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Metabolic syndrome in adult patients with Prader–Willi syndrome

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Abstract *Background and aims:* Prader–Willi syndrome (PWS), the most common genetic cause of obesity, is characterized by elevated morbility and mortality in all ages. In this context, non-obese PWS children showed low frequency of metabolic syndrome (MetS), while a comparable prevalence was observed in obese PWS and obese controls. Aim of this study was to estimate the occurrence of MetS and its components in a large group of PWS adults, according to obesity status.
Methods and results: A cross-sectional study was performed in 108 PWS aged 18.0–43.2 years (87 obese and 21 non-obese) and in 85 controls with nonsyndromic obesity matched for age, gender, and BMI with obese PWS.

Abbreviations: PWS, Prader–Willi syndrome; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; BMI, body mass index; DELETED, interstitial deletion of the proximal long arm of chromosome 15 (del15q11–q13); UPD15, uniparental maternal disomy for chromosome 15; WC, waist circumference; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA-index, homeostasis model assessment index.

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Non-obese PWS showed lower waist circumference, insulin, HOMA-index, triglycerides, diastolic blood pressure, and higher HDL-C than both obese PWS and obese controls ($p < 0.017$). Obese PWS showed higher glucose and systolic blood pressure than both non-obese PWS and obese controls ($p < 0.017$). MetS was found in 1/21 (4.8%) non-obese PWS, 36/87 (41.4%) obese PWS and 39/85 (45.9%) obese controls. Non-obese PWS showed lower frequency for each MetS component as compared with obese PWS and obese controls. PWS patients with deletion of the chromosome 15q11—13 showed a lower risk for low HDL-C ($p < 0.01$) and a trend towards a lower MetS risk ($p < 0.06$) compared to subjects without deletion.
Conclusion: Our findings suggest the main role that obesity status plays on the individual metabolic risk clustering in PWS adults. Early identification of MetS could be helpful to improve morbidity and prevent mortality in such patients.

Introduction

Prader—Willi syndrome (PWS) is a contiguous gene syndrome caused by the non-expression of the paternal alleles in the PWS region of chromosome 15q11—13 [1]. PWS is the single most common known genetic cause of obesity with an estimated population prevalence varying from 1:49,911 up to 1:91,802 [2]. The clinical picture of PWS includes muscular hypotonicity, early childhood-onset obesity, characteristic appearance, hypogonadism, impaired growth hormone secretion, mild or severe mental retardation, and behavioral disturbance [3]. Some of the typical features of PWS seem to reflect a hypothalamic dysfunction [4]. In the early period of life, PWS is characterized by severe neonatal hypotonia, feeding problems and a failure to thrive. In absence of intervention, weight excess typically begins after 2—3 years of age and is later exacerbated by hyperphagia with lack of satiety. Consequently, a disproportionate accumulation of body fat develops as early as in childhood [5] and leads progressively to severe obesity by the adult age [3].

Retrospective studies estimated that yearly mortality rates was 7% in PWS patients older than 30 years [6]. Reduced life expectancy seems to be due to the complications conventionally related to obesity, including cardiovascular and respiratory problems as well as disorders associated with type 2 diabetes mellitus (T2DM) [7]. Nevertheless, the factors determining the evolution to cardiovascular disease and metabolic complications remains to be still elucidated. In non-PWS populations, several studies have shown that individuals with metabolic syndrome (MetS) have an increased risk of T2DM and coronary heart disease or are at a greater risk of developing them [8]. In this light, MetS might be one of the risk factors responsible for excessive mortality in PWS. The metabolic profile of PWS adults, however, is usually characterised by a healthier lipid profile and by a higher insulin sensitivity, compared with matched nonsyndromic obese subjects [9]. These findings seem to be due to an atypically reduced visceral fat depot, which is not common in nonsyndromic obesity [10]. Nevertheless, data on fat distribution in PWS are still conflicting [9,11]. In addition, impaired microvascular function and subnormal exercise capacity have been observed in young adults without ischemic symptoms [12], and several cardiovascular risk factors are already present in pre-pubertal children with PWS [13]. In this context, we have recently demonstrated that non-obese PWS children showed low MetS frequency, while a comparable prevalence was found in obese PWS and obese controls [14].

Since there are no data about the frequency of MetS in adult patients with PWS, the aim of our study was to estimate the occurrence of MetS in a large group of adults with genetically confirmed PWS. We also looked for metabolic differences between obese PWS and non-obese PWS subjects, and between obese PWS and a control group of patients with nonsyndromic obesity, matched for age-, gender- and body mass index (BMI).

Methods

Patients

One hundred and eight patients with genetically confirmed PWS, 47 males and 61 females, aged 18.0—43.2 years, were included in the study (Table 1). All patients showed the typical PWS clinical phenotype [15]. Seventy-three subjects had interstitial deletion of the proximal long arm of chromosome 15 (del15q11—q13) (DELETED), 27 had uniparental maternal disomy for chromosome 15 (UPD15) and 2 individuals had a de novo translocation involving chromosome 15. In addition, a positive methylation test was demonstrated in the remaining 6 PWS but the underlying genetic defect was not identified. The methylation pattern analysis of the PWS region was carried out according to standard diagnostic protocols for Southern blot and bisulphite methylation polymerase chain reaction [16].

At the time of the study, 23 subjects (10 males) had T2DM (15 were treated with oral hypoglycemic agents alone, 5 with insulin, 2 with insulin plus metformin, and one was on diet only). Fifty-two patients (26 males) had hypertension: 25 subjects were taking monotherapy ($n = 9$) or a combination therapy ($n = 16$), while 27 individuals were receiving no treatment. Two individuals were treated for high triglycerides (1 male). Five subjects suffered from hypothyroidism (2 males) and were biochemically euthyroid on thyroxine substitution. Twenty-three females and 3 males were undergoing sex steroid replacement treatment. All PWS were reported to have behavioral problems, and 40 patients were treated with neuroleptics (21 males). Subjects were divided according to the presence of obesity (see below) in obese PWS and non-obese PWS.