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

Antonella Meloni[1], Maria Rosaria Casini[1], Emanuele Miraglia del Giudice[2], Loredana Boccone[1]

1. Ospedale Pediatrico "Microcitemico" - Antonio Cao, Università degli Studi di Cagliari, Azienda Ospedaliera Brotzu, Cagliari (Italy)
2. Seconda Università degli Studi di Napoli, Dipartimento di Pediatria, Napoli (Italy)

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 that 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

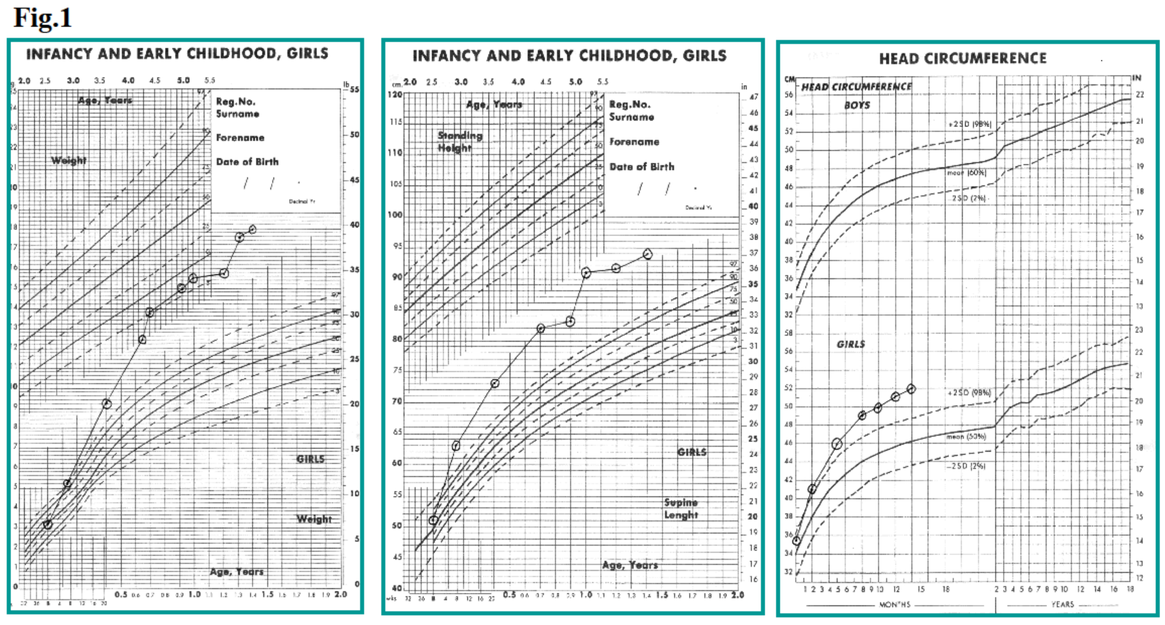
A 10 months old female was referred to our clinic for macrosomia and delayed psycho-motor development. She was the only child of consanguineous parents of Pakistan ethnicity; the family history was not contributory.

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 dismorphisms (telecanthus, strabismus, wide nasal bridge) and pale skin with dark brown hair were noted.

Fig.1



Laboratory

Routine and urine analyses, α-fetoprotein, CEA, β-HCG, metabolic studies, karyotype and molecular testing to identify epigenetic/genomic mutations of chromosome 11p15 (to exclude Beckiwth-Wiedemann syndrome) were all normal.

Endocrine studies revealed normal serum levels of thyroid hormones, prolactin, GH, IGF1 and insulin; decreased serum levels of ACTH and cortisol **(ACTH <5 pg/ml, cortisol <10µg/L)**.

During hospitalization, the patient had a severe hypoglicemia (39 mg/dl) with seizures, due to ACTH deficiency. Immediately glucocorticoid replacement therapy was started.

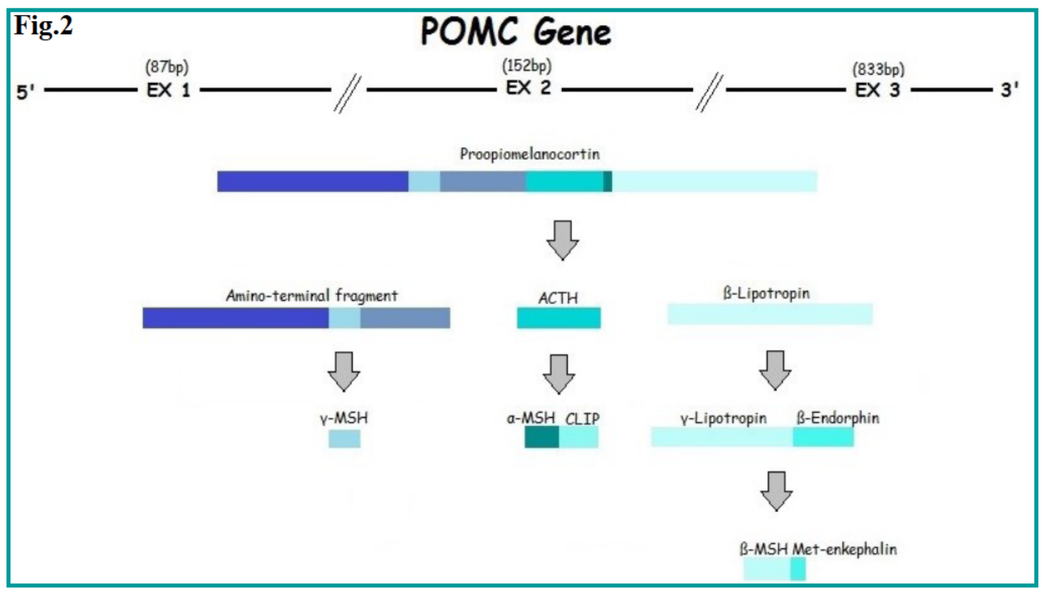
The association of early severe obesity and ACTH congenital deficiency, although our patient did not have red hair, lead to suspiscion of POMC deficiency. So, the next step was been the genetic analysis of POMC gene.

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 than 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.

Fig.2



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 hypogonadotropic 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

. I. Sadaf Farooqi, Genetic and Hereditary aspects of childhood obesity, Best Practice & Research Clinical Endocrinology & Metabolism 2005, Vol. 19, n.3, 359-374
. 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): 4955-62
. Ja Hye Kim, Jin-Ho Choi, Pathophysiology and clinical characteristics of hypothalamic obesity in children and adolescents, Ann Pediatr Endocrinol Meta 2013, 18, 161-167

ESPE 2015
378--P2
Fat Metabolism, Obesity
Antonella Meloni
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com