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# Familial Glucocorticoid Deficiency Presenting as Progressive Hyperpigmentation

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**ABSTRACT**

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disease caused by resistant of ACTH receptor at adrenal cortex leading to (usually) isolated glucocorticoid deficiency with normal mineralocorticoid secretion. Patients with FGD usually presented in neonatal – childhood period with signs /symptoms of glucocorticoid deficiency such as hypoglycemia, hyperpigmentation, Failure to thrive, shock and death if treatment was delayed. Labs usually revealed high ACTH, low cortisol but normal 17 OHP, electrolyte, androgen. Here we describe a three years old, Saudi girl, with history of progressive hyperpigmentation since first year of life, but no history of hypoglycaemia or neonatal jaundice, no history of a lacrimation or dysphagia and positive similar family history. She had generalized Hyperpigmentation with normal female genitalia. Her cortisol was low with high ACTH level, but normal electrolyte, 17 Hydroxyprogesterone, aldosterone, renin, androgen. Familial Glucocorticoid Deficiency was diagnosed and maintenance dose of hydrocortisol was started and patient pigmentation was improved few weeks later.

## Introduction

Familial Glucocorticoid Deficiency (FGD) is a rare autosomal recessive disorder of the adrenal cortex secondary to inactivating mutations of the ACTH receptor genes causing a resistant to ACTH action which will lead to (usually isolated) glucocorticoid deficiency, but combined mineralocorticoid insufficiency and extra-adrenal manifestations have been rarely reported in patient with NNT Gene mutation (Jazayeria et al., 2015). Three genes are responsible for more than 50% of cases of FGD.

Those are MC2R, MRAP and STAR gene mutation causing FGD 1, 2, 3 respectively. Other reported affected genes discovered include TXNRD, NNT (Meimaridou et al., 2013; Jazayeri et al., 2015). Clinical presentation of those types of GFD are similar with few differences like early neonatal presentation in FGD2 (Ramachandran et al., 2003) while type 1 present latter as late as 16 years and usually patients are taller in FGF1 (Ramachandran et al., 2003; Chung et al., 2010). Other reported features include neonatal hypoglycaemia, prolonged neonatal jaundice, neonatal hepatitis (Al-Hussaini et al., 2012; Lacy et al., 1993; Leblanc et al., 1981), convulsion unrelated to hypoglycemia (Ramachandran, 2003), delayed milestones, FTT (Jazayeri et al., 2015; Chung et al., 2010; Rousseau et al., 2007), hyperpigmentation but this can be absent as reported by Turan et al. (2012) and familial focal segmental glomerulosclerosis (Ram et al., 2012).

## Case report

In this report we describe a three years old, Saudi female, who present to our clinic with history of delayed speech and progressive skin hyperpigmentation since age of one year. She was a product of full term pregnancy, NSVD with no birth trauma history and birth weight of 2.8 kg. There was no history of symptomatic hypoglycaemia, a lacrimation, dysphagia or prolonged neonatal jaundice. No history of nausea or chronic abdominal pain.

Child was three years old but her speech was delayed, with normal motor development. Her parents were consanguineous with strong family history of similar presentation in three of her cousin, two females and one male, both had hyperpigmentation at first year of life and diagnosed as isolated cortisol deficiency and are doing fine on Hydrocortisol. Interestingly, one of them was mentally retarded and other had epilepsy.

-Upon examination she had normal growth parameter (Ht at 50 centile) Normal female genitalia.
-Rest of her examination was unremarkable.
Her labs show high ACTH of 120 pmol /L (Normal range 1-6 pmol/l), with low early morning cortisol =76.3 nmol /l. All other investigations were normal including 17 OHP, Aldosterone, Renin, androgen TFT, Glucose and electrolyte.
-Barrium swallow done looking for achalasia but was normal.
-MRI BRAIN done for delayed speech, show incidental finding of small cyst, and pituitary gland was normal.
US Pelvic /ABDOMEN shown normal internal female sexual organs with no adrenal calcification.

Treatment: maintenance dose of hydrocortisol (10 mg/ m2 /day) was started and patient pigmentation was improved few weeks later and ACTH drop to 20 pmol/l.

## Discussion

FGD is a rare AR disease caused by a mutated ACTH receptor at adrenal glumerlosa, leading to and high ACTH level and low cortisol with its consequences. In Saudi Arabia few case reports of FGD have been reported (Hughes et al., 2010; Habeb et al., 2013). We report her a 3 years Saudi old girl who had history of progressive hyperpigmentation since early infancy with low cortisol level and high ACTH with normal electrolyte, Renin, aldosterone and 17 OHP those all going with isolated glucocorticoid deficiency. Differential diagnosis of such presentation usually include FGD, Allgrove syndrome, primary Adrenal failure, congenital adrenal hyperplasia /Hypoplasia (Metherell et al., 2009; Dumic et al., 2012). Allgrove syndrome was unlikely in our patient since there was no a lacrimation nor achalasia.

Primary adrenal failure, usually secondary to infection or old adrenal haemorrhage was rolled out by presence of normal electrolyte, Renin and aldosterone level. Since the level of 17OHP was normal the possibility of Non classical congenital adrenal hyperplasia was ruled out. After those all ruled out then the only possible diagnosis is FGD, which need to be confirmed by genetic study but

was not available in our hospital. Other supporting point toward FGD as a final diagnosis in our patient was strong family history of similar presentation in her cousin who had epilepsy, hyperpigmentation and low cortisol, High ACTH level and normal electrolyte and was doing fine on Hydrocortisol.

In GFD, Electrolyte and blood glass usually normal since electrolyte (Na, K) balance usually under tight control of angiotensin -Renin -aldosterone pathway in the adrenal glomerlosa layer which is not (usually) affected, so level of aldosterone, Renin will be normal or even high trying to compensate hypovolemic state caused by low cortisol which play a role in maintaining normovolemic stat. Combined mineralocorticoid insufficiency and extra-adrenal manifestations have been rarely reported in patient with NNT Gene mutation (Jazayeri et al., 2015). Early diagnosis of FGD is critical to prevent hypocortisolism sequel like hypoglycaemia which has major CNS consequence like CP and delayed treatment could result in death from adrenal crises with simple infection (Habeb et al., 2013).

Treatment with a maintenance dose of hydrocortisol alone and importantly patients should be educated about adjustment of the dose during illness like doubling dose when temperature above 38.5 and triple it with more sickness and keeping emergency pen of Hydrocortsiol IM at home for emergency in case patient get comatose during illness.

## Conclusion

FGF should be kept in mind as a differential diagnosis of any patient who present with signs of hypocortisolaemia and should be diagnosed and treated early to prevent adrenal crises which could kill the patients.

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