Familial Glucocorticoid Deficiency

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Introduction

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive disorder characterized by glucocorticoid deficiency in the absence of mineralocorticoid deficiency, presenting with non ketotic, non hyperinsulinemic hypoglycemia, seizures, hyperpigmentation, recurrent infections, failure to thrive, collapse and coma [1,2]. We report a case of isolated glucocorticoid deficiency in a 3½ year old male child.

Case Report

A 3½ years old male child, third product of 3rd consanguineous marriage was admitted with sudden onset of generalized tonic clonic seizure while undergoing ultrasound of abdomen. He had been fasting overnight. He was found to have hypoglycemia (Blood sugar < 30 mg/dl) and managed with IV dextrose. Child was born by full term normal delivery with uneventful antenatal and perinatal period. There was a history of previous early sibling death at seven months of age following seizures with no known underlying cause. The child achieved his milestones normally as per age. He was noticed to have recurrent episodes of generalized tonic clonic seizure since eleven months of age with no apparent neurological deficit and a normal Electroencephalography (EEG), Computed tomography (CT) scan and Magnetic resonance imaging (MRI) of brain. He was put on long term anticonvulsant therapy with carbamazepine. At two years of age he had an episode of febrile encephalopathy associated with altered sensorium and seizures and available records revealed that he had been managed with antibiotics, anticonvulsants and ventilatory support for a week. During this episode he had documented hypoglycemia (Blood sugar 45 mg/dl), but had not been evaluated further.

On examination his vital parameters were normal. Blood pressure was 94/60 mm of Hg. His height was 102 cm (more than 50th centile for age), weight 14.5 kg (50th centile for the age), head circumference 49 cm. The child was unusually hyperpigmented as compared to other sibling and parents as

seen in (Fig. 1). Systemic examination was unremarkable. The developmental parameters (both motor and mental) were within normal limits. Investigations revealed Hemoglobin-9.8 gm/dL, urine for sugar and ketone bodies was negative. Blood sugar 60 mg/dL (fasting) and 94 mg/dL (postprandial). Other tests revealed blood urea 21 mg/dL, creatinine 0.6 mg/dL and serum sodium 140 mEq/L, potassium 3.6mEq/L. Arterial blood gas study was normal. Radiograph of hand for bone age was ≈ 3-5 years. T3-0.74 ng/ml (normal 0.9-2.6 ng/ml), T4-4.26 mcg/ml (normal 5.5-13.5 mcg/ml) and TSH was 9.07 (normal 0.3- 6.5 µIU/ml). Serum Insulin level was low 0.42 µU/ml (normal 1.7-31 µU/ml), low serum cortisol 0.2 ng/ml (normal 4-22 ng/ml) and significantly high serum ACTH levels 2857 pg/ml (normal 0-46 pg/ml). Plasma rennin activity was normal and 17 OHP was 0.1 µg/ml (normal 0.007-1.7 µg/ml). CT scan of the adrenals was normal. In view of recurrent seizures, hypoglycemia, consanguineous marriage and sibling death due to seizures, generalized hyperpigmentation, low cortisol levels with markedly raised ACTH levels, diagnosis of FGD was made. Child was started on hydrocortisone at 20 mg/day, however when he developed cushingoid features, the dose was reduced to 10 mg/day and on this dose he is maintaining well and has shown remarkable improvement as depicted in Fig. 2.

Discussion

FGD was first described by Shepard et al [3]. The exact incidence of FGD is not known and only isolated case reports have been documented in Caucasians, African-American, East Indian and Middle Eastern populations. This disorder occurs with equal frequency in both males and females. Age of onset of symptoms ranges from birth to nine years, but majority occur in first five years [2].

The exact etiology of this condition is not known, however DNA analysis of all patients with FGD has demonstrated that about 40% of these patients have mutations in melanocortin 2 receptor (MC2-R) or ACTH receptor (ACTH-R) gene with locus at 18 p

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Fig. 1 : Photograph of a child of familial glucocorticoid deficiency showing hyperpigmentation over body and comparison of hand with hand of mother (before treatment).

11.2 and melanocortin 2 receptor accessory protein (MRAP) suggesting this to be the most likely underlying defect. Based on the presence of mutation, FGD is categorized into type 1 (with ACTH receptor mutations) and type 2 (with normal ACTH receptors) [1,4]. On histopathology it is seen that zona fasciculata and zona reticularis of adrenal gland are markedly atrophic while zona glomerulosa is well preserved leading to low plasma cortisol concentrations. Due to the lack of feedback inhibition of the hypothalamus, ACTH levels are markedly raised. Plasma rennin activity and aldosterone concentrations are usually within the reference range [2]. The most common initial presenting feature is hyperpigmentation of the skin and mucous membranes as a result of excessive ACTH. Recurrent hypoglycemia especially during infections or stress is commonly seen. In the neonatal period the presenting symptoms include feeding difficulty, failure to thrive, regurgitation and hypoglycemia manifesting as seizures, lethargy, shock, or sudden death. Some children may present with tall stature and absent adrenarche [5,6]. A positive family

Fig. 2 : Photograph of child showing improvement in hyperpigmentation over body and comparison of hand with hand of mother (after treatment).

history of consanguinity or early unexplained infant deaths or other affected family members supports a diagnosis of FGD. Our case had repeated episodes of unexplained seizures and hyperpigmentation and confirmed to have FGD following intensive investigations. Besides he was also found to have hypothyroidism, which may be associated with glucocorticoid deficiency [7]. The most frequent cause of death in FGD is undiagnosed hypoglycemia due to glucocorticoid insufficiency. Although this disease is easily treatable when recognized, untreated it may be fatal or lead to learning difficulties, spastic quadriplegia or severe mental disability as a result of recurrent hypoglycemia. FGD should be distinguished from other disorders that cause adrenal insufficiency like allgrove syndrome (AAA - Alacrimia Achalasia, Adrenal hypoplasia), congenital adrenal hyperplasia, hypopituitarism, adrenoleukodystrophy and autoimmune polyglandular syndrome type 1 [2]. The diagnosis is confirmed by low serum cortisol and markedly elevated ACTH levels in presence of normal renin-aldosterone

axis. Serum electrolytes, renin and aldosterone and very long chain fatty acids (VLCFAs) are within the reference range. Hypopituitarism can also lead to adrenal insufficiency, but ACTH levels are low in this setting and other pituitary hormones are also low [2]. Adrenal imaging in the form of MRI/CT scanning can be helpful. In FGD the glands are usually small in size [8] in contrast to tuberculosis (calcified adrenal glands), CAH (enlargement), storage disorders and infiltrative disorders (enlargement of the gland) [1]. The mainstay of treatment in FGD is the replacement of glucocorticoids. Family members should be screened with a Cortrosyn stimulation test wherein the cortisol levels are unresponsive to exogenous ACTH stimulation. No restriction of physical activity is necessary in adequately treated cases of FGD. This rare diagnosis needs to be considered when dealing with any case of recurrent hypoglycemia, idiopathic seizures and unexplained sibling death.

Conflicts of Interest

None identified

References

1. Chan LF, Clark AJL, Metherell LA. Familial glucocorticoid deficiency: Advances in the molecular understanding of ACTH action. *Horm Res.* 2008; 69: 75-82.
2. Haqq Andrea, Boston BA. Familial glucocorticoid deficiency, medicine. 2008, www.e medicine.com/ped/topic747.htm-105k.
3. Shepard TH, Landing BH, Mason DG. Familial Addison's disease; case reports of two sisters with corticoid deficiency unassociated with hypoaldosteronism. *AMA J Dis Child* 1959; 97: 154-62.
4. Modan-Moses D, Ben Zeev B, Hoffmann C, Falik-Zaccai TC, Bental YA, Pinhas-Hamiel O et al. Unusual presentation of familial glucocorticoid deficiency (FGD) with a novel MRAP mutation. *J Clin Endocrinol Metab* 2006; 91: 3713-7.
5. Elias LL, Huebner A, Metherell LA, Canas A, Warne GL, Bitti ML et al. Tall stature in familial glucocorticoid deficiency. *Clin Endocrinol (Oxf)* 2000; 53: 423-30.
6. Weber A, Clark AJ, Perry LA, Honour JW, Savage MO. Diminished adrenal androgen secretion in familial glucocorticoid deficiency implicates a significant role for ACTH in the induction of adrenarche. *Clin Endocrinol (Oxf)* 1997; 46: 431-7.
7. Hussein D, Abdul latif, Ambika P, Ashraf B. Reversible subclinical hypothyroidism in the presence of Adrenal insufficiency. *Endocrine Practice* 2006; 12: 572-5.
8. Clark AJ, Weber A. Adrenocorticotropin insensitivity syndromes. *Endocr Rev* 1998; 19: 828-43.

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