

Familial glucocorticoid deficiency presenting with generalized hyperpigmentation in adolescence. Report of three siblings

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ABSTRACT

Background: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterized by glucocorticoid deficiency, high ACTH levels and normal mineralocorticoid levels. FGD is caused due to defects in adrenocorticotrophic hormone (ACTH) signaling. The defect can be caused by mutations in genes encoding the ACTH receptor (melanocortin 2 receptor) or its accessory protein. **Patients:** Here we report three siblings with FGD. The second in order of siblings presented at an age of 15 years with history of diffuse hyperpigmentation since childhood. Their parents were non consanguineous. The patients were hyperpigmented and taller compared with their parents. None of the siblings had ambiguous genitalia or neurological abnormalities. There was no history of tuberculosis in the family. Biochemical investigations revealed low serum cortisol (<1 µg/dl) and elevated plasma ACTH (>1250 pg/ml). Serum electrolytes, aldosterone, and plasma renin activity was normal. Based on the above mentioned data, a provisional diagnosis of FGD was made after ruling out the common causes of glucocorticoid deficiency. **Conclusion:** FGD is a rare autosomal recessive disorder which causes isolated glucocorticoid deficiency. Unawareness about the condition may lead to delayed diagnosis and treatment, which are associated with high rates of morbidity and mortality. Once a diagnosis is made it is easily treatable.

Key words: Familial glucocorticoid deficiency, hyperpigmentations, melanocortin-2 receptor

INTRODUCTION

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterized by glucocorticoid deficiency, high ACTH levels and normal mineralocorticoid levels.^[1] FGD is caused due to defects in ACTH signaling.^[2] FGD may be caused by mutations in the ACTH receptor (melanocortin 2 receptor) gene, classified as FGD type 1, or by mutations in the melanocortin-2 receptor accessory protein, classified as FGD type 2. FGD type 1 accounts for 25% of FGD cases, while FGD type 2 accounts for approximately 15-20% of FGD cases.^[3] Here we report three siblings with FGD.

INDEX CASE

A 15-year-old male presented with progressive diffuse hyperpigmentation since 5 years of age. He had frequent attacks of respiratory infections during childhood which were associated with nausea and vomiting. There was no history of fever and tuberculosis during the past. He was born to non-consanguineous parents after an uneventful full term vaginal delivery, with a birth weight of 2800 g. The patient had a body weight of 46 kg and height of 167 cm (height SDS+0.6, target height SDS-0.25). He had diffuse hyperpigmentation of the skin, palms [Figure 1] and the oral mucosa. He had a blood pressure of 80/60 mm of Hg with an asymptomatic postural drop of 10 mm. Oral candidiasis and tetany were absent. His genitals were normal with a stretched penile length of 12 cm and testicular volume of 16 ml bilaterally. The nervous system examination was normal.

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The biochemical evaluation revealed a glucose 60 mg%; Na⁺ 142.4 mEq/l; K⁺ 4.29 mEq/l; Ca²⁺ 9 mg/dl; alanine transaminase, 28 IU/mL; and aspartate transaminase, 30 IU/mL. His total blood count was normal. Endocrinological analysis revealed a cortisol level <0.1 µg/dl; elevated plasma ACTH (>1250 pg/ml); free T4 0.91 ng/dl; TSH 1.42 µIU/ml. His 17-OH progesterone level was 0.1 ng/mL (normal range: 0.03-0.9 ng/mL); androstenedione, 1.1 ng/ml (normal range 0.7-3.6 ng/ml); dehydroepiandrosterone sulphate, 200 µg/dl (normal range 80-560 µg/dl); plasma renin activity, 5 ng/mL/hour (normal range: 2.35-37 ng/mL/h); aldosterone, 801 pg/mL (normal range: 50-900 pg/mL). The chest X-ray was normal. The adrenals were not visible on ultrasonography, computed tomography and magnetic resonance imaging.

The elder brother who had accompanied the patient had diffuse hyperpigmentation. On enquiring, he and another sibling had similar complaints of progressive hyperpigmentation [Figure 2], intermittent nausea and vomiting starting from 5-6 years of age. The whole family including the parents were subjected to clinical examination and hormonal assays, which revealed findings similar to the index case in two siblings [Table 1].



Figure 1: Patient's photograph showing diffuse hyperpigmentation

A provisional diagnosis of FGD type 1 was made, and the patients were started on glucocorticoid replacement with a plan to follow-up.

DISCUSSION

FGD is a rare cause of adrenal insufficiency, which is inherited in an autosomal recessive manner. Awareness about the condition, proper evaluation to exclude more common causes of adrenal insufficiency and confirmation by genetic studies can lead to early diagnosis and treatment. The common differential diagnoses which should be considered include congenital adrenal hyperplasia, adrenoleukodystrophy, Allgrove syndrome, adrenal hemorrhage, trauma and infections.

The clinical features of FGD types 1 and 2 show striking distinctions in the age of presentation and height. FGD type 1 presents with a variable age of onset, median age is 2.0 years (range 0-16 years; mean age 3.11 ± 3.40 years), while FGD type 2 presents at an earlier age with the median onset at 0.08 years (range 0-1.6 years; mean age 0.31 ± 0.51 years).^[3] Unusually tall stature has been described in many FGD type 1 cases to the literature.^[4] All the symptoms and signs seen in FGD are the result of either hypocortisolemia or elevated ACTH levels. Hypocortisolemia may cause weakness, fatigue, weight loss, anorexia progressing to



Figure 2: Photograph of the whole family showing tall stature and hyperpigmentation

Table 1: Clinical and laboratory data of the patients and their parents

	Age (years)	Sex	Height (cm)	Pigmentation	Cortisol (mcg/dl)	ACTH (pg/ml)
Index case	15	M	167 SDS+0.6	+++	<1	>1250
1 st Sibling	17	M	176 SDS+1	++	<1	>1250
3 rd Sibling	12	F	150 SDS+0.6	+	5.15	53.5
4 th Sibling	9	M	131 SDS+0.2	+	3.1	>1250
Father	40	M	165.5 SDS-1.1	-	11.1	54.3
Mother	35	F	161.5 SDS-0.6	-	15.43	44.3

ACTH: Adrenocorticotropic hormone

nausea, vomiting, diarrhea, constipation, flank or abdominal pain, hypoglycemia and hypothermia. High ACTH causes increased melanin production, resulting in generalized hyperpigmentation. The most frequent cause of FGD death is undiagnosed glucocorticoid insufficiency. Once diagnosed it is easily treatable and if left untreated it may be fatal or lead to severe mental disability as a result of recurrent hypoglycemia secondary to glucocorticoid insufficiency. The treatment of FGD is by replacement with hydrocortisone at a dose of 10-12 mg/m²/day in three divided doses. The suppression of plasma ACTH levels in FGD can be very difficult and should not be used as the goal of treatment.

Our patient presented at the age of 15 years with diffuse hyperpigmentation and tall stature. On evaluation, he was found to have isolated glucocorticoid deficiency with very high ACTH levels. The mineralocorticoid axis was spared as indicated by normal serum K⁺, aldosterone and renin activity. Infections, which are the most common cause of adrenal insufficiency, were less likely as the adrenals were not visible on imaging studies and the chest X ray did not show any signs of infection. Serum for 21-hydroxylase autoantibodies for autoimmune adrenal insufficiency and very long chain fatty acids for adrenoleukodystrophy could not be done. Adrenoleukodystrophy was less likely due to the absence of neurological involvement. The absence of genital ambiguity with normal 17-OH progesterone made the diagnosis of congenital adrenal hyperplasia less likely. Since the patient and two of his siblings had isolated glucocorticoid deficiency with hyperpigmentation and tall

stature, a provisional diagnosis of FGD was made. Genetic studies would have provided a definite answer, which we were not able to do.

CONCLUSION

FGD is a rare autosomal recessive disorder which causes isolated glucocorticoid deficiency sparing mineralocorticoid axis. Unawareness about the condition may lead to delayed diagnosis and treatment, which are associated with high rates of morbidity and mortality. Once a diagnosis is made it is easily treatable.

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