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Growth Hormone Deficiency in Prader-Willi Syndrome

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To search for arguments supporting the presence of a growth hormone deficiency (GHD) in Prader-Willi syndrome (PWS), the clinical and biochemical aspects of PWS are compared with nonsyndromal obesity and to GHD without PWS. Reviewing recently published studies and our own results, it is shown that the following observations support the presence of a hypothalamic GHD in PWS: short adult stature and decreasing growth velocity despite onset of obesity; reduced lean body mass despite increased body fat; relatively low insulin-like growth factor-I (IGF-I) and low insulin levels; as well as the dramatic effect of growth hormone (GH) treatment on growth. GH therapy changes the phenotype of PWS in childhood; height and weight become normal, and, in combination with increased physical activity and control of energy intake, there is a sustained impact on the net loss of body fat. The existence of true GHD in PWS might be difficult to prove because of the obesity-induced counter-regulation, but the GH/IGF axis clearly differs from that in simple obesity. ■

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Background

There is considerable knowledge about genetic mechanisms in Prader-Willi syndrome (PWS) [1–3]. The link, however, between the chromosomal disorder and the clinical manifestations is unknown. It is assumed that there is a dysfunction of several hypothalamic centers, but gonadotropin deficiency is the only clearly documented endocrine hypothalamic disorder [4]. Now, there is growing evidence that a growth hormone deficiency (GHD) due to hypothalamic dysregulation may contribute not only to the abnormal growth pattern, but also to the excess of body fat [5] and the deficit of lean body mass (LBM), with reduced energy expenditure, as a consequence [6].

Growth hormone (GH) response to insulin, arginine, clonidine and dopa is reported to be low-normal or blunted [5, 7–11], as are sleep-induced GH secretion [12] and 24 hour-integrated GH concentrations [8]. But also simple obesity is associated with a decreased circulating concentration of GH, and spontaneous 24 hour GH secretion turned out to be low and similar in both PWS and healthy obese controls [13]. There is evidence, however, that GH secretion in simple obesity is not disturbed, but down-regulated and fully reversible by weight loss. Therefore 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 [14].

To search for arguments supporting the presence of a GHD in PWS, the present paper compares the clinical and biochemical aspects of PWS with nonsyndromal obesity and with GHD without PWS.

Growth

A comparison of the growth dynamics in healthy obese children and in children with PWS reveals a first argument in favor of a GHD. Healthy obese children are taller than normal-weight children. For the prepubertal period after age 4, it has been shown that growth velocity is normal and bone age is already accelerated by up to 2 years [15]; therefore, acceleration of bone age and of

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