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A Female Infant with Familial Glucocorticoid Deficiency Type 1 (FGD1) Presented with Adrenal Crisis in Southwestern Saudi Arabia: A Case Report

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Abstract

An isolated glucocorticoid deficiency with preserved mineralocorticoids is the main characteristic of familial glucocorticoid type 1. We report an unusual presentation of FGD1 in a 40-days-old female infant with shock and mineralocorticoid deficiency. Her parents noted that she started to have generalized hyperpigmentation of the skin and poor feeding, then they presented her to the hospital with severe hypoglycemia, convulsions and shock. Further laboratory investigations showed hyponatremia with hyperkalemia, very high ACTH, and very low cortisol levels during stress. A diagnosis of FGD1 was established by genetic analysis; Whole Exome Sequencing "WES", which, confirmed the diagnosis and showed a pathogenic variant consistent with MC2R, NM_000529.2:c.760T> G (p.Tyr254Asp). To our knowledge, this variant has not previously been reported in association with MC2R-related conditions; and it may have adversely affected the protein structure and/or function and is potentially responsible for the adrenal crisis in this FGD patient. Once the hydrocortisone replacement therapy was started, the patient's dark skin returned to normal color as her parents, and her symptoms significantly improved. We conclude that early recognition of the symptoms and sings of FGD and confirmation by paired investigation of serum cortisol and ACTH levels as well as genetic analysis is essential to establish the diagnosis and start early treatment with hydrocortisone to prevent its-related morbidity and mortality.

Keywords: Adrenal crisis • FGD • Hydrocortisone • Hyponatremia • Hyperkalemia

Introduction

Familial Glucocorticoid Deficiency (FGD) is a rare autosomal recessive disorder characterized by isolated glucocorticoid deficiency without mineralocorticoid deficiency[1]. It is caused by mutations in genes encoding either the ACTH receptor [melanocortin 2 receptor (MC2R)] or its accessory protein [melanocortin 2 receptor accessory protein (MRAP)]. This mutations in *MC2R* gene, also known as adrenocorticotropin (ACTH) receptor, have been associated with glucocorticoid deficiency (GCCD) resulting from defects in the action of adrenocorticotropic hormone (ACTH) to stimulate glucocorticoid synthesis in the adrenal (PubMed: 19500760; OMIM: 607397, 202200). The disorder is known as FGD type 1 and 2, respectively [1,2].

Patients with FGD, are usually characterized clinically by neonatal or early childhood hyperpigmentation, hypoglycemia, seizures, failure to thrive, and recurrent infections. Biochemically FGD is characterized by glucocorticoid deficiency without mineralocorticoid deficiency [3]. Other additional symptoms may develop in some patients due to hypocortisolemia such as weakness, fatigue, weight loss, anorexia, vomiting, flank or abdominal pain, constipation or diarrhea [4]. Recurrent hypoglycemic crises may lead to neurological consequences e.g., intellectual deficits, learning disabilities and sensory or motor defects [5].

Here, we are presenting a case of a 40-days-old girl with FGD type 1 (FGD1), who was presented to the Emergency Department (ED) of Al-Qunfudah general hospital in Southwestern Saudi Arabia with an unusual presentation of FGD 1 showing generalized hyperpigmentation of the skin, severe hypoglycemia with convulsions and shock in addition to hyponatremia and hyperkalemia.

Methodology

After obtaining the informed consent of the girl's parents, an endocrinological analysis and a molecular genetic analysis were performed. Hormones and other biochemical analysis were performed in Al-Qunfudah general hospital laboratories according to the recommended standard methods. Genomic DNA of the girl was extracted from a whole blood sample, and Whole Exome Sequencing (WES) was done in flugent laboratories, Santa Anita Ave, Temple city, California, USA.

In brief, genomic DNA was isolated from the specimen and enriched for the coding exons of targeted genes using hybrid capture technology. Prepared DNA libraries were then sequenced using a Next Generation Sequencing

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(NGS) technology. Following alignment to the human genome reference sequence (assembly GRCh37/hg19), variants were detected in regions of at least 10X coverage. Bioinformatics: Fulgent Germline Pipeline v2019.1 was used to generate variant calls for this test.Ethical approval for this study was obtained from the Biomedical Ethics Committee of Umm Al-Qura University (HAPO-02-K-012-2021-11-500).

Case Presentation

A 40-days-old girl presented to the ED in a seizure. She was born to a non-consanguineous Saudi parents after an uneventful pregnancy with a birth weight of 2.8 kg. The mother noticed generalized progressive darkening of the patient's skin after birth with poor feeding. Then by the age of 40 days, she was presented to the ED with a hypovolemic shock, seizure and generalized hyperpigmentation with normal female genitalia without any signs of achalasia, or alacrima. Capillary blood glucose was 0.9mmol/l, so the patient was resuscitated with normal saline fluid 0.9%, given a bolus dose of 10% dextrose, and continued maintenance before being transferred to the Pediatric Intensive Care Unit (PICU). Initial laboratory findings revealed Na 122 mmol/l (135-145mmol/L), K 8.2 mmol/l (3.5-5.0 mmol/L), plasma glucose 1.6 mmol/L (3.3-7.8 mmol/L), blood gas pH 7.39 (7.35-7.45) HCO_3 18 mmol/l (22-28mmol/L). As a result of the patient's hyponatremia, hyperkalemia, and normal genitalia, the first impression of diagnosis was pseudohypoaldosteronism (PHA) or rare types of salt-losing congenital adrenal hyperplasia (CAH), or lipoid adrenal hypoplasia. Blood sample was extracted to investigate the levels of cortisol, adrenocorticotropic hormone (ACTH), 17 hydroxyprogesterone, aldosterone, and renin. Without waiting for the laboratory results, the patient was given a stress dose of hydrocortisone based on the suspicion of CAH. A summary of clinical and laboratory findings is presented in Table 1. PHA and CAH were ruled out as causes of the infant's condition based on these findings. Achalasia-Addisonianism-Alacrima (AAA) syndrome was also, ruled out by through history taking, detailed physical examination and laboratory investigations. The FGD was diagnosed based on elevated ACTH, low cortisol, and a normal renin-aldosterone axis in response to hypovolemic shock. Hydrocortisone is administered intravenously, then 10 mg/m^2/day orally at discharge. However, there was no family history of similar cases in the girl's family, who is the 4th child for a normal three elder siblings (Figure 1).

The blood was sent for genetic testing, which confirmed the diagnosis of FGD1 and showed a pathogenic variant consistent with MC2R, NM_000529.2:c.760T> G (p.Tyr254Asp). She was discharged after having a stable general condition, and her hormonal and biochemical changes returned to normal (Table 2). The parents were clearly instructed to double the oral dose of hydrocortisone if the baby has undercurrent illness (fever, cough, vomiting and diarrhea). In the routine follow-up after two months of treatment, her symptoms of the FGD had disappeared, she is growing with normal weight and height for age, and her skin color is back to normal (Figure 2).

Discussion

In response to signals and stress, glucocorticoids are synthesized and produced by the adrenal cortex in a circadian manner, they peak in the morning and are lowest at night [1,6]. Hypothalamus releases corticotrophin-releasing hormone (CRH) that stimulates anterior pituitary to secrete adrenocorticotrophic hormone (ACTH) into the general circulation [2,7]. This stimulates the adrenal cortex to synthesize and release glucocorticoids, that are controlled by feedback mechanism in the hypothalamus and anterior pituitary which inhibit further release of CRH and ACTH, respectively [1,8]. Glucocorticoids are steroid hormones that are essential for life by regulating many homeostatic systems in the body, including, cardiovascular, metabolic, reproductive, immune and central nervous systems through intracellular glucocorticoid receptor (GR). FGD is an autosomal recessive disorder resulting from defects in the action of adrenocorticotropic hormone (ACTH) to stimulate glucocorticoid synthesis in the adrenal glands, with normal production of mineralocorticoids [9]. Patients present in early life with low or undetectable cortisol and, because of the failure of the negative feedback loop to the pituitary and hypothalamus, grossly elevated ACTH levels [6,10]. Our case report describes an autosomal recessive disorder of FGD in a 40-days-old girl who was presented with hypoglycemic seizures, hyperpigmentation, hypovolemic shock. Laboratory investigations for the girl's blood samples revealed low serum cortisol levels with high serum ACTH levels, hyponatremia, and hyperkalemia and preserved mineralocorticoid production. After administration of cortisol, her health condition improved, suggesting that her health problem was a glucocorticoid deficiency.

Genetic analysis of the girl's blood confirmed the presence of a mutation in the *MC2R* gene with a homozygous "biallelic" variant in the *MC2R* gene. To our knowledge, this variant has not been reported in association with MC2R-related conditions [8,11]; however, another variant at this position in the gene NM_004333.4:c.741T>G (p.Tyr254Asp) has usually been associated with GCCD1 [2]. Therefore, this identified mutant homozygous likely pathogenic variant that is consistent with diagnosis of a MC2R related condition may have caused the unusual presentation of our FGD girl. It is suggested that the identified variant with the change at the position, NM_000529.2:c.760T>G (p.Tyr254Asp), adversely affected the protein structure and/or function and is potentially a pathogenic variant (PubMed: 12213892) that led to the adrenal crisis findings in addition to the FGD symptoms in our patient [1]. This variant has not been reported in the Broad dataset (individuals without severe

Table 1. Clinical and laboratory information of the four months old girl with glucocorticoid deficiency, at its first presentation to Al-Qunfudah general hospital.

Clinical & Laboratory Data	Results	References
Body weight	3.9 kg	3.4-6.7 kg
Height	56 cm	48-68 cm
Blood Glucose	0.9 mmol/l	(4.4-7.8 mmol/l)
Cortisol	0.88 nmol/L	(80-580 nmol/L
ACTH	>2000 pg/ml	(5-60 pg/mL)
Renin	728 µIU/mL	(2.80-39.90 µIU/mL)
DHEAS	0.006 nmol/L	(2.80-39.90 nmol/L)
17- OH Progesterone	0.4 ng/dL	(36-760 ng/dL)
Aldosterone	69.30 ng/dL	(1.76-23.2 ng/dL)
Sodium (Na^+)	122 mmol/L	(135-145 mmol/l)
Potassium (K^+)	8.3 mmol/L	(3.5-5.0 mmol/l)

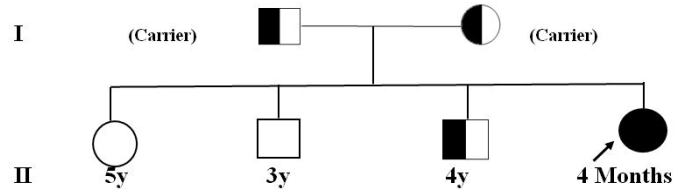

Figure 1. Pedigree of the family of the familial glucocorticoid deficiency case, showing the unaffected parents and siblings.

Table 2. Measurement of glucocorticoid hormones before and after hormonal therapy at Al-Qunfudah general hospital.

Lab	Before Treatment	After Treatment	Reference Range
ACTH	>2000 pg/mL	13.5 pg/mL	5-60 pg/mL
CORTISOL	0.88 nmol/L	322 nmol/L	80-580 nmol/L

Figure 2. Hyperpigmentation of the skin of the FGD girl before treatment and few months after starting cortisol replacement therapy.

childhood onset disease). The physiochemical difference between Tyr and Asp amino acids as measured by Grantham's Distance is 160. This score is considered a "radical" change, indicating that Tyr and Asp have significantly different physiochemical properties (PubMed: 4843792, 6442359). Clark AJL, et al. [1] and Tsigos et al. reported that glucocorticoid deficiency is produced by homozygous or compound heterozygous mutation in the gene encoding MC2R on chromosome 18p11 (GCCD1) [6]. Later on, researchers reported that FGD can be caused by mutations in more than one gene; *MRAP* gene on chromosome 21q22 (GCCD2) [2], chromosome 8q11.2-q13.2 (GCCD3) [4], the *NNT* gene on chromosome 5p12 (GCCD4) and the *TXNRD2* gene on chromosome 22q11 (GCCD5). In patients with abnormal hyperpigmentation, FGD should be considered, rather than waiting for adrenal crisis and life-threatening hyperkalemia to occur. Hydrocortisone treatment should be initiated in all patients without an index case of FGD, as it will ensure safety until the results of the investigation are available.

Conclusion

Early recognition of the symptoms and sings of FGD and confirmation by paired investigation of serum cortisol and ACTH levels as well as genetic analysis is essential to establish the diagnosis and start early treatment with hydrocortisone to prevent its-related morbidity and mortality.

Conflict of interest

The authors declare that there is no conflict of interest for this study.

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