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Research Article

The Incidence of Fractures in Prader-Willi Syndrome across the Age Spectrum

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Abstract

Background: Osteoporosis is a common feature of Prader-Willi Syndrome (PWS), but the true incidence of fractures from infancy through adulthood in this population has not been previously studied.

Objective: Characterize the incidence of fractures across the age spectrum in the Israeli PWS cohort.

Methods: Clinic charts of all 160 individuals with genetically confirmed PWS known to the national PWS multidisciplinary clinic were reviewed. Parents or caregivers were contacted by telephone to confirm and update data regarding the incidence of fractures. Two families were lost to follow-up. The study group consisted of 158 individuals (81 M/77 F) from age 4 months to 52.8 years.

Results: One or more fractures were reported in 35 (22.2%) individuals: 17 M/18 F, ages 4.7-52.8 years (23.2±10.3). For the remaining 123 (76.9%) individuals there was no history of fractures: 64 M/59 F ages 0.4-41.3 years (11.7±10.1). The youngest age at fracture onset was 1.5 years and the oldest was 40 years. Fractures were reported in 5.0%, 25.7% and 50.0% of individuals ages 0.4-11.9, 12-20 and >20 years, respectively. Twenty-four of the 35 individuals with fractures had one fracture; the other eleven had two to three fractures. For adults, BMI was 29.9±5.8 kg/m^2 in the fracture group compared with 35.2±5.8 kg/m^2 in those with no fractures (NS).

Conclusion: Fractures are frequent in individuals with PWS. The incidence correlates with age and is greater in individuals with UPD. Sex and BMI were not risk factors for fracture occurrence. Exercise programs as well as medications may help prevent osteoporosis and should be tailored to each patient's hormonal and anthropometric profile.

Keywords: Prader-Willi syndrome; Fractures; Bone mineral density; Osteoporosis

Abbreviations

BMI: Body Mass Index; PWS: Prader-Willi Syndrome; GH: Growth Hormone; DEL: Deletion; UPD: Uniparental Disomy; IC: Imprinting Center Defect; MOS: Mosaicism; UN: Unknown

Introduction

Prader-Willi Syndrome (PWS) is a neurogenetic disorder characterized by variable expression of physical, cognitive and behavioral impairments. Hyperphagia and morbid obesity, hypotonia, hypogonadism and growth hormone deficiency are among the major features of this syndrome. The genetic basis for PWS is the absence of paternally expressed imprinted genes at 15q11.2-q13 due to deletion of this region on the paternally-inherited chromosome (65-75% of individuals), maternal uniparental disomy (20-30%), or an imprinting center defect (1-3%) [1]. Because of the low bone mineral density (BMD), the risk of fractures is increased, particularly in long bones [2]. Fractures can cause significant pain, disability, reduced quality of life and may result in premature death [3].

The incidence of fractures in PWS was estimated to be 24-44% according to two reports based on relatively small series [2,4]. Among PWS adults, the incidence of fractures was reported to be 44% [5]. There are, however, no data, regarding fracture incidence in a large PWS cohort across the entire age spectrum. In this report, we describe the occurrence of fractures in a large, nationwide cohort of PWS individuals from infancy to adulthood.

Patient Population and Methods

This study was approved by the institutional review board of the Shaare Zedek Medical Center, Jerusalem, Israel. Written informed consent was obtained from participants, parents and/or legal guardians.

Of 160 patients with genetically documented PWS followed in the Israel national multidisciplinary clinic at the Shaare Zedek Medical Center in Jerusalem, 158 (81 males, 77 females) participated in the study. Ages ranged from 4 months to 52.8 years. We divided the patients into three age groups: 79 children (4 months-11.9 years), 35 adolescents (12.0 to 19.9 years) and 44 adults (20.0-52.8 years). Characteristics of the study population including genetic subtypes are shown in (Table 1). 35 of the 81 male participants and 36 of the 77 female participants were or had been treated with recombinant human growth hormone. Four of the 25 male participants and 2 of the

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Table 1: Characteristics of the study population. The male/female ratios, age ranges and mean±standard deviation of age and genetic subtype (DEL: Deletion; UPD: Uniparental Disomy; IC: Imprinting Center Defect; or other) are shown according to each of the three age groups. The genetic subtype "other" includes one patient with a mosaic genotype and one patient diagnosed as PWS on the basis of an abnormal methylation test, but for whom the specific subtype has not yet been determined.

Age group	Children	Adolescents	Adults	Total
Number	79 (50%)	35 (22%)	44 (28%)	158 (100%)
Male/Female	43/36	13/22	25/19	81/77
Age Range(Mean±SD)	4 Months-11.9 Yrs (5.2±3.3)	12.0-19.9 Yrs (15.6±2.1)	20-52.8 Yrs (25.8±10.7)	4 Months-52.8 Yrs (14.3±11.2)
Genetic subtype(DEL/UPD/IC/other)	53/24/0/2	19/15/1/0	26/17/1/0	98/56/2/2

Table 2: Characteristics of PWS patients with a history of fractures compared with those patients with no history of fractures.The age, BMI and genetic subtype are shown according to the three age groups: children younger than 12 years; adolescents 12.0 to 19.9 years; and adults, 20.0 to 52.8 years. The "GH" column indicates the number of patients in each age group who are currently treated or who had received treatment with growth hormone in the past.Genetic subtypes are shown as DEL: Deletion; UPD: Uniparental Disomy; or "other" which includes IC: Imprinting Center Defect; MOS: Mosaicism; UN: Unknown (Positive Methylation Test, but specific subtyping is unknown). One asterisk (*) indicates one patient with mosaicism and one patient whose genetic subtype is unknown; two asterisks (**) indicate patients with an imprinting center defect.

Age Group	Age (Yrs) Range (Mean±SD)		Number of patients		BMI-kg/m² (Mean±SD)		Number of patients treated with growth hormone		Genetic subtype (DEL/UPD/ Other)	
	Fx	No Fx	Fx	No Fx	Fx	No Fx	Fx	No Fx	Fx	No Fx
Children										
Males	4.7-5.4 (5.0±0.53)	0.4-11.8 (4.43±2.95)	2	41			2	26	0/2/0	23/16/2*
Females	5.3-9.4 (7.3±2.92)	0.6-11.9 (6.09±3.68)	2	34			2	25	2/0/0	28/6/0
Adolescents										
Males	12.8-18.4 (16.0±2.86)	12.5-18.6 (15.43±2.25)	3	10			2	4	2/4/0	6/3/1**
Females	13.3-18.6 (16.2±2.27)	12.5-19.2 (15.32±2.03)	6	16			3	7	2/4/0	9/7/2000
Adults										
Males	21.5-35.9 (28.5±4.75)	20.2-41.3 (28.8±6.69)	12	13	29.2±5.6	34.8±5.3	0	1	5/7/0	10/3/0
Females	20.6-52.8 (30.1±10.09)	20.0-40.7 (30.71±6.18)	10	9	30.3±6.6	35.7±6.7	0	0	7/3/0	4/4/1**

19 female participants were or had been treated with sex hormones (testosterone or estrogen preparations). Supplemental vitamin D at a dose range of 600 to 1,000 I.U. daily was prescribed to each patient, but compliance was highly variable.

Demographic parameters including age, weight, height and BMI, as well as history of drug treatment and previous fractures were retrieved from patients' charts. All families were interviewed by telephone to confirm and update data about fracture occurrence.

Statistical Methods

Relations between occurrences of fractures and sex, genotype and age group were analyzed using Chi-square and Fisher exact tests. For the relation between occurrence of fractures and BMI in the adult group, t-test was used to compare BMI between those who have ever had at least one fracture and those who have not. Similar analyses were used to compare various features of patients who had single *vs.* multiple fractures.

Results

Fractures occurred in 4/79 (5.0%) of the children, in 9/35 (25.7%) of the adolescents and in 22/44 (50.0%) of adults. The youngest age at which a fracture occurred was 1.5 years in a boy who is now 5-1/2 years old and who so far has had no subsequent fractures. The oldest patient to report a fracture was a 40 year-old woman.

Characteristics of the patients with no history of fractures including genetic subtypes, GH treatment and BMI according to the three age groups are shown in (Table 2). The same parameters for patients who did have a history of fractures are shown in (Table 2).

There was a significant correlation between fracture occurrence and age ($p<0.001$). A tendency to significant correlation was found between fractures and genotype ($p=0.071$): approximately 25% of the individuals with the deletion genotype had fractures, compared to 50% of these with UPD.

No correlation was found between fracture occurrence and sex, BMI and hormonal replacement therapy (HRT). One of the 4 males who received testosterone had 2 fractures and one of the two females treated with HRT had 3 fractures.

We found no significant differences which distinguished the group with a history of a single fracture from those patients with multiple fractures.

Discussion

This study is the first to describe fracture incidence in a large PWS cohort including all age groups from infancy to adulthood. We found a high incidence (22.2%) of fractures in Prader-Willi Syndrome across the entire age spectrum. Although the incidence of fractures in childhood was relatively low (5.1%), patients continued to experience fractures during adolescence and to an even greater extent in young

adults. Among adolescents 25% had a history of fractures while fractures were noted in half of the young adult patients. Butler, et al. reported a fracture rate of 29% in a population based study which included 66 individuals with a mean age of 19 years (range from 0-41.3 years) [6]. Sinnema, et al. noted a history of fractures in 44% of 102 PWS adults [5]. Kronnen, et al. studied 31 (23 males, 8 females) individuals with PWS with an average age of 22 years (range: 8-39 years). Fourteen had sustained a total of 58 fractures, with 6 patients describing multiple fractures (range 2-7) [2]. Shim, et al. (2010) reported that 9/38 patients with PWS (24.3%) with an average age of 12.0 years (range: 3.6-20.2 years) had a past fracture history [4]. Three of these patients sustained multiple fractures (range: 2-4) and 3 patients underwent surgical treatment. All fractures healed without complications [4].

The youngest patient to sustain a fracture was an 18-month old boy and the oldest patient to report a fracture was a 40 year-old woman. BMI was not a risk factor for fractures in our study population. Consistent with the findings of Butler, et al. we did not find a greater incidence of fractures in females compared to males [6]. In our PWS cohort which included only one individual above the age of 50 years, the incidence of fractures was much greater than in a general population, especially for males. In the general population, approximately one in three women over age 50 will experience osteoporotic fractures, as will one in five men above age 50 years [7-9].

Because our study is retrospective, we were not able to determine the exact ages at which fractures occurred. Other limitations of our study include reliance on parental and caretakers' memories regarding fracture occurrence along with lack of precise information regarding type of fracture, bone density results around the time of the fracture, as well as duration and compliance with hormonal therapy.

Nevertheless, our study showed that people with PWS continue to experience fractures throughout childhood and adolescence and into adulthood. Fractures occur in both sexes and are more frequent among PWS adults compared to a normal population. If most childhood fractures are due to accidents or trauma, other factors, including hormonal and nutritional deficiencies and low levels of physical activity contribute to the high incidence of fractures among PWS adults. Fractures negatively impact quality of life and increase morbidity in the PWS population. Medical personnel and caregivers need to develop specific guidelines for the PWS population to reduce the risk of fractures by correcting hormonal and nutritional deficiencies, monitoring bone density and promoting appropriate exercise programs.

References

1. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012; 14: 10-26.
2. Kroonen LT, Herman M, Pizzutillo PD, Macewen GD. Prader-Willi Syndrome: clinical concerns for the orthopaedic surgeon. J Pediatr Orthop. 2006; 26: 673-679.
3. Gupta A, March L. Treating osteoporosis. Aust Prescr. 2016; 39: 40-46.
4. Shim JS, Lee SH, Seo SW, Koo KH, Jin DK. The musculoskeletal manifestations of Prader-Willi Syndrome. J Pediatr Orthop. 2010; 30: 390-395.
5. Sinnema M, Maaskant MA, Valk HM, Nieuwpoort IC, Drent ML, Curfs LM, et al. Physical health problems in adults with Prader-Willi Syndrome. Am J Med Genet A. 2011; 155: 2112-2124.
6. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Prevalence of and risk factors for physical ill-health in people with Prader-Willi Syndrome: a population-based study. Dev Med Child Neurol. 2002; 44: 248-255.
7. Melton LJ, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL. Bone density and fracture risk in men. J Bone Miner Res. 1998; 13: 1915-1923.
8. Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis? J Bone Miner Res. 1992; 7: 1005-1010.
9. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int. 2000; 11: 669-674.

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