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A Case Report of Familial Glucocorticoid Deficiency

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Abstract: *Familial Glucocorticoid Deficiency(FGD) is a rare autosomal recessive disease characterised by glucocorticoid deficiency leading to hypoglycemia, hyperpigmentation increased serum levels of ACTH without mineralocorticoid deficiency. FGD is an important differential diagnosis of Addison's disease in children and have isolated glucocorticoid deficiency as a result of defects in ACTH action. Recognition of this entity is important to avoid unnecessary treatments with mineralocorticoids .In this paper we report a case of 6 year old male child with isolated glucocorticoid deficiency on the basis of clinical features and laboratory investigations, patient was given appropriate treatment and responded to the treatment.*
Keywords: *Glucocorticoidid deficiency, Addison's disease, Mineralocorticoids, ACTH excess.*

I. Introduction

A rare autosomal recessive disease, Familial glucocorticoid deficiency (FGD) or hereditary unresponsiveness to adrenocorticotropic hormone (ACTH), is characterized byglucocorticoid deficiency, high levels of ACTH and normal mineralocorticoid levels.Mutations of the ACTH receptor, also called as melanocortin−2 receptor (MC2R) contributes to about25% cases of FGD(1,2). The disease manifests with non-ketotic,nonhyperinsulinemic hypoglycemia, seizures,hyperpigmentation, recurrent infections, failure to thrive, sometimes collapse and coma.More recently 15–20% cases of FGD are due to that mutations in melanocortin−2 receptor accessory protein (MRAP), encoding a new interacting partner of the ACTH receptor, and was demonstrated by Metherell et al(3).In this paper we report a case of 6 year old male child with isolated glucocorticoid deficiency.

II. Case Report

A6 year old male child, born of non-consanguinous marriage, presented to us in the OPD with complaints of Hyperpigmentation of skin, unexplained weight loss and fatigue since last 6 months. He had previous history of unresolving cough and fever 5 months back for which he had taken multiple courses of antibiotics and was started on anti-tuberculous treatment. Patient had a history of convulsions and syncope 4 months back with documented hypoglycemia, for which patient was admitted and treated.The elder male sibling also had repeated episodes of convulsionsand died at the age of 3 yr. Motor and mental developmental was normal. On examination, vital parameters were normalhyperpigmentation was evident over the entire body, more prominent over elbows, knees, knucles, toes,palmar creases, oral mucosa and scrotum. His weight was 15.2kg(below 3rdpercentile) and height 109cm(10th-25th percentile).Midparental height is 161cm [between 3rd to 10thpercentile].Investigations were suggestive of normal hemogram, hypoglycemia,hyponatremia with normal serum potassium and calcium,normal thyroid profile. Morning serum cortisol levels and 17-hydroxy progesterone levels were low.Urine was negative for sugar and ketone bodies and ultrasound abdomen was normal.Mantoux test was negative. ACTH was high in presence ofhypocortisolemia, along with pigmentation, confirming primary adrenal failure.Hypocortisolemia with borderline low sodium and normal potassium striked the diagnosis of isolated Glucocorticoid deficiency. With similar history of seizures, pigmentation and sudden death in the elder sibling, genetic etiology was suspected.

Table 1. Laboratory Evaluation of patient: Our patient had no alacrimia or achalasia, ruling out Allgrove's syndrome. X-Linked Adrenoleukodystrophy can present with male-inherited addison's disease, but generally have accompanying neurological problems and mineralocorticoid deficiency. He did not have other markers of Autoimmune Polyendocrinopathy Syndrome [APS] such as hypocalcemia, mucocutaneous candidiasis [APS1] or diabetes and hypothyroidism [APS2]. A mantoux test, chest x-ray and sonography of adrenal glands ruled out tuberculosis.In view ofisolated glucocorticoid deficiency of familial variety, a diagnosis of FGD was made. Patient was started with replacement steroids in the form oral hydocortisone in three daily divided doses. There was marked improvement in child clinical status with weight gain and reduction in pigmentation. Electrolytes are normal with physiological replacement doses of hydrocortisone [12mg/m2/day] and plasma-renin-activity is normal, indicating that there is no mineralocorticoid deficiency.

Table 1 Laboratory Evaluation of patient

Hb	10.8 Gm/Dl
TLC	9700/Cmm
Platelet	4.98 Lakh
Serum Sodium	132 Meq/L
Serum Potassium	4.5 Meq/L
Serum Calcium	8.7 Mg/Dl
Serum Cortisol(8am)	1.34 Mcg/Dl
Serum 17-Hydroxy Progesterone	0.41 Ng/Ml
Blood Sugar(Random)	30 Mg/Dl
Serum ACTH	Above 1250pg/Ml
Plasma Renin Activity	1.9ng/Ml/Hour

III. Discussion

FGD usually presents in infants or in early childhood with failure to thrive, recurrent infections, hyperpigmentation, seizures and severe hypoglycemic episodes that may result in coma or death. These patients have low cortisol and high ACTH levels. It is a rare autosomal recessive disorder characterized by isolated glucocorticoid deficiency with normal mineralocorticoid levels and renin-aldosterone axis[4].

While adult-onset Addison's disease is generally acquired [autoimmune or post-tuberculous]; in children, congenital and inherited disorders prevail. The differential diagnosisincludes congenital disorders such as congenital adrenal hyperplasia(CAH),Adrenoleukodystrophy(ALD), Adrenal Hypoplasia Congenita [DAX-mutations], ACTH resistance syndromes and acquired conditions such as adrenal hemorrhage, trauma and infections[5,].CAHin males can either present in newborn period with salt-wasting crisis or during childhood with precocious puberty. Allgrove's syndrome has associatedalacrimia or achalasia.Congenital adrenal hypoplasia generally has associated cryptorchidism. Out of these genetic causes, FGD and Allgrove's can present with isolated glucocorticoid deficiency.

About 25% of FGD cases (FGD type 1) are contributed bymutations of ACTH receptor (MC2R) present on the ZonaFasciculata cells (1).Mutations in MRAP gene, a gene encoding a small single transmembrane domain protein known as MRAP have been mentioned recently in a group of patients with ACTH resistance syndrome but without any mutations in MC2R gene (FGD type 2). MRAP is an essential cofactor for MC2R expression (3). FGD type 1 are generally tall and present later than FGD type 2 [6]. So far 9 different mutations of MRAP in FGD patients have been described; they all result in either an absent or significantly truncated protein[7]. MRAP mutations comprise approximately 20% of patients with FGD[2].

Although renin-aldosterone axis is unimpaired in most cases, mild salt−wasting at the time of diagnosis have been reported in some cases [8]. In these patients, definitive diagnosis can be made by finding mutations in the MC2R or recently described MRAP gene. In about 55−60% of the FGD cases, the defective genes that cause disease remainunidentified. Mild mutations in the STAR [steroid acute regulatory protein] can present like FGD instead of lipoid congenital adrenal hyperplasia, and are labelled as FGD type 3.

IV. Conclusion

FGD is an important differential diagnosis of Addison's disease in children and have isolated glucocorticoid deficiency as a result of defects in ACTH action. Recognition of this entity is important to avoid unnecessary treatments with mineralocorticoids.

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