

CARDIOVASCULAR CHARACTERISTICS IN PATIENTS WITH PRADER-WILLI SYNDROME

Ingrid-Ioana Stafie¹, Maria-Magdalena Leon^{2,3}, Alexandra Maștaleru^{2,3}, Irina Mihaela Abdulan^{2,3}, Alexandru Dan Costache^{2,3}, Florin Mitu^{2,3,4,5}

¹Saint Spiridon County Hospital, 700111, Iasi, Romania

²Department of Internal Medicine I, Faculty of Medicine, University of Medicine and Pharmacy "Grigore T. Popa", 700115 Iasi, Romania

³Department of Cardiovascular Rehabilitation, Clinical Rehabilitation Hospital, 700661 Iasi, Romania

⁴Academy of Romanian Scientists, 700050 Iasi, Romania

⁵Academy of Medical Sciences, 030167 Bucharest, Romania

Corresponding author

E-mail: leon_mariamagdalena@yahoo.com

Rezumat

Sindromul Prader-Willi (PWS), cea mai comună formă de obezitate sindromică, este cauzat de absența expresiei genelor paterne pe cromozomul 15q11.2-q13 din cauza variațiilor genomice sau epigenetice, cum ar fi metilarea sau acetilarea ADN-ului și histonelor. Sindromul este adesea asociat cu tulburări comportamentale, deficiențe intelectuale, statură redusă, polifagie, hipogonadism și hipotonie musculară, toate provenind din disfuncția endocrină multiplă care caracterizează această condiție. Anomaliile cardiovasculare (CV) pot apărea chiar din primele etape ale vieții, iar pacienții cu PWS au un risc crescut de a dezvolta afecțiuni CV la o vârstă fragedă. Acest risc crescut pentru condițiile CV este atribuit unei interacțiuni complexe între caracteristicile somatice și comportamentale ale sindromului. Majoritatea pacienților cu sindrom Prader-Willi (PWS) prezintă modificări ale axei GH-IGF, indiferent de obezitate. Caracteristicile cardiovasculare specifice ale deficienței de hormon de creștere (GHD) la pacienții adulți cu PWS includ masa cardiacă redusă, fracția de ejeție scăzută și răspunsul cronotrop diminuat la dobutamină.

Cuvinte cheie: obezitate, sindrom Prader-Willi, anomalii cardiovasculare, deficiență de hormon de creștere.

Abstract

The most prevalent type of syndromic obesity is referred to as Prader-Willi Syndrome (PWS), being determined by the lack of expression of paternal genes on chromosome 15q11.2-q13 due to genomic or epigenetic variations, such as DNA and histone methylation or acetylation. The syndrome is frequently associated with behavioral disorders, intellectual deficiencies,



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short stature, polyphagia, hypogonadism and muscular hypotonia, all stemming from the multiple endocrine dysfunctions characterizing this condition.

Cardiovascular (CV) anomalies can manifest even in the early stages of life, and those with PWS have an elevated risk of early onset cardiovascular diseases. The somatic and behavioral aspects of the syndrome interact intricately to cause this increased risk for CV pathologies. Changes in the GH-IGF axis are seen in most Prader-Willi Syndrome (PWS) patients, irrespective of obesity. Specific cardiovascular features of GHD in adult PWS patients include reduced cardiac mass, decreased ejection fraction, and diminished chronotropic response to dobutamine.

Keywords: *obesity, Prader-Willi syndrome, cardiovascular anomalies, growth-hormone deficiency.*

Introduction

There are two types of childhood obesity: non-syndromic obesity and syndromic obesity. Alström syndrome, Bardet-Biedl syndrome, and Prader-Willi syndrome are among the disorders that fall under the category of syndromic obesity. On the other hand, non-syndromic obesity is separated into more prevalent types of polygenic obesity and rarer instances of monogenic obesity⁽¹⁾. Obesity adversely impacts hemodynamics and the structure and function of the cardiovascular system through various mechanisms. It increases the total blood volume and stress on the arterial walls and the left ventricular wall, induces cardiac structural changes, and leads to left ventricular systolic and diastolic dysfunction⁽²⁾.

General characteristics

The most prevalent type of syndromic obesity is referred to as Prader-Willi Syndrome (PWS), being determined by the lack of expression of paternal genes on chromosome 15q11.2-q13 due to genomic or epigenetic variations, such as DNA and histone methylation or acetylation. These variations influence gene expression regulation without altering the DNA sequence. Patients with this syndrome exhibit an increased rate of sudden and unexpected death, with variable causes between children and adults. Cardiovascular and respiratory diseases associated with obesity are often the primary causes of death in adults. The syndrome is also frequently associated with behavioral disorders, intellectual deficiencies, short stature,

polyphagia, hypogonadism, muscular hypotonia, and sleep-wake cycle disturbances, all stemming from the multiple endocrine dysfunction characterizing this condition. Growth is marked by moderate delay in intrauterine and postnatal development, absence of a growth spurt during puberty, and reduced stature at maturity. Although newborns with PWS present below-average weight, between the second and fourth years of life, they become obese due to uncontrolled compulsive appetite. Some PWS subjects have also been found to have premature coronary artery disease^(1,2,3,4).

The estimated incidence of PWS ranges between 1/10,000 and 1/45,000 live births, with an average life expectancy of 29.5 years, and no significant differences in incidence based on sex or ethnicity^(5,6).

Cardiovascular anomalies

Cardiovascular (CV) anomalies can manifest even in the early stages of life, and those with PWS have an elevated risk of early onset cardiovascular diseases. The somatic and behavioral aspects of the syndrome interact intricately to cause this increased risk for CV pathologies⁽⁷⁾. A comprehensive cohort study conducted nationwide in Denmark, which involved 155 patients with PWS tracked from birth until the initial instance of a significant health event, revealed a heightened risk of myocardial infarction, deep venous thrombosis, and pulmonary embolism compared to a similar group from the general population. Consequently, it's crucial to begin monitoring cardiovascular risk factors in adolescence, with annual assessments of electrocardiograms, lipid levels, and pressure profiles. More in-depth examinations, like cardiac ultrasound, 24-hour ambulatory

blood pressure monitoring, or tests for inducible myocardial ischemia, should be conducted as needed⁽⁸⁾.

Endocrine dysfunction

The majority of patients with PWS exhibit alterations in the GH-IGF axis, irrespective of obesity. Between 40-100% are diagnosed with growth hormone deficiency (GHD), as evidenced by various GH stimulation tests, reduced levels of IGF-I, compromised longitudinal growth, and decreased muscle and bone mass. GHD is associated with increased adipose tissue, glucolipidic anomalies, and cardiovascular conditions, most of which are reversible with GH therapy⁽⁹⁾.

The initiation of Growth Hormone (GH) treatment for children with PWS began in the 1990s. Notable improvements in height and body composition were observed, leading to the approval of GH treatment for children with PWS by the U.S. Food and Drug Administration and the European Medicines Agency, regardless of the GH secretory status⁽¹⁰⁾.

Specific cardiovascular features of GHD in adult PWS patients include reduced cardiac mass, decreased ejection fraction, and diminished chronotropic response to dobutamine. GHD also results in a reduced rate of cardiac muscle growth, diminished cardiac performance during exertion, dyslipidemia, and endothelial dysfunction. Twelve months of GH therapy reduced CRP levels, a known marker of cardiovascular risk, and increased left ventricular mass in most patients. GH and IGF-I stimulate genes related to cardiac hypertrophy, underscoring the positive inotropic effects of GH. There is no evidence that GH causes impairments to the right side of the heart. Reduced GH secretion



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is noted in any age group (including adults and subjects under 18 years old) patient with PWS, leading to structural cardiac anomalies and myocardial dysfunctions, resulting in reduced diastolic filling and compromised left ventricular response during intense effort. Patients with GHD often exhibit increased intima-media thickness and a higher frequency of atheromatous plaques, elevating cardiovascular risk.

Both men and women patients over 18 years old with hypopituitarism have a shorter life expectancy, with a mortality rate over twice as high due to cardiovascular conditions. GH/IGF-I mediates cardiac risk regulation in PWS patients. GH deficiency elevates cardiovascular risk, affecting lipoprotein turnover regulation and reducing LDL receptors. GH therapy in PWS optimizes lipid metabolism and body structure over a 12-month period. Although GH reduces LDL cholesterol and increases HDL cholesterol, this positive effect could be neutralized by an increase in lipoprotein (a) (Lp (a)), independently associated with a high risk of atherosclerosis^(3,9,11).

Genetics

In a recent study on PWS, it was found that 61% of patients had a 15q11.2-q13 deletion, 36% showed maternal uniparental disomy, and 3% were due to imprinting defects.

Genetic testing is used to diagnose this disorder. DNA methylation analysis can detect alterations in parent-specific imprinting on chromosome 15, while fluorescence in situ hybridization or microarray-based methods can be used to identify chromosome 15 deletions. Examining DNA polymorphism in affected subjects and their parents is utilized to identify uniparental disomy. Genetic testing is crucial for confirming the diagnosis of PWS, particularly in cases with unusual symptoms or in persons too young for traditional clinical diagnostic methods⁽¹⁾.

In children with PWS exhibiting chromosome 15 anomalies, various cardiac abnormalities have been identified, including microdeletions of genes vital for angiogenesis and cardiac development, such as NR2F2 and ACTC. Cases of dilated cardiomyopathy in infants and adults with PWS have also been reported, which are not related to the absence of essential genes for cardiac structure. Overall, irreversible critical conditions are common reasons for unexpected death among both obese and normal-weight PWS patients, attributable to cardiovascular diseases, either ischemic or non-ischemic, in approximately 40-60% of cases⁽¹²⁾.

Cardiovascular risk factors

Allemand and colleagues emphasized that many cardiovascular risk factors are already

present in prepubertal children with PWS. Body fat percentage increases in all children over 4 years old, whereas 33% of this age group have an elevated waist-hip ratio (WHR). Additionally, 25% of these patients have heightened levels of LDL cholesterol and Apo-B. A significant number of children under the age of 4 exhibited low HDL values. After 3 years of growth hormone (GH) treatment, the body fat percentage reduced to upper normal levels, WHR adjusted, and the ratio of LDL cholesterol to HDL cholesterol balanced in all patients in the three age groups. The adjustment of the ratio is due to the decrease in LDL-C and Apo-B levels and the rise in HDL-C, showing a decrease in atherogenic risk while undergoing GH therapy. An inconsistency is observed in the stability of Apo A-1 levels during GH treatment and the rise in HDL-C, potentially caused by alterations in the composition of HDL particles triggered by GH.

While fat accumulation accounts for 44-53% of body weight in adults with PWS, it has been hypothesized that the reduced presence of atypical visceral fat deposits in obese women with PWS may account for their improved insulin sensitivity and healthier lipid profile in comparison to the matched obese population. Growth hormone treatment enhances various factors that contribute to the development of atherosclerosis in individuals with Prader-Willi syndrome by affecting both body composition and lipid metabolism^(3,12).

Patel and coworkers reported on micro-circulatory dysfunction and increased levels of the high-sensitivity inflammatory marker CRP in adult individuals with PWS, both linked to coronary artery disease. There is a growing awareness that sudden cardiac mortality in individuals with PWS may not solely be attributed to fat. The suggested endocrine disruptions linked to PWS, along with

structural and functional heart abnormalities, are believed to lead to higher rates of cardiovascular illness and death⁽¹¹⁾.

Marcus and colleagues also reported that the values of global peak systolic strain and measurements of the global peak systolic strain rate were significantly reduced in children with PWS compared to healthy control subjects⁽²⁾.

Vascular functionality, measured through arterial stiffness, is an independent indicator for total and cardiovascular mortality. Purtell and colleagues identified microcirculatory dysfunction in individuals with PWS, but compared to normal-weight individuals, they observed no differences in terms of high fasting arterial stiffness. They found that fasting arterial stiffness in individuals with PWS and those who are obese is similarly elevated compared to normal-weight individuals.

Heart rate variability is a robust indicator of cardiovascular risk, possessing a strong capacity to predict mortality in patients who have suffered a myocardial infarction. Additionally, Purtell and colleagues observed that arterial stiffness, another significant cardiovascular risk factor, remains elevated in both individuals with PWS and those who are obese, compared to normal-weight individuals. Their results indicate that these changes in arterial stiffness are associated with adiposity and are not an intrinsic feature of PWS⁽¹³⁾.

A factor that might contribute to cardiovascular alterations in PWS is sleep apnea. The highlighted correlations between nocturnal respiration and cardiovascular characteristics in patients with PWS underscore a possible close link between sleep-disordered breathing and left cardiac mass or heart rate⁽¹²⁾. Hypothalamic dysfunction may be the root cause of certain



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characteristics of the PWS phenotype. Central sleep apnea (CSA) can continue into adulthood. Nocturnal hypoventilation is prevalent and can occur independently of central or obstructive sleep apnea. GH appears to be safe, but, vigilant monitoring for obstructive sleep apnea is crucial. Cardiac autonomic dysfunction happens during slow wave sleep and could raise the risk of cardiovascular events⁽¹⁴⁾.

Abnormal body composition, together with appetite-regulating hormones such as ghrelin and leptin, might affect the cardiovascular system.

PWS is linked to higher concentrations of ghrelin and a higher ratio of acylated to unacylated ghrelin (AG/UAG). While increased quantities of both AG and UAG seem to have beneficial cardiovascular effects, increased concentrations of ghrelin could lead to increased body weight and glucose intolerance⁽⁷⁾. Elevated levels of ghrelin are associated with increased carotid intima-media thickness (cIMT), indicating a potential risk factor for atherosclerosis and coronary artery disease.

The ratio between ghrelin and obestatin, which both derive from the same precursor, varies throughout development. It diminishes from early to late childhood, coinciding with the progression of pancreatic insulin secretion. This reduction appears to be linked with glucose imbalance, a condition more

commonly observed in obese and adult patients than in children and those of normal weight⁽¹⁵⁾.

The baroreflex loop function is indicated by baroreflex sensitivity (BRS). BRS has been demonstrated to predict heart disease mortality independently. The primary cause of impaired baroreflex function in patients with PWS may be a vascular defect resulting from their metabolic profile, which includes obesity, diabetes, and insulin resistance. Alternatively, a neural or autonomic defect may be to blame, which may involve either increased neural input from the hypothalamus to the baroreflex loop or a brainstem defect in and of itself. Autonomic dysfunction has been documented in patients diagnosed with PWS⁽¹⁶⁾.

Schrander-Stumpel and her team analyzed the causes of death in 27 individuals with Prader-Willi Syndrome who were not receiving growth hormone treatment. They found that in infants and children, the primary causes of death were related to respiratory illnesses and sudden deaths due to dysregulation of body temperature. In contrast, in adults, death was often related to obesity and its complications, such as cardiovascular diseases, diabetes mellitus, sleep apnea, and hypertension⁽¹⁷⁾.

Cardiorespiratory causes, including obesity-associated respiratory failure, pulmonary hypertension, obstructive sleep apnea,

arterial hypertension, and diabetes, are common among adults with PWS⁽⁶⁾.

A retrospective study conducted by Whittington and colleagues indicated annual mortality rates of 3% for individuals with PWS across all age categories and 7% for patients over thirty years of age, compared to an annual mortality rate of 1% in the general population. Adult patients with PWS succumb prematurely to complications that have traditionally been linked to obesity, including diabetes mellitus, arterial hypertension, sleep apnea, and cardiopulmonary disorders, despite their metabolic advantages. Numerous researchers have advised rigorous preventative measures against uncontrolled weight gain in PWS in light of this circumstance. Nevertheless, there is an increasing recognition that critical illnesses and untimely deaths among patients with PWS may not be solely attributable to obesity. Annual mortality rates in PWS have been estimated by retrospective studies to be 3% for patients of all ages and 7% for those over 30 years old; a significant number of cardiovascular deaths have been attributed to factors other than obesity. At present, there is no clarity regarding the potential impact of growth hormone deficiency (GHD), an independent contributor to central adiposity, an unfavorable lipid profile, endothelial dysfunction, impaired diastolic and systolic functions, and an elevated risk of ischemic heart disease in hypopituitary populations, regarding adverse health outcomes in PWS⁽¹²⁾.

Conclusions

The prognosis in the case of PWS is intrinsically tied to the efficient management of pathological obesity and its associated complications, including hypoventilation,

heart failure, and diabetes mellitus. The incidence of mortality within the pediatric age group appears to be a rare phenomenon, supported by the fact that the number of reported death cases among infants with PWS is limited⁽¹⁸⁾.

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