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ENDOCRINOLOGY

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Low insulin, IGF-I and IGFBP-3 levels in children with Prader-Labhart-Willi syndrome

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Abstract It is well established that insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein-3 (IGFBP-3) and insulin are low in growth hormone deficiency, but due to their dependence on nutrition, they are elevated in healthy obese children. As the presence of growth hormone deficiency in Prader-Labhart-Willi syndrome (PWS) is still controversial, we studied insulin, IGF-I and IGFBP-3 levels in 19 children with PWS (age range 0.5–14.6 years). Serum concentrations of insulin (SDS: -0.7 ± 0.9, $P = 0.01$) and IGF-I (SDS: $-0.7 \pm 0.8, P = 0.002$) were low, but IGFBP-3 (SDS: -0.3 ± 1.2, $P = 0.2$) was normal compared to normal weight age-matched children. Since children with PWS are typically obese, insulin, IGF-I and IGFBP-3 levels should be compared to normal obese children who present increased levels of these hormones. In comparison to data of healthy obese children reported in the literature, not only IGF-I, but also IGFBP-3 levels are low and fasting insulin levels even very low, suggesting a growth hormone deficiency.

Key words Growth hormone deficiency · Prader-Willi syndrome

Abbreviations *BMI* body mass index · *GH* growth hormone · *GHD* growth hormone deficiency · *IGF-I* insulin-like growth factor 1 · *IGFBF-3* insulin-like growth factor binding protein 3 · *PWS* Prader-Labhart-Willi syndrome · *WfH* weight for height

Introduction

Prader-Labhart-Willi syndrome (PWS) was first described in 1956 [1] and affects 1 in 16.000 live births [2]. The syndrome is caused by a lack of a specific part of the paternal homologue of the long arm of chromosome 15 due to a deletion [3] or to a maternal uniparental disomy [4, 5]. Growth is characterised by moderate intra-uterine and postnatal growth delay, lack of a pubertal growth spurt and short stature as an adult [6]. Infants with PWS are underweight, but between the 2nd and 4th year of life, they become obese as a consequence of uncontrolled compulsive eating. Hypogenitalism, cryptorchidism and incomplete pubertal development are common features in addition to delayed psychomotor development, mental retardation and behavioural problems, especially in older children and adolescents.

The link between the chromosomal disorder and clinical manifestations is unknown. There is evidence that various hypothalamic centres are involved, but until now gonadotropin deficiency is the only clearly documented endocrine hypothalamic disorder in PWS [7–9]. Several lines of evidence suggest, however, that a growth hormone deficiency (GHD) due to hypothalamic dysregulation may contribute to abnormal growth pattern, decreased lean body mass, muscle hypotonia and increased total body fat [10].

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Growth hormone (GH) response to insulin, arginine, clonidine and dopa are reported to be low-normal or blunted [7,10–14], as are sleep-induced GH secretion [15] and 24-h integrated GH concentrations [11]. As similar results were found in simple obesity, a controversy arose as to whether the insufficient GH secretion is the consequence of obesity, or whether this is a case of a genuine GHD due to hypothalamic dysfunction. In contrast to simple obesity however, bone maturation is reported to be often retarded [7], lean body mass to be reduced and insulin-like growth factor I (IGF-I) [10–12], and insulin-like growth factor binding protein-3 (IGFBP-3) [10] to be low or in the low-normal range.

In the past, only little attention was given to insulin levels in PWS children. It was thought that the metabolic characteristics of PWS obesity do not differ from usual exogenous obesity which is characterised by hyperinsulinaemia and insulin resistance [16], leading to type II diabetes in some adolescents and adults.

We have recently reported GH induced changes in children with PWS, namely growth acceleration, dramatically decreasing weight for height with loss of body fat and increasing muscle mass, increasing physical performance and physical activity [17]. As GH treatment-induced changes seemed rather like those observed in GHD than those seen in simple obesity, and with regard to the ongoing debate about GHD in PWS, we studied insulin, IGF-I and IGFBP-3 levels in untreated children with PWS in search for further arguments for GHD in PWS. We thereby focused our attention on insulin levels because elevated plasma insulin is an important argument against a claimed GHD [18, 19] and because plasma insulin was suggested to play a role in the regulation of appetite [20]. In order to study the effect of obesity in PWS we analysed data of young non-obese and older obese PWS children separately.

Subjects and methods

The sample consisted of 19 children with PWS (10 boys, 9 girls) with documented deletion or uniparental disomy of chromosome 15, of whom 14 were prepubertal and 5 had reached pubertal stage 2 or 3 (Tanner). The children were subdivided into two groups. The non-obese group consisted of seven children with weight for height (WfH) below the mean; the other 12 children formed the obese group with a WfH above the mean.

Blood samples were taken between 8 and 9 a.m., after a 12 h overnight fast.

Insulin was determined using an enzyme-linked immunoabsorbent assay (Tosho, Tokyo, Japan). In two of the youngest children (non-obese group) we could not obtain enough serum to measure insulin ($n = 17$). Because of age dependence, results are given in SDS [21], but due to lacking normal data for children below 3 years of age, SDS could be calculated in only 14 patients (including all of the obese group, but only two of seven in the non-obese group). IGF-I was measured in sera after acid ethanol extraction as described [22] and expressed in SDS [23]. Specific radio immunoassays were used to determine serum concentrations of IGFBP-3 [24] and expressed in SDS [24]. All data were processed by GAS 3.0 of Institute for Medical Informatics, IMI, Zurich, Switzerland. Tests of significance were performed with One Sample Wilcoxon test, a P-value of less than 0.05 was considered significant.

Results

Table 1 presents anthropometric measurements of all patients and of the obese and the non-obese groups separately. The mean age of the non-obese group was 1.8 (±1.3) years and 8.3 (±3.4) years in the obese group, illustrating the biphasic weight pattern of the syndrome.

The children of the non-obese group (defined as WfH < 0) were markedly underweight as shown by WfH (SDS: −1.8 (±0.7)) and body mass index (BMI) (SDS: −1.6 (±0.8)), whereas the obese group was markedly overweight (defined as WfH > 0) (WfH SDS: 4.6 (±2.8), BMI SDS: 3.6(±2.7)).

Table 2 presents the laboratory findings in raw values as well as expressed in SDS. In all children ($n = 19$), serum levels of IGF-I were lower compared to age-matched normal weight children (SDS: −0.7± 0.8, $P = 0.002$) [23], they were even lower in the obese group (SDS: $-1.0 \pm 0.8, p = 0.001$ compared to age-matched normal weight children) than in the non-obese group (SDS: $-0.3 \pm 0.8, P = 0.005$ compared to the obese group, Wilcoxon two sample test).

Serum levels of IGFBP-3 of all children ($n = 19$) were normal compared to age-matched normal weight children (SDS: $-0.3 \pm 1.2, P = 0.2$) [24] and lower in the non-obese group than in obese group ($P < 0.001$).

Fasting plasma insulin levels of all but one (see below) children were low (SDS: $-0.7 \pm 0.9, P = 0.01$) [21] compared to age-matched normal weight children. There was no difference between the obese and non-obese children. The basal insulin level of one patient was considerably elevated compared to all others. Therefore he was excluded from the group.

Table 1 Anthropometric data (Obese patients: WfH (SDS) > 0; non-obese patients: WfH (SDS) < 0)

		Age	Height SDS	Weight SDS	BMI (kg/m^2)	BMI SDS	WfH SDS
All patients	Mean ±SD	6.3 (±4.5)	−2.0 (±1.2)	−0.0 (±2.5)	19.5 (±5.7)	1.9 (±3.5)	2.4 (±3.9)
($n = 19$)	Range	0.5–14.6	−4.8–0.2	−3.3–5.9	13–38	−2.5–9.7	−2.8–12.0
Non-obese patients	Mean ± SD	1.8 (±1.3)	−1.9 (±0.9)	−2.2 (±0.7)	14.5 (±1.1)	−1.6 (±0.8)	−1.8 (±0.7)
($n = 7$)	Range	0.5–4.1	−3.9–0.9	−3.3–1.3	14.0–16.4	−2.5–0.3	−2.8–0.6
Obese patients	Mean ± SD	8.3 (±3.4)	−2.1 (±1.4)	1.3 (±2.3)	22.1 (±5.6)	3.6 (±2.7)	4.6 (±2.8)
($n = 12$)	Range	3.7–14.6	−4.8–0.2	−2.1–5.9	18.6–38.0	−0.2–9.7	0.8–12.0

Table 2 Hormonal data

		IGF-I		IGFBP-3		Insulin	
		nmol/l	SDS	μg/l	SDS	pmol/l	SDS
All patients	Mean ± SD	12.2 (±8.4)	−0.7 (±0.8)	2511 (±1085)	−0.3 (±1.2)	30.6 (±24.5)[a]	−0.7 (±0.9)[b]
($n=19$)	Range	1.4–37.6	−2.2–0.6	1000–5200	−2.2–2.8	<15–85	−2.3–1.0
Non-obese patients	Mean ± SD	6.5 (±3.7)	−0.3 (±0.8)	1671 (±519)	−0.8 (±1.3)	14.9 (±5.0)[a]	−0.8 (±0.2)[b]
($n=7$)	Range	1.4–12.1	−1.3–0.6	1000–2400	−2.2–1.2	<15.0–21.0	−0.68/−0.92
Obese patients	Mean ± SD	15.6 (±8.6)	−1.0 (±0.8)	3000 (±1034)	0.06 (±1.2)	37.7 (±26.6)	−0.7 (±1.0)
($n=12$)	Range	5.9–37.6	−2.2–0.1	2100–5200	−1.2–2.8	<15–85	−2.3–1.0

[a] 2 patients are lacking ($n=17$)
[b] 5 non-obese patients without insulin SDS

Discussion

The presence of a GHD in PWS has been a controversial issue in the past. Whereas some authors take a sceptical view [25], others, including all those reporting on GH-treated children with PWS, were convinced of the presence of a GHD, despite the paradoxical fact that all of them have administered supraphysiological doses of GH [26–29]. Furthermore GH treatment-induced clinical changes, which we have reported recently [17], namely marked growth acceleration, increasing muscle mass and decreasing body fat, seemed rather similar to those observed in GHD than to those in normal obesity. It is well established that IGF-I, IGFBP-3 [30] and insulin [18, 19] are low in children with GHD, but elevated in healthy obese children. Therefore we studied IGF-I, IGFBP-3 and insulin levels in children with PWS before any treatment was instituted. Our data provide further arguments in favour of a hypothalamic GHD in PWS.

In our study, IGF-I levels were significantly lower, and IGFBP-3 was normal compared to normal weight children. The levels were not as low as expected in classical GHD, but in obese children, serum concentrations of IGF-I [31] as well as of IGFBP-3 [30] have been reported to be increased by 50% to 100% [30,32,33] compared to normal weight children. Therefore, the obesity-induced counterregulation may explain the fact that IGF-I and IGFBP-3 levels in PWS are not as low as expected in classical GHD.

Both groups, the non-obese young children and the markedly obese older children, had decreased insulin levels. The mean insulin level found in the obese group is very low in relation to the 2–2.5 fold elevation seen in normal obese children [34,35]. Only the oldest male patient who had already reached puberty and was grossly overweight (BMI 38 kg/m^2), had an elevated insulin level. These results contradict, at least in children, the view that the metabolic characteristics of PWS obesity do not differ from usual exogenous obesity [16]. They are also in contradiction with the speculation that insulin levels in PWS were only low before obesity sets in. This was the explanation used in the study in which single children were found to have low insulin levels besides many subjects with high insulin levels [36]. Our data, however, show that not only underweight, but also the overweight prepubertal PWS children have low insulin levels as it is the case in classical GHD [37]. It may thus appear that even in overweight children with Prader-Willi syndrome, there is at first a higher insulin sensitivity compared to both normal weight and obese children, which may only later turn into an insulin resistance. This idea is compatible with the recent hypothesis that insulin resistance in GH deficient adults depends on the absolute amount of body fat and that the BMI has to be at least 27 kg/m^2 to induce obesity-associated insulin resistance [37].

This finding also suggests that insulin resistance or the resulting hyperinsulinaemia is unlikely to be an important cause of obesity in PWS and is consistent with the hypothesis to the contrary that the acquisition of insulin resistance and hyperinsulinaemia represent physiological adaptions to obesity that may further limit fat deposition as was suggested in Pima Indians [38]. In animal models, it was hown that high insulin levels in the brain decrease appetite and food intake [20]. Thus, in PWS, low insulin secretion could therefore be a factor predisposing to weight gain.

In conclusion, insulin, IGF-I and IGFBP-3 levels in children with PWS are low compared to healthy obese children, as reported in the literature and are an argument in favour of the assumed hypothalamic GHD. We hypothesise that in PWS, hyperalimentation could partly counteract the effect of hypothalamic GHD and lead to relatively higher IGF-I and IGFBP-3 levels.

Although the crucial question whether there is a GHD in PWS may not be ultimately answered, several arguments strongly suggest that the hormonal situation differs from that in simple obesity. GHD on its own may already account for several features of PWS.

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References

1. Prader A, Labhart A, Willi H (1956) Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus und Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter. Schweiz Med Wochenschr 86: 1260–1261

2. Burd L, Vesely B, Martsolf J, Korbeshian J (1990) Prevalence study of Prader-Willi syndrome in North Dakota. Am J Med Genet 37: 97–99
3. Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan SB, Crawford JD (1991) Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. N Engl J Med 304: 325–329
4. Nicholls RD, Knoll JHM, Butler MG, Karam S, Lalande M (1989) Genetic imprinting suggested by maternal heterodisomy in non-deletion Prader-Willi syndrome. Nature 342: 281–284
5. Robinson WP, Bottani A, Xie YG, Balakrishman J, Binkert F, Machler M, Prader A, Schinzel A (1991) Molecular, cytogenetic and clinical investigations of Prader-Willi syndrome patients. Am J Hum Genet 49: 1219–1234
6. Butler MG, Meaney FJ (1991) Standards for selected anthropometric measurements in Prader-Willi syndrome. Pediatrics 88: 853–860
7. Bray GA, Dahms WT, Swerdloss RS, Fiser RH, Atkinson RL, Carrel X (1983) The Prader-Willi syndrome. A study of 40 patients and a review of the literature. Medicine 62: 59–80
8. Cassidy SB, Rubin KG, Mukaida CS (1987) Genital abnormalities and hypogonadism in 105 patients with Prader-Willi syndrome. Am J Med Genet 28: 922–923
9. Hamilton CR, Scully RE, Kliman B (1972) Hypogonadotropism in Prader-Willi syndrome: induction of puberty and spermatogenesis by clomiphene citrate Am J Med 52: 322–329
10. Lee PDK, Hwu K, Henson H, Brown BT, Bricker JT, Le Blanc AD, Fiorotto ML, Greenberg F, Klish WJ (1993) Body composition studies in Prader-Willi syndrome: effects of growth hormone therapy. Basic Life Sci 60: 201–205
11. Angulo M, Castro-Magana M, Uy J (1991) Pituitary evaluation and growth hormone treatment in Prader-Willi syndrome. J Pediatr Endocrinol 4: 167–172
12. Costeff H, Horm VA, Ruvalcaba R, Shaver J (1990) Growth hormone secretion in Prader-Willi syndrome. Acta Paediatr Scand 79: 1059–1062
13. Tolis G, Lewis W, Verdy M, Friesen HG, Soplomon S, Pagalis G (1974) Anterior pituitary function in the Prader-Labhart-Willi (PLW) syndrome. J Clin Endocrinol Metab 39: 1061–1066
14. Cappa M, Grossi A, Borrelli P, Ghigo E, Bellone J, Benedetti S, Carta D, Loche S (1993) Growth hormone (GH) response to combined pyridostigmine and GH-releasing hormone administration in patients with Prader-Labhart-Willi-syndrome. Horm Res 39: 51–55
15. Fesseler WH, Bierich FR (1983) Untersuchungen beim Prader-Labhart-Willi Syndrom. Monatszeitschrift Kinderheilkunde 131: 844–847
16. Bray GA (1992) Genetic, hypothalamic and endocrine features of clinical and experimental obesity. Prog Brain Res 93: 333–341
17. Eiholzer U, Gisin R, Weinmann C, Kriemler S, Steinert H, Zachmann M, Prader A (1998) Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance. Eur J Pediatr 157: 368–377
18. Lippe BM, Kaplan SA, Golden MP, Hendricks SA, Scott ML (1981) Carbohydrated tolerance and insulin receptor binding in children with hypopituitarism: responses after acute and chronic human growth hormone administration. J Clin Endocrinol Metab 53: 507–513
19. Costin G, Kogut MD, Frasier SD (1972) Effect of low-dose human growth hormone on carbohydrate metabolism in children with hypopituitarism. J Pediatr 80: 796–803
20. Bray GA, Fisler J, York DA (1990) Neuroendocrine control of the development of obesity: understanding gained from studies of experimental animal models. Front Neuroendocrinol 11: 128–181
21. Lautala P, Akerblöm HK, Viikari J, Louhivuori K, Uhari M, Dahlström S, Dahl M, Lähde PL, Pesonen E, Pietikäinen M, Suoninen P, Knip M (1985) Atherosclerosis precursors in Finnish children and adolescents. VII. Serum immunoreactive insulin. Acta Paediatr Scand (Suppl) 318: 127–133
22. Zapf J, Walter H, Froesch ER (1981) Radioimmunological determination of insulin-like growth factors I and II in normal subjects and in patients with growth disorders and extrapancreatic tumor hypoglycemia. J Clin Invest 68: 1321–1330
23. Zapf J, Froesch ER (1998) Hormonal control of growth. Goodman HM (ed) Handbook of physiology. Oxford University press (in press)
24. Blum, WF, Ranke MB, Kietzmann K, Gauggel E, Zeisel H, Bierich JR (1990) A specific radioimmunoassay for the growth hormone (GH)-dependent somatomedin-binding protein: its use for diagnosis of GH deficiency. J Clin Endocrinol Metab 70: 1292–1298
25. Van Vliet G, Deal CL (1994) Growth hormone and body fat: an overview of studies in hypopituitarism and in exogenous obesity, Clinical issues in growth disorders: evaluation, diagnosis and therapy. Serono Colloquia Europe Series, Freund, p 119–129
26. Angulo M, Castro-Magana M, Mazur B, Canas JA, Vitollo PM, Sarrantonio M (1996) Growth hormone secretion and effects of growth hormone therapy on growth velocity and weight gain in children with Prader-Willi syndrome. J Pediatr Endocrinol 9: 393–400
27. Raiti S, Trias E, Levitsky L, Grossman MS (1973) Oxandrolone and human growth hormone. Am J Dis Child 126:597-600
28. Ruvalcaba RH, Holm, VA (1993) Effects of growth hormone in Prader-Willi Syndrome. A case report. Clin Pediatr (Phila) 32: 292–295
29. Trygstad O, Veimo D (1993) Growth hormone treatment in Prader-Labhart-Willi syndrome (abstract). Pediatr Res (Suppl) 33:40
30. Wabitsch M, Blum WF, Muche R, Heinze E, Haug C, Mayer H, Teller W (1996) Insulin-like growth factors and their binding proteins before and after weight loss and their associations with hormonal and metabolic parameters in obese adolescent girls. Int J Obes 20: 1073–1080
31. Loche S, Cappa M, Borrelli P, Faedda A, Crino A, Cella SG, Corda R, Müller EE, Pintor C (1987) Reduced growth hormone response to growth hormone-releasing hormone in children with simple obesity: evidence for somatomedin-C mediated inhibition. Clin Endocrinol 27: 145–153
32. Van Vliet G, Bosson D, Rummens E, Robyn C, Wolter R (1986) Evidence against growth hormone-releasing factor deficiency in children with idiopathic obesity. Acta Endocrinol (Suppl) 279: 403–408
33. Rosskamp R, Becker M, Soetadji S (1997) Circulating somatomedin-C levels and the effect of growth hormone-releasing factor on plasma levels of growth hormone and somatostatin-like immunoreactivity in obese children. Eur J Pediatr 146: 48–50
34. Deschamps I, Giron BJ, Lestradet H (1977) Blood glucose insulin, and free fatty acid levels during oral glucose tolerance tests in 158 obese children. Diabetes 26: 89–93
35. Knip M, Nuutinen O (1993) Long-term effects of weight reduction on serum lipids and plasma insulin in obese children. Am J Clin Nutr 57: 490-493
36. lllig R, Tschumi A, Vischer D (1975) Glucose intolerance and diabetes mellitus in patients with the Prader-Labhart-Willi-Syndrome. Mod Probl Paediat 12: 203–210
37. Salomon F, Cuneo RC, Umpleby AM, Sonksen PH (1994) Interactions of body fat and muscle mass with substrate concentrations and fasting insulin levels in adults with growth hormone deficiency. Clin Sci (Colch) 87: 201–206
38. Schwartz MW, Boyko EJ, Kahn SE, Ravussin E, Bogardus C (1995) Reduced insulin secretion; an independent predictor of body weight gain. J Clin Endocrinol Metab 80: 1571–1576