

GH treatment, BMI and different genotypes in patients with Prader-Willi syndrome and scoliosis: Is there any relationship?

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ABSTRACT

The purpose of this study is to try to find a protocol defining a clinical diagnostic procedure for the patients to be admitted to the authors' Institute to receive treatment for either suspected or confirmed diagnosis of spine deformity in Prader-Willi syndrome (PWS). The aim is to evaluate every subject from the diagnostic point of view, assessing variability of clinical expression and evolution of spinal deformity in the light of the related genetic aspects, thus providing a univocal protocol. The present series only includes patients (18 cases) with PWS, 7 hospitalized for surgical treatment of scoliosis, 11 followed-up at the authors' institute only for conservative treatment of scoliosis. Both BMI tracks (weight/height²) and BMI Z-score (only for children older than 2 years) were assessed. Moreover, the GH treatment was evaluated for each group of patients as follows: being administered, suspended or no treatment. Finally, the gene was compared with BMI. No relationship was observed either between GH treatment and mean BMI or between genetics and mean BMI. More patients should be seen by the authors to confirm or refute the current findings.

Keywords: Scoliosis; Prader-Willi; GH; BMI

1. INTRODUCTION

The PWS is a rare and complex genetic disorder considered the most common genetic cause of morbid obesity, first described by Prader *et al.* back in 1956 [1].

The prevalence reported in epidemiological studies

varies between 1 in 8000 and 1 in 134,000 whereas the number of births identified as being PWS cases varies between 1 in 15,000 and 1 in 30,000. In 2010, the European Organization for Rare Disease in partnership with Orphanet estimated the number of person living with PWS in Europe to be around 10.7 per 100,000 (1:9346) [2,3].

Genes associated with PWS are known to be expressed from chromosome 15 derived from the father, but not from the mother. Loss of the normal contribution from paternally inherited genes in this interval leads to the PWS phenotype, since maternal genes are normally inactivated. This type of genetic regulation dependent on the sex of the transmitting parent is termed genomic imprinting [4].

The three genetic mechanisms involved in PWS are: interstitial deletions of the paternal chromosome 15, which are of two classes differing by their total length (T1 deletion larger than T2 deletion) [5]; maternal uniparental disomy (mUPD, or two copies of chromosome 15 from mother and none from father), [6] which can be either hetero- or isodisomy (meaning two different maternal chromosomes or two copies of the same maternal chromosome), and imprinting defects [7] and translocations. Recently it has been suggested that additional factors such as maternal age, environmental variables causing genetic errors, the use of reproductive technologies and diagnostic methodology have influenced the previously recognized distribution of genetic subtypes, with mUPD occurring more frequently than previously recognized [8,9].

In Italy PWS is related to deletion for 69% of the cases, mUPD for 30% [10].

The original consensus diagnostic criteria of Holm *et al.*, 1993 [11] was recently revised [12] to indicate when genetic analysis should be performed [13].

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In the foetus and newborn, PWS is generally characterized by decreased fetal movement, prenatal and post-natal hypotonia (or diminish muscular tone) and poor suckling, causing decreased movement, lethargy, abnormal cry, breathing difficulties requiring special feeding techniques and poor reflexes, and resulting in failure to thrive. Whereas hypotonia improves over time, and difficulties in feeding are replaced by normal calorie intake with a beginning of central obesity during the toddler years [14,15].

Characteristic facial features including narrow bifrontal diameter with dolichocephaly (head disproportionately long and narrow), almond-shaped eyes with ocular defects (estropia, myopia), thin upper lip with down-turned mouth and thick saliva.

In preadolescence, mild to moderate mental deficiency, behavioral disorders (e.g. obsessive-compulsive characteristics, self-injury behavior, skin-picking, temper tantrums, manipulative behavior, impulsivity, stubbornness) and cognitive disabilities also become manifest and intensify with age. Musculoskeletal problems may also become apparent, such as scoliosis (abnormal back curvature) [16-20]. Hyperkyphotic deformity can be observed in nearly 40% of the patients [21-23].

The syndrome is associated with growth hormone deficiency (GHD). According to cross-sectional, prospective and retrospective studies, GHD prevalence ranged from 58% to 100% [24,25]. Similar prevalence rates (74%) were observed in the international, observational KIGS database [26].

Obesity is a primary cause of increased morbidity and premature mortality in PWS. It leads to complications such as type 2 diabetes mellitus, hypertension, atherosclerosis, hyperlipidemia, cardiovascular diseases, respiratory insufficiencies, thrombophlebitis, leg edema, and sleep apnea. Increased rates of scoliosis are also observed.

Although the pharmacological therapy with growth hormone (GH) provides satisfactory results, its impact on progression of spinal deformities still remains controversial [21,27].

According to a study conducted in the UK population, mortality rate of individuals with PWS not treated with GH was estimated at 3% per year between age 6 and 56 years and at 7% per year above 30 years of age. Epidemiological data from Italy noted 18 deaths over a 20-year period of observation (4.2%), occurring in both the pediatric and adult subjects (age range: 0.5 - 39.3). Causes of death in children are usually associated with respiratory infection or insufficiency, whereas mortality in adults is found to be primarily circulatory and/or respiratory failure [10].

The various different clinical and pathological conditions with onset during the pediatric and early adolescent

age, and affecting the general aspect and health status, can change or delay treatment of spinal deformities and subsequently entail negative consequences in terms of life quality and expectation. Scoliosis is reported to require active treatment in 15% to 20% of the cases and to behave as an idiopathic scoliosis, with high risk of progression during adolescence [1,22].

Absent, inadequate or delayed treatment of spinal deformities can jeopardize the patient's respiratory and cardiocirculatory "compliance", which is already severely compromised by the other remarkable phenotypic aspects of the syndrome.

2. MATERIALS AND METHODS

The present case series includes 18 patients, 11 of which (9 males and 3 females) were seen at the Rare Disease Outpatients' Unit for conservative treatment; mean age was 4.2 years (range, 0.5 to 16.1). Another 7 patients were surgically treated: they were 5 males and 2 females, aged 12.8 years on average (range, 10 to 14.6 years).

Regarding the patients' origin, 87% came from outside the region (Emilia-Romagna): 61% from the central southern area and 44% from Latium, in particular (**Figure 1**).

For all of the 18 patients, both standard BMI (weight/height²) and the BMI Z-score developed by the Centers for Disease Control and Prevention (CDC) were calculated. The latter is to be preferred when assessing children [28,29] to allow for their classification into underweight/normal weight/overweight/obesity (**Table 1**), although more recent studies tend to attach importance to the use of BMI also for younger patients [30]. As a matter of fact, the values of BMI Z-score are charted for specific



Figure 1. Patients' Origin Region of origin of the patients belonging to the series with PWS.

Table 1. Weight categories corresponding to percentile ranges.

Weight Status Category	Percentile Range
Underweight	Less than the 5th percentile
Healthy Weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obesity	Equal to or greater than the 95th percentile

Z-scores (-2, -1.5, -1, -0.5, 0, 0.5, 1, 1.5, 2), corresponding to as many different growth curves for the children. Scores are used to express the standard deviation from the mean calculated on the reference population. The corresponding percentiles in standard normal distribution are calculated from Z-scores; the different weight categories (underweight/normal weight/overweight/obesity) derive from the percentile ranges. Percentiles are plotted in “growth charts by age” (**Figure 2**) for each gender. Proceeding this way, the BMI of a specific child is plotted on the chart against the other children of the same sex and age.

Anyway, BMI Z-score, can be calculated only for patients older than 2 years and therefore could not have been applied in 5 cases, thus reducing the current case series—which is small, the study involving a rare disease and referring to a single diagnosis and treatment centre—by 30% approximately. Therefore, both BMI indices were used.

The GH treatment was assessed in all of the 18 subjects: being administered, suspended or no treatment.

The genotype is known only for the group of 12 PW patients conservatively treated at the outpatients' unit (deletion of chromosome 15 or uniparental disomy), since the genetic test was not routinely performed when the surgically-treated patients' data were recorded.

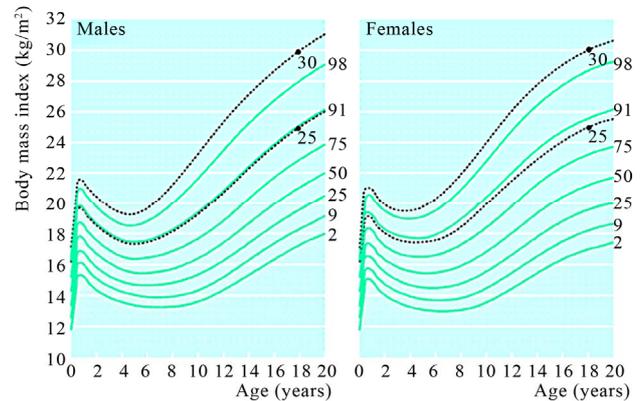
The purpose of the study was to evaluate the relationship between BMI and GH treatment and, only for the outpatients, the relationship between BMI and genotype. The two groups of cases were assessed both separately and as a whole. The statistical tests used were the following: either the Chi-square test or the Fisher's exact test when the BMI-Z score was calculated, and the Wilcoxon test to calculate the differences between the average values for the BMI.

3. RESULTS

Of the 12 outpatients with PWS (**Table 2**), 9 were males and 3 females; 87% came from outside the Region (Emilia-Romagna): 61% from the central southern area, Latium in particular (44%); 11 had received conservative treatment, 1 surgical treatment.

The BMI of the PW children seen at the Outpatients' Unit turned out to be 17.54 (range, 11.49 to 29.48), whereas the BMI Z-score was 0.7 (range, -0.7 to 1.7).

Their medical history revealed the presence, absence

**Figure 2.** BMI for age and sex body mass index for age percentiles by sex.**Table 2.** Characteristics of PWS outpatients.

Characteristics	Values
Patients' number by sex	9 M 3 F
Mean age	4.2 yrs (range, 0.5 to 16.1)
BMI	17.54 (range, 11.5 to 29.5)
BMI Z-score	0.66 (range, -0.7 to 1.7) 70.4% percentile (range, 25.5% to 95.6%)
GH	8 treated 2 suspended treatment 2 not recorded
Genotype	9 microdeletion of chromosome 15 3 uniparental disomy

of suspension of the GH treatment: GH had been administered to 8 patients, suspended in 2 cases and no information was available for the 2 remaining cases.

Many studies (references 1 to 9) refer to the GH treatment in PWS without reaching unambiguous conclusions.

The present case series showed a statistically significant ($p < 0.05$) difference in terms of mean BMI which proved to be lower in children receiving GH treatment (16.8, ± 1.1) than in those who had had it suspended (24.7, d.s. ± 6.8) (**Table 3**).

In addition, genetics was compared with BMI as follows: mean BMI equal to 18 for the 9 patients with microdeletion of chromosome 15 *versus* mean BMI equal to 15 for the 3 patients with uniparental disomy. The difference between BMI in the 2 groups did not result to be statistically significant (**Table 3**).

Considering the other group of 7 PWS patients operated on for scoliosis (**Table 4**), 5 of them were males with mean age of 12.8 yrs (range, 10 to 14.6).

The BMI of the 7 patients with PW operated on for scoliosis turned out to be equal to 29.41 (range, 21.03 to 41.72), whereas the BMI Z-score was 1.8 (range, 0.51 to 2.77). This value was notably higher than that observed

Table 3. BMI relationship with GH and genotype in PW outpatients.

	GH treated	GH interrupted	p
Mean BMI	16.8 (±1.1)	24.7 (±6.8)	0.05
	Microdeletion of chromosome 15	Uniparental disomy	
Mean BMI	18 (±4.1)	15 (±2.8)	n.s.

Table 4. Characteristics of PWS surgically-treated patients.

Characteristics	Values
Patients' number by sex	5 M 2 F
Mean age	12.8 yrs (range, 10 to 14.6)
BMI	29.41 (range, 21.0 to 41.7)
BMI Z-score	1.8 (range 0.5 to 2.8).
GH	4 treated 3 not treated

in outpatients who also were much younger.

The BMI Z-score could be calculated for all of the patients belonging to this group; subsequently, using growth charts by age percentiles, the weight categories could be assessed and the following results achieved: normal weight in 2 cases, overweight in 1 and obesity in 4.

Focus was put on the relationship between weight categories (obesity and overweight were considered as a whole, due to the low number of subjects to be included in the latter) and the corresponding GH treatment: of the 4 cases receiving Gh treatment, 3 (75%) were obese and one overweight; of the 3 who did not receive the GH treatment, 2 were normal weight (75%) and 1 obese. The test proved to be not significant.

Besides, since surgery cannot be considered as an effect modifier of this relationship, outpatients and surgically-treated patients were assessed as a whole. In this case, the authors compared the average BMI for the 2 groups instead of the weight categories deriving from the BMI Z-score: no significant difference was found (**Table 5**).

4. DISCUSSION AND CONCLUSIONS

Before to begin GH treatment, many steps have to be accomplished, starting from genetic confirmation of PWS, On GH treatment regular clinical assessment of height, weight, BMI, body composition, pubertal status, scoliosis, and side effects every 2 - 6 months should be done. At cessation of GH, treatment uncontrolled progression of obesity should be present in terms of how it has been reported in the International—Second Expert Meeting of the Comprehensive Care of Patients with PWS (2008) [31].

Table 5. Mean BMI relationship with GH in PWS patients.

	GH administered	GH suspended	No GH treatment	GH Not recorded	P
Mean BMI	20.7 (±6.1)	24.7 (±6.8)	31.4 (±14.6)	13.3 (±2.6)	n.s.

The only report that state scoliosis evolution and GH treatment is a two-year open label study of Sode-Carlson *et al.* (2011) [32]. This study reported that scoliosis progressed in six of 38 patients, whereas three patients had a decrease of Cobb angle of more than 5°. It is unclear if these observations are the results of GH treatment or the natural history of progression of scoliosis in PWS adults. Similar observations were reported for edema which is often seen in clinical studies of GH treatment in adults [33-35].

In our study, no significant difference in terms of BMI was observed between patients receiving GH treatment and patients who did not receive it. No relationship between GH treatment and mean BMI was seen. Anyway, additional studies can be performed creating a subgroup from the present case series which includes the patients younger than 2 yrs, and replacing the BMI with the BMI Z-score.

No relationship between genetics and mean BMI was found in the outpatients' group.

However, our case series is being too small, as it always happens with rare diseases, and for recording of data incomplete, more patients need to be examined by the authors to confirm or refute these findings.

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