CLINICS

CLINICAL SCIENCE

Prevalence of scoliosis in Williams-Beuren syndrome patients treated at a regional reference center

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OBJECTIVE: This study assessed the prevalence of scoliosis and the patterns of scoliotic curves in patients with Williams-Beuren syndrome. Williams-Beuren syndrome is caused by a chromosome 7q11.23 deletion in a region containing 28 genes, with the gene encoding elastin situated approximately at the midpoint of the deletion. Mutation of the elastin gene leads to phenotypic changes in patients, including neurodevelopmental impairment of varying degrees, characteristic facies, cardiovascular abnormalities, hypercalcemia, urological dysfunctions, and bone and joint dysfunctions.

METHODS: A total of 41 patients diagnosed with Williams-Beuren syndrome, who were followed up at the genetics ambulatory center of a large referral hospital, were included in the study. There were 25 male subjects. The patients were examined and submitted to radiographic investigation for Cobb angle calculation.

RESULTS: It was observed that 14 patients had scoliosis; of these 14 patients, 10 were male. The pattern of deformity in younger patients was that of flexible and simple curves, although adults presented with double and triple curves. Statistical analysis showed no relationships between scoliosis and age or sex.

CONCLUSION: This study revealed a prevalence of scoliosis in patients with Williams-Beuren syndrome of 34.1%; however, age and sex were not significantly associated with scoliosis or with the severity of the curves.

KEYWORDS: Elastin; Scoliosis; Williams-Beuren Syndrome.

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INTRODUCTION

Many studies have identified mutations in the genetic loci encoding proteins that are components of elastic fibers, leading to a wide range of connective tissue disorders, including skeletal, cardiovascular and ocular abnormalities, as well as neurodevelopmental deficits (1-4). One of the most striking aspects of the syndromes that cause musculoskeletal impairment is scoliosis, which occurs frequently in individuals in the same family.

Williams-Beuren syndrome (WBS) is a relatively rare disease, with a frequency of 1:7,500 to 1:20,000 living births (5-7). WBS is caused by a chromosome 7q11.23 deletion in a region containing 28 genes and the gene encoding elastin is situated approximately at the midpoint of this deletion (8-10). Mutation of the elastin gene results in various phenotypic changes, including neurodevelopmental impairment of varying degrees, cardiovascular abnormalities, hypercalcemia, urological dysfunction, and bone and joint dysfunctions (11-13).

Elastin is the best-known protein encoded in scoliosis. As the main component of the tissue extracellular matrix, elastin is fundamental to regulating the distribution of elastic fibers in the intervertebral discs. In patients with scoliosis, disorganization of collagen and elastic fibers is observed, elastic fibers are sparse, and the lamellar structure is lost (14-16).

Few cases of scoliosis have been reported in patients with WBS (17-19), and the descriptions of the deformities have been brief. The prevalence of scoliosis in WBS is not fully understood, and the patterns of the scoliosis curves in patients with WBS have not been studied.

No potential conflict of interest was reported.

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The objectives of the present study were to assess the prevalence of scoliosis in patients with WBS and to determine the association of WBS with the patterns of scoliotic curves.

MATERIALS AND METHODS

Study design and study population

The participants in this observational, cross-sectional study were WBS patients undergoing follow-up at the Genetics Ambulatory clinic of our public university hospital. Hospital das Clínicas is a referral center for genetic diseases that receives patients from other primary and tertiary health centers from all over Brazil. The patients are regularly followed up free of charge within the Brazilian public health system (Sistema Único de Saúde, SUS). WBS patients present with many different comorbidities of the disease, and in our hospital, they are closely monitored by our multidisciplinary team.

For this study, the Genetics Ambulatory clinic provided a list of all of the patients with WBS who were registered at any time for diagnosis or treatment at the institution. The database of the Brazilian Association of Williams-Beuren Syndrome was checked, and 51 patients registered in Brazil were found. Of these patients, 50 were undergoing follow-up at Hospital das Clínicas.

After obtaining approval from the local ethics committee, telephone calls were made by the Spinal Surgery Division of the Orthopaedics and Traumatology Department of the same hospital from June to July 2010 to each of the 50 patients registered with the hospital. The patients were asked to visit the hospital and undergo an orthopedic consultation due to the risk of spinal deformities in WBS patients.

Patients of any age were included, provided they had a complete clinical or cytogenetic diagnosis of WBS and were undergoing follow-up at our institution. The cytogenetic study was performed with fluorescence *in situ* hybridization (FISH).

Clinical interview and examination of the spine

When the patients presented for the interview, they were informed about the study objectives and were given an informed consent form to be signed by themselves or their parents. The orthopedic surgeon obtained each patient's medical history systematically, registering age, sex, previous genetic exams, consanguinity between the patient's parents, other cases of WBS in the family, and the patient's age at menarche. We recorded the age at which the deformities or deviations of the spine first appeared in childhood.

A physical examination was then performed by the same professional, observing the vertebral axis, alignment of the shoulders, the presence of dorsal spinal deviation, the space between the trunk and the elbows, hip function, and musculoskeletal deformities. The Adams test was performed, and the surgeon also examined neurological function.

After the physical examination, the patient was referred for orthostatic panoramic radiography of the spine, with anteroposterior, front, and lateral incidences (right and left), in the Radiological Examination Outpatient service of our hospital. Two experienced orthopedic surgeons from the Spine Surgery division examined the radiographic images, observing the alignment of the spine and shoulders and the hip flexibility, in addition to verifying the spinal deviation. When scoliosis was suspected, the examiner verified the pattern of the primary curve, alignment, and sagittal balance. The Cobb angle was calculated, according to the Scoliosis Research Society criteria and was recorded. Scoliosis was defined as a Cobb angle greater than 10° between the cranial and caudal vertebrae of the spinal curve. The average distance between the two measurements was calculated and used to estimate the prevalence of scoliosis in this study.

Statistical analysis

Inferential and descriptive analyses were used in the presentation of the results. All of the continuous data with a normal distribution were described by the means and standard deviations. For the non-parametric data, the medians and interquartile ranges were used. Categorical data were analyzed as frequencies. Multivariate regression analysis was performed to determine whether some independent variables could explain the severity of scoliosis. For the comparison of simple pairs of data, when necessary, Student's t test was used. The accepted level for type I error in this study was less than or equal to 5%. The statistical software SPSS (Chicago, IL, USA), version 20.0 for Mac, was used for the analysis.

RESULTS

Of the 50 patients with WBS who were initially selected, 2 could not be reached because they had changed their addresses and telephone numbers, 3 lived in other cities and could not attend due to transportation difficulties, and 4 failed to attend the consultations without providing a reason. The remaining 41 patients agreed to participate and presented to be examined in August 2010. The ages of these 41 patients ranged from 2 to 31 years old (mean: 16.3 years), and 25 were male. There were no cases of consanguinity between the parents of any of the patients.

Scoliosis was found in 14 WBS patients, indicating a prevalence of 34.1% in this population. Of the 14 scoliotic patients, 10 were male. Regression analysis did not show a significant difference in the frequency of scoliosis according to sex ($p = 0.393$).

Scoliosis was observed only in patients older than 8 years of age; the 6 patients younger than 8 years of age had a normal vertebral axis. Single, double, and triple scoliosis curves were observed, and no patterns or associated factors could be identified in this sample. Half of the WBS patients with scoliosis had single curves (7 cases), while the other half had double (5 cases) or triple curves (2 cases), as shown in Figure 1. The Cobb angle in the main curve varied from 12° to 94° (mean: 27.6°), as shown in Figure 2. However, descriptive and regression analyses did not reveal a statistically significant association between age and the severity of the curve ($p = 0.124$).

Most of the patients (12 cases) had flexible curves (lateral inclination leading to reduction of the curve of less than 25°), and 2 had rigid deformities (both with triple curves).

DISCUSSION

Scoliosis has been observed in 0.5% to 2% of the population (20-23). Our study showed that the prevalence

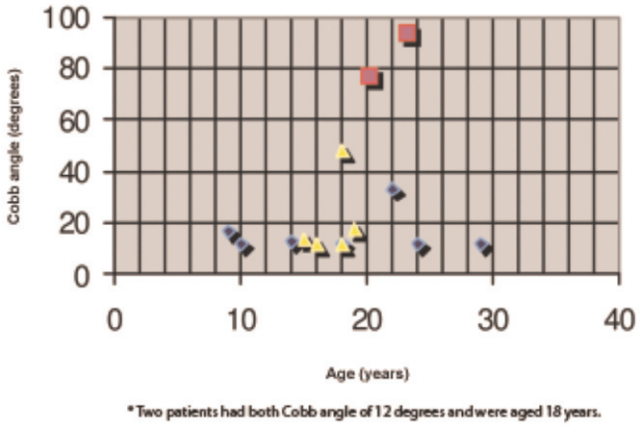

Figure 1 - Pattern of the scoliosis curves in 14 Williams-Beuren syndrome patients according to age: blue points indicate single curves, yellow triangles indicate double curves and pink squares indicate triple curves*.

of scoliosis could be much higher in WBS patients. The explanation for this finding might be related to the gene mutations that are present in genetic disorders. For example, in both Marfan syndrome and neurofibromatosis type 1, approximately 60% of individuals present with scoliosis during growth (24). A review of the literature revealed that scoliosis was observed in 12% (13) to 18% (18,19) of patients with WBS, while the present study showed a prevalence of 34.1%. To our knowledge, this was the first study to evaluate specifically the prevalence of scoliosis in WBS patients in Brazil.

A high prevalence of scoliosis has been identified in many other connective tissue diseases, including Marfan syndrome, neurofibromatosis, Ehler-Danlos, Prader-Willi, Noonan, and Angelman syndromes, mucopolysaccharidosis, and VATER syndrome, among others (24-34). Collagen production is impaired in Ehler-Danlos syndrome and in osteogenesis imperfecta (26,34). Neurofibrin production is a problem that has been associated with neurofibromatosis (24). Defects in 11 enzymes are involved in mucopolysaccharidosis (27,28). Fibrillin-1 (FBN1) and elastin are the two main protein components of elastic fibers and because scoliosis is common in patients with Marfan syndrome, some authors have suggested that FBN1 gene mutations confer a greater risk of vertebral deformity, compared to mutations in the elastin locus (19).

The concurrence of scoliosis with WBS suggests that mutations in the fibrillin-1 gene (responsible for Marfan syndrome) or neurofibromin (responsible for neurofibromatosis type 1) might have greater effects on the development of scoliosis than mutations in the locus encoding elastin.

WBS was first referred to as childhood idiopathic hypercalcemia by Lightwood in 1932 (35). In 1951, Fanconi described children with hypercalcemia, weight and height deficits, mental retardation, typical facies and cranial osteosclerosis as having WBS (36). It was only in 1961 and 1962 that John Williams and Alois Beuren, both cardiologists, published the most important studies that named the syndrome and described the main cardiovascular abnormalities, particularly supra-aortic valvular stenosis (present in approximately 80% of individuals affected by disease) (37). Garcia et al. revealed the main symptoms of the syndrome in 1964 in a case description of supravalvular aortic stenosis in a patient with idiopathic infantile hypercalcemia (38).

The etiology of WBS was not identified until 1993, with the discovery of the gene encoding elastin. Approximately 95% of WBS patients have microscopic deletions (1.5 to 2.0 Mb) (39-41) in the elastin locus, which is detectable by FISH (42,43). The clinical criteria for diagnosis (44) include typical facial features (broad forehead, orbital ridges with a ''startled'' look, short palpebral fissures, epicanthus, excessive subcutaneous tissue around the eyes, saddle nose with a long nasolabial groove, and thick lips), associated with one or more of the following characteristics:

- Cardiovascular anomalies, predominantly supravalvular aortic or pulmonary artery stenosis;
- Irritability;
- Learning difficulties;
- Low stature development;
- Hypercalcemia;
- Overly social personality (''cocktail party''-type personality); and
- Dental anomalies.

Orthopedic disorders have often been described in WBS patients. Joint contractures (45), bilateral extra-sacral folds (46) and clinodactyly (11) affect approximately half of these

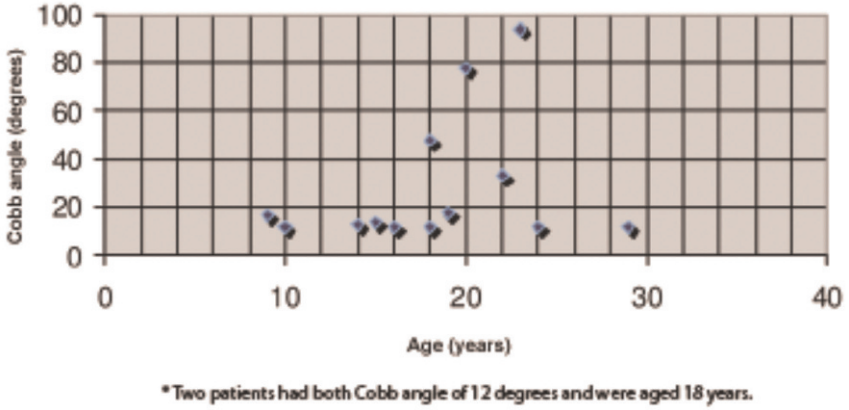

Figure 2 - Cobb angle in the scoliosis main curve in Williams-Beuren syndrome patients according to age*.

patients; limitations of forearm supination and radio-ulnar synostosis are observed in approximately one quarter of patients (47); and hallux valgus is the most frequent alteration, occurring in approximately 78% of patients (13).

Despite extensive involvement of the musculoskeletal apparatus in WBS patients, few studies have shown involvement of the spine.

In 1988, Morris et al. described scoliosis in 12% of patients with WBS in a classic series of 42 individuals aged 1-34 years old (13).

In 1994, Osebold and King published a case report of a 10-year-old girl with WBS, showing characteristic behavior and facies, mental retardation and a growth disorder. This patient had scoliosis that, despite the use of thoracolumbar orthosis, progressed rapidly to 95°, requiring surgical stabilization (17). At that time, the authors reviewed all of the available literature describing the syndrome and found only a single, brief mention of spinal deformity. At the end of the article, the authors implored spine surgeons to be aware that the progression of scoliosis could occur quickly in patients with WBS.

In 2002, Sugayama described a scoliosis prevalence of 20% in 20 patients, aged between 5 and 17 years old (18). In 2010, Morris et al. evaluated 111 patients aged between 8 and 45 years old and observed a scoliosis prevalence of 18% in patients with a confirmed diagnosis of WBS. There was no significant difference between the sexes and severe scoliosis occurred in approximately 5.4% of the cases with the deformity (19).

This research was based on a sample of patients drawn from a population that was regularly followed up at a specialized center in the city of São Paulo, Brazil. São Paulo is the largest metropolis in the country, and it is a reference destination for those seeking tertiary and quaternary health care from all of the regions of the country. Therefore, it would be reasonable to assume that the majority of the cases (if not all cases) in Brazil would be seen at our hospital during follow-up. Nevertheless, we contacted the Brazilian Association of Williams-Beuren Syndrome and we were informed that there were 51 patients registered in Brazil. We could therefore estimate that our population of 50 patients was a good representation of all of the WBS patients in our country.

The prevalence of scoliosis in this study was higher than that in other populations. Of the 50 patients initially identified, 9 failed to attend the medical examinations. Because our hospital is a public institution with a limited budget, it was not possible to provide transportation for patients who alleged that they were unable to attend due to economic problems. Such an inability might be a difficulty affecting the lives of patients with genetic syndromes and scoliosis deformities, leading to decreased access to proper health care. This inability must be noted as a study limitation, because it is possible that some of these absent patients were not interested in coming because they did not believe that they had any spinal deformity. If, once examined, these 9 patients were found to be *negative* for scoliosis, the prevalence of scoliosis among WBS patients would have decreased from 34.1% to 28%, which is nevertheless a high prevalence. However, if the patients had been examined and deemed *positive* for scoliosis, the prevalence would be even higher: 46%. However, this is merely speculative. Only a study designed specifically for the purposes of comparing prevalence would be capable of clarifying the variables that could explain the high prevalence of scoliosis among WBS patients.

Therefore, among the patients with WBS who were followed up at our public university hospital, which is a referral center for the disease in Brazil, the prevalence of scoliosis was 34.1%, without any significant associations between age or sex and the severity of spinal deformity.

This study was approved by our local Ethics Committee (Instituto de Ortopedia e Traumatologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo).

AUTHOR CONTRIBUTIONS

Damasceno ML and Cristante AF designed the study, collected and analyzed the data, wrote the manuscript and revised the final version to be published. Marcon RM and Barros Filho TE assisted with the study design and interpretation of the data, and they revised the final version to be published.

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