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Obesity due to proopiomelanocortin deficiency: three new cases and treatment trials with thyroid hormone and ACTH4-10.

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Abstract

The symptoms of severe early-onset obesity, adrenal insufficiency, and red hair define the proopiomelanocortin (POMC) deficiency syndrome as described so far in two children with complete loss-of-function mutations of the human POMC gene. In POMC deficiency, obesity reflects the lack of POMC-derived peptides as ligands at the melanocortin (MC) MC4 and MC3 receptors, which are expressed in the hypothalamic leptin-melanocortin pathway of body weight regulation. Hypocortisolism and alteration of pigmentation are caused by the lack of POMC-derived peptides at the adrenal MC2 receptor and the skin MC1 receptor, respectively. Here we describe three new cases of complete loss-of-function mutations of the POMC gene. Patients were diagnosed based on the clinical trials of red hair, adrenal insufficiency, and early-onset severe obesity. One previously described translation initiation mutation (C3804A) as well as one new nonsense (A6851T) and two new frame-shift mutations (6996del and 7100 + 2G) were found in homozygosity or compound heterozygosity. The heterozygous parents were found to have high normal or mildly elevated body weight, suggesting a dosage effect of the POMC gene product on weight regulation. To compensate for the lack of hypothalamic melanocortin function, we initiated a trial in the two previously published patients with intranasal ACTH4-10, a melanocortin fragment for which an anorexic effect has been described recently. During 3 months with increasing doses of ACTH4-10, no change of body weight or metabolic rate was observed, suggesting that at least in these two POMC-deficient patients ACTH4-10 is without any compensatory effect. In the same two patients, further investigation revealed a mildly elevated TSH. However, a 1-yr treatment with thyroid hormone did not result in a significant reduction of body weight.

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