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Scoliosis in CHARGE:
A Prospective Survey and Two Case Reports

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CHARGE syndrome was first identified as a cluster of congenital anomalies in 1979 and has since undergone diagnostic criteria modifications to include the major and minor characteristics that occur during infancy and childhood. As the individuals with CHARGE syndrome have aged into their adolescents and adulthood, it has become increasingly common for them to develop scoliosis. This article presents an older population of individuals with CHARGE syndrome and describes the prevalence of scoliosis, and identifiable risk factors for scoliosis. Two case reports demonstrate the variability of scoliosis in CHARGE syndrome. A survey of adults and adolescents with CHARGE syndrome was completed to collect information about late onset medical issues, and those identifying scoliosis as an issue, were further followed for more information. The total population (n = 31) and then the subgroup of individuals with scoliosis (n = 19) were analyzed. Sixty one percent (19 of 31) of this population was diagnosed with scoliosis. The age of CHARGE syndrome diagnosis was later in the scoliosis population (6.3 years compared to 3.7 years in the no scoliosis population). Growth hormone use was reported in 7 of 31 of the individuals; 6 of these subsequently were diagnosed with scoliosis (32% of the scoliosis group). Of the scoliosis subgroup, most were mild scoliosis but eight were diagnosed with moderate to severe scoliosis, and all of these were treated with either a brace (n = 5) or with surgical fusion (n = 2) and one individual had both. Scoliosis in CHARGE syndrome individuals is more common than previously reported, and the age of onset is earlier than when routine monitoring for scoliosis is recommended. The prevalence of scoliosis in the CHARGE syndrome population is higher than in the general population therefore, it is very important for physicians to carefully monitor the spine for the development of scoliosis in children with CHARGE syndrome, especially if they are being treated with growth hormone.

KEY WORDS: CHARGE syndrome; CHARGE association; scoliosis; diagnostic criteria

INTRODUCTION

CHARGE syndrome is a non-random cluster of congenital anomalies with an estimated population-based incidence of 1 in 9,000 live births [Issekutz et al., 2005]. The association of the anomalies was first recognized in 1979 [Hall, 1979; Hittner et al., 1979]. Later the CHARGE acronym was coined to represent coloboma, heart defects, choanal atresia, growth retardation, genital hypoplasia, and ear anomalies [Pagon et al., 1981]. In 1998, a group of geneticists and developmental pediatricians redefined the syndrome using major and minor criteria, thus highlighting more of the common cranial nerve characteristics [Blake et al., 1998]. A number of physical characteristics have recently been identified that are typical of CHARGE syndrome only as the individual matures [Lawand et al., 2003; Blake et al., 2005]. One of these characteristics is the occurrence of scoliosis.

Scoliosis describes a lateral curvature of the spine quantified by the Cobb angle [Dobbs and Weinstein, 1999; Reamy and Slakey, 2001]. The progression of the curvature usually coincides with a period of growth, and so infants and adolescents are very susceptible to developing scoliosis [Dobbs and Weinstein, 1999]. Several factors, such as advanced maternal age, prolonged supine positioning in the crib and intrauterine molding, have been associated with the occurrence of scoliosis, however, most scoliosis is idiopathic in etiology [Dobbs and Weinstein, 1999]. The progression of the curve is influenced by gender, the amount of growth potential remaining and the severity of the curve [Little et al., 2000; Reamy and Slakey, 2001]. There are many scoring systems to assess the severity of scoliosis, however, treatment options are usually based on the severity of the curve, which is best described by the Cobb angle [Reamy and Slakey, 2001]. Children with scoliosis have an increased association with other anomalies such as plagiocephaly, bat-ear deformity, congenital muscular torticollis, hip dysplasia, and hyperactivity [Dobbs and Weinstein, 1999]. Scoliosis and other vertebral anomalies have been described in children with other syndromes, however, scoliosis has been recognized only as an occasional finding in the criteria for CHARGE syndrome [Goldson et al., 1986; Harvey et al., 1991; Labelle et al., 1996; Blake et al., 1998; Tellier et al., 1998; Khadilkar et al., 1999].

This article presents an adolescent and adult population of CHARGE syndrome patients with respect to the prevalence of scoliosis [Blake et al., 2005]. The mean age of CHARGE syndrome diagnosis, scoliosis diagnosis, commencement of walking, and the use of growth hormone were compared between the CHARGE syndrome individuals with scoliosis and those with no scoliosis. The data compare the prevalence of each of the major and minor CHARGE syndrome characteristics in the group with scoliosis to the group without scoliosis. The adults and adolescents with scoliosis are presented individually to demonstrate the variability of scoliosis and the different factors associated with the development and progression of scoliosis. Two CHARGE syndrome patients with varying severities of their scoliosis are discussed in detail, one of whom required corrective surgery.

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METHODS AND PATIENTS

A questionnaire was mailed to 31 families with adolescents or adults with CHARGE syndrome who were known to the CHARGE Syndrome Foundation. This is an international patient, parent, and professional group. At the time of this research, this was the largest population of older individuals with CHARGE syndrome identified whose diagnosis was confirmed clinically by a group of geneticists. This questionnaire gathered information about medical, social, and educational issues for this older population of CHARGE syndrome individuals. The information was entered on a database and was cross-referenced with the CHARGE Syndrome Foundation medical reports that were completed by caregivers and medical doctors of the adolescents and adults with CHARGE syndrome. A 100% return rate was accomplished from the 21 who listed scoliosis as an issue. An additional telephone survey, for which consent was obtained, was completed asking specific questions relating to the scoliosis. As a result of the telephone survey, two patients were excluded from the scoliosis group as they had spinal abnormalities that were not consistent with scoliosis. One of these had osteoporosis, and the other had back pain with no radiological evidence of scoliosis. Pearson's Chi square was used to statistically analyze the two groups of individuals with scoliosis (n = 9) and those without scoliosis (n = 12). The group with scoliosis was analyzed to determine if a relationship existed between the administration of growth hormone, age of walking, family history of scoliosis, and the age of diagnosis of scoliosis or the severity of their scoliosis measured by the most severe Cobb angles of each individual. Two patients were non-randomly selected from this population in order to describe the diversity of scoliosis in CHARGE syndrome. Further consent was obtained from the legal guardian of one male and one female selected for these case reports.

RESULTS

The prevalence of scoliosis among adults and adolescents with CHARGE syndrome was high, with 19 of 31 (61.3%) reporting this diagnosis. There was not a significant sex difference in this population of 14 males and 17 females (Table I).

The mean age at which CHARGE syndrome was diagnosed was later in the group with scoliosis (6.3 years, SD = 3.7), compared to the no scoliosis group (3.7 years, SD = 5.38), although this relationship did not reach significance (Table I). There was no significant difference in the presence of diagnostic features between the groups, although there were two noteworthy points: tracheoesophageal fistula and the characteristic CHARGE face were more prevalent in the group with scoliosis compared to those without scoliosis (Table I).

Growth hormone was used in 7 of the 31 adults and adolescents with CHARGE syndrome and 6 of these (86%) were subsequently diagnosed with scoliosis (32% of the scoliosis group).

There was no statistical difference in the CHARGE syndrome features when comparing males to females among the individuals with scoliosis, however, some trends were noted: genital hypoplasia was more common among males (males = 8/9; females = 5/10; $P = 0.07$) and delayed growth was more common among females (males = 5/9; females = 9/10; $P = 0.09$). However, a bias in ascertainment may have existed given the difficulty of defining hypoplasia of the external genitalia in females.

The average age at which the adult and adolescent population of CHARGE syndrome individuals was diagnosed with scoliosis was 6.25 years (Table II). Males were younger than females upon diagnosis of CHARGE syndrome (5.4 and 7.1 years, respectively). A positive family history of scoliosis in a first degree relative did not appear to affect the severity of scoliosis as all three individuals with a positive family history had mild scoliosis (Table II).

The age in which the individuals with CHARGE and scoliosis began walking was 4.43 years (Table II) and is compared to the mean age of the individuals with CHARGE and without scoliosis (4.0 years). The age at which the individuals with CHARGE syndrome and scoliosis started walking was not influenced by the curvature of their spine. An example is patients nos. 5 and 6 who both walked at 4 years, the former having a Cobb angle of 50 degrees and the latter a Cobb angle of less than 20 degrees. The administration of growth hormone did not lead to an increase in severity of scoliosis. Six of these individuals were treated with a brace either permanently or periodically. One of these patients went on to have surgery. Two other individuals not previously treated with a brace also had a spinal fusion.

Case Report Patient no. 9

This male was born vaginally at 38.5 weeks from an uncomplicated pregnancy to non-consanguineous parents. He weighed 2.9 kg, was 49.5 cm long, he was in the 20th centile for

TABLE I. Characteristics of Adults and Adolescents With CHARGE Syndrome

	Scoliosis, n = 19	No scoliosis, n = 12	*P* value
Female	10	7	ns
Mean age of CHARGE syndrome diagnosis (y)	6.3	3.7	ns
Mean age of diagnosis of scoliosis (y)	8.6	N/A	ns
Use of growth hormone	6	1	<0.05
Mean age of walking (y)	4.2	4.0	ns
Major criteria			
Coloboma	17	11	ns
Choanal atresia or stenosis	13	7	ns
Cranial nerve anomaly	18	10	ns
Characteristic ear anomaly	19	11	ns
Minor criteria			
Genital hypoplasia	13	10	ns
Delayed growth	14	8	ns
Heart defects	15	9	ns
Orofacial clefting	10	7	ns
Trachea-esophageal fistula	6	2	ns
Characteristic face	18	8	0.06

ns, not significant; N/A, data not available; n, number; y, years.

TABLE II. Further Characteristics of Adults and Adolescents With CHARGE Syndrome and Scoliosis: Males (1–9), Females (10–19)

Patient	Diagnosis of CHARGE (y or neonate*)	Diagnostic criteria		Scoliosis diagnosis (y)	Family history of scoliosis	Growth hormone	Most severe Cobb angle	Age of walking (y)
		Major, max = 4	Minor, max = 6					
1	Neonate	3	3	4	N/A	Yes	N/A	2
2	12	3	4	10	+	Yes	<20	2.5
3	Neonate	4	3	11	−	No	<20	3.5
4	21	4	4	7	−	No	<20	3.5
5	1	3	2	9	−	No	50	4
6	Neonate	3	5	8	−	No	<20	4
7	14	4	5	19	−	No	<20	5.5
8	1	4	6	6	−	No	<20	6
9	Neonate	3	5	10	−	Yes	<20	6
Mean male	5.44	3.44	4.11	9.33				4.56
10	N/A	2	4	5	−	Yes	<20	2
11	14	4	5	9	−	No	<20	2.5
12	Neonate	4	3	13	+	Yes	<20	2.5
13	5.5	3	3	7	−	No	50	3
14	4.5	4	5	5	+	No	<30	3.5
15	18	4	5	13	−	No	<20	4
16	17.5	4	3	8	−	Yes	<20	4
17	Neonate	3	3	10	−	No	28	5
18	4	4	4	7	−	No	<20	8
19	Neonate	4	4	3	−	No	<20	8.5
Mean female	7.05	3.60	3.90	8.00				4.30
Mean all	6.25	3.52	4.01	8.67	n = 3	n = 6		4.43

N/A, data not available; *neonate ≤ 1 month; n, number; y, years; +, present; −, absent.

weight and in the 35th centile for length. Immediately following birth he had respiratory distress, which was attributed to his heart defects. He had coloboma, dysphagia, genital hypoplasia, developmental delay, and complex cardiac malformations (truncus arteriosis, interrupted aortic arch, atrial and ventricular septal defects, and a patent ductus arteriosis). He also had orofacial clefting and the characteristic CHARGE face and ear anomalies. These anomalies met the diagnostic criteria for CHARGE syndrome (three major and five minor) and he was diagnosed with CHARGE at 3 months of age. He was diagnosed with scoliosis at the age of 10 years. He developed a rib hump and Sprengle's deformity (Fig. 1). He received growth hormone supplementation beginning at the age of 13 and subsequently had a growth spurt. He was never treated with testosterone. The curvature of patient no. 9's spine was monitored annually at his school and was considered mild until the age of 17½ when he was informed that his curve had progressed slightly beyond mild, but was still not surgical. He has shown persistent short stature below the 5th centile and continues to receive growth hormone supplementation. At the age of 17½ years he measures 148 cm, which is 5 standard deviations below the mean for a male his age and at the 50th centile for a child of almost 12 years.

Fig. 1. Rib hump and Sprengle's deformity of patient no. 9. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Case Report Patient no. 13

Due to a breech presentation at the end of an otherwise normal pregnancy, this female was born by cesarean section at 43 weeks to non-consanguineous parents. She weighed 3.8 kg, was 53 cm long, and was in the 95th centile for both weight and height. Her face had the characteristic CHARGE syndrome appearance, and she had coloboma, external ear anomalies, sensorineural and conduction deafness, and developmental delay. Using the revised diagnostic criteria [Blake et al., 1998], she had three major and three minor CHARGE syndrome characteristics. As an infant she was diagnosed with a dislocated hip, which was treated with a pavlik harness and physiotherapy. It was reported during physiotherapy that she had decreased tone that persisted throughout her childhood. At 12 months she underwent heart surgery to repair a patent ductus arteriosis. A diagnosis of CHARGE syndrome was made at 5½ years and of scoliosis at 7 years. At diagnosis, her Cobb angle was measured at 22 degrees, and this was controlled and even improved somewhat with a back brace (the Cobb angle digressed from 22 to 14 degrees) until the age of 13 years. Menses and a growth spurt occurred spontaneously at 13 years and although she was wearing a brace, her curve progressed from 14 to 50 degrees in 6 months (Fig. 2). A spinal fusion was performed in her 14th year and her Cobb angle has not changed since that time. At 17 years of age, she measured 142 cm tall which is almost 4 standard deviations below the 50th centile for height for her age, but at the 50th centile for a child of 10½ years.

Fig. 2. X-ray of thoracic spine of patient no. 13. Cobb angle measurements are shown.

DISCUSSION

There is an abundance of information regarding the prevalence and natural history of scoliosis in children with no associated anomalies or health problems, but to date there is no discussion about the high prevalence of scoliosis among individuals with CHARGE syndrome. Children with CHARGE syndrome develop and grow at a different rate than other children and so it is difficult to predict the prevalence and progression of scoliosis in these children [Blake et al., 1993; Khadilkar et al., 1999]. Because most children with CHARGE syndrome were diagnosed with scoliosis at a young age, it should be recommended that their spine be monitored during their subsequent periods of rapid growth, as scoliosis tends to progress quickly during such periods of time. Some children with CHARGE syndrome take growth hormone to increase their growth rate, and so it is especially necessary for these children to be monitored frequently although the group presented does not demonstrate an increased severity of scoliosis with the use of growth hormone.

If scoliosis is diagnosed in a child with CHARGE syndrome, the child should be referred to orthopedics and physiotherapy. Physiotherapy has not been proven to affect the progression of scoliosis, however, it is helpful to strengthen the paraspinal muscles [Reamy and Slakey, 2001]. It is imperative that an early diagnosis of scoliosis is made in order for appropriate conservative treatment to follow; a diagnosis of progressive scoliosis may limit treatment to surgical interventions such as spinal fusion [Reamy and Slakey, 2001]. As spinal fusion limits further growth in the spine of any individual, it is important to exhaust all other options, such as Milwaukee braces, before surgery is planned [Reamy and Slakey, 2001]. In children already at risk of short stature, every effort should be made to avoid the imposition of a structural limit to the child's growth.

The prevalence of scoliosis in the CHARGE syndrome population is higher than in the general population, therefore, it is very important for physicians to carefully monitor the spine for the development of scoliosis in children with CHARGE syndrome, especially if they are being treated with growth hormone.

LIMITATIONS OF THE STUDY

As the CHARGE syndrome is becoming more widely known, more young children are being diagnosed with this syndrome. Few children have aged into their adolescence and fewer into adulthood due to the sequelae of fatal medical complications that arise. This makes the compilation of data for this population difficult and thus the numbers in this study are very small. Despite this, significance in the frequency of scoliosis in those individuals who age into their early adulthood is well demonstrated.

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