Familial Glucocorticoid Deficiency in a Newborn Caused by a Mutation in Melanocortin 2 Receptor: Case Report

Familial glucocorticoid deficiency (FGD) is one of the genetic causes of primary adrenal insufficiency (PAI) in children. It is characterized by glucocorticoid deficiency in the absence of mineralocorticoid deficiency. Most of cases are attributable to mutations in one of three genes: MC2R, MRAP, and STAR. NNT and MCM4 genes are recently discovered FGD causal genes. Patients typically present with hyperpigmentation, hypoglycemic seizures in the neonatal period. Herein we report a newborn diagnosed as PAI with generalized hyperpigmentation and hypoglycemia. Genetic analysis revealed c.560.delT homozygous mutation in MC2R gene. FGD should be kept in mind in hyperpigmented newborns with hypoglycemia in whom congenital adrenal hyperplasia is excluded.

Primary adrenal insufficiency (PAI) comprises a large group of disorders characterized by the impaired synthesis and release of adrenocortical hormones. Most of the causes of PAI in childhood have an inherited origin. Familial glucocorticoid deficiency (FGD) is caused by genetic defects within the adrenal gland, it is characterized by unresponsiveness of the adrenal gland to ACTH. Patients with FGD present early in childhood with hypoglycemia that may result in seizures, hyperpigmentation, feeding difficulties, failure to thrive. Familial glucocorticoid deficiency has been identified with mutations in the ACTH receptor/melanocortin 2 receptor (MC2R), the MC2R accessory protein (MRAP) or the StAR protein (StAR) genes. Approximately 50% of cases are attributable to mutations in one of these genes. However nicotinamide nucleotide transhydrogenase (NNT), and mini-chromosome maintenance-deficient 4 homologue (MCM4) gene are recently discovered FGD causal genes.
Herein we report a newborn diagnosed as PAI with generalized hyperpigmentation and hypoglycemia due to a mutation in MC2R gene (c.560delT).

**CASE REPORT**

A female infant (2530 g) was born by recurrent cesarean delivery at 37 weeks of gestation because of preterm labour to a 36-year-old mother. Parents were third degree relatives and they had a healthy, four years old boy. There was no history of medications. After birth, there was respiratory distress, the infant was treated with nasal continuous positive airway pressure (CPAP) and then weaned to room air.

Enteral feeding was began, afterwards the baby appeared more active and signs of respiratory distress resolved with no more oxygen requirement. Hypoglycemia was detected with blood glucose of 40 mg/dl on the second day while she was receiving i.v. glucose at 5 mg/kg/min, treatment with i.v. glucose (8 mg/kg/min) was initiated and then blood glucose levels were detected in normal range. On follow up generalized hyperpigmentation was noticed. Other examinations were normal with normal female genitalia. No clinical evidence of deficient tear production or achalasia was observed (Figure 1).

Additional laboratory studies were performed. Serum electrolytes were normal. Biochemical analysis revealed cortisol deficiency (0.26 mg/dl) with elevated plasma adrenocorticotropin hormone (ACTH) (826 pg/ml) levels. Dehydroepiandrosterone sulfate (DHEAS) levels (1.05 mcg/dl) and 17-hydroxyprogesterone (17-OHP) level (0.21 ng/ml) were normal. Very long-chain fatty acids levels were normal. Karyotype analysis revealed 46,XX. Cranial ultrasonography showed normal findings. The adrenal glands were not visualized on abdominal ultrasound.

According to these findings she was diagnosed as PAI and oral hydrocortisone replacement dose of 20 mg/m² per day was started. Plasma ACTH level was measured 7 days after starting hydrocortisone therapy and was detected as 540 pg/ml.

Molecular genetic analysis blood revealed homozygous c.560.delT mutation in patient in MC2R gene. Heterozygous carrier status of patients was confirmed. Informed consent was obtained from the parents.

**DISCUSSION**

Primary adrenal insufficiency is a potentially fatal medical condition. It is caused by conditions affecting the adrenal cortex resulting in insufficient production of adrenal steroids. Signs and symptoms result from low serum cortisol (such as failure to thrive, hypoglycemia, and lethargy) and high plasma ACTH levels (hyperpigmentation).1,2 Intense generalized hyperpigmentation was the most significant symptom in our patient. The diagnosis was established as PAI with very high plasma ACTH level in the presence of low plasma cortisol level.

Primary adrenal insufficiency is caused by either genetic defects or acquired disease that affect the adrenal function.2 The present case is the report of adrenal insufficiency in a neonate diagnosed as FGD due to a mutation in MC2R gene. Familial glucocorticoid deficiency is a rare autosomal recessive disorder that usually presents in neonatal period or in early childhood.3 The underlying genetic disorder is known in approximately 70% of patients with FGD.5 The MC2R is a member of the melanocortin receptor family, it is predominantly expressed in the adrenal cortex and binds specifically to ACTH.5,7,8 FGD is caused by mutations of MC2R that result in unresponsiveness to ACTH.
Hypoglycemia in the neonatal period is usually seen in patients with FGD, in many cases clinical diagnosis can not be made at this time. Similarly, hypoglycemia did not persist in our patient, she improved quickly with enteral feeding and IV glucose treatment. Excessive skin hyperpigmentation can be recognized in a few cases at early stage. Generalized hyperpigmentation at neonatal period was the most significant symptom in our patient. Clinical, laboratory findings and genetic studies in six patients with a diagnosis of FGD were discussed in a study from Turkey.

Differential diagnosis of adrenal insufficiency includes, congenital adrenal hyperplasia, adrenoleukodystrophy, adrenal hypoplasia, autoimmune disorders, metabolic disorders, syndromic causes and acquired conditions such as adrenal hemorrhage, trauma and infections. We excluded these diseases by history, physical examination and appropriate laboratory findings. Congenital adrenal hyperplasia was excluded by hormone analysis, normal female genitalia and chromosome analysis. Levels of very long-chain fatty acids were normal excluding adrenoleukodystrophy. Syndromic causes were not considered because of the normal physical examination and the absence of alacrima, achalasia. Acquired causes of adrenal insufficiency were unlikely because of her history, age and laboratory findings.

Most of the cases with FGD have an intact renin-aldosterone axis therefore do not require additional mineralocorticoid treatment. Hydrocortisone is the drug of choice for glucocorticoid replacement in children with FGD. In this case oral hydrocortisone replacement dose of 20 mg/m² per day was started and continued as 8-12 mg/m². Our patient responded to hydrocortisone treatment, her skin significantly lightened subsequent to treatment, and continues on replacement.

The long-term neurological consequences of FGD depend on the severity of hypoglycemic episodes during childhood. Our patient did not have persistent hypoglycemia. She is followed by pediatric endocrinology department, her neurodevelopment is appropriate for age.

In conclusion PAI is a potentially life threatening condition in childhood. It is important to be aware of PAI in newborns with generalized hyperpigmentation different from parents. Molecular genetic analysis is essential in confirming the exact diagnosis for congenital forms of PAI.

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Conflict of Interest
Authors declared no conflict of interest or financial support.

Authorship Contributions
REFERENCES


