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Quality of Life in Adolescents and Adults with CHARGE Syndrome

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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. © 2016 Wiley Periodicals, Inc.

Key words: CHARGE syndrome; quality of life; development; adolescent; adult

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INTRODUCTION

CHARGE syndrome, a genetic condition most often caused by a mutation in the *CHD7* gene, affects multiple organs and sensory systems [Blake and Prasad, 2006; van Ravenswaaij-Arts et al., 2015]. The impairments result in many medical, physical, developmental, and behavioral challenges for these individuals [Blake et al., 1998; Hsu et al., 2014]. Although some infants and young children do not survive the first postnatal months and early years, many grow up to live relatively healthy lives [Blake et al., 2005; Blake and Prasad, 2006]. As CHARGE association was only first described in 1979, there is limited research focusing on the specific difficulties encountered as an individual with CHARGE syndrome grows into adolescence and adulthood [Hall, 1979; Blake et al., 2005; Searle et al., 2005; Forward et al., 2007].

A previous study identified numerous new issues that first presented after childhood in CHARGE syndrome, including late pubertal development, scoliosis, sleep apnea, intermittent abdominal pain, retinal detachment, cataracts, migraines, seizures, urinary tract infections, hypoglycemia, and psychiatric and behavioral diagnoses [Blake et al., 2005]. Adolescents and adults with this genetic syndrome also reported little independence with complex tasks such as cooking, shopping, and managing finances [Blake et al., 2005].

Another study investigating older individuals with CHARGE syndrome reported a high incidence of bone issues and delayed puberty, as well as a high failure to meet the recommended calcium and vitamin D daily nutritional intake [Forward et al., 2007]. A case report of a 33-year-old with CHARGE syndrome revealed that gallstones, osteoporosis, and delayed puberty were new medical issues that arose in adolescence [Searle et al., 2005]. As the diagnosed CHARGE syndrome population ages, there is a need for continued investigation of issues regarding adolescence and adulthood.

The life expectancy of many genetic syndromes has been increasing in recent years, resulting in more and more individuals living well beyond adolescence and into late adulthood [Coppus,

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2013; Dykens, 2013]. Therefore, investigations of the natural history of a genetic syndrome, including aging, challenges across the lifespan, and new physical and mental health issues that arise, are critical. Several studies on older populations with syndromes such as Prader–Willi [Sinnema et al., 2012], Williams [Cherniske et al., 2004; Marler et al., 2005], Noonan [Smpokou et al., 2012], and Turner syndrome [Sutton et al., 2005] have been conducted, but little is known about CHARGE syndrome. A recent review highlighted that research on aging, health, and mortality in adults with rare syndromes with intellectual disability is lacking, and should be pursued as it reveals new insights into phenotypic manifestations and treatment options that differ from infants and children with the same genetic disorder [Dykens, 2013].

There is also a need to investigate the quality of life in CHARGE syndrome. Quality of life was first defined as the development of well-being in five areas: physical, material, social, emotional, and productive [Felce and Perry, 1997]. This has been a growing topic of research in the area of genetic syndromes. Recent studies have investigated quality of life among individuals with Velocardiofacial syndrome [Looman et al., 2010], Noonan syndrome [Binder et al., 2012], Prader–Willi syndrome [Mazaheri et al., 2013], Down syndrome [van Gameren-Oosterom et al., 2011], and Turner syndrome [Cohen and Biesecker, 2010; Taback and Van Vliet, 2011].

Previous studies have demonstrated mixed results regarding the quality of life among different genetic disorders [Cohen and Biesecker, 2010]. Children with Velocardiofacial syndrome were found to have a lower quality of life than healthy children and children living with chronic conditions [Looman et al., 2010]. Adults with Noonan syndrome had a higher rate of mortality, lower education, and lived more frequently without a partner [Binder et al., 2012]. Adolescents with Turner Syndrome were found to have a lower quality of life in terms of physical functioning in comparison to typically developing adolescents [Taback and Van Vliet, 2011]. Each genetic syndrome differed in their quality of life, as well as their physical and mental health manifestations as they aged, prompting an investigation in CHARGE syndrome.

The current study explored the areas of physical, emotional, and productive well-being, in addition to quality of life, in adolescents and adults with CHARGE syndrome. In general terms, we wanted to know what life looked like for individuals with CHARGE syndrome as they began to age.

MATERIALS AND METHODS

Participants

Individuals with CHARGE syndrome aged 13 years or older were invited to be included in this study. Participants were recruited in-person at an International CHARGE Syndrome Foundation conference and through the Deafblind program at the Perkins School for the Blind.

Procedure

Ethical approval for this study was obtained through the IWK Health Centre Research Ethics Board in Nova Scotia, Canada. All measures were completed by the participants and/or their caretakers, who were either interviewed in-person or over the telephone, or who completed the surveys independently and returned them. Two measures were used to gather information (Appendix SA). The first was an informational questionnaire used to gather a variety of information including medical, psychological, and developmental histories. This measure also included an adapted Impact of Childhood Neurologic Disability Scale. Second, in order to evaluate quality of life, the Centers for Disease Control and Prevention (CDC) Health-Related Quality-Of-Life (HRQOL) measure [Centres for Disease Control and Prevention Health-Related Quality of Life-14 'Healthy Days Measure', 2011] was adapted for use.

Informational Questionnaire

This questionnaire first assessed the prevalence of CHARGE syndrome major and minor diagnostic features. Second, participants were asked to report timing of developmental milestones or current levels of functioning in the areas of mobility, communication, hearing, and vision. Description of living situation, type of school attended, and type of vocational position held were also requested. Participants were asked to indicate specialists with whom they consulted, and any behavioral or psychiatric diagnoses, and new medical issues. Participants were asked about current levels of independence of functioning on daily living tasks. They rated their level of independence on a four-point Likert scale: 1 = no independence, 2 = a little independent, 3 = somewhat independent, 4 = mostly independent. Lastly, participants were asked to rate how much sensory impairment, behavior, ability to think and remember, balance, and overall health affected various areas of their life in the past 3 months. This was adapted from the Impact of Childhood Neurologic Disability Scale [Camfield et al., 2003]. Although the adapted version of this questionnaire had not been previously evaluated for validity and reliability, when investigating a specific syndrome such as CHARGE syndrome, valid and reliable tools are not available. Therefore, it was necessary to use this investigator-developed and adapted tool in order to gather information.

Health-Related Quality of Life Questionnaire

This scale, adapted from the HRQOL 14-item measure of the CDC [Centres for Disease Control and Prevention Health-Related Quality of Life-14 'Healthy Days Measure', 2011], included items that measured health-related quality-of-life over the previous 30-day period (Appendix SA). Participants were asked about overall physical and mental health and the impact of these on ability to do usual activities (e.g., self-care, work, recreation), as well as the impact of difficulties relating to having CHARGE syndrome (e.g., pain, depression, anxiety, lack of sleep).

Analyses

Information questionnaires were analyzed using descriptive analysis of closed-ended questions. Continuous variables were expressed as mean (M) ± standard deviation (SD) and categorical variables were expressed as frequency (N) and percentage (%). Correlations between sleep problems and anxiety, self-abuse,

conduct problems, and autistic-like behaviors were analyzed using a Spearman's rank-order correlation. A *P*-value of 0.05 or less was regarded as statistically significant. All analyses were done in SPSS Version 20.0.0 (IBM® SPSS© Statistics, 1 New Orchard Road Armonk, NY).

RESULTS

Participants

A total of 53 adolescents and adults with CHARGE syndrome (33 male, 62%) were included in this study. Ages ranged from 13 to 39 years. There were 22 individuals (42%) between the ages of 13 and 17 years, 21 individuals (40%) between the ages of 18 and 25 years, and 10 individuals (19%) between the ages of 26 and 39 years. Forty-nine participants were scattered geographically across the United States, two were from Australia, one from Denmark, and one was from South Africa. Four participants were attending Perkins School for the Blind, and were recruited by staff there. The remaining 49 were recruited at the International CHARGE Syndrome Conference.

Diagnostic Features

The incidence of major and minor diagnostic features of CHARGE Syndrome found in this study sample are listed in Table I, alongside the frequency of these features in the general CHARGE syndrome population depicted by a recent review [Hsu et al., 2014]. This sample reported a higher frequency of cleft lip and palate (42%) compared to the estimated 15–20% frequency in the general CHARGE population.

TABLE I. Diagnostic CHARGE Syndrome Features of the Study Sample, Compared to General CHARGE Syndrome Population Frequencies

Criterion	Study sample number of individuals[a] (%)	Estimated CHARGE syndrome population frequencies[b] (%)
Ear abnormalities	47 (89)	90–100
Growth deficiency	45 (85)	70–80
Developmental delay	45 (85)	70
Choanal atresia/stenosis	34 (64)	65
Cranial nerve dysfunction	44 (83)	50–90
Coloboma	41 (77)	75–90
Distinctive facial features[c]	40 (76)	*
Heart defects	39 (74)	50–85
Genital hypoplasia	32 (60)	50–70
Cleft lip and/or palate	22 (42)[d]	15–20
Urinary tract infections	14 (26)	*
Abnormal temporal bones	12 (23)	*
Tracheoesophageal fistula	5 (9)	*

*Frequency of features not reported.
[a]Sample frequencies are based on parent responses for the current sample.
[b]Medical characteristics and estimated population frequencies are from Hsu et al. [2014].
[c]Includes square face, prominent forehead, flat midface [Hsu et al., 2014].
[d]A much higher frequency than the estimated CHARGE syndrome population frequency.

Developmental and Physical Characteristics

The age at walking and pubertal milestones are displayed in Table II. The means of communication (e.g., verbal, sign language), and the severity of impairment of hearing and vision are also reported. The majority of individuals began walking around the age of 3 years. Pubertal development was incomplete for three-quarters of the study population. Most individuals had delayed and incomplete puberty. A quarter had tried growth hormone and almost half had tried puberty hormone replacement.

The main means of communication was sign language. Hearing and vision impairment were severe as almost three-quarters of the study population had severe to profound hearing loss, and almost half were legally blind or had total blindness in at least one eye.

School, Living, and Work Arrangements

Twenty-six individuals (49%) attended a mainstream school. Seven individuals (13%) attended a residential school and another seven (13%) attended a deaf school. School adaptations were the use of a resource room (n = 8), special needs classroom (n = 15), an aid/interpreter (n = 13), and a deaf-blind program (n = 7). Mean reading levels were grade 4 (SD 4.8) with 20 individuals (38%) unable to read. Math levels also had a mean level of grade 4 (SD 4.7), with 17 individuals (32%) unable to do math. Sixteen individuals (30%) were able to receive educational training beyond high school, which included attending college (n = 9), receiving vocational training (n = 6), and completing a graduate degree (n = 1).

Most individuals lived in a family home (n = 29, 55%), while two (4%) lived in a group home. Eight individuals (15%) lived independently with and without support. Seven of these eight individuals who were able to live independently represented almost a quarter (n = 7/31, 23%) of the adolescents and adults who were 18 years and older.

Medical Specialists Involved in Current Care

Table III depicts the frequency of different types of medical specialists involved in the individuals' current care. The most common medical specialist that followed adolescents and adults with CHARGE syndrome in this study was an Ear–Nose–Throat surgeon. The next three most common specialists were endocrinologists, ophthalmologists, and cardiologists.

New Medical Issues

The most common medical issues that began in adolescence and adulthood were bone health issues (n = 21, 40%), sleep apnea

TABLE II. Developmental and Physical Characteristics of the Study Sample of 53 Adolescents and Adults With CHARGE Syndrome

Characteristics		Mean (SD)	Range
Age at walking	Years	3.4 (3.0)	1–11
	Category	**N (%)**	**N (%)**
Puberty	Incomplete	40 (76)	
	Delayed	35 (66)	
	Tried growth hormone therapy	13 (25)	
	Tried puberty hormone	22 (42)	
Communication	Only sign	21 (40)	
	Primary verbal	20 (38)	
	Sign and verbal	6 (11)	
	Gestures	4 (8)	
	Pictures	1 (2)	
Hearing impairment		Left ear	Right ear
	Profound loss	30 (57)	23 (43)
	Severe	9 (17)	8 (15)
	Moderate	8 (15)	14 (26)
	Mild loss	4 (8)	5 (9)
	Normal	2 (4)	3 (6)
Vision impairment		Left eye	Right eye
	Total blindness	4 (8)	6 (11)
	Legally blind	20 (38)	11 (21)
	Moderate	6 (11)	10 (19)
	Mild	9 (17)	12 (23)
	Normal	10 (19)	10 (19)

(n = 13, 25%), and retinal detachment (n = 8, 15%). Others included seizures/epilepsy (n = 3, 6%) and urinary tract infections (n = 2, 4%). Twenty-one individuals (40%) also reported "other" new medical issues.

TABLE III. Current Medical Specialists Consulted by 53 Adolescents and Adults With CHARGE Syndrome in This Study[a]

Specialist	N (%)
Ear nose throat	25 (47)
Endocrinologist	22 (42)
Ophthalmologist	19 (36)
Cardiologist	18 (34)
Neurologist/neurosurgeon	12 (23)
Psychologist/psychiatrist	10 (19)
Audiologist	10 (19)
Gastroenterologist	9 (17)
Orthopedic surgeon	8 (15)
Deafblind specialist	8 (15)
Physical therapist	6 (11)
Pulmonologist	6 (11)
Retinal specialist	5 (9)
Urologist	5 (9)
Osteopath	2 (4)
Other	25 (47)

[a]Participants identified one or more medical specialists they were currently consulting.

Psychological and Behavioral Issues

Adolescents and adults had more difficulty with sleep (59%) than with any other psychological or behavioral issue (Table IV). Approximately half of participants struggled with aggression, tactile defensiveness, obsessive-compulsive behaviors, self-injurious behaviors, and anxiety. Problems with sleep significantly correlated with anxiety ($r\varphi = 0.30$, $P = 0.04$), self-abuse ($r\varphi = 0.31$, $P = 0.03$), conduct problems ($r\varphi = 0.32$, $P = 0.02$), and autistic-like behaviors ($r\varphi = 0.44$, $P < 0.001$).

Level of Independence

The highest levels of independence in adolescence and adulthood were reported in personal care tasks, such as toileting, dressing, and washing ones' self (Table V). Over half of the individuals reported no independence in managing their own finances, getting themselves to school and work, and shopping. Despite a high level of independence reported for toileting, dressing, and washing ones' self, 53% of individuals still needed help for personal care needs (Table VI). Seventy-nine percent needed help for routine activities (Table VI).

Quality of Life

Individuals rated their health-related quality of life as fair, good, very good, or excellent, with most (40%) rating it as "good" (Table VI). A quarter of adolescents and adults reported that their mental/physical health restricted their daily activities. On average, individuals reported that in the past month they felt full of energy for almost 3 weeks, but did not get enough sleep or rest for over a week (Table VI). Individuals also reported feeling worried/anxious, and poor mental health for an average of 5 days in the past month (Table VI).

The most common interests outside of school were sports, fitness, and swimming (n = 35), technology (e.g., TV [n = 18],

TABLE IV. Psychological and Behavioral Issues Reported by 53 Adolescents and Adults With CHARGE Syndrome in This Study[a]

Psychological/behavioral issue	N (%)
Sleep	31 (59)
Aggression	27 (51)
Tactile defensiveness	27 (51)
Obsessive compulsive	26 (49)
Self-injurious	25 (47)
Anxiety	24 (45)
Attention deficit	14 (26)
Autism spectrum	14 (26)
Tics	9 (17)
Conduct disorder	7 (13)
Depression	4 (8)
Other	4 (8)

[a]Participants identified one or more psychological and/or behavioral issue they were experiencing.

TABLE V. Levels of Independence at Daily Living Skills in 53 Adolescents and Adults With CHARGE Syndrome, Reported in Frequency (N)

Skill	Most	Some	Little	None	No response
Toileting self	36	6	6	5	0
Dressing self	32	10	6	4	1
Washing self	27	7	11	8	0
Own cleaning	13	11	12	17	0
Getting self to school/work	12	6	4	31	0
Own cooking	7	9	14	23	0
Own shopping	6	7	12	27	1
Own finances	5	3	9	36	0

computer [n = 17], videogames [n = 13]), and interacting with animals (n = 11).

This study sample reported more *mentally* unhealthy days per month (mean 5.0, SD 8.0 days) than the general U.S. population (mean 3.5 days, 95%CI 3.4–3.6) [,xps1Health-related quality of life (HRQOL) data," 2010] The mean *physically* unhealthy days per month were similar for both the study sample (mean 3.7, SD 6.8 days) and the U.S. population (mean 3.7 days, 95%CI 3.6–3.8).

TABLE VI. Number of Days in the Last Month Affected by Poor Physical and/or Mental Health of 53 Adolescents and Adults With CHARGE Syndrome

Health-related quality of life item	Count (n = 53)	Frequency (%)
Health is excellent	8	15
Health is very good	16	30
Health is good	21	40
Health is fair	8	15
Mental/physical health restricted daily activities	13/51	25
Need help for personal care needs	28	53
Need help for routine activities	42/51	79

Health-related quality of life item	Number of days in 1 month	Standard deviation
Felt very healthy and full of energy[a]	19.9	10.3
Not enough rest or sleep[b]	7.4	9.8
Worried, tense, or anxious[c]	5.2	7.0
Mental health not good[d]	5.0	8.0
Physical health not good[e]	3.7	6.8
Pain interfered with activities[f]	2.8	5.4
Sad, blue, or depressed[g]	2.3	3.4

[a]n = 45.
[b]n = 47.
[c]n = 40.
[d]n = 47.
[e]n = 51.
[f]n = 50.
[g]n = 41.

Sources of Activity Limitation

Hearing, vision, and balance problems limited daily activities for more than half of the study population (Table VII). Anxiety and emotions were the next most common limitations to activities. Other sources of limitation were problems with walking, sleeping, eating, and breathing.

CHARGE Characteristics Affecting Quality of Life

Table VIII displays the breakdown of how many participants identified certain CHARGE characteristics as affecting various parts of their life "a lot" in the adapted Impact of Childhood Neurologic Disability Scale. Overall health, behavior, and balance most affected the number of social activities in the individual's life. Sensory impairment most affected relationships with friends. The ability to think and remember most affected school and academics.

Table IX describes the quality of life in our study sample with CHARGE syndrome and various other genetic syndromes (e.g., Down syndrome, Turner syndrome). The quality of life between different genetic syndromes cannot truly be compared because of the different age ranges addressed, assessments, definitions of quality of life, and different areas of life addressed in each one. There is a wide range of quality of life described in each genetic syndrome.

Case Histories

To demonstrate the wide range of abilities, differences in quality of life, and types of issues faced in an older CHARGE syndrome population, two adult case histories are presented below.

TABLE VII. Major Sources of Limitations to Daily Activity Reported by 53 Adolescents and Adults With CHARGE Syndrome[a]

Source	Number of individuals (n)	Frequency (%)
Hearing	46	87
Vision	37	70
Balance	28	53
Anxiety	19	36
Emotions	19	36
Walking	18	34
Sleep	15	28
Eating	13	25
Breathing	13	25
Back or neck	9	17
Heart	7	13
Feet	4	8
Depression	4	8
Other	12	23

[a]Individuals reported one or more sources of limitations to their daily activities.

TABLE VIII. Quality of Life Questionnaire[a]: CHARGE Syndrome Factors for Which the 53 Adolescents and Adults Responded as Affecting Areas of Their Life "A Lot"[b]

Areas of life	Overall health (%)	Behavior (%)	Sensory impairment (%)	Balance (%)	Ability to think and remember (%)
Relationship with parents	15	27	23	9	17
Relationship with siblings	13	31	31	6	13
Relationship with partner	0	0	0	2	4
Relationship with friends	13	35	**45**	13	21
Social acceptance	16	**39**	38	11	25
Number of social activities	**20**	**39**	39	**15**	17
School/academics	12	33	38	13	**32**
Work life (n = 51)	4	12	18	4	11
Self-confidence	5	14	14	6	9
Family activities	10	22	19	9	11
Hope for self	13	24	27	6	19

Bolded numbers represent the highest percentage in each category.
[a]Adapted from the Impact of Childhood Neurologic Disability Scale.
[b]Number of respondents ranged from n = 42 to n = 53 for each category and area of life question.

Case 1. A 26-year-old male with CHARGE syndrome had bilateral retinal coloboma, bilateral choanal atresia, characteristic ear abnormalities, a small heart defect (VSD) at birth, and cranial nerve dysfunction, which resulted in difficulties such as problems with facial palsy, balance, swallowing, and smelling. His minor CHARGE syndrome physical features included genital hypoplasia, growth deficiency, developmental delay, distinct facial features, and missing semi-circular canals.

He used a combination of pictures, idiosyncratic behaviors, and sign language as his main form of communication. He had severe to profound hearing loss in both ears, and moderate to severe vision loss in both eyes. He first began to walk at the age of 7 years. Growing up, he attended his neighborhood schools with special education support. At the age of 26 years, he has neither literacy nor math skills.

Medical specialists that were currently involved in his care included an endocrinologist, physical medicine and rehabilitation specialist, physiotherapist, optometrist, and audiologist. New medical issues that began in adolescence and adulthood were bone health problems: osteopenia, osteoporosis, and kyphoscoliosis.

Pubertal development was delayed until age 18. He developed pubic hair at 19 years, completed testes development at 20 years, and began shaving when he was 25 years old, He had undergone puberty hormone treatment due to his delayed development. He also had current feeding difficulties, with an inability to chew. His parent reported some obsessive-compulsive-like behavior.

He was unable to complete any daily tasks with complete independence. He was somewhat independent with toileting and dressing himself. He needed full assistance with shopping, doing his finances, cooking, cleaning, and getting himself to school or work. He was able to live independently (in his own home) with 24-hr assistance and support.

Overall, his parent described his health as "good." His activity was limited by problems with hearing, vision, balance, walking, and his back or neck. He suffered frequent otitis media as a result of structural problems with his Eustachian tubes. His health was poor for 10 of the last 30 days. Pain interfered with his daily activities for 5 days of the month.

His work environment consisted of paid and volunteer activities, including filling bags of dog treats at a pet food store, washing menus at a local diner, and returning donated soda cans daily to raise funds for a charity. Although one-on-one support was necessary for transportation and physical needs, he had become virtually independent with these tasks, once on site.

Case 2. A 31-year-old female with CHARGE syndrome had bilateral choanal atresia, characteristic ear abnormalities, and cranial nerve dysfunction (including the absence of sense of smell). Growth deficiency was the only minor CHARGE syndrome physical feature. Verbal speech was her main form of communication. She had severe to profound hearing loss in both ears, and was farsighted. She first began to walk at the age of 2 years and 2 months old. School adaptations included a teacher of the Deaf and resource room support. Reading and math skills were at a college level.

Medical specialists that were currently involved in her care included an endocrinologist, nephrologist, audiologist, ophthalmologist, and geneticist. A pre-diabetic diagnosis was the only new medical issue arising after childhood.

Pubertal development was delayed until age 17, when she achieved menstruation with hormone therapy. She developed pubic hair at age 13, but did not achieve breast development, and breast implants were inserted at age 16. She was diagnosed with growth hormone deficiency at age 10, and received 5 years of hormone therapy.

She reported anxiety as a psychological issue, which she attributed to the stress of raising her child who also had CHARGE syndrome. She also indicated sleep difficulties.

She was completely independent in all activities of life. She was married, had a child with special needs, and had a graduate degree in school psychology. She indicated no special needs in her adult life.

She indicated that her health was "good," and that she felt healthy and full of energy about 20 of the past 30 days. However, she reported 7 nights of sleeping difficulty in the past 1 month. Her sensory impairment only interfered "a little" with her work

TABLE IX. Quality of Life Among Different Genetic Syndromes

Syndrome	CHARGE syndrome	Noonan syndrome	Velocardiofacial syndrome	Down syndrome	Prader–Willi syndrome	Turner syndrome
Authors	Current study	Binder et al. [2012]	Looman et al. [2010]	van Gameren-Oosterom et al. [2011]	Caliandro et al. [2007]	Tabak and Van Vliet [2011]
Measure	Adapted CDC health-related quality-of-life 14-item	Medical outcome study short form-36 questionnaire	PedsQL 4.0 generic core scales (23-item) and PedsQL multidimensional fatigue scale	TNO-AZL children's quality of life questionnaire	Short form-36 and child health questionnaire-parent form-50	Short form-36
Age (years)	13–39	25–58	2–18	8 years old	5–35	≥18
Quality of life (QoL)	QoL was reported as good (40%). Not getting enough sleep negatively affected QoL. Sleep significantly associated with anxiety, self-abuse, conduct problems, autistic-like behaviors. Wide range in functioning and development.	QoL not statistically different from a healthy reference cohort. Lowest in physical functioning and general health domains.	Lowest in school functioning and cognitive fatigue domains. Children with a learning disability had significantly more fatigue than children without learning disability.	Significantly more emotional and behavioral problems. Lower scores for gross motor skills, autonomy, social functioning, cognitive functioning.	Adults and children had significantly lower physical and mental QoL in most domains.	No significant differences in any QoL domains compared to reference sample.

life, and her overall health affected her relationships with family only "a little."

Her work environment was a full-time school psychologist position with a public school district.

DISCUSSION

This is the first study to investigate the quality of life in adolescents and adults with CHARGE syndrome. As in the case studies described above, features, symptoms, physical health, mental health, and levels of independence in CHARGE syndrome are greatly variable among individuals.

CHARGE Syndrome Characteristics

The adolescents and adults in this study population reported a higher frequency of cleft lip and palate in comparison to the general CHARGE syndrome population frequency [Hsu et al., 2014]. A higher frequency of orofacial clefts was similarly found in a previous study on adolescents and adults with CHARGE syndrome [Blake et al., 2005]. Cleft lip and palate may provide another passage for air, thus aiding in breathing as a neonate and improving survival [Blake et al., 2005].

Developmental Outcomes

The majority of individuals in this study relied solely on sign language. Several individuals used only gestures or pictures to communicate. This highlights the importance of communication adaptations throughout the entire lifespan of an individual with CHARGE syndrome.

Feeding difficulties are extremely common in infancy and childhood, and can persist into adolescence and adulthood [Issekutz et al., 2005; Hudson et al., 2015; Hudson and Blake, 2016]. Feeding issues were identified in this current study population of adolescents and adults, which caused difficulties in their daily living activities. Gastroenterologists and feeding therapists may need to be involved in the care of older individuals, even if these individuals had previously successfully transitioned from tube to oral feeding, or never had feeding interventions in infancy.

A previous study also found pubertal delay to be common in adolescents and adults with CHARGE syndrome [Issekutz et al., 2005]. Similar data on pubertal development was reported in our current study. Parents should be made aware that children with CHARGE syndrome are likely to experience delayed puberty, and that they may need to be followed by an endocrine specialist (as with bone density issues) as they transition into the teen years. The age at which individuals in this study began to walk was around 3 years old, which is consistent with previous findings in CHARGE syndrome [Dammeyer, 2012].

Living Situation and Work

Almost one-fourth of individuals in this sample, aged 18 years and older, were able to live independently, both with and without support. However, most individuals needed help with routine and personal care needs. Parents of children with CHARGE syndrome

should be given information about financial and instrumental programs for even adults with the most severe disabilities to live in their communities with appropriate support. For example, most states in the U.S. have funding waivers to support individuals with disabilities to have the support they need to live in their own home or apartment, even if 24-hr support is needed.

Many of the older individuals were able to receive education beyond high school, and one individual even completed a graduate degree. School adaptations that were found to be helpful included using a resource room; a special needs classroom; an aid, interpreter, or deafblind intervener; and a deafblind program. Most states in the United States will provide education for students with special needs until the age of 21, and one state (Michigan) provides this until age 26. This time would be well spent preparing the student to learn, live, and work in the community.

The type of work individuals participated in varied widely, including paid-work, volunteering, and internships. Examples of volunteering work included volunteering at a church, daycare, nursing home, parent's office, and at an animal shelter. Paid work included working at a grocery store, school bookstore, as a janitor, and at a hotel. Although a paid position in the community garners the most respect for the individual with severe disabilities, volunteer work is also helpful in making community connections, especially when the individual receives disability funding from the government. Individuals who are more capable, but have sensory or other impairments, should be encouraged to seek paid employment with necessary accommodations.

Specialists Needed in Adolescence and Adulthood

Little is known about the type and number of medical specialists needed in adolescence and adulthood in CHARGE syndrome. A previous study on adolescents and adults with CHARGE syndrome found that the top four specialists consulted were ophthalmology, ENT/audiology, endocrinology, and cardiology [Blake et al., 2005]. Further specialists consulted were psychiatry, orthopaedics, and neurology. This present study found the same top four specialists utilized, although lower frequency than the previous study. Between 53% and 93% of the previous study population used each of the top four specialists, while only 34–48% of the current study reported their use.

This current study also identified consultations with additional medical specialists, previously unreported. These include gastroenterologists, deafblind specialists, physical therapists, pulmonologists, retinal specialists, and osteopaths. These additions could be a result of the evolution of knowledge about CHARGE syndrome, as previous study participants were diagnosed at a time when little was known about medical outcomes. Now that more is known, families may be seeking information from these specialists earlier, and intervening with and resolving some of the medical issues before adolescence.

Of interest is the finding that although many mental health conditions were noted in the participants, few participants consulted mental health professionals. Although we do not know why, this could perhaps be explained by communication barriers or the numerous other medical appointments that the individuals must attend due to their complex health needs. Important mental health issues are not always addressed by the professionals and may get pushed to the side in favor of other medical issues. Individuals with CHARGE syndrome are often seen by fewer health professionals than are actually needed due to the extensive and fluctuating list of health care problems.

Pre-Existing and New Medical Issues in Adolescence and Adulthood

Psychological and behavioral issues. The most prevalent mental health difficulties in this study were aggression, tactile defensiveness, obsessive compulsive-like behaviors, and anxiety. Anxiety and emotional dysregulation were the major mental health limitations to daily activity. Mental and physical health restricted the daily activities of many individuals with CHARGE syndrome, and not getting enough sleep, feeling anxious, and having poor mental health interfered with QOL the most. The adolescents' and adults' overall health, behavior, and balance, most negatively impacted social activities and acceptance, as well as relationships with friends. Mental health problems were quite prevalent, but only 19% were seen by mental health specialists.

Sleep. Difficulty with sleep was the most prevalent issue reported in this study. The majority of individuals reported that a lack of rest and sleep affected their daily activities, for over a week each month. Sleep was also identified as a major limitation to daily activities. Sleep has been described as a major area of concern for individuals with other genetic syndromes. A recent review examining sleep in children with neurodevelopmental disabilities found that children with genetic syndromes represented more than 35% of the cases of children referred to a neuropsychiatric center for sleep disorders [Angriman et al., 2015]. This study included children with Down syndrome, Fragile X syndrome, Prader–Willi syndrome, Angelman syndrome, Rett syndrome, Smith–Magenis syndrome, cerebral palsy, and autism spectrum disorders. Further investigation is needed into sleep disorders and issues in CHARGE syndrome. A recent study on children with CHARGE syndrome also identified sleep as a major problem for half of the study population [Dammeyer, 2012].

Many individuals with CHARGE syndrome have restricted vision. Blindness and partial blindness are often associated with difficulty gaining light/dark cues to assist with melatonin release and circadian rhythm regulation [Skene and Arendt, 2007]. Strategies to help individuals with CHARGE syndrome fall and stay asleep may be helpful in addressing this common issue. Interventions such as improving sleep hygiene, for example, reducing screen time before bed, reducing the consumption of rich or sugary foods before bed, and following the same bedtime routine every night, may be helpful.

Sleep apnea has previously been identified as a common medical problem in children with CHARGE syndrome [Trider et al., 2012]. Sleep apnea was the second most common medical issue that first appeared after childhood in this current study, as well as a previous study [Blake et al., 2005]. Surveillance for the emergence of sleep apnea and associated consequences should be continued beyond childhood, into teenage and adult years in CHARGE syndrome. Previous studies on sleep in CHARGE syndrome have identified

that sleep breathing, along with initiating/maintaining sleep, and waking up from sleep were the most problematic areas for these individuals [Hartshorne et al., 2009].

Difficulties with sleep significantly correlated with anxiety, self-abuse, conduct problems, and autistic-like behaviors. Improving sleep may have the potential to positively impact these difficulties, and reducing anxiety-producing factors in the environment may also improve sleep.

Bone issues. Bone health issues, including low bone mineral density, scoliosis, and kyphosis, were the most common medical issue that began in adolescence and adulthood in the current sample. More activity and better nutrition, including adequate intake of vitamin D and calcium, might prevent bone deterioration and decrease the risk of osteoporosis in adulthood, therefore close consultation with an endocrinology is advised.

Quality of life. In this study, teens and adults with CHARGE syndrome and their caregivers reported a positive outlook on overall health. Mentally unhealthy days were greater than average, when compared with the U.S. general population, which may be partially explained by the high level of anxiety reported in our study population. Physically unhealthy days were similar to the general population. This seems astounding, given the physical difficulties and significant burden of malformation and sensory impairment frequently faced by this population. Slow adaptation to physical difficulties may play a part in this.

However, mental and physical health restricted the daily activities of many individuals. Not getting enough sleep, feeling anxious, and having poor mental health interfered with quality of life the most. The adolescents' and adults' overall health, behavior, and balance, most negatively impacted social activities and acceptance, as well as relationships with friends. The ability to think and remember most negatively affected school and academics.

Adolescence is a time of intense peer and social interactions. Developmental delay and communication difficulties, including severe hearing and vision difficulties, may further compound difficulties with relationships. A previous study found that difficulties in reading facial expression of emotion was a social cognition deficit in individuals with Prader–Willi syndrome [Whittington and Holland, 2011]. Another study reported that children with special health care needs who had hearing impairment had more difficulties making friends and had more feelings of anxiety and depression than children with special health care needs but without hearing impairment [Russ et al., 2013].

Most individuals with CHARGE syndrome have a degree of hearing and vision impairment. These sensory deficits appear to contribute to difficulties with social interactions and acceptance. Further complicating social interactions and acceptance for some with CHARGE syndrome is unilateral or bilateral facial palsy, which can significantly or totally mask facial expressions, thereby making it difficult to express emotions to others in speech or sign language. The majority of participants indicated cranial nerve anomalies, which may include facial palsy (cranial nerve VII dysfunction).

Pain was also identified as interfering the quality of life in this study population. Pain can often go unrecognized, especially in individuals with hearing and communication difficulties such as those with CHARGE syndrome. Pain has recently been highlighted as an under-recognized clinical problem in other genetic syndromes such as Noonan syndrome and Down syndrome [Barney, 2015; Vegunta et al., 2015].

Barriers to daily activity were physical health (hearing, vision, and balance difficulties) and mental health (anxiety and emotions). Therefore, appropriate adaptations to accommodate sensory deficits of individuals with CHARGE syndrome should extend through the lifespan. Limitations due to anxiety and emotions may not be as prevalent during childhood, and therefore are important to identify and treat, using first environmental adaptation, and then medical intervention if necessary, during adolescence and adulthood.

Limitations

This study relied on the parents' or adolescent/adults' with CHARGE syndrome recall of medical, social, and educational information. The validated CDC–HRQOL measure and Impact of Childhood Neurologic Disability Scale were also adapted for use by this study population, and were not tested for validity or reliability after its adaptation. Lastly, participants were recruited through an international CHARGE syndrome foundation and a residential Deafblind program. This may not be a representative sample as those with milder features of CHARGE syndrome and those who are not as medically involved may not have been a part of these catchment areas.

Future Directions

Future research should examine adults with CHARGE syndrome as an independent population, without the confounding factor of adolescence and school issues. Future investigations should investigate treatments for sleep difficulties and anxiety, and their effect on the quality of life of individuals with CHARGE syndrome.

CONCLUSIONS

Hearing and vision impairment is extensive in adolescents and adults with CHARGE syndrome, with most having severe to profound loss. Sleep issues, aggression, tactile defensiveness, obsessive compulsiveness, and anxiety were common, although very few individuals were being followed by mental health professionals. New medical issues that appeared after childhood were bone health problems and sleep apnea. Sleep issues also significantly correlated to anxiety, self-abuse, conduct problems, and autistic-like behaviors.

Sensory deficits (hearing, vision, balance), anxiety, and emotional dysregulation limited daily activity. Areas of life that were most impaired were relationships with friends, social activities, and social acceptance. Our study sample reported more mentally unhealthy days than the U.S. population, but a similar number of physically unhealthy days.

Most participants reported a positive outlook on their overall health, including several individuals who completed high school and college education and held volunteer and paid work positions. The quality of life for an individual is not purely determined by a diagnosis of CHARGE syndrome, but extends much further into the realms of social, community, and paid supports, as well as quality and location of supports provided to the individual. Sleep issues and anxiety were highly prevalent in our study population and are potential areas for intervention to improve overall health and quality of life.

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