Case Report

Hypo-cortisolism, early onset obesity and liver disease in a child with homozygous proopiomelanocortin mutation

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ABSTRACT

The peptide derivatives of proopiomelanocortin molecule are involved in energy homeostasis, regulation of food intake, skin pigmentation and augment biliary flow. Homozygous mutation in POMC gene, which is inherited in an autosomal recessive pattern, is associated with hyperphagia leading to early onset obesity, hypoglycaemia and neonatal cholestasis due to cortisol deficiency and red hair pigmentation as a result of alpha MSH deficiency. We report a child having multiple episodes of hypoglycaemia with this disorder who presented like liver disease. Our case report highlights the importance of early suspicion of this rare condition and confirmation with genetic analysis.

Keywords: Proopiomelanocortin, Cortisol, Obesity, Hyperphagia, Cholestasis

INTRODUCTION

Proopiomelanocortin (POMC) gene is expressed at high levels in the arcuate nucleus of hypothalamus. The POMC derived peptides act as ligands on melanocortin receptors which influence energy homeostasis, skin pigmentation and regulate food intake.1 Current report present a child with hypocortisolism, hyperphagia and early onset obesity due to a novel POMC mutation presenting like liver disease.

CASE REPORT

A 4.4 years male child, born of consanguineous union presented with a 4 day history of fever, vomiting, lethargy and generalized tonic clonic seizures. There was history of jaundice and seizures in a sibling who died at day 8 of life. The child had a normal birth history with a birth weight of 3.2 kg. On day 3 of life, he was admitted for refusal of feeds and seizures and was found to have hypoglycaemia (blood glucose 36 mg/dl). Similar episodes of seizures were there at 2, 2.5 and 4 years of age after an acute illness. He used to demand frequent feeds since early infancy with significant weight gain. His developmental milestones were normal.

On examination, patient had respiratory distress, jaundice, ascites and hepatomegaly (liver palpable 13 cms below right costal margin). He was of fair complexion as compared to his parents. Genital and ophthalmologic examination was normal. His weight was 27.5 kg (+3.64 SDS), height 117.5 cms (+2.73 SDS) and BMI 19.92 kg/m² (+2.98 SDS). Patient had a bone age of 4 years. At presentation, his blood sugar was 34 mg/dl which was treated with IV dextrose. Glucose delivery gradually increased to 7 mg/kg/min because of persistent hypoglycemia. Critical sample revealed raised beta-hydroxy butyrate of 4.2 mmol/L (normal; 0.02-0.027 mmol/L), suppressed insulin levels (<1 μIU/ml), low serum cortisol (<0.4 μg/dl), low plasma ACTH levels (<5 pg/ml) and normal thyroid function tests (fT3; 5.04 pg/ml; fT4; 1.20 ng/dl and TSH; 4.59 μIU/ml). Synacthen stimulation test showed no rise in serum cortisol (baseline, 30min and 60 min serum cortisol levels <0.4 μg/dl). Other laboratory workup showed elevated liver enzymes SGOT; 1601 IU/l, SGPT; 1040 IU/l, ALP; 175
IU/l (normal; 54-369 U/l), GGTP-64 IU/l (normal; 9-38 IU/l) with hypoalbuminemia (total protein; 4.9 g%, serum albumin; 2.8 g%) and INR of 1.22. Total bilirubin was 2.9 mg% (direct bilirubin; 2.3 mg%). Work up for hepatitis A, B, C, E and Wilsons disease was negative. Ultrasonography of abdomen showed moderate hepatomegaly with increased echo texture and mild splenomegaly. Liver biopsy showed intrahepatic cholestasis with feathery degeneration of hepatocytes and grade 3/4 fibrosis. Clinical exome study was positive for POMC deficiency secondary to homozygous nonsense mutation in exon 3 of POMC gene resulting in stop codon and premature truncation of the protein at codon 76 (c.226A>T) (p.Lys76Ter). The patient was treated with hydrocortisone 12.5 mg/m²/day. A follow up done one month after hydrocortisone showed improvement in liver functions (SGOT; 46 IU/l, SGPT; 62 IU/l, GGTP-36 IU/l, serum albumin; 4.6 g%) and no further episode of hypoglycemia.

**DISCUSSION**

The proopiomelanocortin (POMC) gene is located on short arm of chromosome 2. The first clinical description of the case of POMC mutation was made by Krude et al following which 14 cases of POMC mutation have been reported. To the best of our knowledge, this is the first case to be reported from India.³ POMC derived peptides like ACTH, alpha MSH, beta MSH, gamma MSH, corticotrophin; like intermediate lobe peptide (CLIP) and beta-endorphins are derived from post translational cleavage of the POMC molecule at specific tissue sites. Alpha MSH acting through MC1 receptors is responsible for skin and hair pigmentation.⁴ ACTH, through its action on MC2 receptors expressed in the adrenals, is responsible for steroidogenesis. Alpha MSH also acts on the MC3 and MC4 receptors which are expressed in the hypothalamic-leptin-melanocortin pathway and plays a central role in energy homeostasis and body weight regulation. From the above discussion, it is evident that, POMC deficiency would result in constellation of manifestations that include hyperphagia, severe early onset obesity, red pigmented hair and hypocortisolism.⁵,⁶

POMC deficiency is inherited in an autosomal recessive manner. The mutations involving the exon 3 of the POMC gene is responsible for most of the cases. Neonates born with POMC deficiency usually have a normal weight at birth.⁷ Hyperphagic behaviour in these children is described as early as 1st month of life, as a result of which, they tend to gain weight rapidly during early infancy as seen in our child. At presentation we thought of a primary liver disease as cause of hypoglycemia. Obesity and very good height was perplexing as one would expect low weight in liver disease. Central hypocortisolism added more confusion. However genetic diagnosis gave answers to the puzzle. Cortisol deficiency is known to be associated with neonatal cholestasis.⁸ Glucocorticoids are known to prevent cholestasis by augmentation of biliary flow.⁹ Early treatment with hydrocortisone is known to reverse the changes of cholestasis with normalization of the liver function as was noted in our patient.

**CONCLUSION**

Early onset obesity, fair skin and hypoglycemia due to central hypocortisolism should be promptly tested for POMC mutation, as early treatment is vital in preventing morbidity and mortality.

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**REFERENCES**

7. Farooqi IS, Drop S, Clements A, Keogh JM, Biernacka J, Lowenbein S, Challis BG, O'Raiffty S. Heterozygosity for a POMC mutation, as early treatment is vital in preventing morbidity and mortality.

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