Prader-Willi Syndrome and Physical Activity

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Prader-Willi syndrome (PWS) is the most frequent cause of genetic obesity, with a prevalence between one in 20,000 and one in 30,000 births. PWS is a complex genetic neurodevelopmental disorder caused by an absence of expression of imprinted alleles of paternal origin on chromosome 15. PWS is characterized by severe hypotonia and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of severe obesity.

Keywords: Prader-Willi syndrome ; syndromic obesities ; physical activity ; sedentary time ; implementation ; systematic review

1. Introduction

Prader-Willi syndrome (PWS) is the most frequent cause of genetic obesity [1], with a prevalence between one in 20,000 and one in 30,000 births [2]. PWS is a complex genetic neurodevelopmental disorder caused by an absence of expression of imprinted alleles of paternal origin on chromosome 15 [1]. PWS is characterized by severe hypotonia and feeding difficulties in early infancy, followed in early childhood by excessive eating and gradual development of severe obesity [1]. Patients with PWS display low to moderate intellectual disability, as well as decreased motor competencies and physical fitness [1][3]. In adulthood, patients with PWS are prone to develop severe complications, such as cardiac or respiratory failure as well as various comorbidities such as scoliosis [4].

Promoting physical activity (PA) is an important objective of the management of PWS in both children and adults [5]. However, less than 10% of children with PWS reach the recommended level of PA [6][7], and this proportion does not exceed 20% in adults [8][9]. Over the last 10 years, a number of studies have assessed habitual PA and, to a lesser extent, sedentary behavior in these patients [7][8][9][10][11]. Most studies used objective methods such as accelerometers that are considered as the method of reference for measuring PA and sedentary time, especially in patients with cognitive impairment for whom self-reporting may be particularly challenging [12]. If most studies have reported a low level of PA in patients with PWS, it is not clear whether the decreased PA is related to obesity per se, or to the physical and intellectual disabilities associated with PWS. It is therefore relevant to synthetize the available literature comparing habitual PA and sedentary behavior in patients with PWS and in controls without obesity, with non-syndromic obesity or with other neurodevelopmental disorders.

A recent systematic review reported beneficial effects of PA interventions, mostly in the forms of supervised exercise training programs, in patients with PWS [3]. The benefits were mainly related to improved physical fitness, while the effects on body composition were not consistent [3]. Given the relatively few studies included and their diversity in terms of population, interventions, and outcomes assessed, this review did not provide a quantitative analysis of findings. Since then, several studies were published [8][13][14][15][16], adding to the body of evidence on the effect of PA interventions in patients with PWS. Importantly, some of these studies described in detail the implementation process of the PA intervention [8][13][16], which is of great importance to facilitate their transferability in real-life settings.

2. Physical Activity in Patients with Prader-Willi Syndrome

The total volume of PA was consistently found to be lower in patients with PWS compared to patients with non-syndromic obesity [8][17][18][19]. Although we have no explanation for this observation, the deficit in lean body mass in patients with PWS compared to people of similar corpulence may explain, at least in part, the lower level of PA observed in patients with PWS. In addition, although data came from only two studies, patients with PWS appear to spend less time in light-intensity PA and more time in a sedentary position compared to patients with non-syndromic obesity [6][8]. The proportion of patients with PWS who met the public health PA guidelines was very low, estimated between 5% and 8% in children [6][7] and between 15 and 25% in adults [8][9] but, in contrast with previous findings, it was not different from that reported in controls with non-syndromic obesity [7][8][9]. This discrepancy can be explained by the fact that PA volume (e.g., daily steps) considers any intensity of PA (light, moderate, or vigorous), whereas PA guidelines are based on the amount of

moderate-to-vigorous PA (MVPA). In the 2020 WHO guidelines on PA and sedentary behavior, children are advised to engage in 60 min/day of MVPA, and adults in 150 to 300 min/week (i.e., at least 30 min/d) of MVPA [20].

They are also advised to limit the amount of time spent being sedentary by engaging in PA of any intensity [20]. Replacing sedentary time by light-intensity PA is indeed increasingly recognized as beneficial for maintaining health status across the lifespan [21]. Interestingly, recent data suggest that the benefit may be higher for individuals with low levels of PA [22], which is most often the case for patients with PWS. Overall, the data included in this review suggest that reaching the recommended level of at least moderate-intensity PA may be particularly challenging for patients with low physical fitness such as patients with PWS [3]. The guidelines based on MVPA should therefore be seen as a goal to strive for rather than a minimum level to be achieved. Promoting light-intensity PA throughout the day may be a complementary and more feasible approach that may bring substantial health benefits in patients with PWS and could represent a first step in progressing towards higher levels of PA.

The most consistent benefit of PA interventions was related to the improvement of physical fitness in both children and adults with PWS. Studies have reported improved walking capacity [8], muscle strength [23][24][25], or gait parameters [26] after a PA program. Such effects are likely to represent important benefits in patients with PWS who typically present with impaired muscle strength, cardiorespiratory fitness, and gait patterns [3]. In contrast, most studies reported no significant effect of PA interventions on weight and fat loss [8][14][27][17][28]. The only study reporting a significant weight loss also included a dietary intervention in addition to several hours of exercise per day, thus preventing the authors from attributing this effect to PA alone [29]. In line with these findings, observational studies reported no significant relation between habitual PA and body fat in either children or adults with PWS [7][10][30][19], which strengthens the conclusion that PA may not have substantial effect on weight loss in patients with PWS.

This is in agreement with the known effect of PA in adults with non-syndromic obesity, in whom only a weight loss of small magnitude (2 to 3 kg on average) is observed after an exercise training program [31]. In children with PWS, PA interventions seem to have a beneficial effect on lean body mass [23][27][17] and bone mineral density, which is an important major health benefit in these patients with low baseline values of lean body mass and bone mineral density [15]. Observational studies have also reported a positive relation between habitual PA and lean body mass [27][18] or bone parameters [11]. Importantly, a large majority of children and adults participating in the PA intervention were on GH replacement therapy at the time of the study or had been on such therapy for extended periods of time before the study [15][23][27][17]. In this context, PA is likely to reinforce the effects of GH therapy, and it has therefore been described as a co-adjuvant intervention to GH therapy in children with PWS [3].

3. Conclusions

Patients with PWS spend less time in light-intensity PA, more time in sedentary occupations, and tend to spend less time in moderate-to-vigorous PA compared to patients with non-syndromic obesity, which results in a lower total volume of PA. Supervised PA programs are feasible in both children and adults with PWS and may provide several benefits related to improved physical function and, in children only, increased lean body mass and bone mineral density. Importantly, these benefits occur even in the absence of weight and fat loss. To facilitate the implementation of PA programs in real-life settings, PA sessions should be supervised by trained PA instructors or by parents provided they receive significant support and guidance on how to conduct and adapt the program. PA programs should be developed jointly by care teams specializing in the management of PWS, by PA instructors, and by parents and professionals involved in the day-to-day education and care of these patients. As for all patients with obesity, but even more so for patients with PWS, the PA program should be individually tailored and should offer a variety of activities that are as enjoyable as possible.

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