Early-onset obesity and adrenal insufficiency associated with a homozigous POMC mutation

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Introduction
Isolated hypocortisolism due to ACTH deficiency is a rare condition that can be caused by mutations in the gene encoding pro-opiomelanocortin (POMC). POMC is the precursor to bioactive peptides: ACTH, β-endorphin, α-, β- and γ-MSH. Mutations in inactive POMC (locus 2p23.3) typically result in secondary adrenal insufficiency, severe obesity and red hair. Fewer than 50 affected individuals have been reported in the world literature.

We describe a girl with POMC deficiency, presenting early onset hyperphagic obesity and hypocortisolism, but without red hair.

Case presentation
A 10 months old female was referred to our clinic for macrosomia and delayed psycho-motor development. She was the only child of consanguineous parents of Pakistan ethnicity; the family history was not contributory.

The patient was born at 39 weeks (weight 3170 g, 50th percentile; length 52 cm, 75th percentile; head circumference 35.8 cm, 50th percentile); her mother developed gestational diabetes during pregnancy and the baby presented neonatal transient hypoglicemia.

Her clinical history was significant for marked weight and length gain since the age of 3 months. On the first clinical evaluation, her weight was 15 Kg (=>97th percentile), length was 82.5 cm (=>97th percentile) and head circumference was 50 cm (97th percentile). (Fig.1)

On physical and neurological examination, axial hypotonia and delayed motor milestones were observed. In addition, some dysmorphism (telecanthus, strabismus, wide nasal bridge) and pale skin with dark brown hair were noted.

Molecular analysis
Methods: genomic DNA was obtained from peripheral white blood cells using a commercial kit. The coding and flanking intronic region of POMC gene was amplified by PCR and then sequenced.

Results: gene sequencing of POMC revealed homozygous c256 C>T mutation causing a stop codon (R86 stop). This mutation is located in the gene region corresponding to γ-MSH; therefore, the production of ACTH and α-MSH is inhibited (Fig.2). Each parent was heterozygous for c256 C>T mutation.

Conclusions
POMC gene mutation should be considered in patient with early-onset severe obesity and secondary adrenal insufficiency, even without red hair. Adrenal insufficiency have to be treated as usual, with substitutive glucocorticoid therapy.

As reported in literature, these patients may develop other endocrine manifestations in adolescence (central hypothyroidism, adolescent-onset GH deficiency and hypogonadotrophic hypogonadism); therefore, they should be followed overtime.

The management of obesity in POMC deficiency remain a challenge but lifestyle measures are necessary to control weight gain.

Bibliography
2. K. Clement et al., Unexpected endocrine features and normal pigmentation in a young adult patient carrying a novel homozygous mutation in the POMC gene, J Clin Endocrinol Metab. 2008 Dec; 93(12): 4954-62