# CHARGE Syndrome:
## Relations Between Behavioral Characteristics and Medical Conditions

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The behaviors and medical problems in 27 persons with CHARGE syndrome were studied, because it was hypothesized that their behavior might be partly dependent on the heterogeneous medical status. With the exception of more tics, cardiac surgery was associated with positive behaviors: less withdrawn behavior, better mood, and a more easy temperament. Tube feeding was also related to positive behavior, since participants with a history of tube feeding showed less intense behavior. Cerebral deficits were associated with three problem behaviors: more intense and withdrawn behavior and a worse mood. Deafblindness was associated with developmental delays in expressive and overall communication level, and recurrent middle ear infections correlated with delays in written language. Of all medical conditions, only the presence or absence of heart defects and cardiac surgery could differentiate between the participants with regard to the number of behavioral problems. Participants with heart surgery especially, had less behavior problems. The number of operations and hospitalizations was not associated with behavior, but the total length of the hospitalizations was. Long hospital stays were associated with less problem behavior, especially internalizing behaviors. Cerebral and heart problems did not result in longer hospital stays, whereas esophageal reflux did. Age effects were reflected in older participants, who showed more internalizing problems. Heart surgery and hospitalization may be protective factors, but the protection might not be the actual surgery or hospital stay, as there may be other variables that are the actual cause, such as reduced vitality or altered parent child interactions after heart surgery. The study could not confirm a significant association between medical conditions and autism found in previous studies. © 2006 Wiley-Liss, Inc.

**Key words:** CHARGE syndrome; heart defects; cerebral defects; temperament; child behavior checklist; deafblindness

## INTRODUCTION

The acronym CHARGE, proposed by Pagon et al. [1981] 2 years after Hall [1979] described an association between choanal atresia and other anomalies, refers to a combination of congenital anomalies consisting of: coloboma, heart disease, atresia of the choanae, retarded growth or development, genital hypoplasia, and ear anomalies including deafness. Agenesis of the vestibular semicircular canals has been suggested as an additional main feature of CHARGE, because in 94%–100% of CHARGE patients the canals are absent [Admiraal and Huygen, 1997; Murofushi et al., 1997; Admiraal et al., 1998; Wiener-Vacher et al., 1999; Abadie et al., 2000; Amiel et al., 2001; Verloes, 2005].

Many additional anomalies can be found in CHARGE syndrome: facial palsy, facial dysmorphism, cleft lip or palate, tracheo-esophageal fistula, gastro-esophageal reflux, renal abnormalities, cerebral malformations, breathing problems, hypotonia, scoliosis, and delayed psychomotor development [Asher et al., 1990; Russell-Eggitt et al., 1990; Blake

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et al., 1993; Edwards et al., 1995; Raqbi et al., 2003; Doyle and Blake, 2005; Strömland et al., 2005].

The initial diagnostic criteria suggested by Pagon et al. [1981] were gradually refined as more was learned about this syndrome. Criteria can be found in Mitchell et al. [1985], Harris et al. [1997], Blake et al. [1998]. The latter proposed four major and seven minor criteria, while recently, Verloes [2005] proposed three major signs (coloboma, atresia of the choanae, and hypoplastic semi-circular canals), which are necessary and sufficient signs of CHARGE, and five minor signs. He also introduced partial and atypical forms of CHARGE besides the typical form. Because diagnostic criteria differ between authors, substantial heterogeneity exists in samples of CHARGE patients.

It has been suggested that CHARGE syndrome is caused by neural crest disorders [Siebert et al., 1985; Wright et al., 1986; Guyot et al., 1987; Lin et al., 1990]. Recently, genetic research resulted in the discovery of two patients with a de novo overlapping micro deletion on chromosome 8q12. Sequence analysis of genes located in this region detected mutations in the CHD7 gene in 10 of 17 individuals with CHARGE syndrome [Vissers et al., 2004].

Depending on the regional differences in the ability of clinicians to make this diagnosis [see Issekutz et al., 2005] and the specific diagnostic criteria used CHARGE syndrome has a prevalence between 1:8,000 and 1:20,000 [Blake et al., 1998; Hartshorne and Hartshorne, 1998; Lewis and Low-ther, 2001; Issekutz et al., 2005].

While the medical aspects of CHARGE syndrome have been described extensively, and although ample anecdotal information is available, there are only a few empirical behavioral and developmental studies. As a result behavioral aspects of CHARGE syndrome are less well-known.

Several behavioral problems were found frequently in persons with CHARGE syndrome. Autistic features were mentioned most often. In an Internet survey of 117 CHARGE patients Hartshorne and Cypher [2004] found large variability in medical and behavioral characteristics in persons with CHARGE. Autistic features, deafblindness, and, to a lesser extend, attention deficit disorder were mentioned frequently. A second study designed to investigate autism in CHARGE syndrome came from the Canadian Pediatric Surveillance Program of 13 children with CHARGE [Smith et al., 2005]. Although most participants did not present with significant behavior problems, evidence of autism spectrum disorder (ASD) was judged moderate to strong in 6 of 10 children above the age of 4–5 years, and all but one showed evidence of ASD. The autistic nature of behaviors in CHARGE syndrome was further studied by Hartshorne et al. [2005a] in a survey of 160 persons with CHARGE. The results showed that persons with CHARGE frequently demonstrated behaviors that are autistic-like in nature, and that they had higher scores on the Autism Behavior Checklist (ABC) than persons with deafblindness, but lower scores than persons with autism. A survey of 71 parents of children with CHARGE by Souriau et al. [2005] also pointed, although indirectly, to autistic-like behavior in persons with CHARGE. All of the children involved in this survey had auditory and visual impairments. Problems were found in impulse control (especially waiting), social relations, functioning in a group, and communication. A large group was restless and seemed permanently on the move or showed aggression toward themselves or others. Souriau et al. [2005] also found a need for external structuring of behavior.

Note that the autistic features seem to be qualitatively different in persons with CHARGE syndrome compared to persons with classic autism. Graham et al. [2005] found that, although in 14 boys with CHARGE in comparison with boys with Down, Prader–Willi, and Williams syndrome the boys with CHARGE had behavior that resembled autistic spectrum disorders (such as socially withdrawn, lack of interest in social contact, reduced seeking of attention from others, hyperactivity and the need to maintain order), these boys were not as socially impaired as in classic autism.

Repetitive and obsessive–compulsive behaviors have been reported by Denno and Bernstein [1997]. They compared seven children with CHARGE with five children with congenital rubella syndrome, one with infantile encephalitis, and one child with multiple impairments as a result of premature birth. Children with CHARGE showed more uncorrectable compulsive behavior, especially repetitive behaviors, than the control group. Recently Bernstein and Denno [2005] found on the compulsive behavior checklist an average of 11.2 repetitive behaviors in 29 students with CHARGE. For 83% of these students the repetitive behaviors interfered significantly with their daily routines. However, in contrast to Denno and Bernstein's results obsessive–compulsive behaviors were found less frequently by Hartshorne and Cypher [2004].

With regard to the level of intellectual functioning Raqbi et al. [2003] found that about 50% of children with CHARGE had good intellectual outcome and 25% had very poor outcome. Poor intellectual outcome in CHARGE syndrome was best predicted by extensive bilateral coloboma resulting in low vision, microcephaly, and brain malformation [Raqbi et al., 2003].

Preliminary results from the Canadian Pediatric Surveillance Program with 13 children with CHARGE syndrome showed that individuals with CHARGE syndrome have relatively low adaptive behavior skills. Gross motor delays were most prominent [Smith et al., 2005]. Delays in adaptive behavior were also found by Salem-Hartshorne and Jacob [2004]. In

a group of 100 persons with CHARGE syndrome and over a period of 4 years the mean adaptive behavior score, measured with the adaptive behavior evaluation scale (ABES), declined significantly. Subsequently these authors studied whether the persons who improved or declined in ABES scores differed significantly from each other. Those who walked earlier, had fewer medical problems, and those who had better vision improved the most in adaptive behavior over time. ABES scores were best predicted by age at walking [Salem-Hartshorne and Jacob, 2004].

Lastly, communication problems were mentioned in persons with CHARGE syndrome [Thelin and Fussner, 2005]. Their results suggested that physical disorders, vision loss and hearing loss adversely affected communication ability, but did not preclude the development of symbolic language in 28 children with CHARGE.

With regard to the association between medical and behavioral problems in CHARGE syndrome several significant associations were found. In both the Hartshorne studies [Hartshorne and Cypher, 2004; Hartshorne et al., 2005a] the number of medical anomalies seemed to be positively associated with autistic characteristics. Hartshorne and Cypher [2004] also found a positive association between deaf-blindness and behavioral problems, between age and the number of behavioral problems, but no association between number of hospitalizations and operations and the number of behavioral problems. Adaptive behavior was significantly associated with the degree of deafblindness, age at walking, degree of hearing impairment, and medical involvement (a combined score for length and number of hospitalizations, surgery frequency, and number of CHARGE symptoms present) in 100 persons with CHARGE [Salem-Hartshorne and Jacob, 2004]. The level of communication and the ability to communicate were largely dependent upon physical disorders, vision loss and hearing loss. Physical and sensory impairments adversely affected communication ability, but did not preclude the development of symbolic language. Success in the treatment of hearing loss with amplification, the ability to walk independently, and communication training before the age of three were related positively with the development of symbolic language [Thelin and Fussner, 2005].

Summarizing, frequently found problems in CHARGE include: autistic features, obsessive–compulsive behavior, poor intellectual outcome, attention deficit disorders, and communication problems. Contradictory results were found for the number of compulsive behaviors, as well as the association between medical history, number of hospitalizations and operations on the one hand and developmental outcome on the other hand. It is not unusual that different studies may come to somewhat

different conclusions regarding the relationships between behaviors in children with CHARGE syndrome and medical problems. Unlike most other genetic syndromes CHARGE syndrome is always highly variable in its manifestations. This makes the diagnosis difficult and leads to heterogeneous samples.

Because of different methodological strategies of these studies it is hard to generalize the results to the total population of persons with CHARGE syndrome. Firstly, sometimes checklists were used and not validated assessment instruments. Secondly, the samples of children with CHARGE in the studies mentioned above do not seem representative of the total CHARGE population. Selection bias is likely to have occurred [Larzelere et al., 2004]. For instance, the Graham et al. [2005] sample consisted only of boys. Denno and Bernstein's [1997] participants came from a residential facility. These participants may be expected to have more severe problems than persons with CHARGE living at home. Souriau's [2005] participants came from organizations for deafblind people and Hartshorne's participants were recruited with the help of patient organizations and by the internet, excluding participants who were not known to patient organizations or who had no access to the internet. Moreover, because of the self-enrollment no information is available on the reliability of the diagnosis CHARGE. Self-enrollment probably also leads to over-enrollment of respondents who experience behavioral problems in their child with CHARGE.

The current study focuses upon behavior problems in persons with CHARGE syndrome, while trying to overcome the abovementioned methodological flaws. Since the number and kind of symptoms differ according to the criteria used to diagnose CHARGE syndrome, and given the established heterogeneity in CHARGE syndrome, the possible behavioral phenotype of CHARGE might be better understood when the discrete symptoms are considered than the diagnosis CHARGE per se. Therefore, the main research question concerns the possible associations between behavior characteristics and medical complications in persons with CHARGE syndrome. A related question is whether persons with few or many behavioral problems can be distinguished from each other by their medical history. Both length of hospitalization, number and etiology of medical complaints was studied. Knowing the behavioral genotype–phenotype relations is thought to be useful in the prevention and treatment of behavioral problems in persons with CHARGE and the transfer of this information to parents and professionals. Otherwise, a recent study of Jongmans et al. [in press] could not find a clear genotype-phenotype correlation concerning the medical complications/congenital anomalies in 47 CHARGE patients with a proven *CHD7* mutation.

## MATERIALS AND METHODS

### Participants

To answer the research questions, the study sample had to be representative for the CHARGE population, and be large enough to cover the variation in medical and behavioral characteristics found in persons with CHARGE. Firstly, participants were recruited from the records of the Department of Otorhinolaryngology of the Radboud University Nijmegen Medical Centre and Viataal, a residential facility for deaf and deafblind persons in Sint Michielsgestel. Both these institutes are national resource centers for CHARGE syndrome. Of the 28 patients contacted the parents of 24 children were willing to participate. Secondly, additional participants were recruited with the help of the CHARGE network of the federation of parent support groups. Nine additional children with CHARGE were recruited this way. Another six families known to the CHARGE network, did not respond to our question to participate. This brings the total response rate to 77% (33 of 43 potential participants). In contrast to the samples of Souriau et al. [2005] and Hartshorne and Cypher [2004] there was no selection based on either problem behavior, access to the internet, or the fact that help was being received from service providers or schools. After enrollment the medical records of the participants were screened for CHARGE symptoms. Although labeled CHARGE patients, eight participants did not satisfy the clinical criteria of Pagon et al. [1981] and of Blake et al. [1998] of whom five also did not have agenesis of the vestibular semicircular canals. These latter five were therefore excluded from the study, while the three patients with vestibular agenesis where included, although they did not show coloboma and/or choanal atresia (see Table I, patients no. 5, 8, 23). They did show, however, several other features of CHARGE according to the criteria of Pagon and Blake. For one person it proved to be impossible to make house calls or appointments. This participant was also excluded, leaving a final sample of 27 participants. CHD7 mutation analysis in 15 of these 27 patients showed 14 mutations, and one deletion of 8q12. All three patients with vestibular agenesis, who did not meet the Pagon's and Blake's criteria, showed a mutation. For the other 12 patients the mutation analysis was not finished as yet in three patients, and has not been performed as yet for the remaining 9 patients.

Participants came from all over the country and varied widely in their parents' Social Economic Status. There were 19 (70%) participants who lived at home receiving special education, day care, or itinerant care. Eight participants lived in a residential facility. There were 23 (85%) participants with severe multiple disabilities. The remaining four participants showed only auditory or communicative disabilities.

### Procedure

After informed and written consent by the participants and/or their parents, medical and psychological records were obtained and analyzed for medical and psychological characteristics of CHARGE. Three questionnaires were sent to the parents to fill in before the home visit. These were the "Temperamentsschaal Voor Zwakzinnigen" (Temperament scale for the mentally retarded) [Blok et al., 1990], the translated Hartshorne questionnaire and the "Child Behavior Checklist" [Achenbach, 1991]. During the home visits these three questionnaires were checked for missing values. Subsequently, a structured interview was held on the basis of the translated Souriau questionnaire [Souriau, 2001], and demographic and family data were gathered. House calls lasted for 75–195 min.

### Instruments

***Medical and psychological records.*** Analysis of medical and psychological records were intended to prepare home visits and to gather objective data, sometimes established a long time ago. Whenever necessary, additional records were obtained from other physicians or psychologists.

***A survey for parents of children with CHARGE regarding behavior problems.*** This questionnaire consists of items grouped in the three categories: demographics, medical, and behavioral [Hartshorne and Cypher, 2004]. The behavioral items contain questions that refer to typical behaviors of some common diagnoses in CHARGE syndrome: autism, obsessive–compulsive disorder, attention deficit disorder, Gilles de la Tourette syndrome, and deafblind specific behaviors. Answers to the 71 behavioral questions were scored on a five point Likert scale. Thus far, no psychometric characteristics have been reported.

***"Questionnaire destiné aux familles d'enfants ayant le syndrome de CHARGE".*** The items in this questionnaire [Souriau, 2001; Souriau et al., 2005] were derived from video analyses of four children with CHARGE. The questionnaire contains 183 items arranged in 10 categories: demographics, medical aspects, sensory functioning, motor development, feeding, autonomy, behavior, social behavior, communication, and cognition. The questionnaire is descriptive and uses yes/no questions, multiple choice questions, and open questions. Thus far, no psychometric characteristics have been reported.

***Temperament.*** The "Temperamentsschaal Voor Zwakzinnigen" (TVZ) [temperament scale for the mentally retarded] is developed for persons with moderate and severe intellectual disability [Blok, 1989; Blok et al., 1990]. The scale consists of 56 five point Likert scale items in seven categories: intensity, soothability, mood, adaptation, approachability,

TABLE I. Demographic and Medical Characteristics of the Participants (n = 27)

| Nr. | Sex[a] | Age (year; month) | Length hospital stay in weeks | Coloboma (r/l)[b] | Heart disease | Choanae atresia (r/l) | Growth retardation | Motor delay | Hypogenitalism | Ear malformation (r/l) | Hearing FI[d] (r/l) | CT-scan/missing vestibular organ (r/l) | Cleft lip or palate | Facial paresis (r/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 16;6 | 2–6 | +/+[c] | + | –/– | + | + | + | +/+ | 115/115 | +/+ | + | –/– |
| 2 | M | 10;1 | >12 | +/+ | + | –/+ | + | + | + | +/+ | 70/60 | +/+ | – | +/+ |
| 3 | M | 9;8 | >12 | +/+ | + | –/– | + | + | + | +/+ | 93/87 | +/+ | – | –/– |
| 4 | F | 6;3 | >12 | +/+ | + | –/– | + | + | ? | +/+ | 110/110 | +/+ | – | –/– |
| 5 | F | 2;9 | 7–12 | –/– | – | –/– | + | + | ? | +/+ | 115/115 | +/+ | – | –/– |
| 6 | F | 15;7 | 0 | +/+ | – | –/– | + | + | + | +/+ | 20/130 | +/+ | – | –/– |
| 7 | F | 33;5 | 2–6 | –/+ | – | +/– | + | + | + | +/+ | 115/125 | +/+ | + | –/– |
| 8 | M | 9;2 | 0 | –/– | – | –/– | + | + | + | +/+ | 125/65 | +/+ | – | +/+ |
| 9 | M | 3;10 | 7–12 | –/+ | + | –/+ | + | + | + | +/+ | 80/>90 | +/+ | – | –/+ |
| 10 | F | 6;7 | >12 | +/+ | + | +/+ | + | + | – | +/+ | 50/50 | – | – | –/– |
| 11 | F | 1;10 | 2–6 | +/+ | + | –/– | + | + | + | +/+ | 50/73 | +/+ | – | –/– |
| 12 | F | 27;10 | >12 | +/+ | + | +/– | + | + | – | +/+ | 50/130 | – | – | –/– |
| 13 | M | 18;11 | 2–6 | +/+ | – | +/+ | + | + | + | +/+ | 95/95 | – | + | –/– |
| 14 | M | 11;3 | 7–12 | +/+ | + | –/– | + | + | + | +/+ | 40/40 | +/+ | – | –/– |
| 15 | F | 9;2 | >12 | –/– | + | +/+ | + | + | + | +/+ | 75/57 | +/+ | + | –/– |
| 16 | F | 4;0 | 2–6 | +/+ | + | –/– | + | + | – | +/+ | 25/90 | +/+ | + | –/– |
| 17 | M | 6;4 | 0 | +/+ | – | +/– | + | + | + | +/+ | 80/60 | +/+ | – | –/– |
| 18 | M | 2;4 | 2–6 | –/– | – | +/+ | + | + | + | +/+ | 40/40 | – | – | –/– |
| 19 | F | 39;6 | 2–6 | –/+ | + | –/– | + | + | ? | +/+ | 130/130 | +/+ | + | +/+ |
| 20 | F | 3;11 | 2–6 | +/+ | – | – | + | + | + | +/+ | 0/0 | ? | – | – |
| 21 | M | 1;10 | >12 | –/+ | + | –/– | + | + | + | +/+ | 85/60 | +/+ | – | –/– |
| 22 | M | 19;1 | 2–6 | +/+ | + | –/– | + | + | + | –/– | 80/30 | +/+ | – | –/– |
| 23 | M | 10;6 | 7–12 | –/– | + | –/– | + | + | + | +/+ | 60/60 | +/+ | – | +/+ |
| 24 | M | 18;6 | 2–6 | +/+ | + | –/– | + | + | + | +/+ | 60/60 | – | + | –/– |
| 25 | F | 1;7 | >12 | –/– | + | +/+ | + | + | – | + | 40/40 | +/– | – | –/– |
| 26 | F | 7;1 | >12 | +/+ | + | +/+ | + | + | – | + | 80/80 | +/+ | – | –/– |
| 27 | M | 5;3 | >12 | +/+ | – | +/+ | – | + | + | +/+ | 0/90 | +/+ | – | – |

aF, female; M, male.
br, right; l, left.
c–, absent; +, present; ?, unknown.
dFI, Fletcher index; that is, mean hearing loss at 500, 1,000, and 2,000 Hz.

sensitivity, and persistence. The scale also rates temperament as easy or difficult by the formula: ½ adaptation + mood + soothability − intensity. Temperament scales describe behavioral styles or the way persons behave, independently from the content of the behavior. The TVZ was added to be able to measure, besides problem behaviors, also some positive behaviors. The TVZ has good psychometric properties [Blok et al., 1990].

*Child behavior checklist.* The child behavior checklist (CBCL) was added to measure behavioral pathology [Achenbach et al., 1987; Achenbach, 1991]. The CBCL has two versions, one for children between 4 and 18 years of age, and one for children age 2 and 3. The CBCL 4−18 consists of 112 items in eight syndrome scales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior. The 2−3 years old version has 99 items in six categories: social withdrawal, depressed, sleep problems, somatic problems, aggressive, and destructive. The CBCL gives scores for the discrete syndrome scales as well as an internalizing, externalizing, and total problem score. Internalizing problems are emotional problems directed inwards, such as somatic complaints, depression, and withdrawn behavior. Whereas externalizing problems are behavior problems directed to the environment, such as aggression, ADHD, and delinquent behavior. Standardized norms are available for non-handicapped [Achenbach, 1991] as well as deaf children [Van Eldik, 1999].

*Communication scale of the vineland adaptive behavior scales.* The Vineland adaptive behavior scales (VABS) measure social adaptation in persons with intellectual disability [Sparrow et al., 1984]. The communication scale consists of 133 items in the categories: receptive communication, expressive communication, written language, and an overall communication score. The scale has to be filled in by parents or care takers. The communication scale of the Vineland was added, because results from a pilot study [Close, 2002] hinted that communication is possibly associated with problem behavior.

### Statistical Analysis

At the outset of the study, it was the intent to examine all possible comparisons between medical symptoms and behavioral variables. Per medical symptom this led to, depending on the participant's age, approximately 30 comparisons. If post hoc correction for multiple comparisons was applied for this number of comparisons the required significance level per comparison would become very small, which would increase the risk of failing to detect a significant difference that is present (type II error). Nonparametric tests are less powerful than parametric tests, so large differences are needed to detect significant differences. This fact in combination with the relatively small number of participants, that participants do not form a sample but represent probably more than half the Dutch population of persons with CHARGE (so generalization is less of a problem), and the exploratory nature of the analyses, made us decide to let power prevail above type I error and adapt the significance level to 0.01 for those analyses that compared groups. To simplify the reporting, only significant differences will be reported.

### RESULTS

The characteristics of the 27 participants are depicted in Table I. Of the 27 participants 14 were male (52%) and 13 female (48%). The ages ranged from 1.7 to 39 years of age (mean and median age: 12 and 9 years respectively). Ten participants were visually impaired (visual acuity less then 6/20 in the better eye), and six were legally blind, with a visual acuity less then 2/20. None of the participants was totally blind. Bilateral hearing impairment was found in 23 participants. Six participants showed profound (>90 dB), three severe (70−90 dB), ten moderate (40−70 dB), and four mild (20−40 dB) hearing impairment. Nine participants had a double sensory impairment. Their visual acuity was less than 6/20 and hearing impairment was more than 30 dB. There were 19 participants (70%) with one or more heart defects, of whom 12 needed cardiac surgery. Patent ductus arteriosus (PDA) was reported in 11 participants, ventricular septal defects (VSD) in 4 participants, and atrial septal defects (ASD) in 7 participants. Central nervous system (CNS) malformations were found in 11 (40.7%) participants. Only three participants had no hospital readmissions after birth, but most participants had extended hospital stays. All participants showed overall motor delay. The total number of medical anomalies, including the ones depicted in Table I, ranged from 8 to 19, with a mean of 11.5 (SD = 2.6).

All behavioral categories from the CBCL and the questionnaires of Souriau and Hartshorne were dichotomized (see Table II). A participant received a pathological score on the CBCL scales whenever their scores fell in the borderline or clinical area. The criteria for the Hartshorne and Souriau questionnaire can be found in Table II. Given the nature of the temperament and Vineland communication scales, these scores were not dichotomized in normal and pathological scores. Subsequently the scores in Table II were accumulated into a total behavioral problem score. Twenty categories concerned participants 4 years and older, 17 categories concerned participants younger than 4 years of age. To prevent overlap the CBCL total, internalizing and externalizing scores were not included in this frequency analysis, nor included in the total behavioral problem score. The mean number of behavioral

TABLE II. Behavioral Problem Categories Based on Checklists

| Behavioral category | Questionnaire |
| --- | --- |
| 1 Autism (mean <3.0) | Hartshorne |
| 2 Deafblind specific behavior (mean <3.0) | Hartshorne |
| 3 Attention deficit disorder (mean <3.0) | Hartshorne |
| 4 Obsessive–compulsive behavior (mean <3.0) | Hartshorne |
| 5 Tic disorder (mean <3.0) | Hartshorne |
| 6 Stimulus sensitivity[a] (5 of 6 items) | Souriau |
| 7 Motor problems (5 of 7 items) | Souriau |
| 8 Dependency[b] (3 of 3 items) | Souriau |
| 9 Sleep disorders (1 item) | Souriau |
| 10 Anxious/depressed behavior (5 of 6 items) | Souriau |
| 11 Movement disruption (5 of 6 items) | Souriau |
| 12 Withdrawn behavior | CBCL |
| 13 Anxious/depressed behavior | CBCL |
| 14 Somatic complaints | CBCL |
| 15 Aggressive behavior | CBCL |
| 16 Delinquent behavior (>4 years) | CBCL |
| 17 Attention problems (>4 years) | CBCL |
| 18 Thought problems (>4 years) | CBCL |
| 19 Social problems (>4 years) | CBCL |
| 20 Sexual problems (>4 years) | CBCL |
| 21 Sleep disorders (2–3 years) | CBCL |
| 22 Destructive behavior (2–3 years) | CBCL |

[a]Stimulus sensitivity means intense or strange responses to normal visual, auditory, or tactual stimuli.
[b]Dependency concerns being largely dependent upon others and not taking self-initiatives.

problem categories was 4.6 (SD = 3.58) with a large range of 0–12 problems. Two persons with CHARGE showed none of the behavioral problems mentioned in Table II.

The number of medical problems was not associated with the number of behavioral problems. There was one significant correlation between number of medical problems and a discrete behavioral problem, namely total score of dependency on parents on the Souriau questionnaire, Rho = 0.45, P = 0.019.

Age of the participants was not associated with the number of medical problems, nor with the number of behavioral problem categories mentioned in Table II. However, age was significantly associated with the number of behavioral problems mentioned in the participant's records, Rho = 0.48, P = 0.012. Correlation analysis with separate behavioral variables showed further that age was significantly correlated with the internalizing T-score of the CBCL, Rho = 0.40, P = 0.041, and the anxious/depressed behaviors of the Souriau questionnaire, Rho = 0.46, P = 0.022.

Several significant negative correlations were found between length of hospitalization and, primarily internalizing, problem behaviors: anxious/depressed Souriau questionnaire, Rho = −0.59, P = 0.002; withdrawn behavior CBCL, Rho = −0.56, P = 0.003; anxious/depressed CBCL, Rho = −0.52, P = 0.007; thought problems CBCL, Rho = −0.54, P = 0.011; and internalizing T-score CBCL, Rho = −0.41, P = 0.037. As an exception, one significant correlation with an externalizing behavior was found, namely delinquent behavior CBCL, Rho = −0.49,

P = 0.024. Note that correlations were calculated on the raw scores. This does not mean that older children had necessarily more or less scores in the clinical range than younger children. Length of hospitalization in weeks was significantly longer for participants with esophageal reflux, T = −3.322, df = 11.676, P = 0.006, than for participants without this defect. Cerebral and heart problems did not result in longer hospital stays.

The relationship between behavioral characteristics and medical symptoms was studied by dichotomizing the medical symptoms into absence or presence. With respect to the CHARGE symptoms, Table III shows that heart defects and subsequent cardiac surgery were associated most frequently with discrete behaviors and behavioral problems. There were 19 participants with heart defects, of whom 12 participants needed cardiac surgery. Separate analyses showed that participants with cardiac surgery did not have motor, cerebral, or neurological disorders more often then participants without cardiac surgery.

Problem behaviors were found for cardiac surgery, heart defect, and cerebral abnormalities (see Table III). Heart defects and cardiac surgery were associated with more tics. Participants with cerebral abnormalities showed more withdrawn behavior, reacted more intense on stimuli, and also showed an overall more negative mood. The presence of coloboma was not associated with significant behavioral problems, but note that only six participants had no coloboma at all.

Developmental delay was found for recurrent middle ear infections and deafblindness. The presence of

TABLE III. Significantly Different Behaviors in Participants With or Without Medical Symptoms

| Medical symptom | Behavioral category (questionnaire) | Explanation | Mann–Whitney | P |
|---|---|---|---|---|
| **Problem behavior** | | | | |
| Heart defect | Tic score (Hartshorne) | Heart defect then more tics | $U=26.5$ | 0.007 |
| Heart surgery | Tic score (Hartshorne) | Heart surgery then more tics | $U=16.0$ | <0.001 |
| Cerebral abnormalities | Withdrawn (CBCL) | Cerebral abnormalities then more withdrawn behavior | $U=30.5$ | 0.006 |
| | Intensity[a] (TVZ) | Cerebral abnormalities then more intense behavior | $U=24$ | 0.003 |
| | Mood (TVZ) | Cerebral abnormalities then worse mood | $U=31$ | 0.004 |
| **Developmental delay** | | | | |
| Recurrent middle ear infections | Written language (Vineland) | Middle ear infections then lower score on written language | $U=39.0$ | 0.009 |
| Deafblindness | Expressive communication (Vineland) | Deafblind then lower expressive communication score | $U=16.0$ | 0.006 |
| | Total communication score (Vineland) | Deafblind then lower total communication score | $U=15.0$ | 0.005 |
| **Positive behavior** | | | | |
| Heart surgery | Withdrawn (CBCL) | Heart surgery then less withdrawn behavior | $U=27.5$ | 0.004 |
| | Mood (TVZ) | Heart surgery then better mood | $U=24.5$ | 0.001 |
| | Approachability (TVZ) | Heart surgery then easier to approach | $U=30$ | 0.003 |
| | Easy-difficult temperament score (TVZ) | Heart surgery then higher total temperament score, that is, more easy temperament | $U=23$ | 0.003 |
| PEG tube | Intensity (TVZ) | PEG tube then less intense behavior | $U=31.5$ | 0.010 |

[a]Intesity refers to extremely intense physical or vocal responses to normal daily events.

recurrent middle ear infections in 17 participants affected their written language performance; they scored lower on the Vineland written language scale. Deafblindness, which was strongly associated with behavioral problems in Hartshorne and Cypher [2004], showed only two significant correlations with behavior. Deafblind participants had lower expressive and total Vineland communication scores.

Associations with positive behaviors were found for heart surgery and tube feeding. Participants who had had heart surgery had higher temperament scores for mood, approachability and easy-difficult temperament. Moreover, cardiac surgery was associated with less withdrawn behavior. A history of tube feeding in 13 participants with serious feeding problems was associated with less intense reactions on stimuli.

A post hoc analysis with two temperament categories (easy/medium vs. difficult) instead of 10 decile scores showed that participants with cardiac surgery had more often high total temperament scores, that is an easy temperament, Chi-square $= 6.5$, df $= 1$, $P = 0.011$. The same was true for participants who had currently feeding problems, Chi-square $= 7.2$, df $= 1$, $P = 0.007$. Whereas participants with cerebral defects had a more difficult temperament, Chi-square $= 6.2$, df $= 1$, $P = 0.013$.

In order to study a possible association between the number of behavioral problems and medical symptoms, two groups were formed based on the mean number of total behavioral problems. The total sample minus one participant, who had too many missing values to calculate a total problem score, was split in half by the median number of behavioral problems. The first group had less than five

behavioral problems (n $= 15$), the second group had more than five behavioral problems (n $= 11$). Only the presence of heart defects and cardiac surgery were associated with less behavioral problems, Chi-square $= 5.06$, df $= 1$, $P = 0.024$, and Chi-square $= 4.55$, df $= 1$, $P = 0.033$ respectively. Not surprisingly the participants with more than five behavioral problems were rated with a more difficult temperament than the participants with less behavioral problems, Mann–Whitney $U = 4.5$, $P < 0.001$.

## DISCUSSION

The research question concerned differences in medical characteristics between persons with CHARGE syndrome as a possible source of individual variation in behavior and behavioral problems. The most prominent result was that heart defects and heart surgery, followed by cerebral disorders, were associated with behavior and behavioral problems most often. The trend seems to be that heart surgery is associated more with internalizing than externalizing behaviors. Furthermore, it seems that a side effect of heart surgery is that children with CHARGE thrive better after heart surgery.

In the present study heart defects showed a prevalence of 70%. Compared to the literature this figure is not uncommon [Lin et al., 1987; Blake et al., 1990; Wyse et al., 1993]. Heart defects and cardiac surgery seemed to act as protective factors for behavioral problems, because they were associated with lower withdrawn scores on the CBCL and higher scores, which is positive, on the temperament scales mood, approachability, and the easy-difficult continuum. The number of behavioral problems was

also lower in the group that had heart surgery. At the same time, they showed more tics. An overall developmental delay in children who had heart surgery is not responsible for the aforementioned results, since participants with heart operations did not have more motor, cerebral, or neurological disorders than participants that did not underwent heart surgery. It is more likely that heart defects requiring surgery have long lasting effects, resulting in more easy going and less intense behaviors, which sometimes lead to tics. However, there is the serious possibility that some of the major findings are unique to the present sample of participants, and not generalizable. Given the inherent difficulties with this kind of research it is important that the findings will be replicated in future research.

Cardiac surgery was more often significantly related to discrete behaviors than heart defects in general. This seems to be in accordance to Lin et al. [1987] who stressed the importance to divide the cardiological manifestations, especially those that are simple atrial septal defects and minor cardiological problems, to those that are major cardiological defects and larger atrioventricular septal defects. In the present study 12 of 19 participants with heart defects underwent cardiac surgery. These 12 participants may be expected to have major cardiac defects. The seven participants with heart defects who did not had an operation can be thought of participants with minor heart defects. This distinction is in accordance with Blake et al. [1990], who defined major and minor heart disease by the fact whether surgery was needed or not. Since cardiac surgery had more significant associations with behavior and behavioral problems than heart defects only, we found a comparable distinction as Lin et al. [1987].

In nonhandicapped children congenital heart disease is known to have effects on cognitive, psychological and behavioral development. Academic difficulties and cognitive deficits are not uncommon [Griffin et al., 2003; Van Rijen et al., 2003; Bass et al., 2004; Shillingford and Wernovsky, 2004]. Less is known about the behavior after heart disease in children with developmental delay, as in children with CHARGE. So one can only hypothesize what causes the aforementioned behaviors. Firstly, heart patients are physically more vulnerable, and lack energy or resilience, which prevents them from showing vivid behavior or more extreme externalizing behavior. The lack of problem behavior might be due to reduced vitality in post-surgery heart patients. In nonhandicapped children one can find some evidence for this hypothesis in the fact that the number of operations and severity of the cardiac defect are related to internalizing behaviors [Utens et al., 1998; Gupta et al., 2001; Yildiz et al., 2001]. Children with a history of cyanosis are especially at risk for significant impairments [Gupta et al., 1998; Griffin et al., 2003]. Secondly, it could be that

persons with CHARGE syndrome and heart defects show primarily internalizing problem behaviors. In nonhandicapped children with heart disease covert behaviors such as depression, anxiety, and fears were reported [Gupta et al., 1998, 2001]. In general, these behaviors are difficult to notice by others, especially when language is also delayed, as was the case in the majority of participants in the current sample. Moreover, whenever participants are not able to give self-reports or fill in questionnaires, these intrapsychic behaviors will go largely unnoticed. Consequently, problem behavior in CHARGE syndrome might be underscored. Lastly, children with CHARGE and heart defects might be treated differently than children with CHARGE without heart defects. For instance they might be subject to less demands and lowered expectations but at the same time receive ample parental attention and support. To study this hypothesis, teaching and child rearing practices need to be included in future prospective research, as was done in studies on social support and parental stress of parents of nonhandicapped children with congenital heart disease [Davis et al., 1998; Visconti et al., 2002].

This study showed that cerebral and neurological disorders not only affected intellectual outcome [cf. Raqbi et al., 2003] but also the behavior of persons with CHARGE, because the participants with cerebral abnormalities were more withdrawn, showed more intense reactions to external stimuli and had lower mood levels. Heart defects and heart surgery, however, seemed only to affect overt behavior and not intellectual functioning. Lin et al. [1990] found that the presence of CNS malformations was most strongly associated with choanal atresia. This association was not found in the current study. Specific information on cerebral and neurological disorders was not gathered in this study. It is therefore not known whether cerebral defects were predominantly forebrain malformations as in Lin et al. [1990]. Whether heart defects and surgery also affected poor life expectancy as in Tellier et al. [1998] has not been studied, because for obvious reasons only surviving persons were included.

The results from the analyses with cerebral abnormalities and heart defects showed that the symptoms needed for syndrome delineation differ from the symptoms important for behavioral variation. Heart defects and subsequent surgery, cerebral abnormalities, and or central nervous system (CNS) dysfunction are not major but minor signs of CHARGE. From a genetics point of view it makes sense to reckon heart defects among the minor signs because it results from relatively nonspecific blastogenic defects. Mental retardation, as the operationalization of CNS dysfunction, is also a minor sign because it is poorly explained on an anatomical or histological basis [Verloes, 2005]. From a behavioral point of view heart defects, heart surgery, and

cerebral abnormalities seem more important, especially because both can independently and in combination lead to negative developmental sequelae.

The results showed, in accordance with Hartshorne and Cypher [2004] and Raqbi et al. [2003] that the number of operations and hospitalizations was not associated with behavioral problems, but total length of hospitalization was. Children who spent more time in hospital had less internalizing problems (anxious/depressed, withdrawn, thought problems, internalizing T-score), and also less delinquent behavior. The explanation could be that these children were more vulnerable and ill, and, as a result, delinquent behavior is impossible to perform, and internalizing problems hard to observe in this group. Alternatively, because of weak physical health parent-child interactions might have been quantitatively and qualitatively different, which might have affected the children's behavior.

One of the research questions concerned differences between persons with CHARGE with none or few and more behavioral problems. Only the presence of heart defects and cardiac surgery was associated with the number of behavioral problems. So, for the number of behavioral problems heart defects and cardiac surgery seem to be relevant and other medical conditions are not. However, other medical conditions might lead to more early deaths as was shown by Blake et al. [1990], Tellier et al. [1998], and Issekutz et al. [2005]. Blake et al. [1990] had a mortality rate of 26% (13 of 50 patients). Of those who died most succumbed in the first year of life, with aspiration of secretions being the major incremental risk factor. Tellier et al. [1998] found that of 47 patients with CHARGE syndrome 23 (49%) died early, mostly before the age of 6 months (83%). Issekutz et al. [2005] had a mortality rate of 13% (10 of 77 patients). The current study only dealt with surviving children. Consequently, the effect of medical conditions can only be studied as far as they are not lethal. Tellier et al. [1998] found that male gender, tracheo-esophageal fistula, midline CNS malformations, and bilateral choanal atresia were significantly more predominant in the children with CHARGE who died early. In the Blake et al. [1990] study bilateral posterior choanal atresia combined with cyanotic heart disease or tracheo-esophageal fistula seemed to predispose to a poor outcome with regard to mortality. With the exception of CNS malformations the above mentioned medical defects were not significantly related to developmental outcome in the current study.

Note, that the present study did not confirm a significant association between medical conditions and autism [cf. Hartshorne and Cypher, 2004; Hartshorne et al., 2005a]. Autism and blindness often coincide, although visual impairment or blindness alone cannot explain the high prevalence of autism in CHARGE syndrome. For instance, Fernell et al. [1999] found autism in three children with CHARGE of whom two did not have coloboma nor low vision. In our opinion the large number of autistic features found in CHARGE syndrome [see Hartshorne and Cypher, 2004; Graham et al., 2005; Hartshorne et al., 2005a; Smith et al., 2005; Strömland et al., 2005] needs to be interpreted with caution. Only Hartshorne et al. [2005a] used a questionnaire that had norms for deafblind persons, the other studies did not. Furthermore, it is very hard to decide whether the behavior of persons with CHARGE is really autistic or does only resemble autistic behavior in appearance but not in function, since the classifying behaviors might be the same but the underlying mechanisms are not. The pathogenesis of heterogeneous etiologies may result in single outcomes such as autistic-like behaviors, while the autistic-like features might only be a single outcome superficially. This correspondence might be only quantitative. Autism and deafness or blindness show overlapping characteristics such as delays in language acquisition, peculiarities in word use and social difficulties in peer relations. Qualitatively, however, there are subtle differences in cause, pathogenesis, manifestation, and persistence of these behaviors [see Jure et al., 1991; Hobson and Bishop, 2003; Knoors and Vervloed, 2003; Pérez-Pereira and Conti-Ramsden, 2005]. Note also that developmental differences imposed by sensory limitations can be mistaken for psychopathology. At the same time differences may be wrongly attributed to sensory impairment and their ramifications overlooked [Smith et al., 2005].

Several lines of investigation are possible for future behavioral research in CHARGE. Firstly, prospective longitudinal research is needed to truly understand the risk factors for behavior in CHARGE. More homogenous cohorts should be formed with regard to CHARGE symptoms in order to be able to assess the effect of discrete medical symptoms on behavior. Persons with CHARGE who thrive well should also be included. An important distinction would be to separate the persons with CHARGE with and without intellectual disabilities. By studying also the context in which these persons live it should be possible to answer the question raised by several authors whether the behavior of persons with CHARGE is adaptive or pathological [see Brown, 2005; Hartshorne et al., 2005b; Salem-Hartshorne and Jacob, 2005]. It would also be interesting to see whether the amount of social support and parental stress affects behavior in persons with CHARGE syndrome as it does in children with congenital heart disease [Davis et al., 1998; Visconti et al., 2002]. Recently, Nicholas [2005] in a case study suggested that attention and executive functioning might be at risk in CHARGE syndrome. Research on more than one subject is needed to study this possible relationship between cerebral dysfunction in CHARGE and executive functioning.

Many children with CHARGE have communication problems and are not properly understood by their parents or care takers [Daelman, 2003]. We agree with Van Dijk and De Kort [2005], and Thelin and Fussner [2005] that early intervention with regard to language and communication is needed. Although other problem behaviors, such as autistic features, tics, stereotyped behavior and emotional instability, occur often, they do not seem to be a distinct feature in CHARGE syndrome, because a lot but not all persons with CHARGE syndrome show them. The clinical observation that behavioral problems occur frequently should not contaminate our view on individual variation within CHARGE syndrome, because survey studies are inadequate in helping to understand the problems of a particular individual [Van Dijk and De Kort, 2005].

## ACKNOWLEDGMENTS

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