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Early diagnosis in familial glucocorticoid deficiency

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ABSTRACT

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive condition, characterized by marked atrophy of zona fasiculata and reticalaris with preservation of zona glomerulosa. Out of more than 50 published cases, 18 patients died as a result of glucocorticoid insufficiency. The main objective of this report is to emphasize the early diagnosis and treatment in our 17 month-old patient. Her presenting features following an upper respiratory tract infection were hypoglycemia, seizures as well as deep hyperpigmentation of the limbs and lips. A low cortisol concentration, elevated ACTH level and normal electrolytes and aldosterone level all supported the diagnosis of primary glucocorticoid deficiency. Parents were counseled about the diagnosis, management and the lifelong requirement of steroids. FGD is an easily treatable disease when recognized but frequently missed due to a non-specific presentation. FGD is a treatable disease, delayed diagnosis and treatment can lead to significant morbidity.

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Introduction

Familial glucocorticoid deficiency (FGD) is a rare autosomal recessive condition with a prevalence of $< 1{:}1000000$, characterized by isolated glucocorticoid deficiency and an elevated level of adrenocorticotropic hormone (ACTH) in the presence of normal aldosterone function.[1,2] It may present in the first year of life or early childhood in the form of hypoglycemia, seizure and increased pigmentation that may lead to death or severe mental disabilities if left untreated or inadequately treated.[1,4] FGD is a rare disease and only isolated case reports are documented.[4,5] From the original descriptions from 1959 to1995, about 50 cases have been reported.[2] The incidence of FGD may be underestimated because some patients may have episodes of recurring hypoglycemia or convulsions, but FGD may remain undiagnosed for many years.[2,7] Out of more than 50 published cases, 18 patients died as a result of glucocorticoid insufficiency.[2] Here, we report a case of a 17 month-old Indian girl with familial glucocorticoid deficiency. The main objective of this report is to emphasize the early diagnosis and treatment in our patient, therefore avoiding likely debilitating and fatal sequelae.

Case presentation

A 17 month-old Indian girl, previously healthy was referred from a private medical center where she was treated a week earlier for an upper respiratory tract infection. One day before hospitalization she developed recurrent episodes of vomiting, decreased oral intake and urine output and a fever which was treated with acetaminophen. On the day of admission the patient had a generalized tonic clonic seizure lasting 15 minutes, was found to be hypoglycemic 12 mg/dl (0.6 mmol/l), and managed with dextrose 50%, 2 doses of diazepam followed by a loading dose of phenytoin. There was no history of sick contact, travel, head trauma or family history of febrile seizure or epilepsy. The parents were first degree cousins.

On examination she was found to have a temperature of 36 °C, respiratory rate 24 breaths/minute, peripheral pulse of 145 beats/minute and blood pressure of 72/30 mmHg. Her anthropometric measurements showed a length of 82 cm, (z score 0.54), and weight 9 kg (z score −1.02).

Specifically, the patient was noted to have generalized symmetric deep hyperpigmentation of the limbs and the lips (Fig. 1). There was no organomegaly, no

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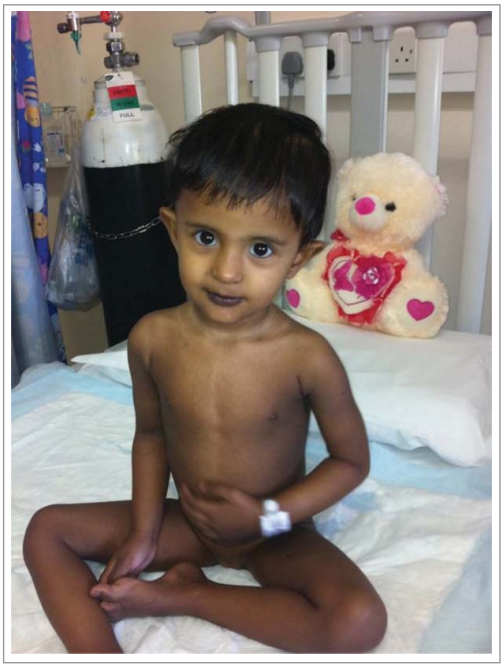

Figure 1. Generalized hyperpigmentation of the skin.

ambiguous genitalia and no dysmorphic features detected.

The full septic workup including the lumbar puncture, were all normal. Ketosis was documented in the early phase of illness (urine ketones was positive).

The patient was initially admitted as a case of dehydration, hypoglycemia and seizures to rule out meningitis, started on intravenous fluid and intravenous ceftriaxone at meningitic doses.

As this patient was more hyperpigmented in comparison to her parents and presenting with hypoglycemia during her illness, she was evaluated for cortisol deficiency. Being deeply pigmented and presenting with a hypoglycemic seizure during a minor illness, a low cortisol concentration, elevated ACTH level and normal electrolytes all supported the diagnosis of primary glucocorticoid deficiency (Table 1). Absence of ambiguous genitalia, aldosterone concentration within normal range and consanguinity suggested a diagnosis of familial primary glucocorticoid deficiency. Parents were counseled about the diagnosis, management and the lifelong requirement of steroids. They were advised about readjustment of the dose with intercurrent illness or stress and referred to genetic counselling as well. Elevated ACTH level and unresponsiveness of cortisol level after ACTH stimulation test all supported a diagnosis of FGD. Molecular genetics study was not done due to financial constraint. She was discharged on oral hydrocortisone at a dose of 2.5 mg Q8 hr with regular follow up scheduled.

Table 1. Represent the electrolyte and the hormonal work up.

Lab values	Initial Result	Reference Range
Na	140 mmol/l	135–148 mmol/l
K	4 mmol/l	3.5–5.8 mmol/l
Ca	2.38 mmol/l	2.2–2.7 mmol/l
Mg	0.89 mmol/l	0.7–0.9 mmol/l
Glucose	12 mg/dl	60–105 mg/dl
Cortisol	89 nmo/l	165–828 nmol/l
ACTH	>440 pmol/l	0–10 pmol/L

This table showed a low cortisol concentration, elevated ACTH level and normal electrolytes all supported the diagnosis of primary glucocorticoid deficiency.

Discussion

FGD is an easily treatable disease when recognized.[7] It is frequently missed due to a non-specific presentation.[4,5,7] Untreated FGD is associated with high mortality and morbidity.[7] Other causes of adrenal insufficiency should be considered such as congenital adrenal hyperplasia, adrenal hypoplasia and Allogrove or Achalasia-Addisonianism-Alacrimia (AAA) syndrome and ruled out by thorough history, detailed physical examination and appropriate investigations.[1,2,7]

FGD is a rare autosomal recessive disease, characterized by marked atrophy of zona fasiculata and reticalaris with preservation of zona glomerulosa.[5] So plasma cortisol level will be low as zona fasiculata is the responsible layer for glucocorticoid formation, while mineralcorticoid level will be normal as the zona glomerulosa is well preserved.[5,7] As a compensatory feedback of low cortisol, high ACTH level will be noticed and those patients become pigmented as a result of excessive ACTH stimulation of melanocyte stimulating hormone receptors (melanocortin-1 receptor) on cutaneous melanocytes leads to increase melanin production and generalized hyperpigmentation.[3,4,5,7]

FGD can present in the form of recurrent episodes of hypoglycemia which is a non- specific presentation secondary to glucocorticoid deficiency and can lead to severe mental disability if not treated.

FGD is classified into 2 types: type 1 and type 2.[3,5,6,7] Type 1 is characterized by mutation in ACTH Receptor [melanocortin 2 receptor (MC2R)] gene.[3,5,6,7,8] Type 2 is characterized by a mutation in ACTH accessory protein [melanocortin 2 receptor accessory protein (MRAP)].[5,7]

25% of FGD cases have mutation in MC2R while only 15 to 20% of FGD cases have mutations in MRAP.[5,7] Mutations in mini chromosome maintenance deficient 4 homolog (MCM4) and nicotinamide nucleotide transhydrogenase (NNT) genes have been noticed in FGD cohorts.[9] MCM4 plays a role in DNA replication while NNT is involved in antioxidant defense.[9] This reflects the various pathogenetic mechanisms implicated in adrenal disorders.[9]

Patients with FGD could have normal lifespan and able to have their own children if adequately replaced with glucocorticoid and educated properly regarding the dose adjustment during the time of illness and stress.[2]

Conclusion

FGD is a treatable disease, delayed diagnosis and treatment can lead to poor clinical outcome.

Abbreviations

AAA	Allogrove or Achalasia-Addisonianism-Alacrimia syndrome
ACTH	adrenocorticotropic hormone
FGD	Familial glucocorticoid deficiency
MC2R	melanocortin 2 receptor gene
NNT	nicotinamide nucleotide transhydrogenase genes

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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