A Pilot Study Evaluating Therapeutic Response of Different Dosage of Oral Glucocorticoid in Two Children with Familial Glucocorticoid Deficiency Presenting with Diffuse Mucocutaneous Hyperpigmentation

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Abstract

Introduction: Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive potentially life-threatening condition, characterized by glucocorticoid deficiency, preserved aldosterone/renin secretion, and secondary rise in plasma adrenocorticotropic hormone level. This occurs due to either mutation in adrenocorticotropic receptor (25%, FGD Type-1) or in the MC2 receptor accessory protein (15%–20%). However, in about 50% patients, no identifiable mutations have been identified. Clinically, it manifests with weakness, fatigue, weight loss, anorexia, nausea, vomiting, diarrhea, abdominal pain, hypoglycemia, and hypothermia. Progressive mucocutaneous pigmentation is a conspicuous presentation. Repeated hypoglycemia may result in seizure, persistent neurological, severe mental disability, and even sudden death. Standard therapy is oral glucocorticoids (10–15 mg/m²). Patients and Results: Two familial cases of FGD were put on progressively increasing doses of oral glucocorticoids (10 mg, 15 mg, and 20 mg/m²/day, each for 6 weeks) to achieve the best response without any adverse effects. One patient had excellent improvement with 15 mg/m²/day, and another required 20 mg/m²/day. The latter patient had excellent overall improvement with only moderate improvement in pigmentation. Conclusion: Glucocorticoids replacement with optimum dose is necessary in FGD to promote physical and neurological growth and to prevent adrenal crises, hypotension, hypoglycemia, and sudden death. Higher dose than mentioned in literature (15 mg/m²/day) may be required in selected cases. Mucocutaneous pigmentation may require even higher dose than we used. More studies are required.

Key Words: Diffuse mucocutaneous hyperpigmentation, familial glucocorticoid deficiency, Oral glucocorticosteroid,

What was known?
Systemic problems and mucocutaneous pigmentation in FGD is principally managed with oral glucocorticoid replacement therapy. Maximum dose known to be used so far is 15 mg/m²/day.

Introduction

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive potentially life-threatening condition,[1,2] first described by Shepard, Landing, and Mason in 1959.[3] Little more than fifty cases are reported in literature,[4,5] Age of onset is birth to 9 years. Approximately, 50% of cases occur in the 1st year of life.

This is characterized by glucocorticoid deficiency, elevated plasma adrenocorticotropic hormone (ACTH) level, and preserved aldosterone/renin secretion. Clinically, it manifests with weakness, fatigue, weight loss, anorexia, nausea, vomiting, diarrhea, abdominal pain, hypoglycemia, and hypothermia and diffuse mucocutaneous pigmentation.

Repeated hypoglycemia may result in seizure, persistent neurological deficit, and severe mental disability. Undiagnosed glucocorticoid insufficiency may even lead to death due to various mechanisms. Death due to repeated seizure and intercurrent infections are reported.

This is considered a heterogeneous disease. There is mutation in adrenocorticotropic receptor (25%, FGD Type-1)

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The zona fasciculata of the adrenal gland that secrete cortisol is markedly atrophic. Cortisol level is low with a secondary rise in ACTH level. Zona glomerulosa is well preserved. Thus, serum mineralocorticoids and plasma renin level are usually unaffected.

Generalized, intense hyperpigmentation of the skin and mucous membrane, a striking feature of FGD results from high ACTH level. This starts at very early age. FGD is one of the important etiologies that need consideration in any case of early-onset generalized pigmentation like carbon baby syndrome.

Replacement of glucocorticoids is the principle treatment. This avoids adrenal crises and allows normal growth. The usual dose of oral corticosteroid, as per published literature is 10–15 mg/m²/day. Both overdose and undertreatment are detrimental. Adequacy may be judged clinically with the improvement of disease parameters, linear growth, normal blood pressure and sugar value, and absence of steroid overdosage like Cushingoid features. Hyperpigmentation fades once proper treatment is initiated with glucocorticoid.

There have been so far no trials or even case report with dose higher than 15 mg/m²/day that is the highest limit of standard recommended daily replacement dose in FGD. We report this due to the extreme rarity of the cases and to present the response of higher doses of oral corticosteroid replacement therapy in this pilot study.

Study Report

Two familial cases, one female, aged 2 years and one male, aged 1.5 years, both having born after consanguineous marriage (2nd degree in both) [Figure 1] presented to us within a short gap with the complaints of lower respiratory tract infection (RTI), severe weakness, failure to thrive and intensely dark generalized pigmentation of skin and mucosa.

Symptoms started with poor appetite, repeated vomiting, gross weakness, and progressively increasing mucocutaneous pigmentation. Age of onset was around 6 months in the male and about 4 months of age in the female child. They suffered from recurrent lower respiratory tract and skin infection.

Investigations revealed hypotension, hypoglycemia, normal electrolyte level, normal thyroid and parathyroid function, very low serum cortisol (1.22 μg/dl in male, 1 μg/dl in female, normal value - 5–25 μg/dl), high plasma ACTH (>1250 pg/ml in both, 0–46 normal value), normal plasma renin value, normal levels of plasma 17-hydroxy progesterone, and normal arterial blood gas (ABG). Lacrimal gland was of normal size in ultrasonography (USG), and barium swallow study of the upper gut revealed normal appearance. Adrenal gland was not visualized with USG and computed tomography scan of abdomen. Skin biopsy (from back) revealed intense basal layer melanization without any basal layer liquefaction. There was mild lymphomononuclear cell infiltration in the dermis [Figure 2]. With the constellation of features, the cases were diagnosed as FGD.

Both the cases were put on oral corticosteroid 10 mg/m²/day. Both the patients showed a partial response after 6 weeks. Dose was increased to 15 mg/m²/day. With this higher dose, which was still within the standard recommended dose, the female child had complete improvement in all parameters and but the male child improved only partially with persistence of weakness, lethargy, poor appetite. Mucocutaneous pigmentation persisted at almost same state. He also had two episodes of lower RTI also during this. His serum cortisol was still low and plasma ACTH was high. A further dose escalation by 5 mg/m²/day was planned. The institutional ethics committee approved this study of dose escalation.

After this 20 mg/m²/day dose for another 6 weeks, the male child showed excellent recovery in appetite, muscle

Figure 1: Pedigree of the affected patients (square = male, circle = female)

Figure 2: The photomicrograph (×100, H and E) showing mild hyperkeratosis, prominent basal pigmentation, and unremarkable dermis. The close up image (×400) showing large, darkly stained keratinocytes at basal and supra-basal layers
strength, and physical activity. There was no RTI during this period.

Both the patients were maintained on these doses (female with 15 mg/m²/day and male with 20 mg/m²/day). They were followed up monthly. After 6 months, both the children were active, had normal growth and did not have any clinical signs of FGD. The female patient showed significant improvement in pigmentation, but the male child had improved moderately at 6 months [Figure 3]. Plasma ACTH level was still higher (990 pg/ml) in the male child.

There was no increased incidence of infections. Blood sugar, ABG, and blood pressure were measured repeatedly, and these were within normal limit. There were no signs of cortisol overdose like hypertension and Cushing syndrome in both.

Discussion

Generalized hyperpigmentation during neonatal till early childhood can be caused by metabolic, endocrine, and other systemic and dermatological conditions. Hyperthyroidism, hypothyroidism, acromegaly, Addison’s disease and Cushing’s syndrome, chronic hepatic disease and chronic renal disease are known to present with diffuse generalized hyperpigmentation. Dyschromatosis symmetrica hereditaria, congenital diffuse melanosis,[9] familial progressive hyperpigmentation,[10] and erythema dyschromicum perstans and carbon baby syndrome are important conditions that develop pigmentation very early in life. Carbon baby syndrome[11] is a diagnosis by exclusion for diffuse generalized pigmentation and has no systemic abnormality. Bronze baby syndrome[12] occurs among neonate with hepatic dysfunction and undergoing phototherapy. In addition to the presence of specific features, these conditions lack any abnormality of cortisol secretion and ACTH level.

FGD may also be closely simulated by other causes of adrenal insufficiency such as congenital adrenal hyperplasia (CAH), adrenal hypoplasia, polyglandular autoimmune syndrome, adrenoleukodystrophy, hemorrhage, trauma and infections of the adrenal gland, and Allgrove syndrome (AS). AS characterized by alacrima-achalasia-adrenal insufficiency neurologic disorder occurs due to a defect in a WD-repeat regulatory protein.[5] Adrenoleukodystrophy, an X-linked recessive disorder is caused by the accumulation of unsaturated fatty acids with a chain of 24–30 carbons, (hexadecanoate mostly) in the adrenal cortex and brain and is manifested with diffuse pigmentation that spares palms, soles, groin along with neurologic abnormality. Features of CAH are ambiguous genitalia, hyperplasia of adrenal gland, and low 17-hydroxyprogesterone. Polyglandular autoimmune syndrome is characterized by involvement of thyroid, parathyroid gland, diabetes mellitus as well as mucocutaneous candidiasis.

FGD is rare. Thus, therapeutic trials on this condition are lacking. Published literature that comprised mostly case reports and standard textbooks has suggested a dose range of 10–15 mg/m²/day. To the best of our knowledge, there have been no earlier reports where dose higher than this dose were used or required.

Escalation of a dose of oral corticosteroid was done cautiously and under supervision with close clinical and laboratory monitoring. No adverse effects of overdosing were detected with 20 mg/m²/day dose for 6 months. All other parameters such as lethargy, weakness, and apatite were improved satisfactorily. However, improvement in mucocutaneous hyperpigmentation was moderate in one while other one had an excellent recovery.

As per our knowledge, dose escalation in FGD above 15 mg/m²/day was never tried.[6] Based on these findings, we suggest, increment of daily oral corticosteroid replacement dose in selected cases of FGD showing poor efficacy with standard dose for attaining optimum benefit. Stringent clinical and laboratory monitoring is required to detect any untoward effects early in all such cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.
What is new?
In rare circumstances, FGD may respond incompletely to 15 mg/m²/day dose. Under strict monitoring, dose of oral corticoids may be increased up to 20 mg/m²/day. Although systemic problems improved completely, mucocutaneous pigmentation may respond partially even at this dose.

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