

Introduction to Series

Behavior in CHARGE Syndrome: Introduction to the Special Topic

Timothy S. Hartshorne,* Margaret A. Hefner, and Sandra L.H. Davenport

Central Michigan University, St. Louis University, Bloomington, Minnesota

Challenging behavior in children with CHARGE syndrome has been increasingly a concern of parents, educators, and health professionals. This article introduces the special topic in the American Journal of Medical Genetics on behavior in individuals with CHARGE syndrome. It provides background on CHARGE syndrome, diagnostic criteria, and the relationship of sensory and other physical deficits with both development and behavior. Four themes related to our developing understanding of behavior in CHARGE are described: children with CHARGE have behaviors different from those seen in other syndromes with or without deafblindness. The behavior they display is often very adaptive to their environment and to their own disabilities. These behaviors may be partially related to problems with arousal and self-regulation. And, finally, all papers point to behavior as communication, especially within relationships, where it is essential for maximizing intellectual and social outcomes. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

This series of articles in the Journal is devoted to behavior in CHARGE syndrome. Sorting out which behaviors may be characteristic of CHARGE is a challenge in children who have their own distinct personalities, have many medical problems which may lead caretakers to cater more to them than if they were healthy and, most importantly, have major sensory input issues of vision loss, hearing loss, vestibular dysfunction and decreased or absent olfaction. As the articles that follow show, although many behavioral issues may be due to lack of sensory input, others may be an intrinsic part of the syndrome.

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*Correspondence to: Timothy S. Hartshorne, Psychology Department, Central Michigan University, Mount Pleasant, MI 48859. E-mail: tim.hartshorne@cmich.edu

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DIAGNOSIS

The association of choanal atresia and multiple anomalies was first identified by Hall [1979]. The acronym CHARGE was suggested by Pagon et al. [1981], based on some of the more common features: C, coloboma of the eye; H, heart defects; A, atresia of the choanae; R, retardation of growth and/or development; G, genitourinary anomalies; E, ear anomalies and/or deafness. Even then it was noted that several important, probably distinctive features (e.g., facial palsy and swallowing disturbances) were not covered by the acronym, and today the acronym is no longer used for diagnostic purposes. Although CHARGE was originally described as an association, it has become clear to those geneticists who have seen hundreds of these children over more than two decades that a subgroup exists with a distinctive set of clinical features that qualify clinically as a syndrome [Davenport et al., 1986a; Blake et al., 1998; Lubinsky, 1994; Graham, 2001]. Such a group of children look as much alike as a group of children with Down syndrome. This has led to a more refined diagnostic system [Blake et al., 1998] based on four major features, a number of minor features and additional described characteristics (Table I). Based on considerable experience, the diagnostic criteria suggested by Blake et al. have been modified by the co-authors (Hefner and Davenport) in their clinical work. The following reflects these modifications (the original updated criteria can be found in Issekutz et al., this issue).

The four major diagnostic features represent characteristics that are very common in CHARGE but rare in other syndromes: coloboma; choanal atresia; cranial nerve involvement; and characteristic ear abnormalities. The presence of three or four of these features should presume a diagnosis of CHARGE syndrome. The minor features are still very common in CHARGE, but also common in many other conditions: cleft lip or palate, congenital heart defects; genitital hypoplasia; tracheoesophageal fistula; growth delay; characteristic CHARGE face, and upper body hypotonia. The presence of three minor features along with two major features should also presume a diagnosis of CHARGE syndrome. CHARGE should also be considered in any infant with one or two of the major criteria and several of the minor features. There is no one feature of CHARGE that is universal. Every feature can vary from severe to absent in different individuals with CHARGE syndrome.

EMERGING FEATURES

Recently it has been suggested that partial or complete hypoplasia of the semicircular canals on temporal bone CT-scan should be added to the list of major characteristics [Amiel et al., 2001]. Gross motor delay in children with CHARGE can be attributed in large part to vestibular dysfunction since the Mondini defect and the associated vestibular anomalies are a frequent finding [Tellier et al., 1998; Wiener-Vacher et al., 1999; Satar et al., 2003]. However, the delay can also be affected by lack of upper visual fields secondary to ocular

TABLE I. CHARGE Syndrome Diagnostic Criteria

Major features	Minor features
Coloboma	Cleft lip or palate
Choanal atresia	Congenital heart defect
Cranial nerve anomalies (1, 7, 9, 10)	Growth deficiency
Characteristic CHARGE ear (outer, middle, or inner)	TE fistula or esophageal atresia
	Typical CHARGE face
	Genital hypoplasia
	Upper body hypotonia

Definite CHARGE syndrome: Three or four majors or two major and three minor features.

colobomas, myopia, upper body hypotonia, and even fatigue due to heart disease and illness.

GENETICS

As of this writing, one major causative gene for CHARGE has been identified [Vissers et al., 2004] as CDH7, on chromosome 8. Numerous candidate genes that are associated with overlapping phenotypes have been ruled out as a cause of CHARGE, including PAX2 [Schimmenti, Lisa, personal communication; Tellier et al., 2000], and PITX2 [Martin et al., 2002]. Although the vast majority of children in whom CHARGE is suspected are tested with FISH for del 22q11.2, to date we do not know of any individual with clinical CHARGE syndrome who is positive for the deletion. Genes in the vicinity of chromosome translocations in children with features of CHARGE have not been shown to cause CHARGE in other individuals. Sanlaville et al. [2002] used comparative genomic hybridization to look for an etiology of CHARGE. Lalani et al. [2003] used SNP information from the Human Genome Project to search for potential genes for CHARGE. Because not all children with CHARGE appear to have mutations in the CHD7 gene, the clinical diagnostic criteria published in Blake et al. [1998] and modified by Davenport and Hefner help define which children fit best into this group. Of the four major diagnostic criteria, the ear anomalies are the most distinctive for this syndrome [Davenport et al., 1986a; Admiraal et al., 1998], and in the extreme may be nearly pathoneumonic.

COGNITIVE ABILITY

The R in the original CHARGE acronym stood for mental retardation. Early reports suggested that 100% of children with CHARGE had mental retardation. This is clearly not true. At least a dozen individuals with CHARGE syndrome are in or have finished college and many teens and young adults clearly have normal intelligence. As with all the features of CHARGE, a spectrum exists from low to high intellectual functioning in different individuals. Reports of low IQ are frequently underestimates or simply in error because the psychologist may not be able to communicate adequately with the child and/or may not have enough experience with vision or hearing loss to choose the right test instruments or make the proper adaptations.

A major impediment to learning is dual sensory loss (known as “deafblindness” even if both the hearing and vision losses are mild), which affects 80%–90% of individuals with CHARGE [Davenport et al., 1986b; Blake and Brown, 1993; Edwards et al., 1995]. This leads not only to problems acquiring language and developing symbolic communication but also to problems understanding what is in the environment and what is happening around them. Very few parents or teachers have any prior knowledge about how to work with children who have combined vision and hearing loss. Therefore, immersion in an appropriate language setting (e.g., total communication for

children who are deafblind) rarely happens the way it does for children with just hearing loss or just vision loss. In addition, since these children can neither “overhear” nor “oversee” what others are doing, or the consequences of their peers’ actions, they miss out on incidental learning about appropriate social interactions.

Complicating these sensory issues are the numerous medical issues that are nearly ubiquitous in this population. Neurogenic swallowing problems often result in frequent aspiration, chronic recurrent middle ear infections and sinus infections. Heart anomalies and multiple other medical problems result in frequent hospitalizations, surgeries, and clinic visits, especially during the first few years of life. Given these potentially life-threatening and debilitating illnesses, the fitting of hearing aids and glasses or implementing appropriate early intervention and educational programs are often put on hold, even for several years. This is to the detriment of the child’s ultimate ability to communicate and learn [Thelin and Fussner, this issue].

BEHAVIOR IN CHARGE

It could appear, therefore, that most of the developmental delay and behavioral issues in children with CHARGE syndrome are due to “input impairment” (deafblindness). However, this oversimplifies the situation, as illustrated by two newly identified adults. In the last few years, two women in their 40s approached us (Davenport and Hefner) independently to confirm their self-made diagnoses of CHARGE syndrome (they do not know one another). One is nearly blind and has hearing loss. The other has significant hearing loss with good vision, speaks for herself but requires either voice-over or sign language for input. Both clearly have CHARGE by either old or new diagnostic criteria. Both have normal intelligence—they are college graduates, one with three masters degrees. As part of the conversations, each inquired whether obsessive-compulsive disorder (OCD) was part of CHARGE, as OCD tendencies were personal challenges for them. The OCD tendencies seen in many of the children and young adults with CHARGE may be one of the true behavioral manifestations of the syndrome.

In addition to these and other reports of OCD, for many years parents have reported issues described as autism, attention deficit, and tic disorders in their children. Behavior has been a major topic of discussion at the biennial CHARGE syndrome conferences since 1995, where the first formal presentation of behavioral issues in CHARGE was presented by Denno and Bernstein (not published, but the follow-up is in this series). Behavioral questions have formed the basis of ongoing studies, many of which are presented in this series.

PREVIOUS STUDIES OF BEHAVIOR IN CHARGE

Fernell et al. [1999] presented three case histories of children with CHARGE in Sweden who scored in the severe autism

range using the Childhood Autism Rating Scale [Schopler et al., 1988]. They felt the apparent autism might be due to a neuroendocrine dysfunction in CHARGE.

The first large sample study of behavior in CHARGE was conducted by Hartshorne and Cypher [2004]. They created a list of behaviors associated with disorders that were reported to appear in children with CHARGE (autism, attention deficit disorder, obsessive-compulsive disorder, tic disorder, and deafblindness). This list of behaviors was used to create a web-based survey, completed by parents of 100 individuals with CHARGE. Three behaviors emerged as the most typical in children with CHARGE: "extreme preference for certain toys, people, food, etc.," "restricted range of interests and/or pre-occupation with one narrow interest," and "significant difficulty in ability to make same age friendships." Obsessive-compulsive behaviors were less typical than those in the other categories. However, this may be the result of the specific behaviors listed in the survey. Children classified as "deaf-blind" based on their having both vision and hearing deficits had more significant behavior difficulties than those without dual sensory loss.

CURRENT STUDIES ON BEHAVIOR

At the Sixth International CHARGE Syndrome Conference in 2003 nine papers were presented at a full day Symposium on Behavior in CHARGE. Eight of these form the basis for this series, with three invited additional papers. Four themes emerge from these papers.

First, while there is clearly overlap, the behavior of children with CHARGE syndrome differs from that of children with other syndromes or causes of deafblindness. Bernstein and Denno's updated study at Perkins School for the Blind, Deafblind Program confirms that students with CHARGE who are classified as deafblind show a different pattern of behavior from other students who are deafblind in the same setting. Their study used the Child Behavior Checklist [Achenbach, 1991] and The Compulsive Behavior Checklist [Gedy, 1992]. Graham et al. illustrate some of the differences between behavior in some boys with CHARGE and that in boys with other genetic conditions using the Profile of Fundamental Goals and Motivation Sensitivities [Reiss and Havercamp, 1998], the Child Behavior Checklist [Achenbach, 1991], and the Aberrant Behavior Checklist [Aman and Singh, 1986]. Hartshorne, Grialou, and Parker's [2005] research using the Autism Behavior Checklist [Krug et al., 1993] shows a particular pattern of subscale scores for CHARGE that differs from those with autism and from those who are deafblind due to other causes. Finally, Smith et al.'s survey using several different instruments finds evidence for autism spectrum disorder in the CHARGE population, but cautions that assessment of this population is very difficult. The case histories of their children provided by Lauger, Cornelius, and Keedy demonstrate some of the variability as well as similarity found among children with CHARGE.

The second theme is that the behavior of children with CHARGE is very often adaptive to the environment and to their own disabilities. There is great creativity in the way children use behaviors to adapt to different situations. Brown, looking at the impact of sensory issues, and van Dijk et al. exploring extremely challenging behavior, both provide many examples of this. Behavior does not develop in a vacuum, but emerges as an adaptation to what the person is experiencing. Salem-Hartshorne and Jacob reveal the difficulties children with CHARGE experience in developing the kinds of typical adaptations to their environments that most children develop. However, the level of adaptation many children achieve (despite enormous handicaps) often illustrates the underlying (normal) intelligence in many of these children.

Third, behavior in CHARGE may be related in part to problems with arousal and self-regulation. These problems may be due to decreased sensory input and possibly to brain anomalies. Nicholas, using an extensive battery of test instruments, including the BRIEF [Gioia et al., 2000], shows how neurological executive functions, which are the abilities needed to control and to regulate organized behavior, may be affected in children with CHARGE. Several of the papers address stress as a serious issue for children with CHARGE and note that it can affect self-regulation and other behaviors.

Finally, communication, and especially communication within relationships, is essential for maximizing intellectual and social outcomes in these children. All of the papers in this series point to behavior as communication. Souriau et al. and van Dijk and de Kort in particular demonstrate the importance of establishing a communication link with the child with CHARGE. Thelin and Fussner emphasize the importance of total communication training early and throughout childhood. They correlate linguistic success (development of symbolic language) with age of walking, postulating that the child can then voluntarily move to the physical space in which communication can take place most effectively (the "communication bubble").

Behavior is nearly impossible to study in a controlled experimental way. It is always subject to the observations and biases of the observer. Nevertheless, multiple studies, from four different countries, using a variety of test instruments, came up with similar themes and similar behavioral patterns in children with CHARGE. Taken together, the articles in this series show the emergence of behavioral phenotypes that are perhaps specific to CHARGE syndrome.

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