# ABSTRACTS FROM THE LAB

CHARGE Syndrome Research Lab at Central Michigan University

#### Introduction

The CHARGE Research Lab at Central Michigan University began to form around 1999. Throughout its history it has been supported by the CHARGE Syndrome Foundation both in terms of financial support and publicity for its studies. In the next pages are abstracts of the Lab's major publications.



#### **Cranial Nerve Manifestations in CHARGE Syndrome**

Blake, K. D., Hartshorne, T. S., Lawand, C., Dailor, A. N., & Thelin, W. J. (2008). Cranial nerve manifestations in CHARGE syndrome. *American Journal of Medical Genetics*, *146*, 585-592.

Cranial nerve (CN) anomalies have been regarded as a major criterion for a clinical diagnosis of CHARGE syndrome for some time. However, there have been relatively few studies of the extent of this involvement. A detailed questionnaire (in French or English) was distributed to all physicians who participated in the 2001–2004 Canadian Paediatric Surveillance Program (CPSP), and who identified themselves as caring for an individual with CHARGE syndrome. Clinical data were collected from multiple sources for each individual, including evidence of CN dysfunction. Evidence for CN anomalies recorded by the clinical presentations and evidence from specialized testing, were: weak chewing and/ or sucking (CN V), facial palsy (CN VII), sensorineural hearing loss (CN VIII), balance vestibular problems (CN VIII), and swallowing problems (CN IX/X). Data were analyzed as to the frequency of the CN anomalies and compared to the literature. At the time of this study, there were 99 individuals identified with CHARGE syndrome across Canada. The CHARGE syndrome diagnosis was confirmed by geneticists across the country. Gene testing was not available at the time of this study. Of these 92% exhibited symptoms of at least one CN anomaly, and 72% reported involvement of more than one. Isolated CN involvement was rare. Ascertainment was highest for CN IX/X, and lowest for VIII vestibular. The frequency of CN involvement was generally higher than that reported in the literature.

*Keywords:* CHARGE syndrome, cranial nerves (CNs), surveillance, sensorineural hearing loss, facial palsy, swallowing dysfunction

#### Postopertative Airway Events of Individuals with CHARGE Syndrome

Blake, K., MacCuspie, J., Hartshorne, T. S., Roy, M., Davenport, S. L. H., & Cortsen, G. (2009). Postoperative airway events of individuals with CHARGE syndrome, *International Journal of Pediatric Otorhinolaryngology*, *73*, 219-226.

#### Summary

Objective: CHARGE syndrome is a heterogeneous genetic disorder comprising multiple congenital anomalies. Major clinical diagnostic criteria include ocular coloboma, choanal atresia/stenosis, characteristic ear abnormalities, and cranial nerve abnormalities. CHARGE syndrome is caused by a mutation in the geneCHD7located on chromosome 8. Patients with

CHARGE syndrome require multiple anesthetics for surgical and otorhinolaryngology procedures. This study describes the postoperative anesthetic related airway events (i.e. re-intubations for apneas and desaturations, airway obstruction due to excessive secretions) of nine individuals with CHARGE syndrome.

Methods: Detailed chart audits were performed on nine patients diagnosed clinically with CHARGE syndrome who had undergone surgery at a single tertiary health centre. The CHARGE characteristics present in each individual, the number and types of surgeries and anesthetics, and the related postoperative airway events were determined.

Results: The mean age of the population at chart review was 11.8 years (8.0). The total number of anesthetics was 147, with a mean of 16.2(8.4). Of the 215surgical procedures (mean 21.9,12.2), 30% were otorhinolaryngological. Post-operative airway events occurred after 35% of anesthetics. Surgeries resulting in the most airway events involved the heart (65%), the gastrointestinal tract (39%), and airway diagnostic scopes, i.e., bronchoscopy, laryngoscopy, and nasopharyngoscopy (36%). Combining multiple surgical procedures under one anesthetic did not increase the risk of postoperative airway events. As individuals aged, they had fewer surgeries and anesthetics, as well as a lower risk of postoperative airway events.

Conclusion: Individuals with CHARGE syndrome face a significant risk of postoperative airway events with anesthesia, and this is exacerbated by the high number of surgeries they require. Surgeons and anesthesiologists should be aware of potential for postoperative airway events in individuals with CHARGE syndrome and plan accordingly.

# Quality of Life in Adolescents and Adults with CHARGE Syndrome

Hartshorne, N., Hudson, A., MacCuspie, J., Kennert, B., Nacarato, T., Hartshorne, T., & Blake, K. (2016). Quality of life in adolescents and adults with CHARGE syndrome. *American Journal of Medical Genetics,* Article 9999A, 1-10.

Health-related Quality of Life and the Impact of Childhood Neurologic Disability Scale were collected for 53 patients with CHARGE syndrome aged 13–39 years with a mean academic level of 4th grade. The most prevalent new and ongoing issues included bone health issues, sleep apnea, retinal detachment, anxiety, and aggression. Sleep issues were significantly correlated with anxiety, self-abuse, conduct problems, and autistic-like behaviors. Problems with overall health, behavior, and balance most affected the number of social activities in the individual's life. Sensory impairment most affected relationships with friends. Two contrasting case studies are presented and demonstrate that the quality of life exists on a broad spectrum in CHARGE syndrome, just as its physical features range from mild to very severe. A multitude of factors, including those beyond the physical manifestations, such as anxiety and sleep problems, influence quality of life and are important areas for intervention. *Keywords:* CHARGE syndrome, quality of life, development, adolescent, adult

#### **Challenging Behavior in CHARGE Syndrome**

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

Little is known, beyond anecdotal reports, concerning the challenging behaviors of some children with CHARGE Syndrome. One hundred respondents from the US (74%) and 7 foreign countries, primarily mothers (91%), completed a web-based survey regarding the behaviors of a person with CHARGE (median age of 7). Included was a medical history and a list of 71 behaviors based on the diagnostic categories most frequently reported anecdotally. Findings supported these reports. Behaviors typical of autistic disorder, attention deficit/hyperactivity disorder, obsessive-compulsive disorder, Tourette syndrome, and deaf-blindness were characteristic of these children. Those who were deaf-blind received higher ratings on these challenging behaviors.

*Keywords:* CHARGE, behavior, deaf-blind, psychiatric, developmental disabilities, OCD, autism, tics, ADHD

#### **Autistic-Like Behavior in CHARGE Syndrome**

Hartshorne, T. S., Grialou, T. L., & Parker, K. R. (2005). Autistic-like behavior in CHARGE syndrome. *American Journal of Medical Genetics*, *133*, 257-261.

Children with CHARGE syndrome frequently exhibit moderate to severe behavior difficulties, and are often diagnosed with obsessive-compulsive disorder, attention deficit disorder, Tourette syndrome, and autism. Hartshorne and Cypher (2004) surveyed parents of 100 children with CHARGE worldwide and confirmed the prevalence of behaviors that are associated with these disorders. They also found behaviors that could be described as typical of persons who are deafblind. The present study examined whether the autistic like behaviors of children with CHARGE are more similar to those of children who are deafblind, to those of children who were autistic or are unique to CHARGE. Surveys including the Autism Behavior Checklist (ABC) were mailed to families of 204 children with CHARGE, and 160 usable surveys were returned (78%). Total scores on the ABC for children with CHARGE were significantly different from the norms for those with autism, and those who were deafblind. However, the variance for CHARGE was larger than for the normative groups, and 27.5% of those with CHARGE could be classified as autistic. The pattern of subscale scores for those with CHARGE differed from the other normative groups. *Keywords:* CHARGE, autism, deafblind, rubella, behavior

#### **Executive Function in CHARGE Syndrome**

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

This study addressed the presence of executive dysfunction in children with CHARGE syndrome, a genetic disorder with multiple physical anomalies and severe challenging behaviors. Ninety-eight children were included in the study. More than half received clinically significant scores on the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) scales of Shift, Monitor, and the Behavioral Regulation Index, with additional high scores on Inhibit and the Global Executive Composite. Associations were found with the age the child first walked, scores on the Autism Behavior Checklist (ABC; Krug et al., 1993), and

being classified as deafblind. Difficulties with making transitions and flexible problem solving, monitoring their work and their effect on others, and acting on impulse, may be related to the behavioral difficulties exhibited by children with CHARGE. Interventions targeting improved self-regulation may help to manage this challenging behavior.

### Sleep Disturbances in CHARGE Syndrome: Types and Relationships with Behavior and Caregiver Well-being

Hartshorne, T. S., Heussler, H. S., Dailor, A. N, Williams, G. L., Papadopoulos, D., & Brandt, K. K. (2008). Sleep disturbances in CHARGE syndrome: Types and relationships with behavior and caregiver well-being. *Developmental Medicine and Child Neurology*, *51*(2), 143-150.

Children with CHARGE syndrome frequently develop moderate to severe behavior difficulties and are often diagnosed with obsessive-compulsive disorder, attention deficit disorder, Tourette syndrome, and autism. Anecdotal reports have indicated that sleep is also affected. However, the prevalence and types of sleep disturbance have not been identified. This study investigated sleep disturbances in 87 children with CHARGE syndrome, aged 6-18 years (mean 11 y, SD 3y 8mo). There were 52 males and 35 females represented. Instruments included measures of sleep (Sleep Disturbances Scale for Children [SDSC]), behavior (Developmental Behaviour Checklist [DBC]), and carer well-being (Malaise Inventory). On the SDSC, 57.5% received scores considered significant for sleep disturbances, with disorders of initiating and maintaining sleep, sleep breathing, and sleep-wake transition being the most common. The SDSC was significantly correlated with the DBC (p=0.010) and the Malaise Inventory (p=0.003). Regression analysis found that both problem behavior and sleep disturbances contributed to the prediction of scores on the Malaise Inventory. Being both deaf and blind (p=0.001), experiencing frequent middle-ear infections (p=0.015), and starting to walk at an older age (p=0.007) were associated with more sleep disturbance. Craniofacial anomalies were not. The study highlights the importance of addressing the sleep difficulties associated with CHAGE syndrome relating both to airway management and to disorders of initiating sleep.

### Prevalence of Genetic Testing in CHARGE Syndrome

Hartshorne, T. S., Stratton, K. K., & van Ravenswaajj-Arts, C. M. A. (2011). Prevalence of genetic testing in CHARGE syndrome. *Journal of Genetic Counseling*, *20*, 49-57.

Parents of 145 individuals with a clinical diagnosis of CHARGE syndrome, ages 2 to 39 years, indicated in a survey whether their child had been tested for the CHD7 mutation, which is the only gene presently known to be associated with CHARGE. More than two thirds (68%) of the affected individuals had never been gene tested. Of the 46 who had been tested, 74% tested positive for the mutation. Half (50%) of those who underwent testing did so as a part of a conference blood draw by Baylor College of Medicine in 1999. Children who were tested were

significantly younger than those who had not been tested. A second group of 43 parents were informally surveyed at a conference in 2009. More than half of their children had been tested, and nearly 70% were positive for the mutation. Reasons given by these parents for testing included confirming the diagnosis and assisting research. Reasons given for not testing included lack of opportunity, no known benefit, and lack of insurance coverage.

# CHARGE Syndrome: An Introduction for Speech Language Pathologists

Hartshorne, T. S., & Hissong, K. N. (2014). CHARGE Syndrome: An Introduction for Speech-Language Pathologists. *SIG 16 Perspectives on School-Based Issues*, *15*(2), 94-102. doi:10.1044/sbi15.2.94.

CHARGE syndrome, identified in 1979 and a gene found in 2004, is a highly variable disorder, making "typical" CHARGE hard to describe. Few children will have all of the characteristic anomalies. Therefore, it is essential to know what the anomalies are and be able to know how the specific child is affected in order to plan well for treatment. Characteristic behaviors, which can be challenging, can be understood as attempts to self-regulate and must be understood. These children manage best in an environment that is predictable. Children with CHARGE are multisensory impaired, which can severely restrict their "communication bubble." Building communication is essential for children with CHARGE and the role of the speech-language pathologist is critical to their success in life.

#### **Behavior in CHARGE Syndrome**

Hartshorne, T. S., Stratton, K. K., Brown, D., Madhavan-Brown, S., & Schmittel, M. S. (2017). Behavior in CHARGE syndrome. *American Journal of Medical Genetics 175*, 431-438.

Unusual behavior is often associated with genetic syndromes, and may constitute a behavioral phenotype. In contrast to providing a psychiatric diagnosis, a behavioral phenotype describes what is unique to the behavior associated with different syndromes. While behaviors in CHARGE are as complex and variable as other aspects of the syndrome, there are some commonalities that raise the question of common sources for these behaviors. This article addresses how pain, sensory issues, and anxiety may impact the behavior of individuals with CHARGE syndrome, and how the development of self-regulation skills might help to mitigate some of the behaviors.

Keywords: behavior, CHARGE syndrome, pain, self-regulation, sensory impairment

# Participation in and Barriers to Recreation Participation in CHARGE Syndrome

Imel, G. E., Slavin, L. J., Hartshorne, T. S., & Kanouse, K. S. (2020). Participation in and barriers to recreation participation in CHARGE syndrome, *Palaestra*, *34*(1), 38-43.

Participation in recreational activities is a critical component in an optimal quality of life. However, individuals with disabilities often face many barriers to traditional recreational activities. Individuals with CHARGE syndrome commonly experience multisensory impairments, balance problems, and breathing problems, making participation particularly challenging. The purpose of this study was to obtain parent perspective on their child's participation in recreation and the barriers they encounter. Parents of 71 individuals with CHARGE reported their children were actively participating in a wide range of recreational activities. However, there were barriers to participation with lack of knowledge of opportunities being the greatest barrier. Balance and breathing issues were related to less participation, but not sensory impairments including deafblindness.

Keywords: Recreation participation, barriers, deafblindness, CHARGE Syndrome

# Parent Survey of Sleep Problems Among Children with CHARGE Syndrome

Kennert, B. A., Hartshorne, T. S., Kanouse, S., & Johnson, C. (2020). Parent survey of sleep problems among children with CHARGE syndrome. *Research in Developmental Disabilities*, *101*, Article 103614. https://doi.org/10.1016/j.ridd.2020.103614

Sleep problems are common among children, especially those with developmental disabilities, visual impairments, and behavioral problems. Past research has indicated a particularly high prevalence of clinically-relevant sleep problems for children with CHARGE syndrome, who often possess all three of these qualities. To gather additional information regarding the nature of these sleep problems and how they are most commonly treated amongst parents, an explorative survey was conducted with 30 parents of children with CHARGE syndrome with comorbid sleep problems using the Sleep Disturbance Scale for Children, as well as demographic and sleep questionnaires developed for use in this study.

Our findings indicated that problems of sleep initiation and maintenance were most commonly reported, consistent with previous research. Parents most often reported the following factors suspected of contributing to sleep problems: self-regulation difficulties, teeth grinding, hormonal imbalance, problem behaviors, and anxiety. The most commonly administered treatments were reported to be the use of positive bedtime routines, melatonin treatment, the use of a weighted blanket, and prescription medications, respectively. While parents reported overall that they felt all three of these intervention strategies were slightly effective at improving their child's sleep problem, the use of positive bedtime routines and melatonin treatment were perceived as more effective by parents. These results aid professionals in the selection of future research and intervention strategies to recommend for parents of children with CHARGE syndrome.

# Attachment, Bonding, And Parental Stress in CHARGE Syndrome

Reda, A. M., & Hartshorne, T. S., (2008). Attachment, bonding, and parental stress in CHARGE syndrome. *Mental Health Aspects of Developmental Disabilities*, *11*(1), 1-12.

Parents of 25 children with CHARGE syndrome, ages 12-50 months, completed measures of child attachment, parental bonding, and family stress. Twelve children were classified as securely and 13 insecurely attached. The time it took to appear attached and parents to feel bonded were related, as were length of time to appear attached and strength of parental bonding. Visual impairment was related to an insecure attachment as well as parenting stress. Twelve parents had scores indicating significant stress. Parenting stress was related to problems with bonding, and having a challenging child was related to insecure attachment. Being able to hold the child and a shorter stay in the hospital after birth were related to more secure attachment.

*Keywords:* attachment, CHARGE syndrome, intellectual disability, mental retardation, parenting, psychiatric, stress

### The Development of an Educational Checklist for Individuals with CHARGE Syndrome

Slavin, L. J., & Hartshorne, T. S. (2019). The development of an educational checklist for individuals with CHARGE syndrome. *International Journal of Developmental Disabilities*. https://doi.org./10.1080/20473869.2019.1642639

CHARGE syndrome is a rare genetic disorder which can impact every sensory system and is often associated with significant medical, communicative, developmental, and behavioral difficulties. Due to the rarity and complexity of CHARGE syndrome, educators often lack the expertise required to effectively understand and accommodate the needs of these students. Therefore, an educational checklist (i.e. "Checklist") was developed to provide a comprehensive tool that educators and related professionals can utilize to aid in the education of individuals with CHARGE syndrome. The Checklist was developed through collaboration with an international panel of experts; CHARGE Syndrome Research Lab at Central Michigan University (CMU); and a select group consisting of parents, professionals, and state deafblind project employees. The Checklist outlines major CHARGE characteristics, resulting educational needs, team members, consulting professionals, and suggested methods of accommodation. The Checklist may be utilized to develop and inform services for individuals with CHARGE syndrome in the schools.

Keywords: CHARGE syndrome, checklist, IEP, special education, multidisciplinary team

#### Identifying Pain in Children with CHARGE Syndrome

Stratton, K. K., & Hartshorne, T. (2018). Identifying pain in children with CHARGE syndrome. *Scandinavian Journal of Pain, 19*(1), 157-166. https://doi.org/10.1515/sjpain-2018-0080

Background and aims: The objective was to conduct the first investigation to identify the frequency and intensity of pain experiences for individuals with CHARGE syndrome and to review the use of two established non-vocal pain assessments with children with CHARGE, the NCCPC-R (Non-Communicating Children's Pain Checklist-Revised) and the PPP (Pediatrics Pain Profile).

Methods: Parents of children with CHARGE were enrolled. Participants completed a pain questionnaire and the NCCPC-R and PPP twice, once for a baseline measure and second during a painful experience for their child.

Results: A moderate negative correlation between the mean intensity of pain and the mean duration of pain among individuals with CHARGE was found,  $\rho = -0.34$ . There was a tendency for intensity of pain to increase for sources of pain that were of shorter duration. The NCCPC-R and PPP were found to identify pain when compared to baseline performance (no pain) with a large effect, d = 1.3. For the NCCPC-R, the difference between these ratings was significant beyond the 0.05 level, t (40) = 8.15, p = 0.000, 95% CI [16.93, 28.10]. Similarly, for the PPP, the mean pain ratings were significantly greater than the mean ratings for no pain, with significance beyond the 0.05 level, t (51) = 9.59, p = 0.000, CI 95% [11.74, 17.96].

Conclusions: Evidence exists that children with CHARGE experience pain. While the NCCPC-R and PPP were found to identify pain; future research should consider the development of a pain assessment individualized to pain behaviors present in CHARGE syndrome, given this population's unique expression of pain.

*Keywords:* CHARGE syndrome, CHARGE association, pain, behavior, communication, non-vocal

### Audiologic and Educational Issues in CHARGE Syndrome

Thelin, J. W., Hartshorne, T. S., & Hartshorne, N. S. (1999). Audiologic and educational issues in CHAGE syndrome. *Journal of Educational Audiology*, *7*, 34-41.

CHARGE syndrome is a group of congenital anomalies that can have complex effects on health and on many aspects of development. The prevalence of ear anomalies and hearing loss is 90% and, in any individual, all parts of the auditory system may be involved. The first part of this article deals with the presence and consequences of anomalies, medical and health factors, and special issues that need to be considered in the assessment and treatment of hearing loss. The second part of the article deals with the selection of a mode of communication and with the recommendation for inclusive education for a child with CHARGE. The role of the audiologist in the formulation and attainment of educational goals is stressed.

#### The Experience of Siblings of Individuals with CHARGE Syndrome

Vert, R., Olson, T. A., Kim, S. Y., Stratton, K. K., Hoesch, H. M., & Hartshorne, T. S. (2017). The experience of siblings of individuals with CHARGE syndrome. *Journal of Intellectual and Developmental Disability*, *42*(3), 240-248. http://dx.doi.org/10.3109/13668250.2016.1234594 *Background* We investigated the experience of siblings of children with CHARGE syndrome (n= 29). Siblings of children with a disability are an understudied population, and, to our knowledge, this is the first investigation of the sibling relationship in CHARGE.

*Method* Participants were asked to complete 5 measures: (a) Sibling Evaluation Questionnaire, (b) UCLA Loneliness Scale, (c) Network Orientation Scale, (d) Family Hardiness Index, and(e) Family Member Well-Being Index.

*Results* Participants accepted their sibling with CHARGE, with the relationship being neither highly negative nor positive. Although siblings reported to be somewhat less lonely, they were no less likely to access social support than college-aged peers. Participants did not indicate adjustment issues; however, more than half of the siblings reported avoiding adding to their parents' stress. Further, they rated their own personal wellbeing very positively.

*Conclusion* In spite of acknowledging stress within the family, these siblings represent themselves as well adjusted with a somewhat typical sibling relationship. *Keywords:* CHARGE syndrome, siblings, disability, wellbeing, intellectual disability

# Psychiatric Diagnoses and Psychotropic Medications in CHARGE Syndrome: A Pediatric Survey

Wachtel, L. E., Hartshorne, T. S., & Dailor, A. N. (2007). Psychiatric diagnoses and psychotropic medications in CHARGE syndrome: A pediatric Survey, *Journal of Developmental Physical Disability*, *19*, 471-483.

Many children diagnosed with CHARGE syndrome demonstrate behavioral difficulties in addition to visual, hearing and other systemic impairments. Previous research has reported that children with CHARGE have increased rates of self-injury and aggression, as well as increased frequency of obsessive compulsive and autism spectrum disorders. This study asked parents to report not only the diagnoses given for their child's behavior problems, but also whether psychotropic medication interventions were prescribed, and which agents were chosen. Results of this study showed that according to parental report, anxiety disorders and pervasive developmental disorders were the most common psychiatric diagnoses assigned with antidepressant and antipsychotic medications the most frequently prescribed psychopharmacological agents.

Keywords: CHARGE syndrome, deafblindness, autism, anxiety, psychotropics