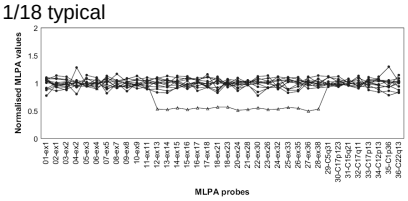
atypical Verloes: 2 majors or 1 major and 2 minors

Deletions of *CHD7*

Results:

One patient with deletion exon 13-38

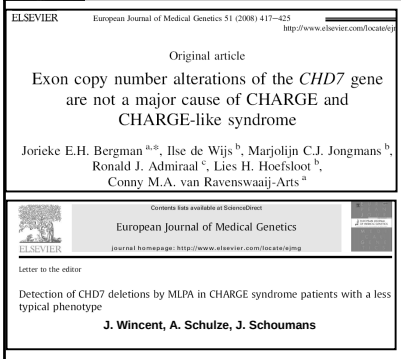
1/54 suspected, 1/18 typical



Conclusion:

Whole exon deletions are not a common cause of CHARGE syndrome

CHD7 diagnostics


ELSEVIER European Journal of Medical Genetics 51 (2008) 417–425

Original article

Exon copy number alterations of the *CHD7* gene are not a major cause of CHARGE and CHARGE-like syndrome

Jorieke E.H. Bergman [a,*], Ilse de Wijs [b], Marjolijn C.J. Jongmans [b], Ronald J. Admiraal [c], Lies H. Hoefsloot [b], Conny M.A. van Ravenswaaij-Arts [a]

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Letter to the editor

Detection of CHD7 deletions by MLPA in CHARGE syndrome patients with a less typical phenotype

J. Wincent, A. Schulze, J. Schoumans

Nijmegen:
302 mutation pos.
1 gene deletion
1 intragenic del.

4/18, 3 atypical

Always perform MLPA

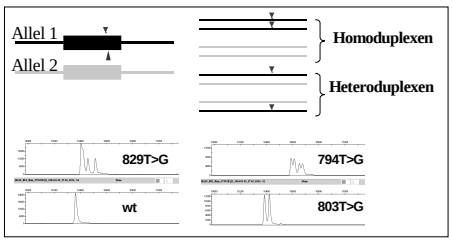
The Dutch experience

450 patients suspected for CHARGE syndrome:

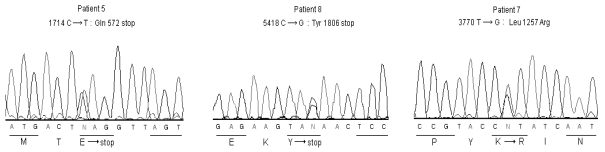
1 whole gene deletion	**(array CGH)**
1 intragenic deletion	**(MLPA)**
302 mutations	**(sequencing)**

Sequencing

Heteroduplex pre-screening



Sequencing



The Dutch experience

450 patients suspected for CHARGE syndrome:

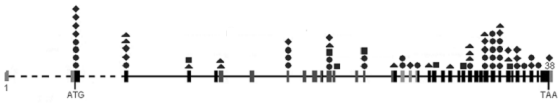
1 whole gene deletion (array CGH)

1 intragenic deletion (MLPA)

302 mutations (sequencing)

Frame shift	92
Missense	55
Splice	48
Stop	107
Totaal	**302**

Genotype-phenotype effect?



- Nonsense mutation (n=31)
- Missense mutation (n=7)
- Splice site mutation (n=15)
- Frameshift mutation (n=17)
- Chromodomain
- SNF2 domain
- Helicase domain

108 patients suspected for CHARGE syndrome

70 patients *CHD7* affected: **~ 65%**

Phenotype study

- 47 mutation positive patients
- 22 males, 25 females
- 2 sib pairs
- Age 0 – 40 years

Clinical features in *CHD7* pos.

	This study N=47(%)	Tellier et al. N=47 (%)	Issekutz et al. N=77 (%)
Coloboma	70	79	77
Heart defects	67	85	84
Choanal atresia	34	57	64
Growth deficiency	69	75	58
Micropenis/cryptorchidism	77	53	65
Ear-anomaly/deafness	100	100	96
Cleft lip/palate	36	17	18
TE fistula	15	15	19

Jongmans *et al*. JMG 2006

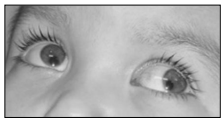
Tellier *et al*. AJMG 1998

Issekutz *et al*. AJMG 2005

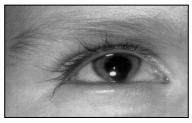
Outline of the presentation

- ✓ **The clinical diagnosis of CHARGE syndrome**
- ✓ **the *CHD7* gene**
- ✓ **DNA-diagnostics in CHARGE syndrome**
- ✓ **Future studies**

Research

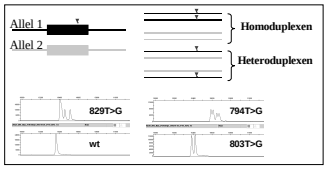
Coloboma is found in 75-90% of CHARGE patients

Coloboma cohort

Methods:

CHD7 analysis (heteroduplex and sequencing) of 16 coloboma patients



Patients:

10 coloboma patients from Oxford (10)

79 coloboma patients from Edinburgh (6)

Coloboma cohort

Results:

No mutations were found in 16 patients

Conclusion:

CHD7 mutations are not found in isolated coloboma patients

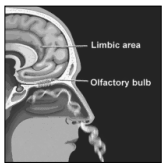
Future research

Other cohorts:

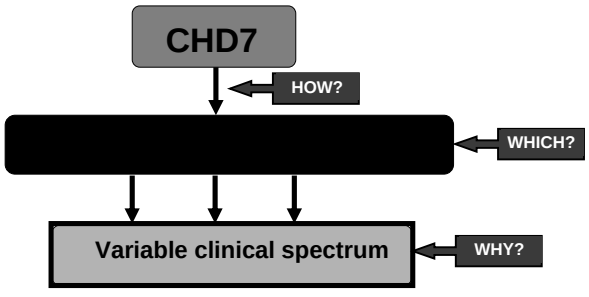
- Kallmann syndrome

= hypogonadotropic hypogonadism + anosmia

- Semicircular canals
- Heart defect
- Oesophageal atresia
- Atresia of choanae



Future research



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HUMAN GENETICS NIJMEGEN

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- **N. Janssen**

- G. Bocca
- R. Free
- L. Kapusta
- R. Admiraal

- J.M. Hagen, Amsterdam
- D. Donnai, Manchester
- P. Helderman, Leiden
- J. Verheij, Groningen
- W. Crowley, N. Pitteloud, S. Seminara, Boston
- N. Sato, T. Ogata, Tokyo
- K. Steel, E. Bosman, Cambridge

Contact:
c.m.a.van.ravenswaaij@medgen.umcg.nl

Sensory Information

Platform Presentation #2
9:40 – 10:05 AM
Trillium Ballroom II, Conference Center

VISION ISSUES FOR PEOPLE WITH CHARGE SYNDROME

David Brown

Education Specialist
California Deaf-Blind Services

Presenter Information: *David Brown* began his career in the United Kingdom but now provides educational services in California. He has written and spoken widely on CHARGE syndrome and deaf-blindness.. He is an extraordinarily perceptive observer of individuals with deaf-blindness. His descriptions of the challenges faced by specific individuals with multiple anomalies and the effects on individual behavior have provided a model for the study of CHARGE syndrome and have shaped the body of knowledge that has been amassed over the past two decades.

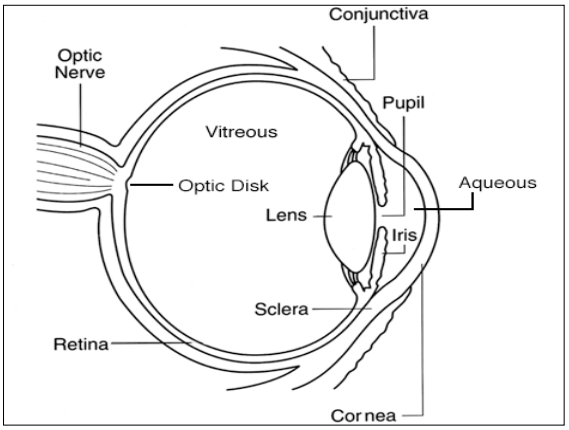
ADDRESS: 885 Corbett Avenue, San Francisco CA 94131
TEL: 415-405 7559; EMAIL: davidb@sfsu.edu

Presentation Abstract: Many of the anomalies found in CHARGE Syndrome carry significant implications for the development of functional vision skills. Some of these anomalies are specifically associated with eye defects, but many are not so are constantly overlooked or misunderstood as contributing to functional vision difficulties. This session will examine all these anomalies, their behavioral implications, and strategies for intervention.

Visual issues for people with CHARGE Syndrome

CHARGE Foundation Conference 2009
Chicago, Illinois

David Brown
Education Specialist
California Deaf-Blind Services
San Francisco State University

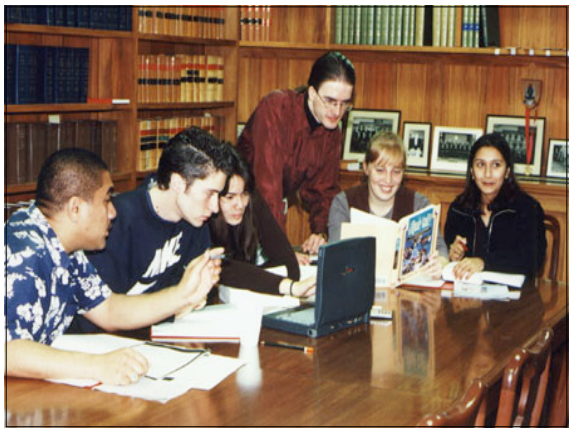


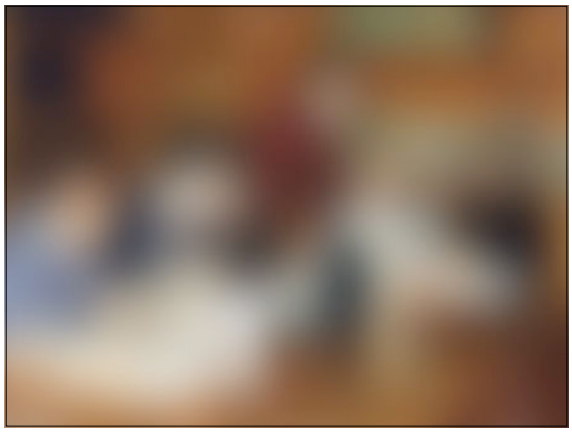
High Risk Signs of Vision Loss

- Atypical appearance of the eye
- Unusual eye movements
- Unusual gaze or head positions
- Absence of visually directed behaviors

The Five Types of Vision Loss

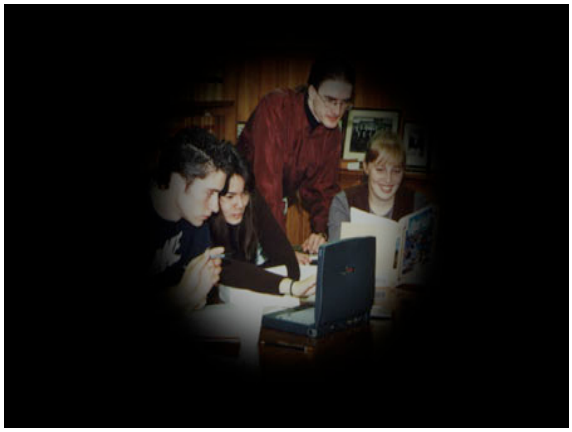
1 Loss of visual acuity: visual images appear blurred, visual detail is missing



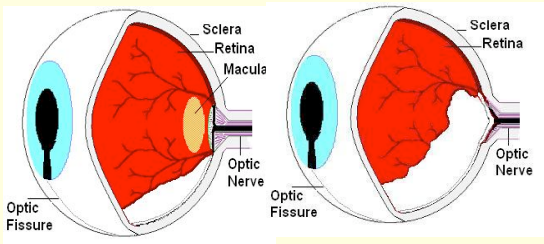


The Five Types of Vision Loss

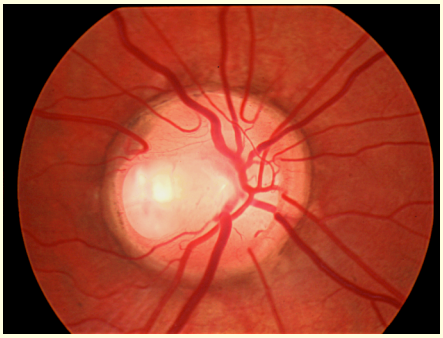
2 Loss of visual field: part (or parts) of the visual field is blurred or completely missing



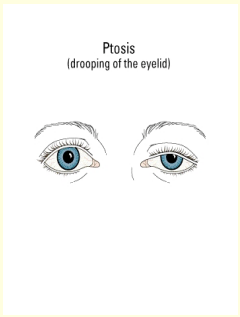
Retinal Coloboma



Optic Nerve Coloboma

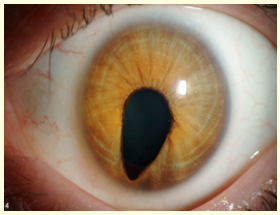


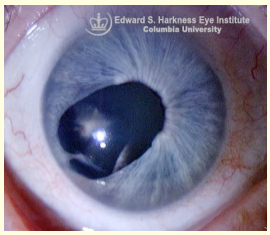
Facial palsy & ptosis



Facial palsy & ptosis

Iris coloboma



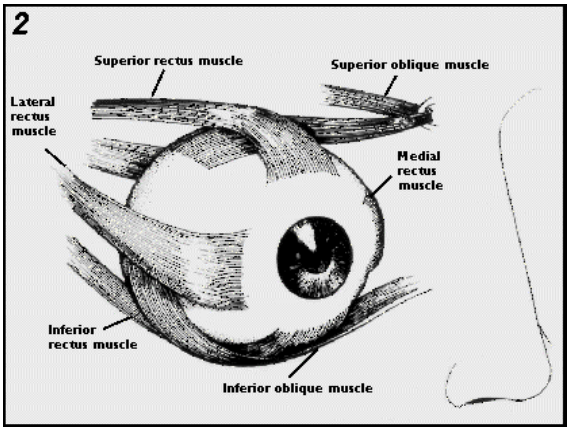


The Five Types of Vision Loss

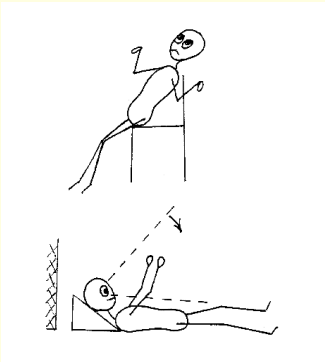
3 Loss of contrast sensitivity:the relative difference between the lightness and darkness of objects and their background is hard to perceive

The Five Types of Vision Loss

4 Loss of ocular motor control: the ability to control eye movements, particularly when performing visual tasks (eg fixating, tracking, scanning) is compromised



T Geniale (1991)



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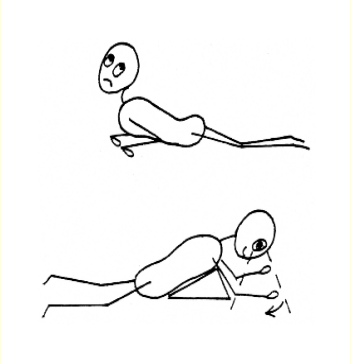

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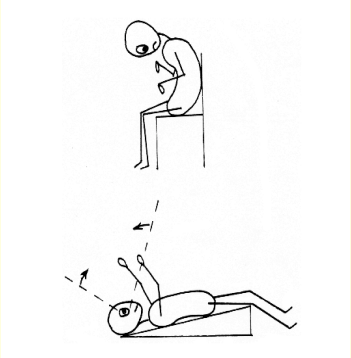
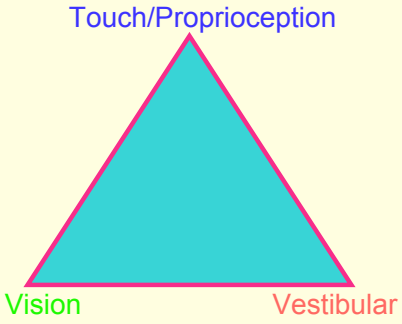
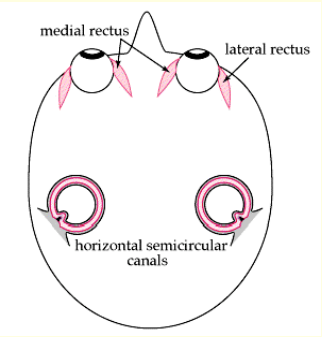


T Geniale (1991)

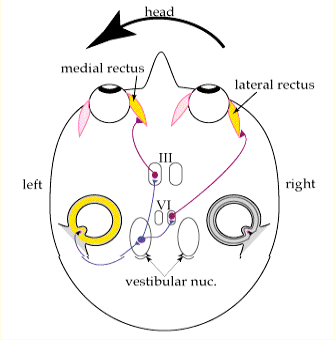
The Equilibrium Triad



The Vestibulo-ocular Reflex (1)



The Vestibulo-ocular Reflex (2)

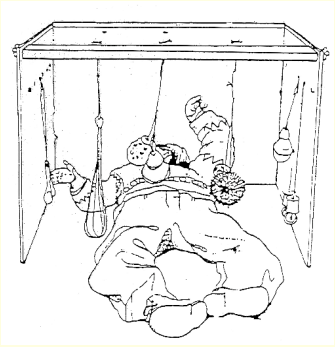


This is normal viewing posture…

…when you have no vestibular sense, upper visual field loss, poor tactile & proprioceptive perception, & low muscle tone.

The Little Room

The Be-Active Box



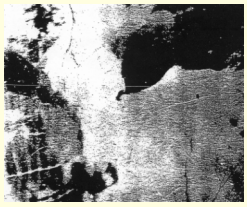
The Five Types of Vision Loss

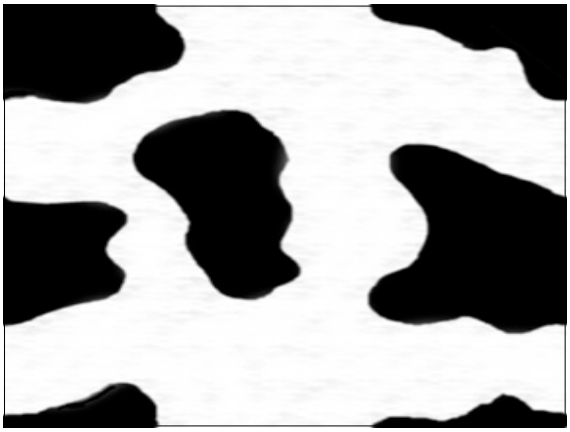
5 Loss of visual processing: the brain is unable to make correct sense of the information it is receiving through the eyes

Whose perception counts?

The brain, the organ that is responsible for your conscious experience, is an eternal prisoner in the solitary confinement of the skull…and must rely on information smuggled into it from the senses…the world is what your brain tells you it is, and the limitations of your senses set the boundaries of your conscious experience.

Coren, Porac & Ward "Sensation & Perception" (1984, p2)





We don't see with our eyes - we see with our brains

When you are assessing vision - don't think 'eyes', think 'child'

We don't hear with our ears - we hear with our brains

When you are assessing hearing - don't think 'ears', think 'child'

Natalie Barraga (1976)

Visual functioning is related in part to the condition of the eye. More explicitly, visual functioning is determined by the *experiences*, *motivations*, *needs* and *expectations* of each individual in relation to whatever visual capacity is available to *satisfy* *curiosity* and accomplish activities for *personal* *satisfaction*.

Vision Issues for People with CHARGE Syndrome

David Brown, CHARGE Foundation Conference 2009

In this presentation I plan to focus on the multi-layered complexity of the vision issues faced by many people with CHARGE Syndrome, with a special emphasis on early childhood when good visual motivation and good visual behaviors can be established.

There is a common tendency to assume that the actual condition of the eyes, particularly any eye defect that might be present, is what determines functional vision skills. While it is, of course, important to know about the condition of the eyes, and to seek appropriate help from medical specialists to evaluate this and to intervene where possible, there are also many other factors that need to be understood, evaluated, and worked on.

For individuals with CHARGE Syndrome the following would be a helpful list to remember:

- The eyes, and ocular defects
- The nerve pathways that connect the eyes to the brain
- The brain itself
- Muscle tone, and the obstacles that abnormal muscle tone present to effective use of vision
- Broader issues of postural control, and energy levels and fatigue
- Distractibility and the place of vision in the individual's hierarchy of the senses (ie. is vision an important resource for this person, or does it seem very low priority for them?)
- Expectations, previous experience, and motivation of the individual (and of the people around them)
- Environmental factors such as visual clutter, physical placement of things in relation to the individual, lighting levels, other distractions that might compete for the individual's attention

We have to remember that we don't see with our eyes, we see with our brains – all that the eyes can do is collect visual information for our brains to 'see' (ie. it is the brain, not the eyes, that has to perceive, to interpret and recognize, and to make decisions based on what the eyes are showing it). We also need to remember that in any group of people with visual impairments the individual with the best functional vision skills might not be the individual with the most vision!

Medical Information

Platform Presentation #3
10:05 – 10:30 AM
Trillium Ballroom II, Conference Center

CHARGE SYNDROME: THE "R" AND THE "G"

Jeremy Kirk, M.D.

Diana, Princess of Wales Children's Hospital
Birmingham, UK

Presenter Information: *Dr. Kirk* is a paediatrician and a long-time contributor to the knowledge base on CHARGE syndrome in the area of endocrinology and growth.

By his own description: he is London born and bred, now Head of pediatric endocrinology at the Diana Princess of Wales Children's Hospital in Birmingham, Britain's own "Second City". .Last remaining member of the UK CHARGE "Brit Pack" still living in the UK.! Associate Professor (Reader) in the University of Birmingham, Council Member of the Royal College of Paediatrics and Child Health, and past secretary of British Society for Paediatric Endocrinology and Diabetes. Has a special in interest in growth and gonadal problems. Medical Advisor to UK CHARGE Family Support Group.

ADDRESS: Diana, Princess of Wales Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, United Kingdom; TEL: +44 121 333 8188; EMAIL: Jeremy.Kirk@bch.nhs.uk

Presentation Abstract: Both growth problems (failure to thrive, short stature, delayed/absent puberty) and also genital problems (micropenis/undescended testicles) are part of the original acronym of CHARGE. Whilst these problems are commonly seen in CHARGE, other more pressing medical and surgical problems often mean that they are not always recognized or treated appropriately. We have been collecting data on these problems from within our local clinic, and also national/international groups, in order to provide best practice.

CHARGE Syndrome: the “R” and the “G”

Dr. Jeremy Kirk
Consultant Paediatric Endocrinologist
Diana, Princess of Wales Children’s Hospital, Birmingham
United Kingdom

CHARGE: the “R” and the “G”

C

H

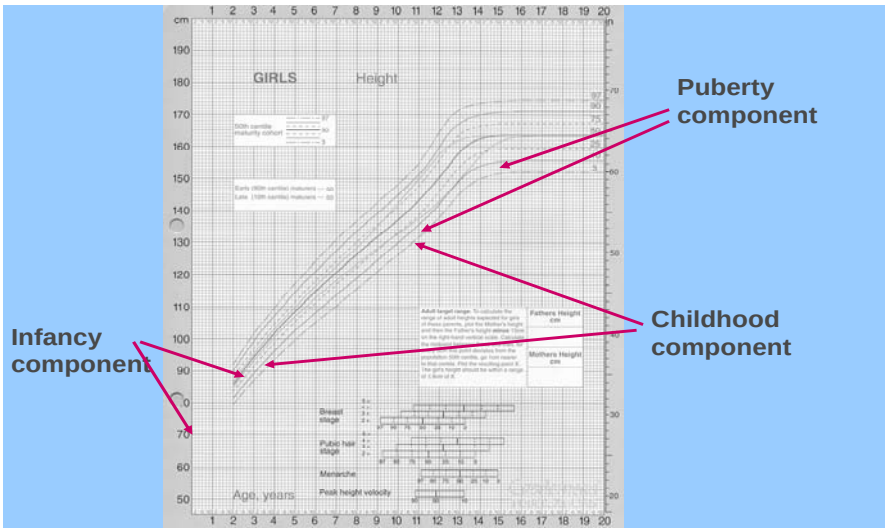
A

R etarded Growth

G enital Hypoplasia

E

Different growth components: all affected in CHARGE



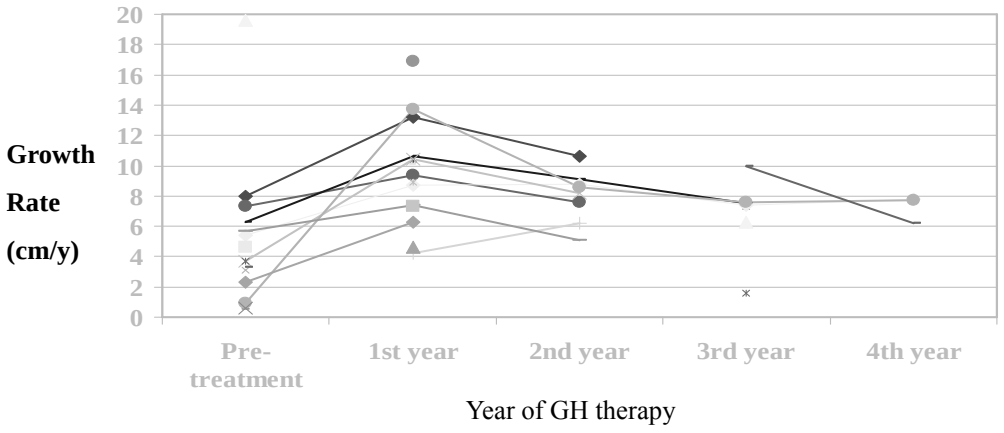
GH-deficiency and underactive pituitary (hypopituitarism)

- Incidence unknown in CHARGE syndrome.
- Probably more common than general population, especially in children with clefting.
- Data on growth hormone (GH) therapy in CHARGE obtained from 2 large international GH databases (NCGS (USA) & KIGS (Europe)).

GH therapy in CHARGE (USA)

- National Cooperative Growth Study (NCGS).
- 26 patients (19 female) aged 0.5-16.7 years. All but one patient were prepubertal.
- Most patients were short (23 had heights below 2nd centile)
- 22 had anterior pituitary function testing; 17 were GH-deficient.

GH therapy in CHARGE (USA)

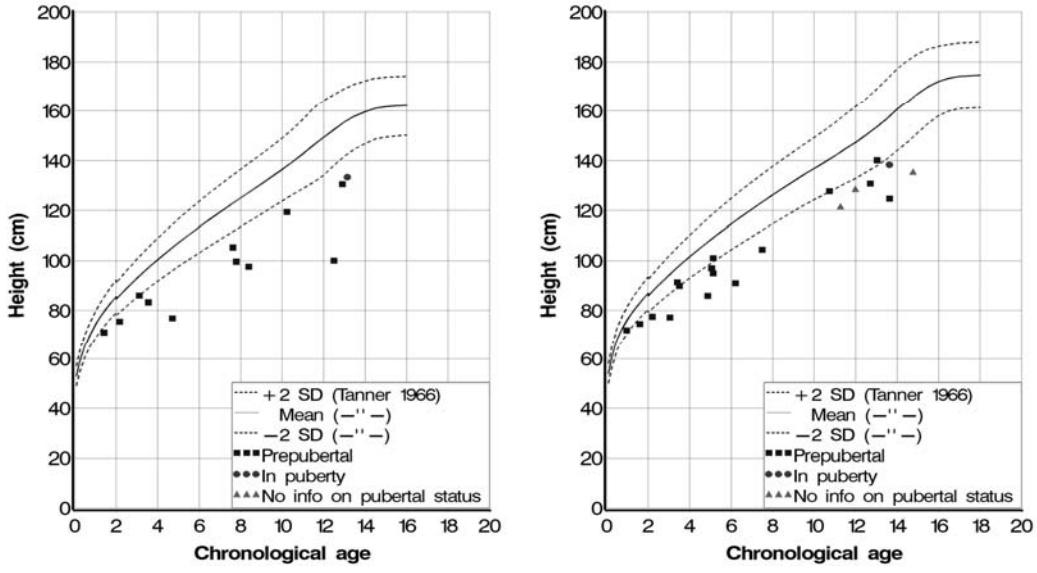


GH therapy in CHARGE (KIGS; European)

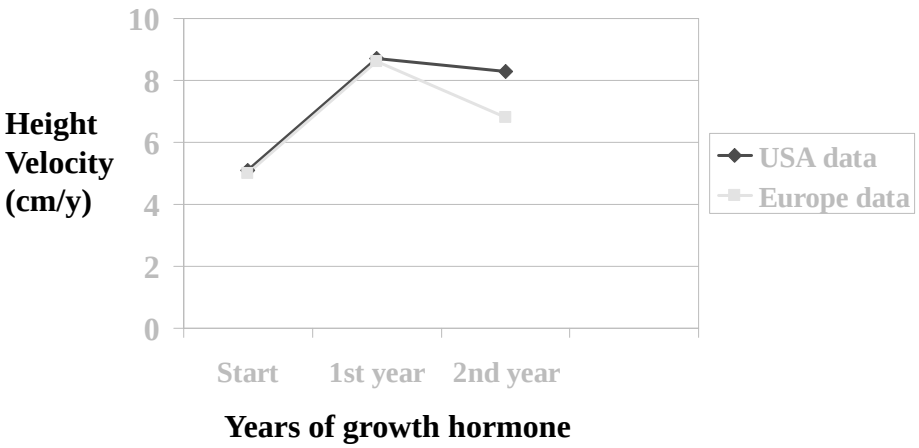
- 32 patients (12 female) average age 7.44 years. All but two (1 male, 1 female) were pre-pubertal.
- Most patients were short (27 (84%) had heights below 2nd centile)
- 26 have had anterior pituitary function performed. Mean GH level was 9.38 μg/L (normal > 10), with 19 (73%) GH-deficient.

CHARGE syndrome (KIGS; Europe): Baseline data

Height at GH start. ***Girls (left) & Boys (right)***



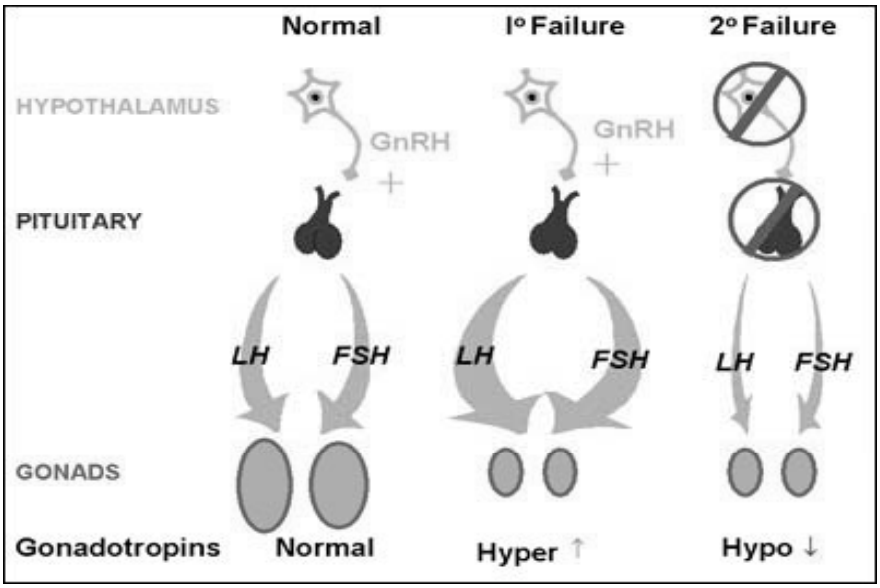
Comparison of US and European data



GENITAL AND PUBERTAL ABNORMALITIES

GENITAL PROBLEMS IN CHARGE

INFANCY	*Frequency*
Males:	
• Micropenis	85%
• Undescended testicles	60%
Females:	
• Underdeveloped labia	Very common
ADOLESCENCE	
• Delayed/arrested puberty	Very common
ADULTHOOD	
• Infertility	Unknown



Forms of gonadal failure: central vs. peripheral

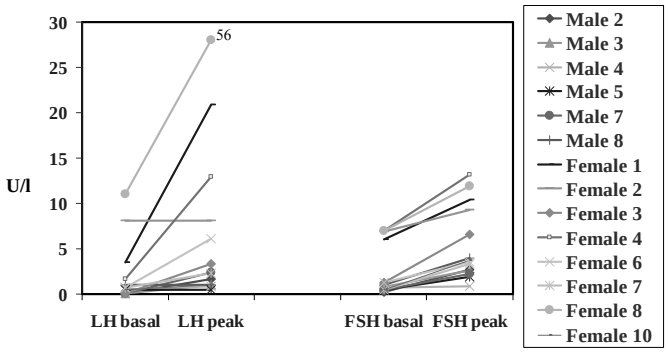
BCH experience: adolescents

- 19 patients (9 male) investigated at average age of 14.7 years (range 10.6-19.4.
- Of the boys 5 had micropenis, and 4 undescended testes requiring surgery (orchidopexy).
- 6 patients (all female) have spontaneous signs of puberty (Breast Stage 2 or Testicular volume >4ml), and 2 have had spontaneous menstruation.
- 9 have had pelvic USS scan, with pubertal uterus in 4.

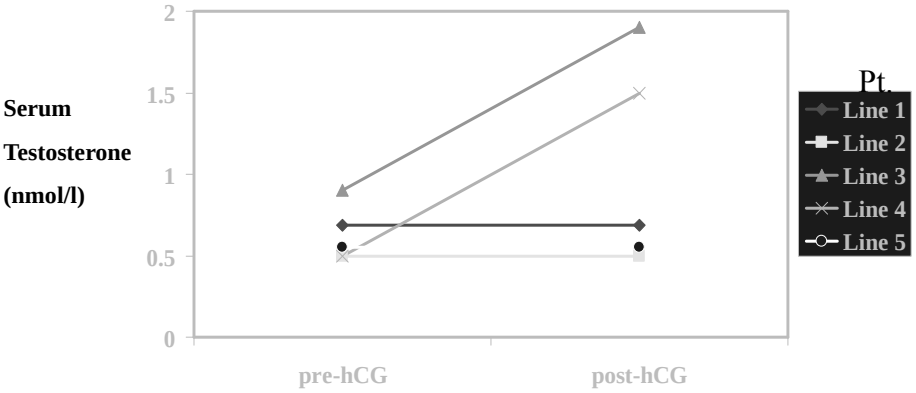
BCH experience: adolescents

- Four patients have been treated with GH: none are growth hormone deficient.
- 10 (4 males) have achieved final height, which is in the normal range ≥-2SDS (2^{nd} centile) in 5 (range -7.5 to -0.7).
- 14 patients have had genetic testing for CHD7, and 8 patients (57%) have been identified as having a mutation.

LHRH testing in CHARGE (N=13)



hCG testing in males with CHARGE (N=5)



Progress

- The seven oldest patients in Birmingham have required sex hormone replacement (oral ethinyl oestradiol in the girls, and testosterone (intramuscular depot in 3, oral in 2) in the boys.
- This has been reflected in the other patients in the UK.

HRT: Concerns in CHARGE

- Worsening behaviour.
- Inappropriate sexual behaviour.
- Menstrual bleeding (in girls).
- Persistent erections (priapism) in boys.

These concerns must be balanced against the long-term risk of osteoporosis, as much bone strength is laid down in late teens under the influence of sex hormones.

Adults with CHARGE (*LaRosa et al., 2009)*

- 8 subjects, 4 males and 4 females (aged 20-28 years), attending adult endocrine clinic.
- 3 had received GH therapy; 2 were GH deficient.
- All had received sex steroid therapy; none had attempted fertility.

- Outcomes on height and bone density compared with age matched subjects affected by primary (Klinefelter Syndrome-Premature Ovarian Failure) and secondary hypogonadism (Hypogonadotrophic Hypogonadism).

Data on patients with CHARGE syndrome and matched hypogonadal groups (*LaRosa et al., 2009*)

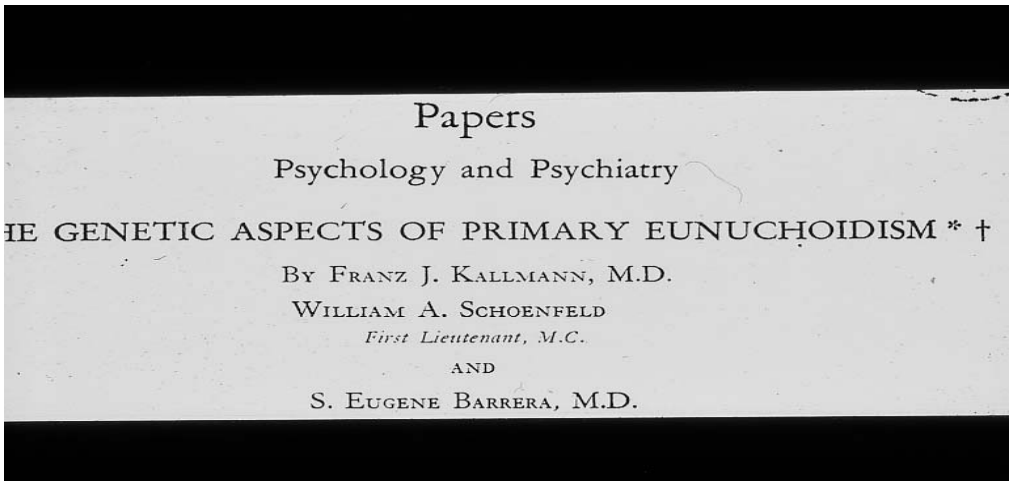
	CHARGE	Hypo-hypo	Klinefelter/ POF
Age	21.5	22	21.7
Height (cm)	158.6	165.4	172.5
Height SDS	-1.6	-1	-0.3
BMI	21.5	25.4	22.9
Spine T-score	-2.4	-1	-1.1
Hip T-score	-0.6	-0.2	-0.3

Adult data (N=11 (*UCLH & BCH*)

- All had low bone mineral density BMD., 8/11 (73%) had osteopenia and 5/11 (46%) had osteoporosis.
- Vitamin D was measured in 6 subjects and was low in 1.

CHARGE and Kallmann Syndrome overlap

Kallmann syndrome



Papers

Psychology and Psychiatry

HE GENETIC ASPECTS OF PRIMARY EUNUCHOIDISM * †

By Franz J. Kallmann, M.D.

William A. Schoenfeld

First Lieutenant, M.C.

and

S. Eugene Barrera, M.D.

Kallmann syndrome (KS)

An association of:

- Central hypogonadism (hypogonadotrophic hypogonadism).
- Absent sense of smell (anosmia).

- Other clinical features eg. absent kidney, mirror movement (synkinesia) are also variably described.

Kallmann syndrome (KS)

- May occur sporadically, or be inherited in an autosomal dominant, recessive or X-linked recessive form.
- A number of different genes (~5) have now been identified, and account for ~30% of all cases.

Common features of CHARGE syndrome and KS (FGFR1 type)

- Anosmia.
- Hypogonadotrophic hypogonadism.
- Cleft lip and palate.
- Hearing impairment.
- External ear abnormalities.
- Iris coloboma.

KS and CHARGE syndrome

- 36 patients with KS and 20 patients with normosmic idiopathic hypogonadotropic hypogonadism (nIHH) in whom mutations in 4 Kallmann had been excluded were screened for mutations in CHD7.
- Three of 56 KS/nIHH patients had mutations in CHD7.

Jongmans et al. 2008

Hypogonadotrophic hypogonadism and anosmia in CHARGE

- Retrospective review of 32 patients with CHARGE.
- 19/20 boys had micropenis and/or cryptorchidism.
- 7/9 nine boys tested < 5 months had v. low testosterone levels. LH response to GnRH stimulation was variable during the first year of life and didn't correlate with clinical abnormalities.
- No girls >12 yr (n = 7) were in spontaneous puberty, and 5 had a decreased gonadotrophin response to GnRH stimulation.
- Olfactory evaluation (n = 10) and MRI (n = 18) of the forebrain revealed defective sense of smell and abnormal olfactory bulbs in all cases.
- Mean height of 25 children >5 yr of age was –2 ± 0.2 SD score.

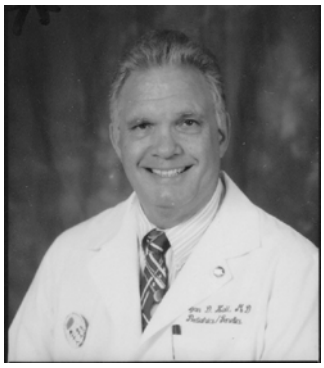
Pinto et al., 2005

THE CHARGE SYNDROME FOUNDATION

SPECIAL GUEST PRESENTATION

Platform Presentation #4
11:00 – 11:25 AM
Trillium Ballroom II, Conference Center

Non-CHARGE Multiple Congenital Anomaly (MCA) Syndromes Associated With Choanal Atresia/Stenosis (CAS)



BRYAN D. HALL, M.D., F.A.A.P.

In 1979, Dr. Hall was the first to recognize the pattern of anomalies that today is called CHARGE syndrome.

Presenter Information: *Dr. Bryan Hall* is Emeritus Professor of Pediatrics and Retired Chief of Genetics/Dysmorphology at the University of Kentucky, School of Medicine in Lexington, KY. His career as a pediatrician and geneticist has spanned 44 years. He is a member of many professional organizations and is the author of 129 articles in medical, genetic, and scientific journals. Though Dr. Hall's official status is "retired", he still is actively practicing in outreach clinics in Kentucky. It was his insightful observations over 30 years ago that led geneticists and physicians to recognize that what we now call CHARGE was not an unrelated collection of congenital anomalies that were treated as individual disorders. The significance of his observations and their value to every parent who has had a child with CHARGE has been very great.

Presentation Abstract: Choanal atresia (CA) is a common feature of the CHARGE syndrome. CA is particularly useful because it is not as common a component of other multiple anomaly syndromes (MAS) as its companion CHARGE features making its presence more specific in the diagnostic consideration of the CHARGE syndrome. However, over 45 MAS have CA as a significant feature which can result in an erroneous diagnosis of CHARGE syndrome. These 45 disorders are tabulated and a brief discussion of how each differs from CHARGE will be presented.

Non-CHARGE Multiple Congenital Anomaly (MCA) Syndromes Associated With Choanal Atresia/Stenosis (CAS)

Bryan D. Hall, M.D., F.A.A.P.
Emeritus Professor of Pediatrics
Retired Chief of Genetics/Dysmorphology
University of Kentucky, Lexington, KY, USA

Why is it important to Know MCA Syndromes Associated with CAS?

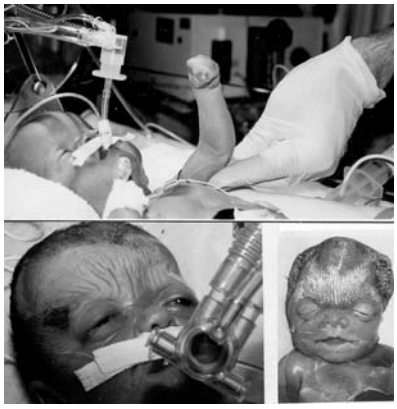
1. Presence of CAS invariably raises CHARGE syndrome in the differential diagnosis
2. May help avoid error in diagnosis
3. 30-40% of patients with CAS have other anomalies, thus, representing an MCA syndrome, of which, CHARGE syndrome is the most common
4. Clinical differentiation of CHARGE syndrome from other MCA syndromes is problematic in neonates and infants

Non-CHARGE MCA Syndromes: Criteria for Inclusion

1. CAS in at least 2 cases of an MCA syndrome
2. One case of CAS qualifies if the MCA syndrome is genetic, chromosomal, or teratogenic

Craniosynostosis Syndromes Associated with CA Stenosis

Diagnosis	% of cases when CAS is present	Number of cases
Apert syndrome	26%	
Pfeiffer syndrome	50%	
Beare-Stevenson syndrome	80%	
Crouzon-Acanthosis nigricans	41%	
Antley-Bixler syndrome	60%	

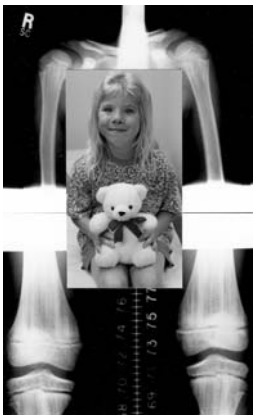


Apert syndrome

Beare-Stevenson syndrome

Skeletal Dysplasia/Dysostosis Associated with CAS

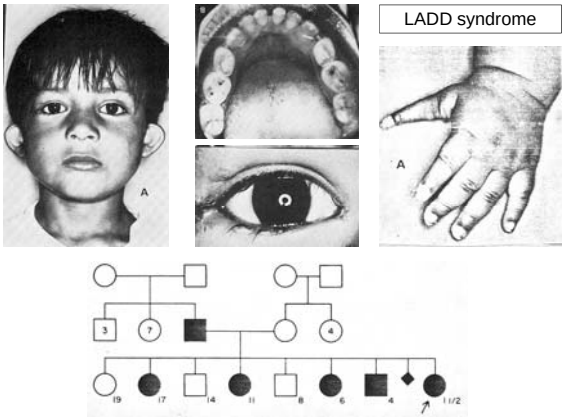
Diagnosis	% of cases when CAS is present	Number of cases
Achondroplasia		3
Osteopathia striata		2
Lenz-Majewski syndrome	> 80%	
Raine syndrome	70%	
Jansen metaphyseal dysplasia		1
Campomelic dysplasia		1
Cranio-Facio-Skeletal dysplasia		1



Osteopathia striata

Ectodermal Disorders Associated with CAS

Diagnosis	% of cases when CAS is present	Number of cases
LADD syndrome	15%	
EEC syndrome		3
CAS/scalp defects		2
Johnson-McMillin syndrome		3
Hay-Wells syndrome		1
Oculo-ectodermal syndrome		1



LADD syndrome

Teratogens Associated with CAS

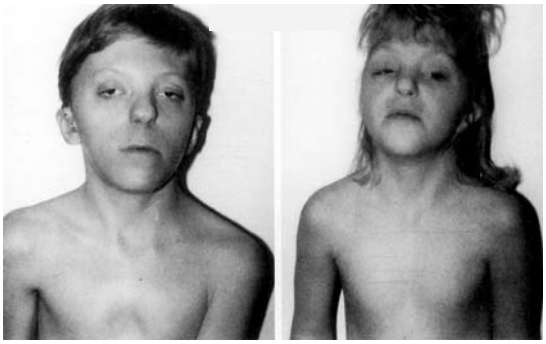
Teratogen	% of cases when CAS is present	Number of cases
Thalidomide	2.3%	
Methimazole	16.4%	
Fluconazole		1
Valproic acid		2
IDM embryopathy		3

Methimazole Embryopathy

Age: 1½ years. Note, right iris coloboma, upslanted eyes, short palpebral fissures, inverted V-shaped mouth

Chromosome Disorders Associated with CAS

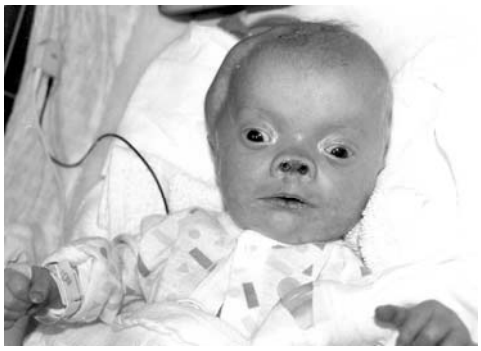
Chromosome Abnormality	% of cases when CAS is present	Number of cases
1p36.3 del/dup		1
1q42-pter dup		3
3p13-p21.1 del		3
3p21.2-p12 del		1
4p16.3 del / 6p21.3 dup		1
6p21-pter dup, 6p22 dup	10%	
t(6p;8q)	?	?



4p16.3 deletion/6p21.3-pter duplication in children with Noonan phenocopy. Male had unilateral choanal atresia.

Chromosome Disorders Associated with CAS (continued)

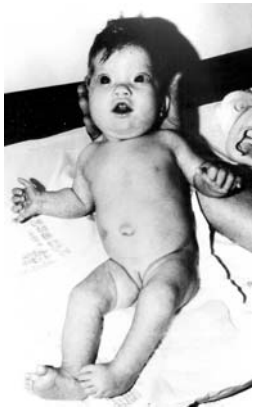
Chromosome Abnormality	% of cases when CAS is present	Number of cases
7p11.23 dup		1
7p15-qter del		4
7p/p15-pter		1
8q22-pter dup		1
9p22 del		2
9p23 del		1



8q duplication/triplication

Chromosome Disorders Associated with CAS (continued)

Chromosome Abnormality	% of cases when CAS is present	Number of cases
14.12p12.2-qter del		1
12p tetrasomy	8%	
13q21.1-q33.1del		1
13q22-q33 del		1
14q22-q24.3 dup		1



13q22-q33 deletion: This patient had both choanal atresia and coloboma

Chromosome Disorders Associated with CAS (continued)

Chromosome Abnormality	% of cases when CAS is present	Number of cases
Trisomy 18/21	Tri-21: (4 / 5581)	2, 4+
18p tetrasomy	11%	1/9
18q del/2q37.3-qter		1
Iso 18p/18q		2
22q11.2 del (VCF)		2 (?)
22q12.2-q13.1 del		1
Xp22.31 del		2

22q11.2 deletion

Iso18p

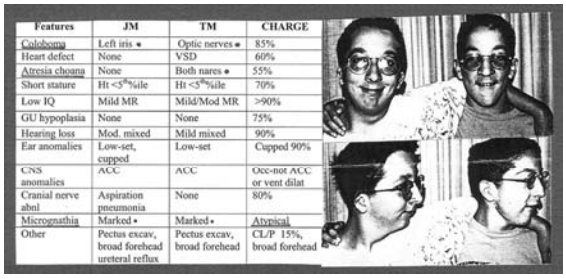
Non-CHARGE MCA Syndromes Associated with CAS

Diagnosis	% of cases when CAS is present	Number of cases
CAS/sodium diarrhea	54.6%	11/19
Acro-Renal-Ocular syndrome		1
Bamforth-Lazarus syndrome	>50%	6
Burn-McKeown syndrome	100%	4/4
COACH syndrome	??	??

Choanal atresia/sodium diarrhea

Non-CHARGE MCA Syndromes Associated with CAS (continued)

Diagnosis	% of cases when CAS is present	Number of cases
Marshall-Smith syndrome	18%	
Schinzel-Giedion syndrome		4
Pallister-Hall syndrome	8%	
Edwards-Young syndrome	33%	1/3
Goldblatt-Viljoen syndrome		2
Graham Xq13 mutation		1/2

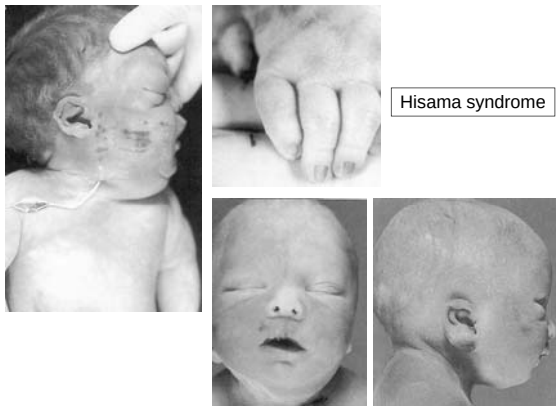


Features	JM	TM	CHARGE
Coloboma	Left iris •	Optic nerves •	85%
Heart defect	None	VSD	60%
Atresia choana	None	Both nares •	55%
Short stature	Ht <5th%ile	Ht <5th%ile	70%
Low IQ	Mild MR	Mild/Mod MR	>90%
GU hypoplasia	None	None	75%
Hearing loss	Mod. mixed	Mild mixed	90%
Ear anomalies	Low-set, cupped	Low-set	Cupped 90%
CNS anomalies	ACC	ACC	Occ-not ACC or vent dilat
Cranial nerve abnl	Aspiration pneumonia	None	80%
Micrognathia	Marked •	Marked •	Atypical
Other	Pectus excav, broad forehead ureteral reflux	Pectus excav, broad forehead	CL/P 15%, broad forehead

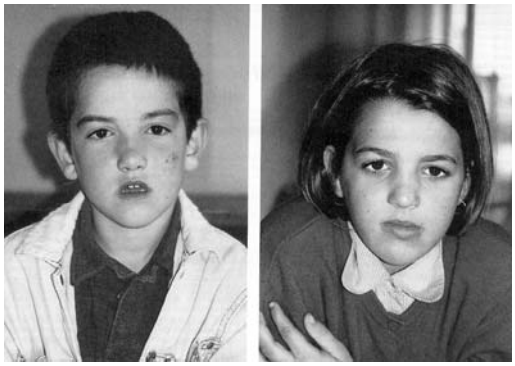
Graham's X-linked mental retardation syndrome with mutation at Xq13

Non-CHARGE MCA Syndromes Associated with CAS (continued)

Diagnosis	% of cases when CAS is present	Number of cases
Qazi/Dumie syndrome		3-4
Hisama syndrome	50%	2/4
Ramos-Arroyo syndrome		3
CAS/anal atresia		2
Coffin-Siris syndrome		2
Kallmann syndrome		2



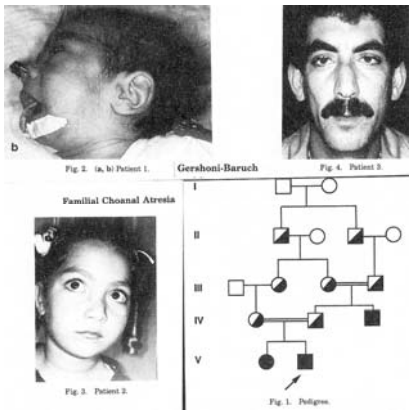
Hisama syndrome



Ramos-Arroyo syndrome

Non-CHARGE MCA Syndromes Associated with CAS (continued)

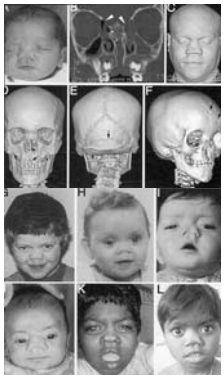
Diagnosis	% of cases when CAS is present	Number of cases
Gershoni-Baruch syndrome		3
Al-Gazali-Kakadekar syndrome		2/2
Lammer-Holmes syndrome		1
Meinecke-Blunck syndrome		1/2
Branchio-Oto-Facial syndrome		2
Branchio-Oto-Renal syndrome		1
Joubert syndrome		1



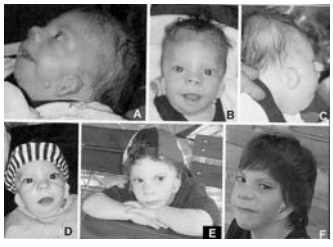
Gershoni-Baruch syndrome

Non-CHARGE MCA Syndromes Associated with CAS (continued)

Diagnosis	% of cases when CAS is present	Number of cases
Frontonasal		??
Frontorhiny	9%	1/11
Wiezorek syndrome	100%	3
Treacher Collins syndrome		2
Otocephaly-agnathia		3



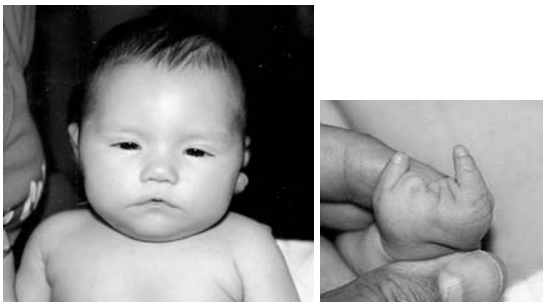
Frontorhiny



Wieorek mandibulofacial dysostosis

Non-CHARGE MCA Syndromes Associated with CAS (continued)

Diagnosis	% of cases when CAS is present	Number of cases
Moebius syndrome		3
Lowry-McKeown syndrome		1
Unknown MCA syndrome (familial)		
FOXE1 mutation (? Bamforth-Lazarus syndrome)		2+



Moebius syndrome with ectrodactyly

MCA Syndromes with Both CAS and Coloboma

Chromosomal

1. 1p36.3 del, 1q42-pter dup
2. 3p21.2-p12 del
3. t(6p;8q), 6p22 dup
4. 8q22-pter dup
5. 14q22-q24.3 dup
6. 22q11.2 (?)

MCA Syndromes with Both CAS and Coloboma (continued)

MCA

1. Acro-Renal-Ocular syndrome
2. BOF syndrome
3. Graham XLq13 MR syndrome
4. Frontorhiny

Teratogens

1. Thalidomide
2. Methimazole
3. IDM Embryopathy

Numerical Categorical Breakdown of Non-CHARGE Syndromes Associated with CAS

Category	Number
Craniosynostosis	5
Skeletal disorders	7
Ectodermal	6
Teratogens	5
Chromosomal	25
MCA syndromes	33
Total	81

Summary

1. There are many syndromes associated with CAS.
2. Craniofacial defects are most frequently associated with CAS.
3. Chromosomal disorders and multiple congenital anomaly syndromes are the categorical groups with the highest association with CAS.

Information on Behavior

Platform Presentation #5
11:25 – 11:50 AM
Trillium Ballroom II, Conference Center

BEHAVIOR ANALYSIS AND CHARGE SYNDROME

Laurie S. Denno, MA, LMHC, BCBA
Behavior Analyst
Deafblind Program
Perkins School for the Blind
Watertown, MA

Presenter Information: *Laurie Denno* is a practicing behavior analyst with over 30 years of experience working with children and adults with developmental disabilities, including over 20 years of experience working with deafblind children and young adults, many of whom have CHARGE syndrome. Laurie's main interests are in implementing proactive behavior treatment that stresses teaching socially appropriate behavior and independence to all learners and using positive behavior supports in a school-wide manner. Laurie is a Doctoral Candidate in Applied Behavior Analysis at Simmons College and will be doing her dissertation on assisting parents of children with CHARGE syndrome to speak effectively with a consulting psychiatrist about their children's behavioral difficulties.

ADDRESS: Perkins School for the Blind, 175 N. Beacon Street, Watertown, MA 02472; TEL: 1-617-972-7891; EMAIL: Laurie.Denno@perkins.org

Presentation Abstract: A behavior analyst with 18 years of experience in working with individuals with CHARGE syndrome, and 30+ years of professional experience, will present an overview of how behavior analysts complete a functional analysis of challenging behavior. A functional analysis of behavior is the first step in designing effective and individualized treatment for children with challenging behavior. Treatment will be completely unique to every student in relationship to their family, their school and their social environment. Failure to complete this step is the single most common cause of failure in behavior treatment. Finding competent behavioral professionals can be difficult. How to find behavioral professionals will be discussed.

1st CHARGE Syndrome Conference for Professionals, Indian Lakes Resort, Bloomingdale, IL, July 23, 2009

Behavior Analysis and CHARGE Syndrome

Laurie S. Denno, M.A., BCBA®
Behavior Analyst
Perkins School for the Blind
laurie.denno@perkins.org

What is Applied Behavior Analysis?

- Philosophy and science of behavior based on over 50 years of carefully controlled research which has identified basic principles of how people learn behavior
- Looks at behavior in the context of the environment
- While often used to decrease troublesome behavior, primarily a teaching strategy
- Goal: teaching socially significant behavior

Functional Behavior Assessment

- Looks at behavior in the context of the environment where it occurs
- Contextual variables are who is there, what are the requests, materials, noise-level, lighting, past learning history, etc.
- What happens before the behavior of interest and what happens after that behavior
- What is the function of the behavior?
- This is called the functional relation: it's the relation between the behavior and the environment

Functions of Behavior

- What does the individual get from or for the behavior?
- Two main functions; get something or avoid something
- Attention, social feedback, eye contact
- Tangible items
- Sensory input
- Escape and/or avoid less preferred things and sometimes pain or discomfort
- Behavior can have more than one function

Treatment Decisions

- Design treatment based on the function identified in the assessment
- Each treatment is uniquely designed for an individual based on their learning history and the environment where they spend their time
- There is no one treatment for “aggression” or SIB
- Often treatment is a combination of environmental changes to prevent the behavior of interest and consequence changes to increase acceptable, adaptive behavior

Beware!

- Everybody thinks they are an expert in applied behavior analysis because everybody has behavior
- People use reinforcers to increase behavior and punishers to decrease behavior without an assessment. Sometimes this works and they get reinforced by their success.
- Highly specialized field and there should be no treatment without a complete assessment and a qualified professional

Antecedent Interventions and CHARGE Syndrome

- Antecedents are the things that happen before behavior; behaviors can have many antecedents
- Antecedents “set the scene”, lead to or have signaled certain functional relations in the past and therefore result in specific behavior
- Sensory issues
- Communication issues/directions
- Physical issues/anxiety
- Materials

Consequence Interventions and CHARGE Syndrome

- A consequence is the thing that happens after a behavior; a behavior can have completing consequences
- Using reinforcers
- Using time out
- Using “relaxation techniques”
- Using punishment. DON’T DO IT. Instead teach the child “to do” something.

Questions to Ask

- What do you want the child to do?
- Where and with whom do you want them to do it?
- What are the consequences that will teach the child to do the behavior?
- What behavior do you want the child to stop doing?
- What behavior will you teach the child to do to replace the behavior they do now?

Get Professional Help

- Look for a Board Certified Behavior Analyst (BCBA)
  - Master's Degree in ABA, behavioral education, special education or maybe psychology with a specialization in ABA
  - Will have practiced at least 1500 hours with 75 hours of direct clinical supervision
  - Passed a rigorous exam

- Find a BCBA at bacb.com
- Search by zip code or city
- A BCBA may not know about CHARGE syndrome but they know about behavior
- Behavior is learned the same way by all children and you can educate them about deafblindness and issues in CHARGE syndrome

My Work as a BCBA

- Positive Behavior Supports implementation school-wide at Perkins
- Starting my dissertation on helping parents of children with CHARGE syndrome locate and speak knowledgably with a psychiatrist for behaviors of concern have not responded to good ABA
- Looking for volunteer parents to help test my self-directed training package
- Pick up my work on the Adults with CHARGE syndrome survey

Behavioral Information

Platform Presentation #6
11:50 AM – 12:15 PM
Trillium Ballroom II, Conference Center

UPDATE ON THE CHARGE BEHAVIORAL PHENOTYPE

Timothy S. Hartshorne, Ph.D.

Department of Psychology
Central Michigan University
Mt. Pleasant, MI

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. His current project is editing a book, along with Sandy Davenport, Meg Hefner, and Jim Thelin, on CHARGE which should be published in 2010.

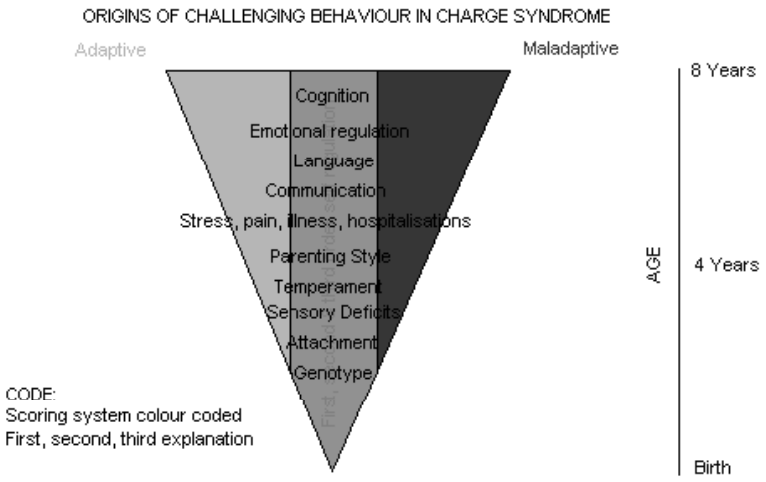
ADDRESS: Sloan Hall 215, Central Michigan University, Mount Pleasant, MI 48859
TEL: (989)774-6479 office; FAX: (989)774-2553; EMAIL: tim.hartshorne@cmich.edu ;
WEB: www.chsbs.cmich.edu/timothy_hartshorne

Presentation Abstract: The special issue of the American Journal of Medical Genetics was a collection of studies and information that described a behavioral phenotype that was unique to CHARGE syndrome. This update is describes the further development of this concept. The presentation includes discussion of behaviors, sensory deficits, parenting, physical illness, sleep, stress, communication and cognitive ability.

1st CHARGE Syndrome Conference for Professionals, Indian Lakes Resort, Bloomingdale, IL, July 23, 2009

Update on the CHARGE Behavioral Phenotype

Tim Hartshorne
Central Michigan University
tim.hartshorne@cmich.edu



George Williams, 2005

"A pattern of behavior that is reliably identified in groups of children with known genetic disorders and is not learned."
(Harris, 1995)

If I behave like this, I probably have CHARGE syndrome

Factors Contributing to Challenging Behavior

- Vulnerabilities related to cognitive impairment
- Individual child's life experiences
- Factors in the immediate environment
- The specific genetic cause

Factors related to the genetic cause are relatively less under the child's control.

Attachment Problems

- May arise from low or absent levels of:
  - "visual, vocal or other forms of reciprocity occurring from the neonatal days on."
- A huge issue for CHARGE babies from the first hours onwards with sensory deficits, medical issues, pain, separation, parent shock, etc.
- 20% of parents had delayed bonding, and nearly a half reported delayed attachment from the child.

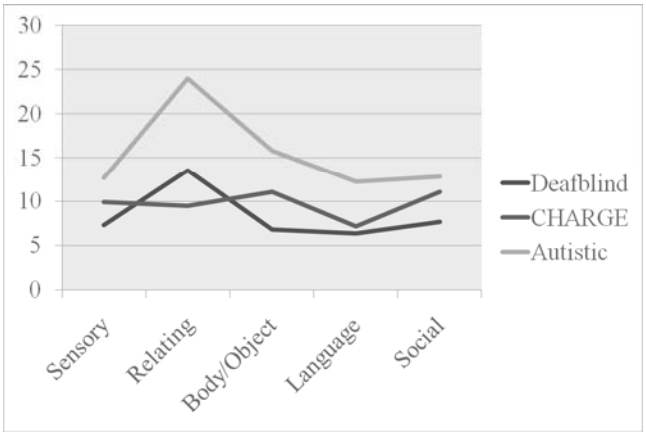
Reda, N. M. & Hartshorne, T. S. (2008). Attachment, bonding, and parental stress in CHARGE syndrome. *Mental Health Aspects of Developmental Disabilities*, *11*, 10-21.

Sensory Deficits

- Hearing – sensorineural hearing loss
- Vision – coloboma
- Smell – anosmia
- Taste – prefer strong tastes
- Tactile – defensiveness
- Vestibular – missing semi-circular canals
- Proprioceptive – muscle weakness

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 vocalize



Hartshorne, T. S., Grialou, T. L., & Parker, K. R. (2005). Autistic-Like Behavior in CHARGE Syndrome. *American Journal of Medical Genetics, 133A,* 257-261.

How do you parent a child with CHARGE?

- Do you use time out?
- Do you use food as a reinforcer?
- Can you explain the reason for behavior?
- Can you say “no”?
- Can you manage your level of stress?

Parenting Style

- *The Malaise Inventory.* This 24-item questionniare was developed by Rutter, Tizard, and Whitmore (1970) as a brief measure of mother’s mental well-being. The items refer to emotions and somatic complaints. In a sample of 87 parents of children with CHARGE, one third achieved a clinically significant score.

Hartshorne, T. S., Heussler, H. S., Dailor, A. N., Williams, G. L., Papadopoulos, D., and Brandt, K. K. (2009). Sleep Disturbances in CHARGE Syndrome: Types and Relationships with Behaviour and Caregiver Well-Being. *Developmental Medicine and Child Neurology, 51*, 143-150.

Parenting Style

The *Parenting Stress Index Short Form* (PSI-SF) (PSI, Abidin & Ona, 1995) is a 36-item self-report measure that was used to identify stressors that are being experienced by the family that relate to parenting. Twelve of 25 parents of children with CHARGE achieved a clinically significant score.

Reda, N. M. & Hartshorne, T. S. (2008). Attachment, bonding, and parental stress in CHARGE syndrome. *Mental Health Aspects of Developmental Disabilities, 11*, 10-21.

Pain, Illness, Hospitalizations

- Delays in coming home from birth (with mother to more than 13 weeks)
- Number of surgeries (1/4 had 13 or more)
- Number of hospitalizations (1/4 had 13 or more)
- Need to better understand the impact of pain on the development of behavior

Hartshorne, T. S., & Cypher, A. D. (2004). Challenging behavior in CHARGE syndrome. *Mental Health Aspects of Developmental Disabilities, 7*(2), 41-52.

SLEEP

Scale	Mean	SD	% clinical
• Initiating/Maintaining	62.05	15.31	
• Breathing 59.63		15.21	
• Arousal	48.57	5.87	
• Transition 57.08		13.77	
• Somnolence	51.76	11.62	
• Hyperhydrosis	49.91	10.01	
• Total	59.29	13.11	57.5%

Mother well being was associated with the child's sleep.

Hartshorne, T. S., Heussler, H. S., Dailor, A. N., Williams, G. L., Papadopoulos, D., and Brandt, K. K. (2009). Sleep Disturbances in CHARGE Syndrome: Types and Relationships with Behaviour and Caregiver Well-Being. *Developmental Medicine and Child Neurology, 51,* 143-150.

Stress

- Child
- Parent
- Family
- School

Communication/Language

Makes reactions or noises or behaviors which can be difficult to interpret	20	16.1%
Uses behaviors such as gestures, sounds, body movements	12	9.7%
Uses single words, signs, picture symbols, or object symbols to represent basic needs	15	12.1%
Uses some 2- to 5-word phrases and sentences using speech, signs, picture symbols, etc.	17	13.7%
Uses verbal or sign language in complete sentences	59	47.6%

All children were 4 or older

Categories of Self-Regulation

- Sleep
- Feeding
- State control
- Self-calming
- Sensory reactivity
- Mood regulation
- Emotional and behavioral control

Initiating research on emotion regulation

Sensory Profile

- Four factors on Sensory Profile significant
  - Low endurance/tone
  - Poor registration
  - Fine motor/perceptual
  - Sensation seeking
- Suggestive of a Regulatory Disorder

Hartshorne, T. S., Grialou, T. L., Russ, J. M., Nicholas, J., & Dunn, W. (2004). Executive dysfunction and sensory processing in CHARGE syndrome. Society for the Study of Behavioural Phenotypes, Barcelona, Spain

Cognitive Ability

- *Adaptive Behavior Evaluation Scale* with 100 Children with CHARGE
- Showed a higher range of ability than once thought: 54 had scores > 70 (Mean=100; SD=15)
- Those who walked earlier, had fewer medical problems, and had better hearing and vision scored higher on the ABES.
- The majority of the variance in ABES scores was explained by age at walking.

Salem-Hartshorne N, Jacob S. 2004. Characteristics and development of children with CHARGE association/syndrome. Journal of Early Intervention Vol 26(4): 292-301.

EXECUTIVE FUNCTION

Inhibit	**64.02**	**46.6**
Shift	**65.42**	**57**
Emotional Control	58.44	31.9
Initiate	60.93	40.2
Working Memory	62.67	12.3
Plan/Organize	60.66	41.2
Organization of Materials	52.10	12.3
Monitor	**64.44**	**54.8**
Behavioral Regulation Index	63.79	50.6
Metacognition Index	61.64	45
Global Executive Composite	63.00	49.4

Hartshorne, T. S., Nicholas, J., Grialou, T. L., Russ, A. M. (2007). Executive function in CHARGE syndrome. *Child Neuropsychology, 13*, 333-344.

A CHARGE Behavioral Phenotype (first draft)

- Low normal cognitive functioning
- Very goal directed, persistent, and sense of humor
- Socially interested but immature
- Repetitive behaviors; increase under stress
- High levels of sensation seeking
- Under conditions of stress and sensory overload
  find it difficult to self-regulate and easily lose behavioral control
- Difficulty with shifting attention and transitioning to new activities; easily lost in own thoughts

Medical Information

Platform Presentation #7
2:30 – 2:55 PM
Trillium Ballroom II, Conference Center

ANESTHESIA COMPLICATIONS IN CHARGE SYNDROME

Kim Blake, M.D.
&
Jill MacCuspie

Dalhousie University
Halifax, Nova Scotia

Presenter Biography: *Dr. Kim Blake* began her involvement with CHARGE more than 25 years ago at Great Ormand Street Hospital in the UK, where she lectured on CHARGE and published several of the earliest papers describing the syndrome. She was instrumental in organizing the UK family support group. Since moving to Canada, she has continued to be involved with the CHARGE Syndrome Foundation. She has been an invited speaker at every conference and received funding from the Foundation for several of her research projects. Kim's research career continues to focus on CHARGE, particularly the issues of the adolescent and adult population. She routinely involves students in her research, both educational and clinical. Most of her students have had abstracts and/or papers published, some even with first authorship. Kim has recruited many local medical faculty members in her research and developed a center of excellence for research and knowledge in CHARGE syndrome. She is regularly asked to present on CHARGE syndrome, both nationally and internationally. Her most recent research projects are on the effects of anesthesia in CHARGE syndrome and the feeding difficulties in children with CHARGE syndrome.

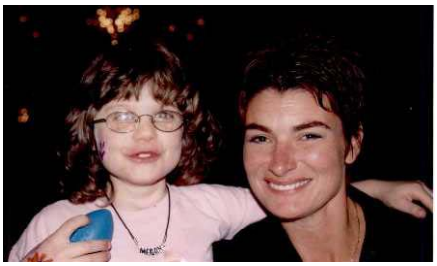
ADDRESS: Dalhousie University, 5850/5980 University Ave, Halifax, NS B3K 6R8
TEL: 902-488-0128; FAX: 902-470-6913; EMAIL: kblake@dal.ca

Jillian MacCuspie is entering her third year of medical school at Dalhousie University in Nova Scotia, Canada. She was first introduced to CHARGE Syndrome in 2006 as a student working with Dr. Kim Blake and has had a keen interest in it ever since. Her work on CHARGE Syndrome includes a paper on anesthesia management published with Dr. Blake, and a case study on the use of Botox to reduce salivary secretions in an infant with CHARGE Syndrome. After medical school Jillian is planning on pursuing a career in pediatrics.

Presentation Abstract: Why is anesthesia important? How many surgeries is my child likely to have? Why is it important to combine procedures with one anesthesia?

ANESTHESIA COMPLICATIONS IN CHARGE SYNDROME

Dr. Kim Blake, MB, MRCP, FRCPC



1st Professional CHARGE Syndrome Conference
July 24-26, 2009
Chicago, Illinois

kblake@dal.ca

There are Always Risks of Complications with Anaesthesia

- "…you sign a consent"
- Are you informed?

- Are Individuals with CHARGE Syndrome More at Risk?

Growing up With CHARGE Syndrome

Kennedy

Age 0-2 years: 7 surgeries

Age 2-4 years: 3 surgeries

Age 4-6 years: 6 surgeries

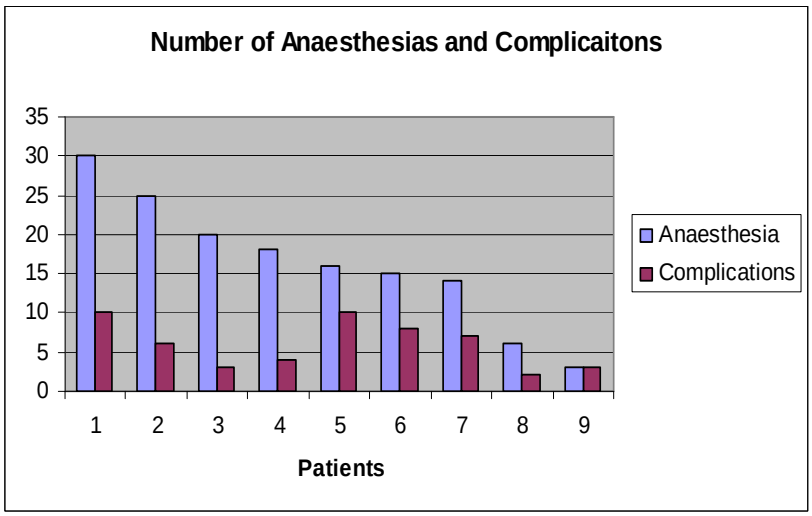
= many anesthesias

Postoperative Airway Events of Individuals with CHARGE Syndrome

- Detailed chart reviews on nine patients
  - Mean age 11.8 years (± 8.0)
  - 215 surgeries (average 22 per child)
  - 147 anesthesias (average 16 per child)
- Postoperative events (reintubation for apneas and desaturations, airway obstruction due to excessive secretions)

Blake K, MacCuspie J, Hartshorne TS, Roy M, Davenport SLH, Corsten G.*International Journal of Pediatric Otorhinolaryngology*, *Vo. 73*, *February 2009*

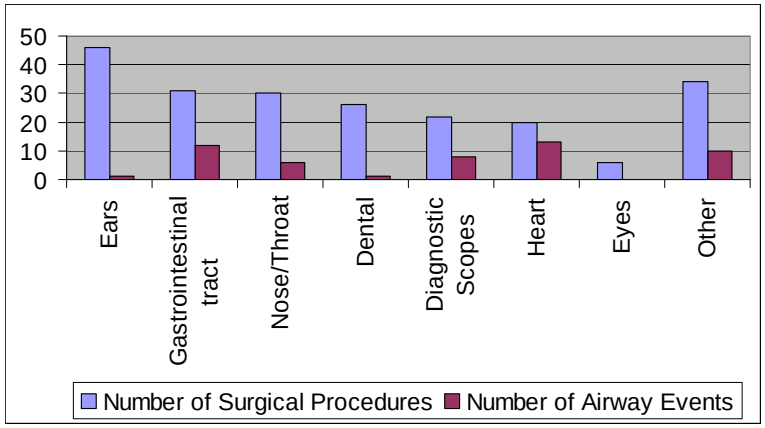
Results



35% (51/147) of anesthesias resulted in complications (>60% were major)

Results

Anesthesia related complications occurred most often with heart, diagnostic scopes (L/B/E) gastrointestinal tract procedures



Results

Number of surgical procedures per anesthetics with resulting postoperative airway events.

Number of surgical procedures	Number	Post-operative Events	Percent resulting in airway events
1	94	37	39% (n= 37/94)
2	36	8	22% (n= 8/36)
3+	15	5	33% (n= 5/15)

P=0.1 Combining multiple procedures under one anesthesia does not lead to an increase in post-operative events.

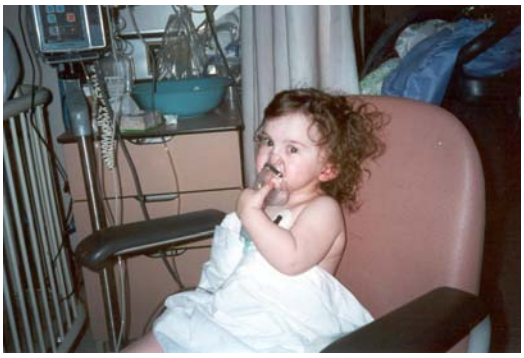
Results

Feeding procedures and rates of postoperative airway events.

	Number of Anesthesias	Airway Event	No Airway Event	Significance
G/J tube	82	36	46	Yes p=0.0092
No G/J tube	63	15	48	
Nissens fundoplication	79	33	46	Yes p=0.049
No Nissens fundoplication	66	18	48	

Having a G/J tube or Nissens fundoplication increases your child's risk of post-operative airway events

MacKenzie's Story



- 27 surgical procedures
- 18 anesthesias
- 4 complications
- Multiple ICU admissions
- Post tonsils/adenoids - improved

Discussion

- 35% of anesthesias resulted in post-operative complications
- Heart, diagnostic, and gastrointestinal tract procedures result in the most complications
- At least one complication occurred with every type of surgery except for eyes

Discussion

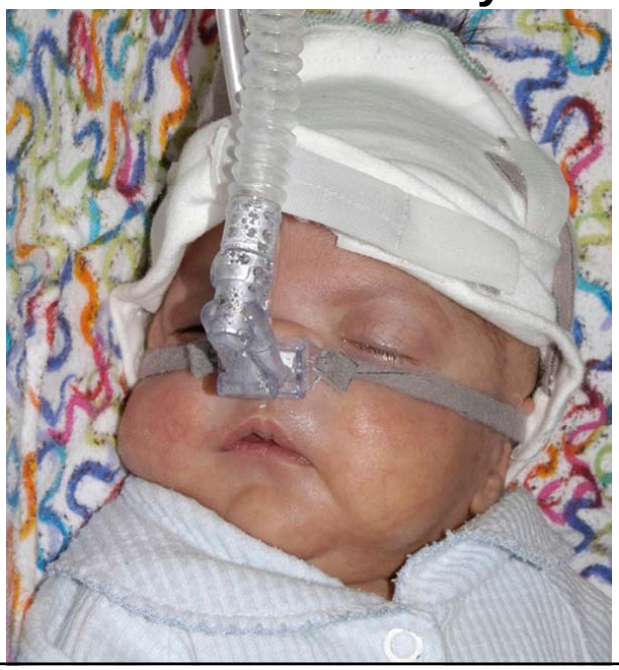
- High risk of complications in individuals with Nissen fundoplication or gastrotomy/jejunostomy tube
- Low risk with cleft palate
- What about individuals with CHD7 mutations who have mild clinical criteria?
  - Will they be at risk in the future?
  - Have they actually been challenged with surgeries?

Take Home Messages

CHARGE children are at high risk of post-operative anesthesia complications. Combining procedures during one anesthesia does not increase the risk of post-operative airway events.

The anesthesiologist needs to be aware that, even with simple procedures, the individual with CHARGE syndrome is at high risk of complications.

Frederick's Story

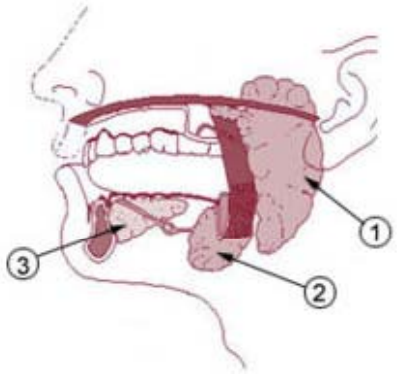


Freddy at 2 Months

- Difficulty with intubation
- ToF repair, vascular ring repair, PDA ligation
- Increased oral secretions
- Multiple attempts at extubation

Site of Botox Injections

1. Parotid glands
2. Submandibular glands
3. Sublingual glands



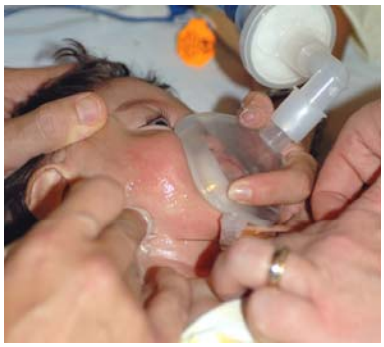
Botox 7.5 units was injected into salivary glands 1 and 2 on each side

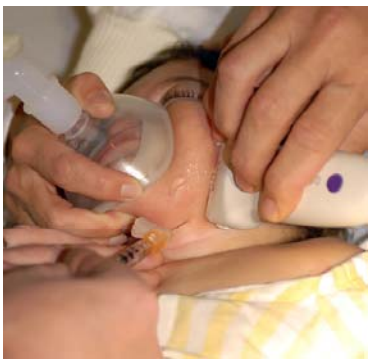
Freddy at 7 Months

- Aspiration pneumonia from oral secretions
- Gastroesophageal reflux
- Required ventilation

Botox Injection

Submandibular Gland Via Ultrasound and Parotid Gland by Palpation





10 Units/gland

Botox Injection

Prophylactic Use to Prevent Increase in Oral Secretions and Aspirations (4-5 monthly)

Waiting for picture

Thank you to all the Children and their Families

UK CHARGE Family Support Group Picnic 1991

Developmental and Medical Information

Platform Presentation #8
2:55 –3:20 PM
Trillium Ballroom II, Conference Center

SMELL AND PUBERTY IN CHARGE SYNDROME

Jorieke Bergman, M.D.
&
Conny van Ravenswaaij-Arts, M.D., Ph.D.

University Medical Center
Groningen, The Netherlands

Primary Presenter Information: *Dr. Bergman* is a clinical geneticist in training and PhD-student She studied medicine at the Utrecht University in the Netherlands and started specializing in clinical genetics in Groningen in 2006. In 2007 she received a grant that allowed her to start a PhD project on CHARGE syndrome that is currently still ongoing. As part of this PhD project she studied smell and pubertal development and causes of post neonatal death in patients with CHARGE syndrome In addition, mouse studies were performed in the Wellcome Trust Sanger Institute in Cambridge, Great Britain in order to gain insight into the underlying mechanisms of smell deficit and pubertal delay in CHARGE syndrome. She is also coordinator of the multidisciplinary CHARGE outpatient clinic in the Netherlands and is actively involved in the Dutch CHARGE parent support group.

ADDRESS: University Medical Center Groningen, P.O. Box 30.001 Groningen, the Netherlands
TEL: 0031(0)503617229, FAX: 0031(0)503617231, EMAIL: j.e.h.bergman@medgen.umcg.nl

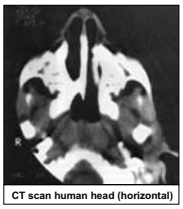
Presentation Abstract: Smell deficiency and delayed/absent puberty often occur in CHARGE syndrome, but few studies have looked at these features in adolescent patients. Therefore, we studied smell and puberty development in 22 adolescent CHARGE patients and showed that puberty and smell problems always co-occur. Therefore, a smell test can possibly predict whether puberty will occur spontaneously or not. This will prevent delay of hormonal pubertal induction, resulting in an age-appropriate puberty in smell deficient CHARGE patients.

University Medical Center Groningen

Smell & puberty in CHARGE syndrome

Jorieke Bergman
MD-medical research trainee
Department of Genetics
UMC Groningen, the Netherlands
CHARGE conference 2009 (Chicago)

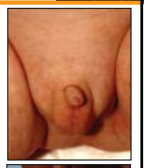
CHARGE syndrome

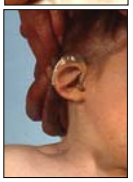


CT scan human head (horizontal)

Birth incidence ~1/10,000
CHD7 mutations (AD)

Coloboma
Heart defect
Atresia of choanae
Retardation
(growth and development)
Genital anomalies
(delayed puberty)
Ear abnormality
(including deafness)

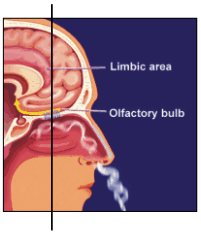




Additional features: balance disturbance and anosmia

Sanlaville& Verloes 2007

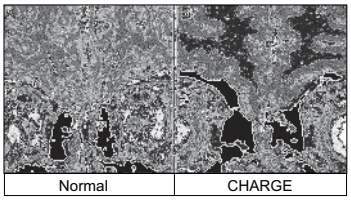
Background: smell



Coronal view

Anosmia: inability to smell due to olfactory bulb hypoplasia

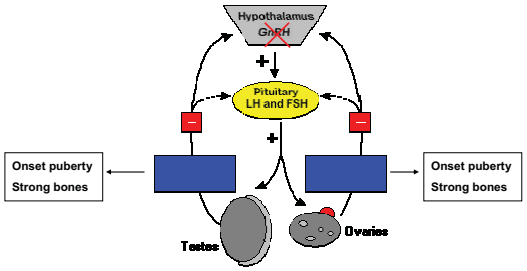
MRI brain scan



Normal | CHARGE

Pinto et al 2005

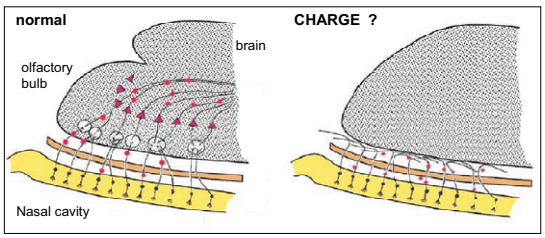
Background: puberty



Hypogonadotropic hypogonadism (HH): delayed or absent puberty secondary to gonadotropin-releasing hormone (GnRH) deficiency

Anosmia & HH

Link anosmia & HH: migration GnRH neurons alongside olfactory neurons



olfactory neurons • Gonadotropin releasing hormone (GnRH) neurons

Cariboni&Maggi 2006

Aim & hypothesis

Aim
To study smell and pubertal development in adolescent CHARGE patients

Hypothesis
Anosmia might predict the occurrence of HH in CHARGE patients

Significance

Significance
Start with hormone replacement therapy at a normal age in anosmic CHARGE patients

- Fewer social problems
- Reduced osteoporosis risk

Methods

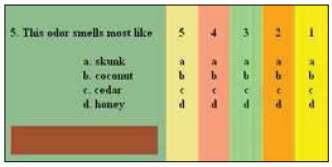
Patients
• 26 *CHD7*-positive CHARGE patients aged 10 years or older that were seen at the CHARGE outpatient clinic in the UMCG

Assessment of pubertal development
• Evaluation by a paediatric endocrinologist (Tanner stadia, anthropometry, biochemical evaluation)

Smell test
• UPSIT

UPSIT

University of Pennsylvania Smell Identification Test



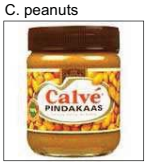
For children of 5 years and older

UPSIT picture book

A. gasoline

B. pizza

C. peanuts



D. lilac

UPSIT problems

Problems
• Communication difficulties
• Mental retardation
• Tube feeding
• Bilateral atresia of choanae

→ Retrospective collection of MRI brain scans for analysis of olfactory bulbs

Results

Smell
- 13/18 patients could not smell (72%)
- Parents often thought their child could smell, when the child could not

Puberty
- 13/19 patients had delayed/absent puberty (68%)
- 8 patients have started hormone treatment

Conclusion

100% association between anosmia & HH
- 8 patients with anosmia and HH
- 4 patients with normal smell and puberty

Smell testing can be used to predict the occurrence of HH in CHARGE patients

Significance: earlier start of hormone replacement therapy in anosmic CHARGE patients
- fewer social problems
- reduced osteoporosis risk)

University Medical Center Groningen

Genetic Information

Platform Presentation #9
3:20 – 3:45 PM
Trillium Ballroom II, Conference Center

INSIGHTS INTO THE FUNCTION OF CHD7 REVEALED THROUGH GENOMICS

Peter C. Scacheri, Ph.D.
Assistant Professor, Department of Genetics
Case Western Reserve University, School of Medicine
Cleveland, OH

Presenter Information: Dr. Scacheri is currently an Assistant Professor in the Department of Genetics at Case Western Reserve University School of Medicine. His laboratory, which consists of four graduate students, two postdoctoral fellows, and two technicians, is investigating the function of the CHD7 protein and its role in CHARGE syndrome. Specifically, the Scacheri lab is using genomics to identify genes that are improperly expressed during development when CHD7 is mutated. Dr. Scacheri's research on CHARGE syndrome is supported by an R01 grant awarded from the National Institute of Child Health and Human Development.
Case Western Reserve University, School of Medicine, 10900 Euclid Ave; BRB 627, Cleveland, OH 44106, EMAIL: pxs183@case.edu

Presentation Abstract: To gain insight into CHD7 function, we identified sites on DNA where the CHD7 protein binds. We found that CHD7 often binds a specific type of DNA element that functions to activate gene expression. The binding of CHD7 to these elements, known as gene enhancers, differs dramatically between cell types and various stages of development. These results suggest that dysregulation of specific developmental genes due to CHD7 mutation lead to the multiple birth defects observed in CHARGE syndrome. An electronic version of this presentation can be obtained by contacting Dr. Scacheri by email.

1st CHARGE Syndrome Conference for Professionals, Indian Lakes Resort, Bloomingdale, IL, July 23, 2009

Sensory Information

Platform Presentation #10
4:10 – 4:35 PM
Trillium Ballroom II, Conference Center

IMPACT OF COCHLEAR IMPLANTS FOR CHILDREN WITH CHARGE SYSNDROME: PRELIMINARY FINDINGS

Susan M. Bashinski, Ed.D.
Associate Professor – Special Education,
Curriculum & Instruction Department, East Carolina University
and
Kathleen Stremel Thomas, M.A.
Director, National Consortium on Deafblindness (NCDB),
Western Oregon University

Presenter Information:

Dr.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 IHE level. She is currently a member of the faculty at East Carolina University. Susan has written numerous research articles, book chapters, and manuals associated with topics relevant to learners who experience significant support needs, including deaf-blindness. She has directed numerous federal and state grants in low-incidence disabilities. Susan has extensive experience providing professional development and technical assistance across the United States and internationally, particularly in the areas of language and communication development, augmentative communication, and nonsymbolic communication intervention strategies for learners who have low-incidence disabilities, including deaf-blindness.

Kathleen (Kat) Stremel Thomas has worked in the area of communication & language assessment, intervention, generalization and evaluation for students with severe disabilities, including deaf-blindness, for the past 39 years. She has written numerous book chapters and articles and continues to conduct workshops nationally and internationally. Kathleen's primary experience includes working with infants, toddlers, and young children within natural environments. She served as the Director for the National Consortium on Deaf-Blindness for the past 11 years. Kat is now involved in Cochlear Implant research and intervention for children who are deaf-blind with Cochlear Implants.

Presentation Abstract: Presenters will share preliminary findings from their ongoing research study investigating outcomes for children with deaf-blindness, who have received a cochlear implant. Participants in this study are diverse; the second largest group, by etiology, is children with CHARGE syndrome. In addition to sharing research findings they have to date, researchers will present suggestions parents might utilize to promote their children's communication development and listening skills. Sound inventories for home, school, and community environments, developed by the researchers, will be discussed.

1st CHARGE Syndrome Conference for Professionals, Indian Lakes Resort, Bloomingdale, IL, July 23, 2009

IMPACT OF COCHLEAR IMPLANTS FOR CHILDREN WITH CHARGE SYNDROME: PRELIMINARY FINDINGS

International CHARGE Syndrome Conference
July 23- 25, 2009

Presented by:
Susan M. Bashinski
Kathleen Stremel Thomas

Department of Education
Office of Special Education Programs
(Grant # H327A050079)

to The Teaching Research Institute, University of Kansas &
Midwest Ear Institute

Presentation Objectives

Parents should leave this session with:

1. suggestions for interacting with their child in ways that will help to promote communication development
2. ideas regarding how they might help their child *learn to use* auditory input, within natural environments
3. suggestions for establishing a "listening environment"
4. Information that might be helpful when considering whether or not to seek a cochlear implant for their child

Participating States

• **Arizona**	• **Massachusetts**
• California	• Mississippi
• Connecticut	• Missouri
• Delaware	• Nebraska
• Florida	• New York
• Georgia	• North Carolina
• Illinois	• Ohio (CCHMC)
• Kansas	• Oklahoma
• Louisiana	• Oregon
• Maryland	• Pennsylvania
	• Texas

Participants with CHARGE Syndrome

- A total of 93 children are participating in this study (with at least one assessment)
- Of this number, 16 participants have CHARGE (the second largest group, by etiology)
- Of the total 93 participants, the number of implants has been reported for 76 children; 11 of these have bilateral implants (14.5%)
- Of the 16 participants who have CHARGE, 3 have bilateral implants (18.8%)

Participants with CHARGE

Gender	*n*	%
Female	3	19
Male	13	81

Participants with CHARGE

Race	*n*	%
African American	3	19
Caucasian	11	69
Latino	2	13

Participants with CHARGE

Age at first implant	*n* (of 14)	%
≤ 12 mos.	3	21.4
13–24 mos.	2	14.3
25–36 mos.	4	28.6
37–48 mos.	3	21.4
49–60 mos.	2	14.3
> 5 years	0	0

Age at which Participants Received Their First Implants

- The average age at which **ALL study participants received a first implant was 36 months (i.e., 3.0 years)**
- **The average age at which study participants with CHARGE syndrome** received a first implant was **30.7 months** (i.e., ~2 years, 7 months)

Participants with CHARGE (with implant age data, n = 14)

	Age of child (months)	Age at Implant (months)	Time in Sound (months)
Mean	70	30.7	39.1

Auditory Development

- Research regarding auditory brain development *should* guide the way we teach children to listen and to use auditory input
- We hear with our brains, not our ears
- A child's brain must be accessed and stimulated in order to develop (Cole & Flexer, 2007)
- Acoustic accessibility of intelligible speech is essential for brain growth
- We are either "growing" the brain or we are not ..!

Research on CI and Children with Multiple Disabilities

- Edwards (2007) reviewed the limited research currently available regarding cochlear implants and children with multiple disabilities
- General findings include:
  - Cognitive functioning is one of the strongest predictors of progress in developing speech perception and speech production
  - Parents report satisfaction with CI due to increased eye contact, awareness of the environment, and response to requests

Observations, to Date

- Younger participants in study, as a group, received their implants at earlier ages
- Participants in study, who had more additional disabilities, as a group received their implants at older ages
- Population of children with DB is extremely diverse; receiving a cochlear implant is *not* associated with any particular etiology

Observations, to Date

- A number of children with deaf-blindness (including CHARGE), who receive implants, do not have pre-linguistic skills
- A child's early communication skills, auditory and speech perception, speech development, and language development must be assessed so the habilitation program can be individualized
- Though a child may receive diagnostic therapy, she needs to learn to *use auditory skills* in authentic environments
- What do we want as outcomes? Are we willing to do what it takes?

Observations re: Outcomes

- Tremendous variability appears to exist in outcomes for children with CHARGE, who receive a cochlear implant

Optimal Outcomes appear to be associated with:

- Children wearing the implant(s) during all waking hours
- Children having their implant(s) mapped frequently
- Interventions focusing on the *auditory* signal
- Intervention focusing on family-child interactions, with an interventionist as "coach"

Preliminary Finding: Age at Implant

The impact of the AGE at which the child received his / her first cochlear implant **was significant on skill development**, as measured by the *Reynell-Zinkin* assessment…

Preliminary Finding: Age at Implant

- Participants who received the first implant at an earlier age appear to demonstrate increased:
  - response to sound
  - verbal comprehension
  - expressive language
  - social adaptation skills
- That is, the **earlier** a child received his / her first implant appears to be associated with **more rapid, significant progress in these areas.**

Preliminary Finding: Time in Sound

The impact of the amount of **TIME IN SOUND** (that is, the length of time the child has had a cochlear implant) **was significant on skill development**, as measured by the *Reynell-Zinkin* assessment…

Preliminary Finding: Time in Sound

- Participants with longer time in sound appear to demonstrate increased:
  - response to sound
  - verbal comprehension
  - expressive language
  - social adaptation skills
- That is, the **more time** a child has been receiving auditory input via a CI appears to be associated with **more rapid, significant progress in these areas**.

Preliminary Finding: Degree of Vision Loss

Although NOT statistically significant, the assessment **scores* for participants with total blindness were lower** than those for children who were reported to have some functional vision—**when scores WERE controlled for age**

*as measured by the *Reynell-Zinkin* assessment

Case Studies – Children with CHARGE Syndrome

See PowerPoint slides
for detailed data display

Examples of What We Need to Teach

- Pre-linguistic communication (a *necessary, but not sufficient* condition for auditory development)
- Differing responses to familiar speech
- Differing responses to environmental sounds
- Differing responses to music
- Differing responses to unfamiliar speech
- Expanding receptive vocabulary and receptive language comprehension

Examples of What We Need to Teach (con't)

- Use of vocalizations as communication
- Differing levels of vocal imitation
- Use of vocal inflection and intonation
- Expanding expressive vocabulary
- Use of expanded expressive language
- Use of speech to communicate
- Use of intelligible speech

Facts

- Many children with DB, who receive a cochlear implant, do not receive intervention or therapy specific learning to listen / use the implant
- Variability in child outcomes indicates the need for individualized and adaptive approaches across receptive and expressive language, as exemplified by:

Auditory – Verbal Continuum

A…..AV…..AV…..AV…..V

(Nussbaum, Scott, Waddy-Smith, & Koch, 2006)

- Children who are deaf-blind might need more than programming across an Auditory – Verbal continuum to support their communication growth

How Do We Teach?

- Establish a "*listening environment*"
- Coach families
- Use auditory – verbal techniques
- Be conscious of the sign – oral continuum
- Use natural routines and activities to embed opportunities for listening and communicating

"Auditory Sandwich"

<u>Definition</u>:

- During an interaction with a child who has received an implant, lead with auditory stimuli
- WAIT for a response from the child
- Implement visual, tactile, and / or kinesthetic cues the child needs for support
- Include spoken language directly in the interaction with the child, *after* other modality cues (Nussbaum, Scott, Waddy-Smith, & Koch, 2006)

EXAMPLE: "Auditory Sandwich"

1. Say, "Get your bib…"
2. WAIT for a response to this verbal cue
   (IF no response, then…)
3. Say, "Get your bib" while pointing or gesturing in the direction of the bib
4. Say, "You have your bib!"

Establishing a Listening Environment

- Position oneself to best interact with the child, in the specific routine
- Use speech that is rich in melody, intonation, and rhythm
- Speak at typical volume
- Minimize all background noise
- Use speech that is repetitive
- Use acoustic "highlighting" techniques

(Estabrooks, 2001)asc ssss

SAMPLE: Home & Community Environments Inventory

Child's Name: Ashley **Sex:** Female
Birthdate: 11/11/1989 **Today's Date:** 11/5/2009

Directions: Please check the sounds that are in your environment (on the left-hand side). Columns on the right-hand side can be used as an assessment to determine your child's detection and identification of specific sounds.

Sounds in Your Home & Community Environment	Your Child's Responses to the Sounds		Motivating Sounds to Target for Learning
	Detection	Identification	
Home Environment – Kitchen and Utility Room:			
X Microwave bell	☐	☐	A good majority of the sounds are only identified in context and Ashley following who is doing the task.
X Oven door opening/closing	X	☐	
X Oven/egg timer	☐	☐	
X Oven temperature setting (beeps)	X	X	
X Refrigerator opening/closing	X	X	
X Drawer opening/closing	X	X	
X Dishwasher	☐	☐	
X Toast popping up in toaster	X	X	

Inventory of Sounds in Home and Community Environments

See Handouts for copy of this sound inventory

SAMPLE: School & Educational Environments Inventory

Child's Name: Ashley **Sex:** Female
Birthdate: 11/11/1989 **Today's Date:** 11/5/2009

Directions: A child's educational team should work together to identify sounds available in various school environments (left-hand side). Columns on the right-hand side can be used as an assessment to determine the child's detection of, and attention to, specifi sounds.

Sounds in Your Child's School / Educational Environments	Your Child's Responses to the Sounds		Motivating Sounds to Target for Your Child to Learn
	Detection	Identification	
Physical Contexts / Settings:			Attention to sounds in general ed classroom; arrangement of open environments to promote sound detection in limited spaces.
X gymnasium	☐	☐	
X corridor	X	X	
X playground	☐	☐	
X general education classroom	X	☐	
Sound Sources:			
X human - adult	X	☐	
X human – child	☐	☐	
X mechanical (toy, fire / tornado warning)	X	X	
X digital (recorded speech, voice output)	☐	☐	

Inventory of Sounds in School and Educational Environments

See Handouts for copy of this sound inventory

Other Activities for Suggesting to Families

- Maintain a joint focus on objects and activities
- Play ritualized games
- Sing and read nursery rhymes (younger children)
- Name objects in the environment
- Describe the location of objects
- Call the child's attention to environmental sounds
- Read to your child
- Play music and instruments

Key Findings from Family Survey

See PowerPoint slides
for detailed data display

References

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- Edwards, L. C. (2007). Children with cochlear implants and complex needs: A review of outcome research and psychological practice. *Journal of Deaf Studies and Deaf Education, 12*, 258-268.
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- Nussbaum, D., Scott, S., Waddy-Smith, B., & Koch, M. (April, 2006). Spoken language and sign: Optimizing learning for children with cochlear implants. Paper presented at Laurent Clerc National Deaf Education Center, Washington, DC.
- Taylor, E., Stremel, K., & Bashinski, S. M. (2008). *Cochlear implants for children with combined hearing and vision loss*. OSEP *grant: #H327A050079.*

THANK YOU!

We appreciate your interest and attendance!

If you have questions, or would like additional information, please don't hesitate to contact us:

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252.737.1705

Kathleen Stremel Thomas
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913.677.4562

Sensory & Educational Information

Platform Presentation #11
4:35 – 5:00 PM
Trillium Ballroom II, Conference Center

THE NICU EXPERIENCE: ITS IMPACT AND IMPLICATIONS

Barbara Purvis, M.Ed.
Technical Assistance Provider
National Consortium on Deaf-Blindness
Shawnee Mission, KS

Presenter Information: Barbara has worked in both general and special early childhood education, including specialized training to provide developmental care to preterm and medically fragile infants in intensive care nurseries. She first met children with CHARGE Syndrome when working as an early intervention provider and, with NCDB, has continued her work on behalf of children with combined vision and hearing loss. Having "transitioned" three daughters, including one who received special education supports, Barbara is an experienced advocate for individuals with disabilities.

4330 Shawnee Mission Pkwy, Suite 108, Shawnee Mission, KS 66205; EMAIL: barbara.purvis@hknc.org : TEL: 913-677-4562

Presentation Abstract:
Preterm infants complete their development in an environment markedly different than their mother's womb. The multi-sensory experiences in an intensive care nursery impact immature systems in ways that interfere with typical prenatal development. Regardless of whether they are born early, children with CHARGE Syndrome often spend extended time in the NICU, encountering experiences difficult for their compromised sensory systems to handle. This session examines implications of the NICU experience for both infants and families.

1st CHARGE Syndrome Conference for Professionals, Indian Lakes Resort, Bloomingdale, IL, July 23, 2009

The NICU Experience: Its Impact and Implications

Barbara Purvis, M.Ed.

CHARGE Conference for Professionals

June 23, 2009 – Bloomington, IL

Overview

1. Impact on Babies and Families

Sensory and developmental implications

Providing supportive care

2. Implications for Service Providers

Increased level of awareness and sensitivity

Importance of early collaboration

IMPACT on BABIES

- Increased survival rate of younger, lower birth weight and medically fragile infants
- NICU is a very unnatural environment
- Babies with (or suspected of having) CHARGE already have altered sensory systems
- Immediate medical concerns take priority over developmental and educational concerns

IMPACT on FAMILIES

- Emotional roller coaster
- Information overload
- Bonding is difficult
- Job stress
- Financial stress
- Strained relationships
- Early challenges can have long-term implications

PRENATAL SENSORY DEVELOPMENT

- **Typical sensory development follows a sequential maturation process**

Tactile ➔ Vestibular ➔ Gustatory ➔ Olfactory ➔ Auditory ➔Visual

- **Each system interacts with and impacts every other system**
- **Any compromise to one system affects much more than just the compromised system**
- **Infant outcomes can be improved through intervention that supports the developing infant and its vulnerable sensory systems**

What is DEVELOPMENTALLY SUPPORTIVE CARE?

- Based on NIDCAP principles (*Newborn Individualized Developmental Care and Assessment Program*)
- Assesses overall nursery environment
- Assesses individual infant's environment
- Provides individualized care to babies
- Provides recommendations to family and medical staff to enhance infant development

NIDCAP ASSESSMENT

- Observe and record a caregiving procedure
  - Heart and respiration rates
  - Oxygen saturation levels
  - Color
  - State
  - Responses to handling/changes in environment
  - Stress signals
  - Self-calming behaviors
  - Motor activity
- Use information to report infant progress and make recommendations for individualized care

Supportive Care Practices

- **Attention to environment**
  - ➔ Overall nursery environment
    - Arrangement of equipment and supplies
    - Ideas for decreasing light, sound, activity levels
  - ➔ Individual infant's bedspace
    - Type and configuration of bedding/clothing
    - Appropriateness of pacifier
    - Ideas to assure bedspace is appropriate based on baby's current gestational age

Supportive Care Practices

- **Positioning**
  - ➔ Encourage hands-to-mouth, midline alignment
  - ➔ Arms and legs flexed and tucked
  - ➔ Nests to provide security, boundaries to facilitate self-regulation/provide proprioceptive input
  - ➔ Kangaroo holding
- **Feeding**
  - ➔ Determine readiness
  - ➔ Choose appropriate nipple
  - ➔ Model appropriate strategies for staff, families

Supportive Care Practices

- **Care giving strategies**
  - ➔ Education regarding infant cues
  - ➔ Planning to minimize handling, over-stimulation
- **Education and support for families**
  - ➔ Principles of developmentally supportive care and recommendations individualized for their baby
  - ➔ Reading infant stress signals
  - ➔ Strategies for being involved in their baby's care
  - ➔ Resources and referral to early intervention programs/support groups/social service agencies

Implications for Service Providers

Increased awareness and knowledege of developmental implications

- Altered development often results in
  - Challenges with state regulation
  - Challenges with attention
  - Challenges with sensory integration
  - Challenges with sensory defensiveness

Implications for Service Providers

Increased awareness and sensitivity

The…infant is in various stages of development to which we place unrealistic demands. The infant is at the mercy of its care providers . . . How we provide care and what we do or don't do can have a lasting effect on the infant and family.

Linda M. Lutes, M.Ed., Infant Development Specialist

Implications for Service Providers

Increased awareness and sensitivity

- Give families of young children space and time – they need and deserve it
- Realize that family behaviors viewed as barriers may have deep-rooted origins resulting from the family's NICU experiences
- Be careful how you "use your words"

Implications for Service Providers

Increased collaboration

- Develop a team for coordinated care – medical, developmental and educational
- Start as early as possible
- Find out about NICU and PICU experiences of children you work with
- Education early intervention providers about CHARGE
- Use what you've learned to inform your intervention and instruction

Selected Resources

Als H (1999) *Reading the premature infant*. In Goldson E (ed.) Nurturing the Premature Infant: Developmental Interventions in the Neonatal Intensive Care Nursery. New York: Oxford University Press, 18-85.

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Selected Resources

Fern, D. and Graves, C. (1996). *Developmental Care Guide for Families with Infants in the NICU* (1996), Weymouth, MA: Children's Medical Ventures.

Newborn Individualized Developmental Care and Assessment Program (NIDCAP) Program Guide (1998) National NIDCAP Training Center, Boston, MA: Children's Medical Center Corporation.

Understanding My Signals: Help for Parents of Premature Infants (1989, 1996) Hussey-Gardner, B. Palo Alto, CA: VORT Corporation

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VandenBerg KA (1993) Basic competencies to begin developmental care in the intensive care nursery. *Infants and Young Children* 6:52-59.

Zaickin, J. (1996). *Newborn Intensive Care: What Every Parent Needs to Know* (1996) Petaluma, CA: NICU Ink.

Contact Information

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Medical Information

Platform Presentation #12
5:00 – 5:25 PM
Trillium Ballroom II, Conference Center

CAUSE OF DEATH IN CHARGE SYNDROME AFTER THE NEONATAL PERIOD: A REPORT OF SIX CASES

Jorieke Bergman, M.D.[1], Kim Blake, M.D.2, Rolien Free[1], & Conny van Ravenswaaij-Arts, M.D., Ph.D.[1]

[1]University Medical Center, Groningen, NL
[2]Dalhousie University, Halifax, NS, CA

Primary Presenter Information: *Dr. Bergman* is a clinical geneticist in training and PhD-student
She studied medicine at the Utrecht University in the Netherlands and started specializing in clinical genetics in Groningen in 2006. In 2007 she received a grant that allowed her to start a PhD project on CHARGE syndrome that is currently still ongoing. As part of this PhD project she studied smell and pubertal development and causes of post neonatal death in patients with CHARGE syndrome In addition, mouse studies were performed in the Wellcome Trust Sanger Institute in Cambridge, Great Britain in order to gain insight into the underlying mechanisms of smell deficit and pubertal delay in CHARGE syndrome. She is also coordinator of the multidisciplinary CHARGE outpatient clinic in the Netherlands and is actively involved in the Dutch CHARGE parent support group.

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TEL: 0031(0)503617229, FAX: 0031(0)503617231, EMAIL: j.e.h.bergman@medgen.umcg.nl

Presentation Abstract: CHARGE syndrome is a multiple congenital anomaly syndrome that can be life-threatening in the neonatal period. Previous studies have shown that complex heart defects, bilateral choanal atresia, esophageal atresia, and brain anomalies can cause neonatal death. However, little is known about the causes of death later in childhood.

Our goal was to study the post-neonatal causes of death in CHARGE syndrome patients. Therefore, we retrospectively collected the medical data of six deceased CHARGE patients (aged between 11 months and 9 years of age) and analyzed the causes of death. In four patients respiratory aspiration most likely contributed to premature death. One patient died because of postoperative complications and one patient choked during eating. Cranial neuropathies were present in all deceased children and were most likely the primary causative factor, predisposing the patients to swallowing problems and gastro-esophageal reflux disease.

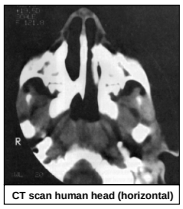
From our small cohort, we conclude that respiratory aspiration and postoperative airway events are a common cause of death in post-neonatal children with CHARGE syndrome. The shared underlying pathogenic mechanism is cranial nerve dysfunction. We recommend that every CHARGE patient with feeding difficulties is assessed by a multidisciplinary team in order to evaluate cranial nerve function and swallowing. Treatment of swallowing problems and gastro-esophageal reflux disease should not be delayed. Surgical procedures should be combined whenever possible and one should be aware of the increased risk of postoperative complications and intubation problems.

University Medical Center Groningen

Cause of death in CHARGE syndrome

Jorieke Bergman
MD-medical research trainee
Department of Genetics
UMC Groningen, the Netherlands
CHARGE conference 2009 (Chicago)

CHARGE syndrome

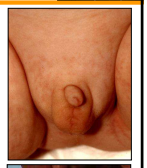


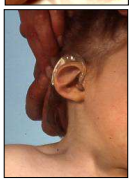
CT scan human head (horizontal)

Birth incidence ~1/10,000
CHD7 mutations (AD)

Coloboma
Heart defect
Atresia of choanae
Retardation
(growth and development)
Genital anomalies
(delayed puberty)
Ear abnormality
(including deafness)

Balance disturbance, anosmia and many other features



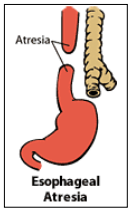


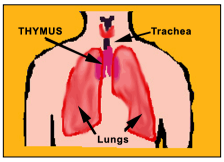
Sanlaville& Verloes 2007

CHARGE can be life threatening

Cause of death in the neonatal period:

- Complex heart defects
- Bilateral choanal atresia
- Esophageal atresia
- Thymus aplasia → severe T-cell deficiency
- Brain anomalies





Observation

Multidisciplinary CHARGE outpatient clinic UMCG
Follow up of patients

→ **3 died suddenly after the neonatal period**

Aims

1. To estimate the incidence of post-neonatal death in CHARGE syndrome
2. To study the causes of post-neonatal death in CHARGE syndrome
3. To identify risk factors for premature death in CHARGE syndrome

Methods

Retrospective collection of patients that died after 11 months of age with definite CHARGE syndrome

Recruitment through:

- CHARGE outpatient clinic (n=3)
- Dutch patient organization (n=1)
- Database search UMCG genetics (n=1)
- Canadian database of Prof. Blake (n=2)

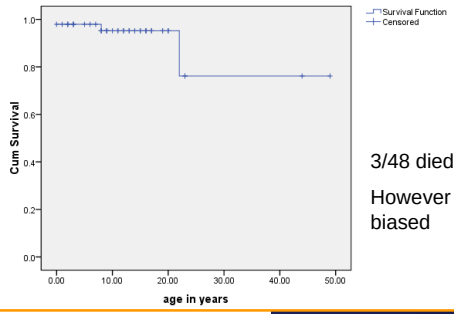
In total 7 patients

Methods

1. Kaplan Meier survival curve of 48 patients that were seen at the CHARGE outpatient clinic
2. Chart review (to analyze cause of death)
3. Comparison of features of deceased and surviving CHARGE patients

Results (1)

Kaplan Meier curve Survival Function



3/48 died (6.3%)

However cohort is biased

Results (2)

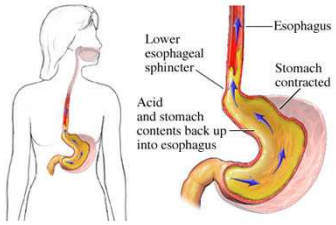
CHD7 mutation: frameshift

Patient A: died age 8 years, choked during eating

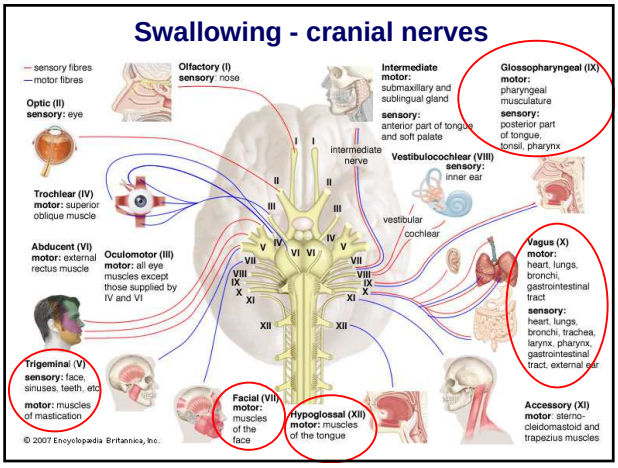
History: esophageal atresia, ASD/VSD, brain anomalies, feeding and breathing difficulties, GERD, aspiration pneumonias

Cranial nerve dysfunction: VII, IX, X

Gastro-esophageal reflux disease (GERD)



Swallowing - cranial nerves



Results (2)

CHD7 mutation: frameshift

Patient B: died age 22 years, pneumonia – respiratory aspiration / circulatory arrest

History: neonatal convulsions, cleft palate, feeding and breathing difficulties, GERD, aspiration pneumonias

Cranial nerve dysfunction: VII, IX, X

Results (2)

CHD7 mutation: frameshift

Patient C: died 11.5 months, viral airway infection - respiratory aspiration / circulatory arrest

History: neonatal convulsions, unilateral choanal atresia, feeding and breathing difficulties, GERD, barium swallow: abnormal

Cranial nerve dysfunction: VII, IX-X

Results (2)

Patient D: died 14 months, respiratory aspiration / circulatory arrest

History: esophageal atresia, complex heart defect, brain anomalies, feeding difficulties, GERD, aspiration pneumonias

Surgery Fallot's tetralogy (13 months)

Cranial nerve dysfunction: IX-X

Results (2)

Patient E: died 27 months, respiratory aspiration

History: Fallot's tetralogy, bilateral choanal atresia, feeding difficulties, GERD

Cranial nerve dysfunction: IX-X

Patient F: died 9 years, respiratory aspiration

History: epilepsy, DORV, unilateral CLP, unilateral choanal atresia, feeding difficulties, GERD, recurrent bowel obstructions

Cranial nerve dysfunction: V, VII, IX-X

Results (2)

CHD7 mutation: nonsense

Patient G: died 14 months, postoperative complications

History: DORV, bilateral choanal stenosis, brain anomalies, cleft palate, feeding and breathing difficulties, GERD, aspiration pneumonias

Cranial nerve dysfunction: IX-X

Results (3)

Features	Surviving (>10 years) n=25	Deceased (<10 years) n=6	P-value
Male gender	48%	83%	0.185
Heart defect	**28%**	**83%**	**0.022***
Esophageal anomaly	4%	33%	0.088
Brain anomaly	77% (n=17)	100% (n=3)	1
GERD	**25%**	**100%**	**0.002***
Feeding problems	58%	100%	0.074
Feeding + breathing problems + GERD	**17%**	**67%**	**0.029***

Discussion

Postneonatal demise is an underestimated complication in CHARGE syndrome (3/48 in our cohort = 6.3%)

Important causes of death:

- Respiratory aspiration (CN defects) or circulatory arrest (CHD, brain anomaly)
- Postoperative mortality (CN defects)
- Choking (CN defects, corrected esophageal atresia)

(Literature: few reports, in agreement with our data)

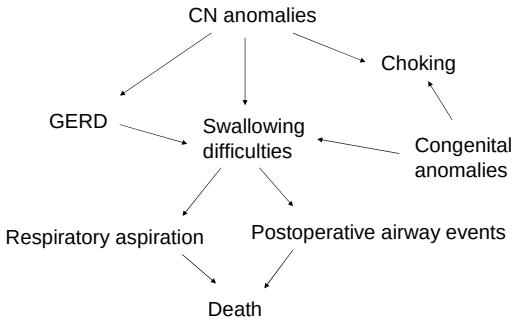
Risk factors:

- Cranial nerve defects, feeding/breathing difficulties and GERD
- Congenital heart defects
- Possibly: brain abnormalities (3/7), esophageal atresia/fistula (2/7)

Limitations of our study

- No autopsy data!
- Cranial nerve dysfunction not systematically tested
- Complex disorder, other congenital defects could have contributed to the demise

Overview



Recommendations

Assessment of CHARGE patients with feeding difficulties:

- Evaluation of CN function
- Swallowing studies, esophageal studies (GERD)
- Early treatment of swallowing problems or GERD (medication, surgery)
- When high risk of choking → educate home carers in Heimlich maneuver and CPR
- Careful preoperative assessment, longer surveillance after surgery (combine procedures whenever possible)

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We are indebted to the families that cooperated in this study

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