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Primary Cortisol Deficiency and Growth Hormone Deficiency in a Neonate With Hypoglycemia: Coincidence or Consequence?

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Cortisol and growth hormone (GH) deficiencies are causes of neonatal hypoglycemia. When they coexist, a pituitary disorder is suspected. We present an infant with hypoglycemia in whom an ACTH receptor defect was associated with transient GH deficiency. A full-term boy with consanguineous parents presented with hypoglycemia (serum glucose 18 mg/dL) at 4 hours of life with undetectable serum cortisol (<1 μg/dL). Examination showed diffuse hyperpigmentation with normal male genitalia. Patient developed hyperbilirubinemia and elevated transaminase levels. GH levels of 6.8 ng/mL and 7.48 ng/mL during episodes of hypoglycemia, peak of 9.2 ng/mL with glucagon stimulation, and undetectable IGF-1 suggested GH deficiency. Thyroid function, prolactin, and gonadotropins were normal. Baseline ACTH was elevated at 4868 pg/mL, whereas serum cortisol remained undetectable with ACTH stimulation. Hydrocortisone replacement resulted in normalization of blood glucose and cholestasis with decline in ACTH level. GH therapy was not initiated, given improvement in cholestasis and euglycemia. An ACTH receptor defect was confirmed with molecular genetic testing that revealed homozygosity for a known mutation of the melanocortin 2 receptor (*MC2R*) gene. At 12 weeks, a random GH level was 10 ng/mL. IGF-1 was 75 ng/mL and 101 ng/mL at 7 and 9 months, respectively. This report describes glucocorticoid deficiency from an *MC2R* mutation associated with GH deficiency. With glucocorticoid replacement, GH secretion normalized. Our findings are consistent with a previously stated hypothesis that physiologic glucocorticoid levels may be required for optimal GH secretion [1].

Freeform/Key Words: cortisol deficiency, growth hormone deficiency, hypoglycemia, adrenocorticotrophic hormone

Neonatal adrenal insufficiency commonly presents with persistent hypoglycemia, hyponatremia, hyperkalemia, acidosis, and hypotension. Cortisol deficiency may result from a primary adrenal process, owing to maldevelopment, malfunction, or destruction of the gland or secondary to dysfunction of the hypothalamic-pituitary-adrenal axis. High ACTH and electrolyte abnormalities are seen in patients with primary adrenal pathology, whereas low ACTH, without electrolyte imbalance, is noted in secondary adrenal insufficiency, given

Abbreviations: DOL, day(s) of life; FGD, familial glucocorticoid deficiency; GH, growth hormone; GHRH, GH-releasing hormone; HC, hydrocortisone; LFT, liver function test; MC2R, melanocortin 2 receptor; MRAP, melanocortin 2 receptor accessory protein; OMIM, Online Mendelian Inheritance in Man; TSH, thyroid-stimulating hormone.

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normal aldosterone production via the renin-angiotensin-aldosterone pathway. When ACTH deficiency is associated with other pituitary hormone deficiencies, such as growth hormone (GH) and thyroid-stimulating hormone (TSH), hypopituitarism is the likely etiology.

A rare cause of congenital cortisol deficiency is hereditary unresponsiveness to ACTH, also known as familial glucocorticoid deficiency (FGD). This disorder, initially reported in 1959 as "familial Addison's disease," described two sisters who presented in their second year of life with generalized hyperpigmentation, weakness, and hypoglycemic convulsions but without evidence of salt wasting [2].

The exact prevalence of FGD is unknown, but is estimated to be <1:1,000,000 [3]. This condition is characterized by isolated glucocorticoid deficiency with elevated levels of ACTH in the presence of normal aldosterone function. FGD may present early in the neonatal period or later in childhood with varying severity of symptoms related to low cortisol, resulting in hypoglycemic convulsions, jaundice with liver dysfunction, failure to grow, and recurrent infections. Hyperpigmentation, which is a constant feature, results from elevated melanocyte-stimulating hormone, associated with high ACTH levels. There is a high risk of morbidity, including a range of neurologic sequela and even mortality, if not appropriately recognized and treated [4].

The mode of transmission for FGD is autosomal recessive, and it is most commonly caused by mutations in the genes encoding either the ACTH receptor, known as melanocortin 2 receptor [*MC2R*; Online Mendelian Inheritance in Man (OMIM) #607397], or its accessory protein, MC2R accessory protein (*MRAP*; OMIM #699196), implicated in 25% and 20% of cases, respectively. FGD has also been reported to be caused by mutations in the genes encoding nicotinamide nucleotide transhydrogenase (OMIM #607878), thioredoxin reductase 2 gene (OMIM #606448), mini chromosome maintenance-deficient 4 homolog gene (OMIM #602638), and achalasia-adrenocortical insufficiency alacrimia (Allgrove, Triple A, Aladin) gene (OMIM #605378) [5–7].

The combination of primary cortisol deficiency and GH deficiency has been rarely reported. We present a newborn with hypoglycemia, undetectable cortisol, elevated ACTH levels, low GH, and abnormal liver function tests (LFTs), later diagnosed to have FGD as a result of an ACTH receptor defect. The GH deficiency was transient and seemed to correct with cortisol replacement.

1. Patient Report

The patient, an African baby boy born by normal spontaneous vaginal delivery at 40 weeks gestation to likely consanguineous parents (from Guinea, Africa), was transferred to our institution at 3 weeks of life. He was born appropriate for gestational age for weight and length and had Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Neonatal course was substantial for hypoglycemia (serum blood glucose of 18 mg/dL at 4 hours of life), which required continuous intravenous dextrose infusion. Serum sodium, potassium, and bicarbonate levels were normal. The New York State newborn screen for thyroid, congenital adrenal hyperplasia, X-linked adrenoleukodystrophy, and metabolic disorders was normal. Urine and serum organic acids, ammonia levels, and glucose-6-phosphate-dehydrogenase levels were normal. On two occasions of spontaneous hypoglycemia, serum cortisol was undetectable, GH was inappropriately low (7.48 ng/mL and 6.8 ng/mL), IGF-1 was undetectable (<10 ng/dL), and insulin was undetectable (Table 1). Serum TSH, free thyroxine, luteinizing hormone, follicle-stimulating hormone, and testosterone were normal for age (Table 2). Combined pituitary hormone deficiency was suspected as a result of the combination of cortisol and GH deficiency. The patient developed elevated direct and indirect bilirubin, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase levels (Table 3). Abdominal ultrasound and upper gastrointestinal series were normal. He was started on hydrocortisone (HC) replacement of 15 mg/m^2 on day of life (DOL) 19 and transferred to our institution on DOL 21 for further evaluation.

Table 1. Critical Samples During Hypoglycemia

	Preserved Blood Glucose, mg/dL	Cortisol, μg/dL	GH, ng/mL	Insulin, mIU/mL	Free Fatty Acids, mEq/L	Betahydroxybutyrate, mM
Reference range	65–199	3–23	5–27	1.9–23	0.1–0.6	0.02–0.27
DOL 10	22	<1	7.48	<0.2		
DOL 18	21	<1	6.8	<0.2	0.31	0.9

Abbreviation: DOL, day of life.

On physical examination, the patient was in no distress and had substantial generalized hyperpigmentation (Fig. 1). There were no midline defects, and external genitalia were normal with bilaterally descended testes.

An ACTH stimulation test (Cosyntropin 125 μg) indicated undetectable baseline and stimulated cortisol levels (Table 4), with baseline ACTH level markedly elevated at 4868 pg/mL (normal: 5– 46 pg/mL). Pituitary MRI, with and without contrast, was normal. The adrenal glands were "diminutive" on ultrasound. A glucagon stimulation test (glucagon 0.1 mg/kg), performed to assess GH reserve, indicated a glucose of 38 mg/dL and a GH of 9.2 ng/dL at 120 minutes after glucagon (baseline sample was insufficient for analysis; Table 5). Given the remarkably elevated ACTH level and undetectable cortisol, an ACTH receptor defect was suspected. Next-generation sequencing and deletion/duplication analysis of *MC2R*, *MRAP*, and nicotinamide nucleotide transhydrogenase genes was performed, and a known homozygous variant in the *MC2R* gene—c.634delA (p.R212Efs*4; NM_000529.2)—was identified. This single base pair deletion caused a frameshift mutation at position 212, leading to a premature stop codon. This pathogenic variant is predicted to cause loss of function of the *MC2R* gene and its product, the ACTH receptor, confirming the diagnosis of FGD.

With HC replacement, blood glucose, hyperbilirubinemia, and LFTs normalized (Table 5). There was a substantial decrease in ACTH levels associated with decreased skin pigmentation (Fig. 2).

A random GH level at 12 weeks of life was 10 ng/mL. IGF-1 levels were 75 ng/mL at 7 months and 101 ng/mL at 9 months, both normal for age (Table 5). GH therapy was considered but not implemented, given normalization of glucose, LFTs, and IGF-1. Until his last visit at 1 year of age, the patient continued to grow and develop normally (Fig. 3).

2. Conclusion/Discussion

The patient described had severe cortisol deficiency as a result of an ACTH receptor defect from an *MC2R* gene mutation. He also had evidence of GH deficiency, suggested by suboptimal GH levels in response to both hypoglycemia and glucagon stimulation. Whereas the patient's GH levels were detectable, they were significantly lower than expected for age. In the first few days to weeks of life, neonates normally have GH levels ranging from 20 to 50 ng/mL [8]. In the event of neonatal hypoglycemia or stress, GH levels increase further [9]. The initial

Table 2. Baseline Endocrine Evaluation

	TSH (DOL 7), mU/mL	Free Thyroxine (DOL 7), ng/dL	Prolactin (DOL 26), ng/mL	IGF-1 (DOL 9), ng/mL	LH (DOL 42), mIU/mL	FSH (DOL 42), mIU/mL	Testosterone (DOL 42), ng/dL
Reference range	0.9–7.7	0.89–1.76	2.6–13.1	15–109	0.02–7	0.16–4.1	60–400
Value	3.401	1.39	55	<10	2.3	1.2	333

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 3. Follow-up of Laboratory Data Over the Course of Treatment of This Patient With ACTH Resistance

	Reference Range	DOL 9	DOL 24	DOL 37	DOL 41	3 mo	7 mo	9 mo
HC dose, mg/m^2		0	15	50[a]	50[a]	37	13	9.375
Cortisol, μg/dL	6.7–22.6		<1	<1				
ACTH, pg/mL	7.2–63.3		3885	4449	332	<5		660
Aldosterone, ng/dL	5–90		22					
IGF-1, ng/mL	15–109	<10	15				75	101
IGF-BP3, mg/L	1.11–3.18		0.65					
AST, IU/L	0–75	40	33	102	98	100	49	49
ALT, IU/L	0–29	6	8	46	59	88	25	20
GGT, IU/L	10–54	553	93	630	930	517	44	
Total bilirubin, mg/dL	0–1.5	16.4	11.9	8.2	5.2	0.3	0.2	<0.2
Direct bilirubin, mg/dL	0–0.4	1.9	6.2		4	0.3		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP3, binding protein 3; GGT, γ-glutamyltransferase; HC, hydrocortisone.
[a]Patient needed stress dosing given fever and respiratory syncytial virus infection.

IGF-1 level was undetectable, consistent with GH deficiency, although IGF-1 levels alone are not reliable to assess the GH axis in newborns [10]. Although subsequent formal GH sufficiency was not assessed using stimulation testing, the normal linear growth and normal IGF-1 level at 7 and 9 months suggested that GH secretion was restored.

Concurrent GH insufficiency in the setting of severe primary cortisol deficiency has been reported infrequently [11]. This report is about transient GH deficiency associated with severe glucocorticoid deficiency, owing to a pathogenic variant of the *MC2R* gene mutation, c.634delA. This variant is noted in gnomAD to have an allele frequency of one in 30,938. The variant c.634delA has been previously reported in ClinVar to be associated with glucocorticoid deficiency [12]. Similar to our patient, a sibling pair with the same genetic variant was

Figure 1. At presentation at 3 wk, diffuse hyperpigmentation was noted. Difference in skin color seen between patient's face and mother's hand.

Table 4. ACTH Stimulation Test (125 μg Cosyntropin)

Time	Cortisol, μg/dL	ACTH, pg/mL
Reference range	6.7–22.6	7.2–63.3
Baseline	<1 μg/dL	4868
60 min	<1 μg/dL	

diagnosed at 1 and 16 months of age because of hypoglycemia, undetectable cortisol, elevated ACTH levels, and normal electrolytes. The two siblings were reported to have normal aldosterone levels with high plasma renin activity [13]. The GH–IGF-1 axis was not evaluated in the reported siblings. Our patient had normal aldosterone levels and transient mild hyponatremia without hyperkalemia that resolved with HC; thus, mineralocorticoid deficiency was unlikely.

Transient GH deficiency associated with severe congenital cortisol deficiency owing to ACTH deficiency ((*T-Box factor pituitary*) gene mutation) and resistance (*MRAP* gene mutation) was reported in two infants. In both cases, the diagnosis was initially based on low GH levels during spontaneous hypoglycemic episodes in the neonatal period, at 2 and 4 weeks, respectively, with a GH peak of 3.4 μg/L in patient 1 and 7.6 μg/L in patient 2. Both patients were treated with HC and GH. The retesting of their GH axis at 8 months and 3 years, respectively, indicated normal GH reserve [1]. The authors hypothesized that appropriate glucocorticoid levels may be required for the development and function of somatotrophs and concluded that evidence of normal circulating cortisol is required when testing GH secretory capacity. Our patient's data support this hypothesis. In another report, GH deficiency of unknown duration was documented in a 2-month-old infant with severe complete generalized glucocorticoid resistance from a mutation in the glucocorticoid receptor [14].

In six adults with cortisol deficiency, as a result of chronic ACTH deficiency, a transient state of GH deficiency, ranging from reduced to undetectable GH levels, was reported to be reversed after 3 to 24 months of HC replacement [15–17]. In a study of seven adults with Addison's disease, an increased GH output by augmentation of GH pulse amplitude and interpulse levels was documented following physiologic HC replacement. The authors suggested that this effect on GH release resulted from attenuated hypothalamic somatostatin secretion by cortisol [18].

In vitro studies in rat pituitary glands have shown that glucocorticoid receptors localize predominantly within corticotrophin and GH-secreting cells [19]. Experiments in pituitary cells from humans and animals have indicated that administration of corticotrophin stimulates GH synthesis and secretion [20–22]. Glucocorticoids have been shown to increase transcription of GH messenger RNA in various cell cultures, which may lead to increased production of GH [23]. Adrenalectomy markedly decreases the expression of GH-releasing hormone (GHRH) and GH secretagogue receptors on pituitary cells [24–26]. Glucocorticoids also increase the response of somatotrophs to GHRH secretagogues by enhancing the expression of GHRH and GH secretagogue receptors on pituitary cells [27, 28]. These studies support the hypothesis that physiologic cortisol levels are required for adequate production and secretion of GH. It is well documented, however, that long-term exposure to supraphysiologic endogenous or exogenous corticosteroids results in a reduced GH response and

Table 5. Glucagon Stimulation Test (0.1 mg/kg Glucagon)

	Time, min					
	0	**30**	**60**	**90**	**120**	**130**
Blood glucose, mg/dL	89	106	95	57	38	43
GH, ng/mL					9.2	

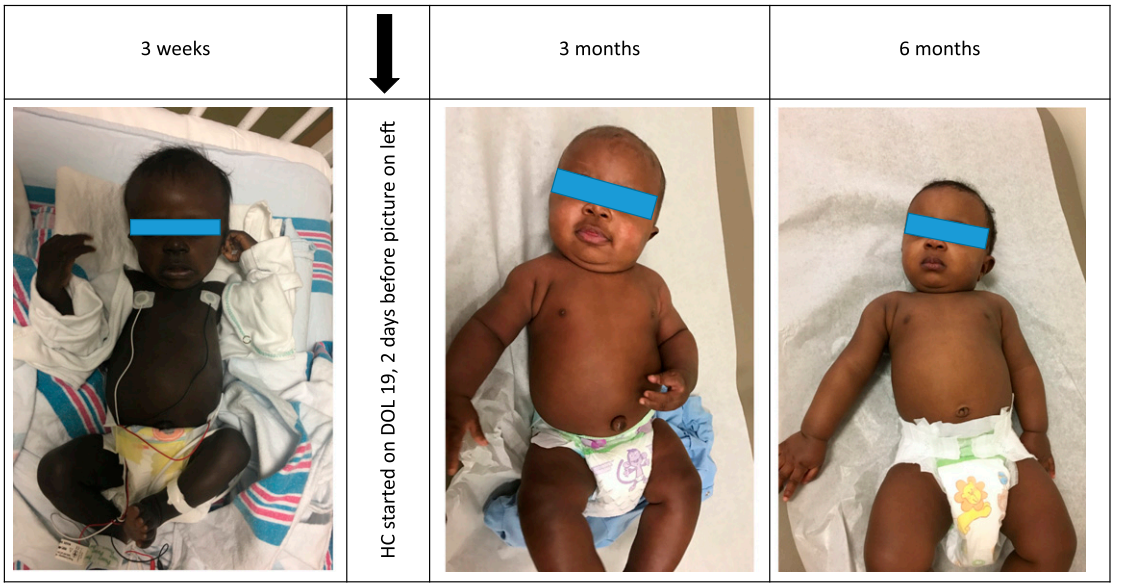

Figure 2. Follow-up photographs demonstrate decreased hyperpigmentation associated with decrease in ACTH levels. Treatment with HC was started at 19 DOL.

can negatively affect growth in children [29]. A study in six adult patients evaluating the effect of increasing doses of corticosteroids on GH levels reported that when serum cortisol levels exceeded the threshold of 25 μg/dL, GH secretory responsiveness to GHRH was acutely decreased [30]. Hence, it appears that corticosteroids have a complex dose-dependent effect on GH secretion, which can be stimulating or inhibiting.

In our patient, treatment with HC alone was effective, not only in the achievement of euglycemia but also in the abatement of the cholestasis and normalization of the LFTs. Although cholestasis, along with abnormal LFTs, has been reported in neonates with

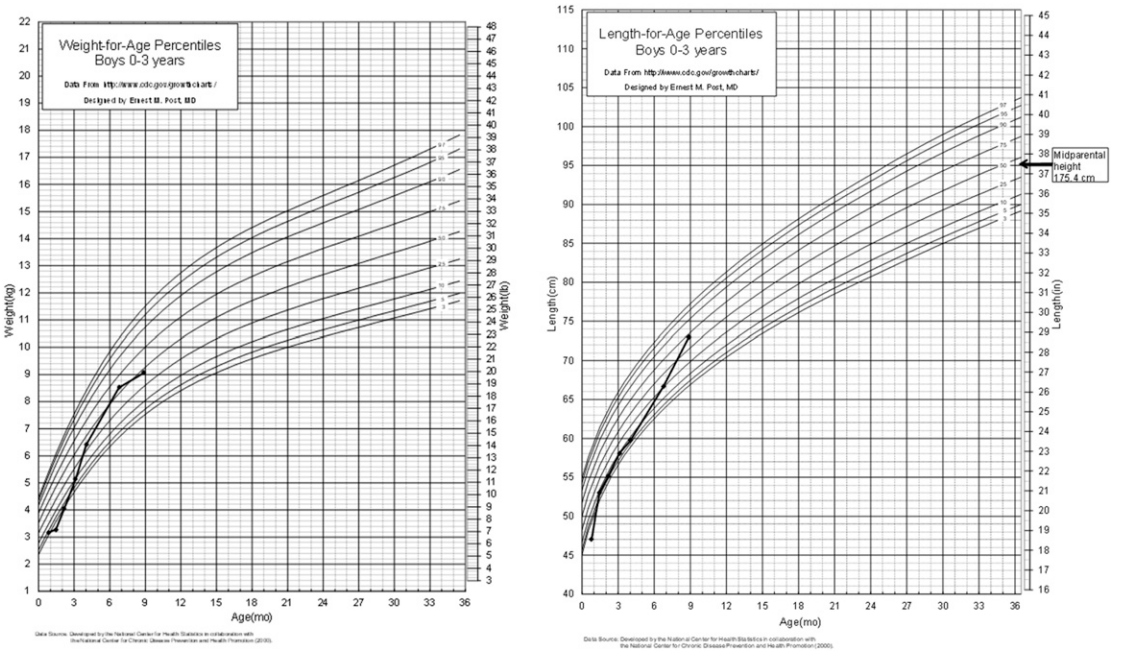

Figure 3. Centers for Disease Control and Prevention growth charts showing improvement in weight and length with HC treatment.

multiple pituitary hormone deficiencies [31], GH deficiency, and isolated hypothyroidism, it has been reported infrequently in isolated cortisol-deficient states [32]. It is possible that the resolution of cholestasis and normalization of LFTs resulted from correction of cortisol deficiency and perhaps also from improvement of GH secretion. In our patient, treatment with supraphysiologic doses of HC leads to decreased and even undetectable ACTH concentrations at 3 months. Because of rapid weight gain, the dose of HC was decreased. On lower HC doses, the patient continued to grow well with no hypoglycemia but had elevated ACTH levels, however significantly lower than pretreatment values. Given rapid fluctuations in ACTH and variability with acute stressors, such as phlebotomy, we chose to rely on a clinical picture for titration of HC dosing. Our approach was consistent with the Endocrine Society Clinical Practice Guideline for Diagnosis and Treatment of Primary Adrenal Insufficiency that suggests "…monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels…" and that "Measurement of plasma ACTH is typically above the normal range and is not useful for routine monitoring" [33].

In conclusion, we present a patient with severe congenital cortisol deficiency, owing to a mutation in the *MC2R* gene with transient GH insufficiency. Our findings support the suggestion that physiologic circulating cortisol appears to be required for optimal GH secretion. Further studies are required to elucidate the complex relationship between cortisol and GH secretion.

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Subjects (or their parents or guardians) have given their written, informed consent.

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