American Journal of Medical Genetics Part A 143A:839–845 (2007)

Risk Factors for Poor Bone Health in Adolescents and Adults With CHARGE Syndrome

Karen E. Forward,[1] Elizabeth A. Cummings,[2] and Kim D. Blake[2]*

[1]Dalhousie University Medical School, Halifax, Nova Scotia, Canada
[2]Department of Pediatrics, IWK Health Center, Halifax, Nova Scotia, Canada

Received 17 May 2006; Accepted 20 November 2006

CHARGE syndrome, is associated with genital hypoplasia, feeding difficulties and delayed puberty. In this study we examined the prevalence of risk factors for poor bone health in adolescents and adults with CHARGE. Questionnaires assessing fracture history, dietary intake of calcium and vitamin D, pubertal status and activity level using the Habitual Activity Estimation Scale (HAES) were completed by caregivers. Control data were collected for the HAES. When available, reports from dual-energy X-ray absorptiometry (DEXA) were obtained. Thirty individuals with CHARGE syndrome (n = 15 males; n = 15 females; age range 13 to 34 years; mean age 19.6 years) were recruited. Traumatic bony fractures were identified in 30% of the population. The recommended nutritional intake (RNI) for calcium and vitamin D were not met by 41% and 87% of the population, respectively, and 53% required past tube feeding. Delayed puberty was experienced by 87% with only 4 individuals (2 female, 2 males) having experienced normal puberty. Hormone replacement therapy (HRT) was taken by 33% of females and 60% of males. According to the HAES, adolescents with CHARGE syndrome (13–18 years) were significantly less active than controls. Individuals with CHARGE syndrome age 19 and older were also less active than controls, although this difference was not significant. DEXA scan data was obtained, however, due to small sample size (n = 10) and confounding variables (i.e., short stature, pubertal stage, height, weight), it was difficult to draw meaningful conclusions. Feeding difficulties, inactivity and hypogonadism are predisposing factors for the development of poor bone health among individuals with CHARGE syndrome. Education is necessary to raise awareness regarding the importance of HRT, proper nutrition and weight-bearing activity for healthy bone development and maintenance in individuals with CHARGE syndrome.

Key words: CHARGE syndrome; CHARGE association; adolescent; bone density; hypogonadism; HAES; osteoporosis; hormone replacement therapy (HRT); bone health

How to cite this article: Forward KE, Cummings EA, Blake KD. 2007. Risk factors for poor bone health in adolescents and adults with CHARGE syndrome. Am J Med Genet Part A 143A:839–845.

INTRODUCTION

Hall originally described CHARGE syndrome as a non-random collection of congenital anomalies in 1979 [Hall, 1979]. The incidence of CHARGE syndrome has varied in the literature with one epidemiological study reporting 1:8,500 live births [Issekutz et al., 2005]. The diagnosis of CHARGE syndrome can be made clinically by recognizing the major, minor and occasional clinical features of the syndrome [Blake et al., 1998]. The four major criteria (coloboma, choanal atresia, characteristic ear anomalies and cranial nerve dysfunction) are clinically diagnostic of CHARGE syndrome when clustered together [Blake et al., 1998]. Minor criteria include genital hypoplasia, developmental delay, cardiovascular malformations (i.e., atrioventricular canal defect, tetralogy of Fallot), growth delay, orofacial cleft, tracheoesophageal-fistula and distinctive facial characteristics. Many of the occasional criteria (i.e., abdominal abnormalities, thymic/parathyroid hypoplasia or anomalies of the kidney, spine, nipple, or hand) are now thought to be more common than previously suggested [Issekutz et al., 2005]. In addition, CT scan or MRI may be used to identify semicircular canal agenesis and/or hypoplasia which is frequently evident in individuals with CHARGE syndrome and may be pathognomonic [Amiel et al., 2001; Graham, 2001].

*Correspondence to: Kim D. Blake, M.D., Department of Pediatrics, IWK Health Center, 5850/5980 University Avenue, PO Box 3070, Halifax, NS B3J 3G9. E-mail: kblake@dal.ca
DOI 10.1002/ajmg.a.31670

Several genetic anomalies have been documented among patients with the features of CHARGE syndrome [Graham, 2001; Sanlaville et al., 2002; Lalani et al., 2003]. Of these, a chromodomain helicase DNA-binding protein mutation on the *CHD7* gene of chromosome *8q12* represents the likely cause of CHARGE syndrome for most affected individuals, with 58% showing identifiable mutations [Vissers et al., 2004; Lalani et al., 2006]. Expression of the *CHD7* gene early in development likely contributes to pharyngeal arch, neural crest, internal ear and central nervous system development [Sanlaville et al., 2006].

Many individuals with CHARGE syndrome demonstrate incomplete or delayed puberty [James et al., 2003; Blake et al., 2005; Issekutz et al., 2005]. This pubertal delay is particularly marked in males- many of whom require hormonal therapy before developing secondary sexual characteristics [Blake et al., 2005]. The rise in sex-steroids accompanying puberty is also essential for optimal bone mineralization and accrual. To achieve peak bone mass in early adulthood, sex steroids must be present in sufficient quantities to promote bone accumulation and bone mineral deposition. Adolescents failing to achieve adequate bone mineralization during this developmental window may become increasingly susceptible to osteopenia, osteoporosis and fractures [Rabinovich, 2004]. The link between poor bone health and delayed pubertal status has been previously established in chronic conditions such as Prader–Willi syndrome [Butler et al., 2001], galactosaemia [Rubio-Gozalbo et al., 2002], Turner syndrome [Gravholt et al., 2003], and chronic kidney disease [Cunningham et al., 2004]. This link, however, has not yet been established in patients with CHARGE syndrome.

A nutritionally complete diet containing the recommended daily amounts of calcium and vitamin D is vital for the development of healthy bones and the prevention of osteoporosis. Achieving adequate nutritional intake, however, can be difficult for individuals with CHARGE syndrome, who may have severe gastroesophageal reflux [Blake et al., 1993], aspiration [Blake et al., 1990], swallowing dysfunction, and cranial nerve abnormalities [White et al., 2005]. Often extensive, complex medical management and multiple surgeries are required in childhood. Many rely on nasogastric or gastrostomy tube feeding for prolonged periods [Blake et al., 1993].

Weight bearing physical activity, another factor contributing to the development of strong and healthy bones, is also important in preventing low bone mass [Brown and Josse, 2002]. To date, however, there has been no research looking at the activity level of individuals with CHARGE.

The objective of this study was to investigate nutritional, hormonal and activity-related risk factors for compromised bone health in adolescents and adults with CHARGE syndrome. Because of the rarity of this condition and the global distribution of participants, we conducted a questionnaire geared towards caregivers in order to increase the number of eligible participants.

MATERIALS AND METHODS

Questionnaires were sent to the caregivers of 45 individuals 13 years of age or older with CHARGE syndrome. Thirty caregivers returned completed questionnaires. The characteristics of non-participants (n = 15) were unknown and their DEXA scan results were unavailable.

Participants were identified and recruited internationally among attendees of The 6th International CHARGE Syndrome Conference (Cleveland, July 25–27, 2003) and through support groups (The CHARGE listserv, a parent-run electronic mail list; CHARGE USA; The OZ CHARGE Association; The Deaf-Blind Institute; The Australasian CHARGE Group; and The Deafblind International CHARGE Network). Thirty participants who: (1) met the diagnostic criteria for CHARGE syndrome described by Blake [Blake et al., 1998]; (2) reported that they had genetic testing to rule out chromosome *22q11* deletion; and (3) had a caregiver who completed and returned a questionnaire, were enrolled in the study. The study included individuals age 13 or older because by this time, most adolescents should exhibit some evidence of pubertal development. The study protocol, information letter and the questionnaire were approved by the Izaak Walton Killam (IWK) Health Center Ethics Review Board and by the CHARGE Foundation USA Advisory Board. Consent to participate in the study was implied by returning the completed questionnaire. The questionnaire contained the categories below:

Bone Health

Family history of osteoporosis was reported as was any history of bone and/or joint pain, scoliosis, fracture and medication use. Caregivers rated their personal knowledge of bone health in the CHARGE population on a scale from 1 to 5 (1 = very little, 5 = expert).

Nutrition

The daily doses of supplementary calcium, vitamin D, cod/halibut liver oil and multivitamins were reported if taken. Dietary calcium consumption was estimated using the number of servings of dairy products consumed per day (serving = 1 cup milk or yogurt, 1″ square of hard cheese) and the number of servings of calcium-containing foods consumed in an average week (broccoli- 3/4 cup; calcium fortified

orange juice, soy or rice milk, cottage cheese- 1/2 cup; ice cream- 1/2 cup; pudding- 1/2 cup; sardines/kippers canned with bones- 1/2 can; salmon canned with bones- 1/2 can; processed cheese spread (i.e., Cheese Whiz)- 3 tbsp.; processed cheese- 2 slices).

Puberty and Growth

Caregivers described the adolescent/adult's pubertal course and Tanner stage using standardized pictures [Schlossberger et al., 1992] as well as the duration and type of hormone replacement, if applicable. Body mass index (BMI) was calculated based on reported height and weight. Adult participants were classified as overweight (BMI between 25 and 29.9 kg/m^2), normal weight (BMI between 18.5 and 24.9 kg/m^2) or underweight (BMI under 18.5). Adolescents 13–20 years old were classified as overweight (BMI above the 95th centile), normal weight (BMI between the 5th and 95th centile) and underweight (BMI under the 5th centile) according to gender-specific normative data from Centers for Disease Control (CDC) 2000 Growth Charts. The participants' heights were also compared to CDC 2000 data [Kuczmarski et al., 2000].

Activity

Activity level was assessed using the Habitual Activity Estimation Scale (HAES), a validated tool that estimates activity levels on a typical weekday (Tuesday, Wednesday, or Thursday) and weekend day (Sunday) over a 2-week period [Boucher et al., 1997]. Control data for the HAES was obtained from healthy junior high school, high school and university volunteers age 13–35 years.

DEXA Scan

Individuals who had undergone a DEXA scan provided a copy of the report. When available, lumbar spine (L2–L4) baseline and post-treatment z-scores were recorded along with age, height, weight, Tanner stage and treatment type. Total body DEXA values were rarely available and were not included. Heights and weights for both adolescents and adults were plotted against the CDC Growth charts for females and males aged 2–20 years [Kuczmarski et al., 2000]. The effect of various treatments (i.e., hormonal replacement therapy, bisphosphonates and vitamins) were examined by comparing baseline z-score to post-treatment z-score. For the purpose of this study, we presented z-scores. In the clinical setting, physicians may standardize Lunar and Hologic bone mineral density (BMD) values to facilitate comparison [Hui et al., 1997]. DEXA scans were performed with Hologic QDR 2000 (Hologic, Inc., Waltham, MA) or Lunar DPX-L (Lunar Corp., Madison, WI) equipment, as available in the clinical centers where subjects were followed.

Statistics

Statistical analyses were performed with Microsoft Excel 2000 (Microsoft Corporation, 1999). Results were given as a mean $\pm$ SD unless otherwise specified. Comparisons between data sets were conducted using Students *t*-tests with *P* values of less than 0.05 considered significant.

RESULTS

Thirty questionnaires (67%) were completed and returned. Ten caregivers (33%) included copies of DEXA scans.

The mean age of the participants was 19.6 $\pm$ 5.2 years and ranged from 13 to 34 years. The gender distribution was 50% male. The majority of the participants (n = 26) were Caucasian. Regarding genital manifestations of CHARGE syndrome, 11 males (73%) were reported to have micropenis and undescended testes, respectively. Six females (40%) had hypoplastic labia.

Bone Health

Four participants (13%) complained of bone pain. Scoliosis was reported in 15 individuals (50%) in keeping with reports of an increased incidence of scoliosis in CHARGE syndrome [Doyle and Blake, 2005]. Family histories were not significant for juvenile-onset osteoporosis. Nine individuals (30%) sustained previous fractures, all of which were the result of trauma.

With regard to medication, 5 individuals used short-course (<10 days) corticosteroids in the past. No long-term corticosteroid use was reported. Seventeen caregivers (57%) reported their knowledge of bone health in CHARGE as a "1" or "2", while 13 caregivers (43%) reported knowledge as a "3" or "4", on a scale of 1 (very little) to 5 (expert).

Nutrition

Of the 30 participants, 22 (73%) experienced past feeding difficulties including gastroesophageal reflux, aspiration, regurgitation of formula, poor oral motor coordination, asymmetric swallowing and rejection of food with certain textures. Sixteen individuals (53%) were fed by either a nasogastric tube (75%) and/or by a gastrostomy tube (75%). The mean duration of tube feeding was 8.2 $\pm$ 6.7 years. Four individuals (mean age: 16.8 $\pm$ 3.1 years) continued to be fed via gastrostomy tube because of chronic aspiration and difficulty swallowing.

Table I reports calcium intake of the study population. Only four individuals (13%) met the

TABLE I. Percentage of Adolescents (13–18 years) and Adults (19–35 years) With CHARGE Syndrome Meeting the RNI for Calcium Through Diet Alone and Through a Supplemented Diet

	Diet (%)[a]	Diet and Supplement (%)[a]
Calcium		
Adolescents (n = 15)	31	50
Adults (n = 14)	43	64
Total (n = 29[b])	38	59

[a]The adolescent and adult RNIs are 1,300 mg/day and 1,000 mg/day, respectively [Blake et al., 1993].
[b]One individual was omitted from nutritional analysis due to incomplete information.

recommended nutritional intake (RNI) for vitamin D (400 IU/day) via supplementation.

Puberty and Growth

Two (13.3%) females underwent spontaneous puberty, while the remainder experienced delayed or arrested puberty. One female taking hormone replacement had agenesis of the ovaries and uterus. Her puberty data was excluded from further analysis. The mean age of females (n = 8) not taking hormonal replacement therapy (HRT) was 17.5 ± 2.7 years (range: 13–21 years). Among these females, five reported Tanner stage 1–3 breast development and three reported Tanner 4–5 development. With respect to pubic hair distribution, six females reported Tanner stage 1–3 development while two reported Tanner stage 4–5. The mean age of females (n = 6) taking HRT was 19.3 ± 4.3 years (range: 14–26 years). Breast development and pubic hair development in this group was reported as Tanner stage 1–3 in two individuals and 4–5 in four individuals, respectively. Statistically, these groups were not significantly different with respect to age ($P = 0.365$), breast Tanner stage ($P = 0.139$) or pubic hair Tanner stage ($P = 0.208$).

Two males (13%) without genital manifestations of CHARGE syndrome underwent spontaneous puberty. The remaining thirteen males all had undescended testis and/or micropenis and experienced delayed puberty. The mean age of males (n = 6) not taking HRT was 17.5 ± 4.8 years (range: 14–17 years). Tanner stages for both pubic hair distribution and genital development in the non-HRT group were reported as 1–3 in four males and 4–5 in two males. Among males taking HRT (n = 9), the mean age was 22.1 ± 6.6 years (range: 14–34 years). Pubic hair Tanner stage was reported by one male as 1–3 while the remaining eight males reported Tanner stage 4–5 development. Two males achieved Tanner stage 1–2 for genital development while seven reported Tanner stage 4–5 growth. For males who received HRT, mean Tanner stages were significantly more advanced than those who had not received HRT (Tanner genital: $P = 0.043$; Tanner pubic hair: $P = 0.021$).

Current growth data was reported for 14 females and 13 males. Of these participants, 3 (11%) were overweight, 20 (74%) were in the normal weight range and 4 (15%) were underweight. One individual was within the 50–75th centile for height, 8 individuals (30%) were between the 10 and 25th centile and 15 (56%) were under the 5th centile for height.

Activity

Activity data is presented in Table II. Those individuals with CHARGE syndrome aged 13–18 years spent fewer hours engaging in activity than controls during both weekdays ($P = 0.001$) and weekends ($P = 0.001$). Among subjects with CHARGE syndrome, hours of activity were not significantly different between the 13–18 year and over 19-year age groups on weekdays ($P = 0.67$) or weekends ($P = 0.24$). Younger controls (13–18 years) were significantly more active than older controls (19 years and older) on both weekdays ($P = 0.018$) and weekends ($P = 0.001$). Data from one female over age 19 with CHARGE was incomplete and omitted from analysis.

DEXA Scan

Ten Caucasian individuals (7 males, 3 females) had previous DEXA scans for review. Of these, four individuals had multiple DEXA scans. Hologic QDR machinery was used for seven while the remaining three were scanned using Lunar equipment.

The three females took HRT (oral contraceptive pills) and ranged in age from 16 to 26 years, achieving Tanner stage 4–5 pubic hair and breast development. Of the males with DEXA scans (n = 7), five (71.4%) had both a micropenis and undescended testes while two had either a micropenis or undescended testes. One individual was reported to have growth hormone deficiency. Males ranged in

TABLE II. Habitual Activity Estimation Scale (HAES) Used to Estimate Time Spent Active During Weekdays and Weekends for Adolescents 13–18 years and 19+ with CHARGE Syndrome Compared to Same-Age Controls

	CHARGE syndrome	Controls
Subjects 13–18 years old:		
Number of participants	15	38
Mean age (years ± SD)	15.7 ± 1.5	15.1 ± 1.2
Weekday activity (hours ± SD)	5.6 ± 2.8[a]	8.9 ± 2.9[a]
Weekend activity (hours ± SD)	4.3 ± 3.4[b]	7.8 ± 3.5[b]
Subjects 19+ years old:		
Number of participants	14	27
Mean age (years ± SD)	23.5 ± 4.7	25.1 ± 3.2
Weekday activity (hours ± SD)	6.1 ± 2.9	6.9 ± 3.5
Weekend activity (hours ± SD)	5.7 ± 3.0	5.7 ± 2.9

Statistically significant: [a]$P = 0.0008$, [b]$P = 0.0015$.

age from 16 to 34 years. The four males who took past or present HRT achieved Tanner stage 4 pubertal development whereas the two males who did not have HRT reached Tanner stage 2 development. DEXA scan data is featured in Table III.

DISCUSSION

There is relatively little information on the medical challenges faced by teenagers and adults with CHARGE syndrome, especially with regard to bone health [Blake et al., 2005]. Risk factors for poor bone health and osteoporosis in young patients include poor nutrition, prolonged inactivity or immobility, chronic inflammatory conditions, glucocorticoid use, hypogonadism and growth hormone deficiency [Brown et al., 2002]. The etiology of low BMD among these conditions is variable. However, there is universal concern that the affected individuals may be at risk for future osteopenia and osteoporosis if peak bone mass is not attained. Adolescents with CHARGE syndrome have many risk factors (particularly relating to nutrition, primary hypogonadism and inactivity), making them vulnerable to the development of low bone density. We found that caregivers lack information about bone health with over half claiming to know very little on the topic.

Bone pain and fractures are clinical manifestations of osteoporosis. Only a few subjects in our study population reported bone pain. However, pain in this population is likely underreported due to high pain tolerance [Souriau et al., 2005] and difficulties in verbal and non-verbal communication [Hefner and Davenport, 2002; Thelin and Fussner, 2005]. The fractures sustained by our study participants were related to trauma and not suggestive of fragility fracture and occurred at a similar rate to that reported in the general population [Cooper et al., 2004].

The majority of participants experienced feeding problems during their lives and required substantial tube feeding. Although most were able to make the transition to oral feeding, a small number continued to depend on formula feedings via a gastrostomy tube. Previous studies have shown that formula dependent individuals, such as those with phenylketonuria may demonstrate increased susceptibility to fracture, osteopenia or osteoporosis if the amount of formula ingested is less than recommended [Marcus et al., 2000]. To ensure the daily requirement of calcium, vitamin D and other essential nutrients is met, it is important to consume the recommended amount of formula and for caregivers to seek nutritional advice.

Nutritional intake of calcium and vitamin D was highly variable. The RNI of calcium for adolescents aged 9–18 years is 1,300 mg/day while for non-pregnant women and men aged 19–50 years it is 1,000 mg daily [Brown et al., 2002]. In our subjects, nearly 70% of adolescents and 60% of adults did not obtain sufficient calcium from the foods they consumed. When supplemental calcium was considered, 50% of adolescents and 36% of adults still did not meet the RNI. Failing to consume adequate amounts of calcium during adolescence is a risk factor for future low BMD [Matkovic et al., 2004]. Very few participants consumed supplemental vitamin D, which is important for the development of healthy bones and the prevention of osteoporosis [Brown et al., 2002]. It is recommended that both adolescents and adults under 50 years of age have 400 IU of vitamin D daily [Brown et al., 2002]. Some experts suggest that malnourished pediatric patients should take double this amount- 800 IU of vitamin D daily [Alp et al., 2006].

During puberty, androgens and estrogens influence the growth and development of bone [Rabinovich, 2004]. The majority of males in our study failed to develop adult secondary sexual characteristics without hormonal intervention. Genital manifestations of CHARGE syndrome, micropenis and/or bilateral undescended testes, affect approximately 73% of males as noted both in our study and in the literature [Tellier et al., 1998]. Previous studies have suggested that females may be more likely than

TABLE III. Lumbar (L2–L4) z-Score, Gender, Age, Tanner Stage, Height and Weight Centiles and Treatment Type (Tx) from 10 Caucasian Individuals With CHARGE Syndrome

Gender	Age	Ht, centile	Wt, centile	Tanner stage	Pre Tx. Z-score	Tx. duration (y)	Post Tx. Z-score	Tx. type
F	16	<3rd	<3rd	5	−1.9	1	−1.7	HRT
F	18	5–10th	10–25th	5	−0.9	n/a	n/a	HRT, Calcium[a], Vitamin D[a]
F	26	<3rd	<3rd	4	−3.7	n/a	n/a	HRT, Calicum, Vitamin D
M	16	<3rd	<3rd	4	−4.0	n/a	n/a	HRT
M	17	<3rd	75–90th	2	−4.7	n/a	n/a	Calcium[a], Vitamin D[a]
M	20[b]	10–25th	5–10th	4	−1.2	6	−1.4	HRT, Calicum, Vitamin D
M	22[b]	n/a	n/a	5	−3.4	n/a	n/a	HRT, Calicum[a], Vitamin D[a]
M	26[b]	3rd–10th	5–10th	4	−4.3	n/a	n/a	HRT
M	26	10–25th	10–25th	2	−4.0	2.5	−2.7	Calcium, Vitamin D, Bisphosphonates
M	34	<3rd	<3rd	4	−4.6	7	−3.4	Calicum

[a]Vitamin D or Calcium intake below RNI.
[b]Lunar DPX-L Equipment. All other individuals were scanned using Hologic DEXA equipment.

males to undergo spontaneous puberty without HRT, however, this was not observed in our data, rates of spontaneous puberty were equal in males and females [James et al., 2003; Blake et al., 2005]. Furthermore, females with CHARGE syndrome who are given HRT do not reliably exhibit advanced Tanner stage in contrast to the majority of males given HRT who subsequently exhibit Tanner stage 4–5 development. In the literature, rates of female genital hypoplasia in CHARGE syndrome are approximately 28%, however, this is a subtle finding and likely goes underreported [Tellier et al., 1998].

Individuals with CHARGE engaged in fewer hours of activity per day than controls on both the weekdays and weekends, however, differences in activity level were only significant in the 13- to 18-year-old. Caregivers often commented that the adolescent was more active during the week when one-on-one care was available. Furthermore, many caregivers noted that the adolescent/adult was more motivated to be active with one-on-one care. Previous research by Boucher, who used the HAES for children with cystic fibrosis, showed that parents underestimated the activity level of teenage children when compared to the adolescent self-reporting [Boucher et al., 1997]. It was suggested that as adolescents with CF became more independent, they typically spent less time with their parents thus parents could not predict their activity level as accurately. Among adolescents/adults with CHARGE who are more closely supervised, this would be less of an issue. The correlation between high-impact/weight-bearing activity and increased BMD in the literature highlights the importance of encouraging adolescents and young adults to become more physically active and include resistance activities.

The DEXA scan data must be interpreted with caution. Firstly, DEXA scans are difficult to interpret in the healthy adolescent and this problem is magnified in CHARGE individuals. The areal BMD measured by DEXA scan in individuals who are shorter than average may be mistakenly interpreted as low because of smaller bone size. The pubertal delay seen in CHARGE also makes DEXA comparisons to age matched controls difficult to interpret. For an accurate DEXA scan comparison (z-score or t-score) one must control for age, height, weight, gender, pubertal status and race [Writing Group for the ISCD Position Development Conference, 2004]. In this group, DEXA scans may be more useful for documenting changes in BMD over time after the initiation of HRT and nutritional replacements. DEXA results may suggest low BMD but should not be used in CHARGE patients to diagnose osteoporosis, as guidelines suggest that fragility fractures must be present to make this diagnosis in adolescents and young adults [Rabinovich, 2004]. Among our population, a great deal of heterogeneity was observed with respect to the management of low bone density and the intake of vitamin D and Calcium was below the RNI.

In conclusion, adolescents and adults with CHARGE syndrome possess a multitude of risk factors predisposing them to the development of low bone mass in adolescence and possible osteoporosis in adulthood and require a multidisciplinary approach for prevention and treatment. Caregivers and physicians should anticipate likely pubertal delay in this population and treat hormone deficiencies accordingly with HRT to promote bone mineralization and to ensure the adolescent develops secondary sexual characteristics. To ensure that calcium and vitamin D intake is adequate, nutritional advice should be sought. Efforts should be made to encourage weight-bearing activities whenever possible. Osteoporosis prevention begins when bone mass is accumulated during childhood and adolescence [Steelman and Zeitler, 2001]. By recognizing that individuals with CHARGE are at increased risk of developing low BMD and by intervening early in life to promote factors positively influencing bone mass accrual, it is hoped that the risk of developing osteoporosis in the future may be reduced.

ACKNOWLEDGMENTS

We are indebted Beth Flanigan for the development of the questionnaire and to Dr. Stephanie Kaiser for her scientific expertise. This research was supported by a summer studentship awarded jointly by Dalhousie University Summer Studentship Program and the IWK Health Center in Halifax, NS.

REFERENCES

Alp H, Orbak Z, Kermen T, Uslu H. 2006. Bone mineral density in malnourished children without rachitic manifestations. Pediatr Int 48:128–131.

Amiel J, Attiee-Bitache T, Marianowski R, Cormier-Daire V, Adadie V, Bonnet D, Gonzales M, Chemouny S, Brunelle F, Munnich A, Manach Y, Lyonnet S. 2001. Temporal bone anomaly proposed as a major criteria for diagnosis of CHARGE syndrome. Am J Med Genet 99:124–127.

Blake K, Kirk JM, Ur E. 1993. Growth in CHARGE association. Arch Dis Child 68:508–509.

Blake KD, Davenport SL, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM Jr. 1998. CHARGE association: An update and review for the primary pediatrician. Clin Pediatr 37:159–173.

Blake KD, Russell-Eggitt IM, Morgan DW, Ratcliffe JM, Wyse RK. 1990. Who's in CHARGE? multidisciplinary management of patients with CHARGE association. Arch Dis Child 65:217–223.

Blake KD, Salem-Hartshorne N, Daoud MA, Gradstein J. 2005. Adolescent and adult issues in CHARGE syndrome. Clin Pediatr 44:151–159.

Boucher GP, Lands LC, Hay JA, Hornby L. 1997. Activity levels and the relationship to lung function and nutritional status in children with cystic fibrosis. Am J Phys Med Rehabil 76:311–315.

Brown JP, Josse RG. Scientific Advisory Council of the Osteoporosis Society of Canada. 2002. clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 167:S1–S34.

Butler MG, Haber L, Mernaugh R, Carlson MG, Price R, Feurer ID. 2001. Decreased bone mineral density in Prader-Willi syndrome: Comparison with obese subjects. Am J Med Genet 103:216–222.

Cooper C, Dennison EM, Leufkens HG, Bishop N, van Staa TP. 2004. Epidemiology of childhood fractures in Britain: a study using the general practice research database. J Bone Miner Res 19:1976–1981.

Cunningham J, Sprague SM, Cannata-Andia J, Coco M, Cohen-Solal M, Fitzpatrick L, Goltzmann D, Lafage-Proust MH, Leonard M, Ott S, Rodriguez M, Stehman-Breen C, Stern P, Weisinger J, Osteoporosis Work Group. 2004. Osteoporosis in chronic kidney disease. Am J Kidney Dis 43:566–571.

Doyle C, Blake K. 2005. Scoliosis in CHARGE: A prospective survey and two case reports. Am J Med Genet Part A 133A: 340–343.

Graham JM Jr. 2001. A recognizable syndrome within CHARGE association: Hall-Hittner syndrome. Am J Med Genet 99:120–123.

Gravholt CH, Vestergaard P, Hermann AP, Mosekilde L, Brixen K, Christiansen JS. 2003. Increased fracture rates in Turner's syndrome: A nationwide questionnaire survey. Clin Endocrinol 59:89–96.

Hall BD. 1979. Choanal atresia and associated multiple anomalies. J Pediatr 95:395–398.

Hefner MA, Davenport SLH. 2002. A management manual for parents and professionals, version 2.1, section IV-2C Influence of sensory loss on development: The communication Bubble. 2002 Columbia, MO: CHARGE Syndrome Foundation.

Hui SL, Gao S, Zhou XH, Johnston CC Jr, Lu Y, Gluer CC, Grampp S, Genant H. 1997. Universal standardization of bone density measurements: A method with optimal properties for calibration among several instruments. J Bone Miner Res 12:1463–1470.

Issekutz KA, Graham JM Jr, Prasad C, Smith IM, Blake KD. 2005. An epidemiological analysis of CHARGE syndrome: Preliminary results from a Canadian study. Am J Med Genet Part A 133A:309–317.

James PA, Aftimos S, Hofman P. 2003. CHARGE association and secondary hypoadrenalism. Am J Med Genet Part A 117A: 177–180.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. 2000. CDC growth charts: United states. Adv Data 8:1–27.

Lalani SR, Safiullah AM, Fernbach SD, Harutyunyan KG, Thaller C, Peterson LE, McPherson JD, Gibbs RA, White LD, Hefner M, Davenport SL, Graham JM, Bacino CA, Glass NL, Towbin JA, Craigen WJ, Neish SR, Lin AE, Belmont JW. 2006. Spectrum of *CHD7* mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation. Am J Hum Genet 78: 303–314.

Lalani SR, Stockton DW, Bacino C, Molinari LM, Glass NL, Fernbach SD, Towbin JA, Craigen WJ, Graham JM Jr, Hefner MA, Lin AE, McBride KL, Davenport SL, Belmont JW. 2003. Toward a genetic etiology of CHARGE syndrome: I. A systematic scan for submicroscopic deletions. Am J Med Genet Part A 118A:260–266.

Marcus R, Leary D, Schneider DL, Shane E, Favus M, Quigley CA. 2000. The contribution of testosterone to skeletal development and maintenance: Lessons from the androgen insensitivity syndrome. J Clin Endocrinol Metab 85:1032–1037.

Matkovic V, Landoll JD, Badenhop-Stevens NE, Ha EY, Crncevic-Orlic Z, Li B, Goel P. 2004. Nutrition influences skeletal development from childhood to adulthood: A study of hip, spine, and forearm in adolescent females. J Nutr 134:701S–705S.

Rabinovich CE. 2004. Osteoporosis: A pediatric perspective. Arthritis Rheum 50:1023–1025.

Rubio-Gozalbo ME, Hamming S, van Kroonenburgh MJ, Bakker JA, Vermeer C, Forget PP. 2002. Bone mineral density in patients with classic galactosaemia. Arch Dis Child 87: 57–60.

Sanlaville D, Etchevers HC, Gonzales M, Martinovic J, Clement-Ziza M, Delezoide AL, Aubry MC, Pelet A, Chemouny S, Cruaud C, Audollent S, Esculpavit C, Goudefroye G, Ozilou C, Fredouille C, Joye N, Morichon-Delvallez N, Dumez Y, Weissenbach J, Munnich A, Amiel J, Encha-Razavi F, Lyonnet S, Vekemans M, Attie-Bitach T. 2006. Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development. J Med Genet 43:211–317.

Sanlaville D, Romana SP, Lapierre JM, Amiel J, Genevieve D, Ozilou C, Le Lorch M, Brisset S, Gosset P, Baumann C, Turleau C, Lyonnet S, Vekemans M. 2002. A CGH study of 27 patients with CHARGE association. Clin Genet 61:135–138.

Schlossberger NM, Turner RA, Irwin CE Jr. 1992. Validity of self-report of pubertal maturation in early adolescents. J Adolesc Health 13:109–113.

Souriau J, Gimenes M, Blouin C, Benbrik I, Benbrik E, Churakowskyi A, Churakowskyi B. 2005. CHARGE syndrome: Developmental and behavioral data. Am J Med Genet Part A 133A:278–281.

Steelman J, Zeitler P. 2001. Osteoporosis in pediatrics. Pediatr Rev 22:56–65.

Tellier AL, Cormier-Daire V, Abadie V, Amiel J, Sigaudy S, Bonnet D, de Lonlay-Debeny P, Morrisseau-Durand MP, Hubert P, Michel JL, Jan D, Dollfus H, Baumann C, Labrune P, Lacombe D, Philip N, LeMerrer M, Briard ML, Munnich A, Lyonnet S. 1998. CHARGE syndrome: Report of 47 cases and review. Am J Med Genet 76:402–409.

Thelin JW, Fussner JC. 2005. Factors related to the development of communication in CHARGE syndrome. Am J Med Genet Part A 133A:282–290.

Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, van Kessel AG. 2004. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36:955–957.

White DR, Giambra BK, Hopkin RJ, Daines CL, Rutter MJ. 2005. Aspiration in children with CHARGE syndrome. Int J Pediatr Otorhinolaryngol 69:1205–1209.

Writing Group for the ISCD Position Development Conference. 2004. Diagnosis of osteoporosis in men, premenopausal women, and children. J Clin Densitom 7:17–26.