



A Novel Presentation of Proopiomelanocortin (POMC) Deficiency

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Abstract

Proopiomelanocortin (POMC) deficiency is a rare form of monogenic obesity which typically presents in infancy with hypoglycemic seizures and reduced cutaneous pigmentation. Over time, these patients develop morbid obesity along with multiple endocrinopathies including adrenal insufficiency, hypogonadism, hypothyroidism and growth hormone deficiency. Here, we describe an 11 year old male with adrenal insufficiency, seizure disorder, morbid obesity, and intellectual disability of unknown etiology recently confirmed to have POMC deficiency based on whole-exome sequencing (WES). This case highlights the advances in molecular genetic testing and opportunities for diagnosis in patients with complex medical histories or atypical clinical manifestations.

Introduction

Proopiomelanocortin (POMC) deficiency, a rare form of monogenic obesity, is characterized by early-onset marked obesity, adrenal insufficiency and reduced cutaneous pigmentation. In the first months of life, most children with POMC deficiency experience hyperphagia, cholestasis, and adrenal insufficiency. POMC deficient patients commonly present with severe hypoglycemia and seizures in the neonatal period as well as hyperbilirubinemia. Hyperphagia is apparent soon after birth leading to rapid weight gain throughout the first year of life and severe childhood obesity. Central hypothyroidism, adult-onset growth hormone deficiency and hypogonadotropic hypogonadism have also been observed in POMC deficient patients [1].

POMC, the polypeptide precursor of several biologically active peptides, is cleaved by a series of prohormone convertases to produce adrenocorticotrophic hormone (ACTH) and the three melanocyte-stimulating hormones (MSH): alpha, beta and gamma. These hormones are the endogenous ligands of the melanocortin family of receptors (MCR) of which there are five known members. The hair and skin manifestations, adrenal insufficiency and obesity are caused by lack of activation of the MC1, MC2, and MC4 receptors respectively [2]. POMC deficiency may be initially diagnosed clinically due to the unique constellation of symptoms and then confirmed by mutation analysis.

Here we report a case of POMC deficiency confirmed via whole exome sequencing (WES) with a unique presentation, including lack of neonatal hypoglycemia and red hair, as well novel clinical manifestations including duodenal perforation, a seizure disorder not related to hypoglycemia, severe developmental delay and autism.

Case Presentation

An 11 year old male with a history of adrenal insufficiency, seizure disorder, acquired primary hypothyroidism and morbid obesity was referred for genetic evaluation of profound developmental delay, seizures and continued rapid weight gain. He was born at 40 weeks gestation via spontaneous vaginal delivery to a 28 year-old mother with A1 (diet-controlled) gestational diabetes and a 30 year-old non-consanguineous father, both of Hispanic ethnicity. His birth weight was average for gestational age at 3153 grams. After delivery, he was admitted to the neonatal intensive care unit (NICU) for seizures secondary to presumed hypoxic ischemic encephalopathy. He had no documented hypoglycemia during this period. He remained hospitalized for two months for hyperbilirubinemia, intra-hepatic cholestasis and persistent seizures. He was subsequently diagnosed with a seizure disorder and progressive intra-hepatic cholestasis and was discharged to home on medical therapy. He was then readmitted at 5 months of age with spontaneous duodenal perforation and septic shock. During this admission, the patient had refractory hypotension and a low morning cortisol level of 1.7 ug/dL. He was started on hydrocortisone therapy which was

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Table 1: Laboratory Evaluation.

Date	Test	Result	Range
10/2003	AM Cortisol	1.7 ug/dL	3-21ug/dL
12/2003	Baseline Cortisol	<0.2 ug/dL	3-21 ug/dL
12/2003	ACTH	<1 pg/mL	9-52 pg/mL
12/2003	Stimulated Cortisol	1.5 ug/dL	3-21 ug/dL
5/2004	TSH	10.45 mU/L	0.5-4.0 mU/L
5/2004	Free T4 (equilibrium dialysis)	0.9 ng/dL	0.8-2.0 ng/dL
5/2004	Total T4	6.3 ug/dL	4.5-11 ug/dL

weaned after recovery from his acute illness. At 7 months of age, physiologic dosing of hydrocortisone was initiated after cosyntropin stimulation testing revealed undetectable baseline cortisol and ACTH levels and a low stimulated cortisol level of 1.5ug/dL. The results of his endocrine testing are listed in Table 1.

The patient was noted to have rapid weight gain between 8 to 12 months and his weight was >99th percentile by 21 months of age. He continued to have exponential weight gain despite dietary modification and increased physical activity. He was started on levothyroxine supplementation at 18 months of age for persistently elevated thyroid stimulating hormone (TSH) levels in the context of negative thyroid antibodies. He has profound developmental delay and autism and continues to have seizures twice monthly despite antiepileptic medications. There has been no reported hypoglycemia during any of his seizures to date. His linear growth rate has been appropriate throughout childhood. He was recently referred to our genetics clinic for a new consultation by the neurologist for genetic testing related to his seizures and autism. On exam, his height, weight and body mass index were: 151.9 cm (72%, Z = 0.58), 68.6 kg (99%, Z = 2.25), and 29.23 Kg/m² (99%, Z = 2.25) respectively. He was a well-appearing, non-dysmorphic male with tan skin and dark brown hair. He was in early puberty with Tanner II pubic hair and 4cc testes bilaterally. He had marked acanthosis nigricans of the posterior neck, axillae and groin. Molecular genetic studies were obtained with informed consent from the patient's mother. Genomic DNA was extracted from peripheral blood samples.

Results

A karyotype was performed on a sample of this patient's blood to rule out the presence of chromosomal aneuploidies and unbalanced translocations. This result was normal, 46, XY. Whole genome single nucleotide polymorphism (SNP) microarray analysis was performed to rule out the presence of chromosomal microdeletions and microduplications greater or equal to 50 kilo bases in size. No abnormalities were detected via microarray; however, this patient was noted to have areas of homozygosity, consistent with a family history of consanguinity and increasing the risk for the presence of an autosomal recessive disorder in the patient. Fragile X syndrome PCR analysis and Prader-Willi syndrome methylation studies were within normal limits. Metabolic screening studies including plasma amino acid levels, urine organic acids, urine orotic acids, and plasma ammonia levels, were performed to assess the likelihood for an underlying inborn error of metabolism. While the patient's initial plasma amino acid levels were suggestive of hyperornithinemia, his follow-up additional metabolic studies were within normal limits. His lipid profile showed a low HDL level, otherwise within normal limits.

Clinical whole exome sequencing was then performed at Ambry Genetics via their ExomeNext™ assay in an attempt to identify an

underlying genetic cause for the patient's phenotype, given his previous uninformative workup. A blood sample from the patient's biological mother was submitted to aid in the analysis. While testing a trio, typically the proband and two first degree relatives, increases the likelihood of a definitive result, the biological father was unavailable to provide a sample for analysis. Testing revealed homozygous frame shift deleterious mutations in this patient's proopiomelanocortin (POMC) genes, at chromosomal location 2p23.3. The mutation, c.20_21ins25, is a frameshift mutation altering the translation of the proopiomelanocortin protein. This mutation is classified as known disease-causing/pathogenic and is consistent with a diagnosis of POMC deficiency. The patient's mother was identified as a carrier of a heterozygous POMC gene c.20_21ins25 mutation. It is suspected that this patient's father is also a carrier of the same mutation, though confirmation was not possible.

Discussion

POMC deficiency has been previously described as a syndrome of central adrenal insufficiency, obesity and characteristic hair and skin pigmentation which may be associated with childhood and adolescence-onset central hypothyroidism and hypogonadotropic hypogonadism. This case illustrates a unique instance of POMC deficiency in which the patient did not have hypoglycemia documented in the neonatal period or external abnormalities in hair and skin pigmentation. Additionally, his seizure disorder and developmental delay is thought to be secondary to perinatal anoxic brain injury and not from hypoglycemia secondary to congenital ACTH deficiency as has been previously described in cases of POMC deficiency [3-6]. Instead, his adrenal insufficiency was diagnosed at 5 months of age during evaluation for refractory hypotension concomitant with sepsis. The patient's lack of characteristic neonatal hypoglycemia and red hair/fair skin coupled with his history of seizure disorder and developmental delay likely obscured his diagnosis and led to a considerable delay in obtaining confirmatory genetic testing.

In this case study, we successfully confirmed the genetic diagnosis in a patient with POMC deficiency after 11 years of extensive inpatient hospitalizations and outpatient care. Given his history of developmental delays/intellectual disabilities (ID) and seizures, this patient went through an extensive series of testing without informative answers [7,8]. The lack of major facial dysmorphisms, absence of congenital anomalies, along with an unclear etiology of early adrenal insufficiency made clinical diagnosis difficult until WES identified this single frameshift mutation. In our patient as well as those in recent studies, this case highlights how a definitive diagnosis of a genetic disorder can provide valuable information about prognosis, anticipatory guidance, and recurrence risk [9]. In children, this knowledge becomes increasingly important in terms of intervention, medical therapy and preventative health care. Accurate diagnosis for patients with POMC deficiency can allow for timely surveillance and management of hypoglycemia as well as treatment of ACTH, TSH, GH, LH, and FSH deficiencies. Unfortunately, the true prevalence of POMC deficiency remains unknown as these syndrome likely remains under diagnosed [1]. With improving our knowledge of genetic mechanisms causing neonatal hypoglycemia or metabolic disorders in early childhood, further studies of earlier treatment approaches can be tailored for the individual patient to maximize neurodevelopmental outcomes.

Advances in molecular testing are becoming increasingly available in the clinical setting. There are over 340 genes just associated with

epilepsy, many of which have overlapping phenotypic features [7]. The improvements in sequencing technology and bioinformatics, turnaround time as a commercial service, and better insurance coverage for testing have allowed patients and family to access this diagnostic tool. WES is becoming more cost effective compared to traditional protocols involving serial genetic testing, particularly for conditions characterized by genetic heterogeneity [9]. There are limitations to whole exome sequencing which may be overlooked by nongeneticists, particularly when receiving a negative WES result. Mutations and/or causal variants may be in an exon of a gene that is poorly covered in the assay. Disease causing variant(s) may also be in non-coding regions of the genome such as deep intronic or promoter regions. As with any genetic test, it is important that families be counseled about risks, benefits, limitations of genetic testing by certified geneticists and/or genetic counselors. As molecular testing improves at an exponential rate, it is important for families to understand that future diagnostic opportunities may exist in the short and long term despite given a negative test result.

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