Title: Familial Hyperinsulinism due to HNF4A Deficiency and Benign Premature Adrenarche: A Case Report

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Highlights:

1. Familial Hyperinsulinism due to HNF4A deficiency (FHI-HNF4A) is a form of diazoxide-sensitive; diffuse hyperinsulinism, characterized by transient or persistent hyperinsulinemic hypoglycemia, and subsequent propensity to develop MODY1.
2. By altering the HPA and HPG axes, hyperinsulinism may lead to increased levels of circulating androgens, which has been demonstrated in conditions with insulin resistance and subsequent hyperinsulinism, such as polycystic ovary syndrome (PCOS).
3. Regulation of HNF4A by many factors indirectly regulates hepatic SHBG synthesis, as HNF4A plays an imperative role in the regulation of SHBG.
4. The association of elevated insulin levels, insulin resistance, and functional hyperandrogenism has been previously described in youth with benign premature adrenarche (BPA) and polycystic ovarian syndrome (PCOS) however there have been no reports in a patient with FHI-HNF4A.
5. These findings may suggest that patients with FFI-HNF4A may be at greater risk for insulin induced hyperandrogenism and therefore diazoxide dosage should be titrated to insulin levels to prevent functional hyperandrogenism and its sequelae.
6. If HNF4A defects play a role in altering SHBG levels, it may be clinically relevant to screen patients with BPA for these alterations.

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Discussion Points:

1. Familial Hyperinsulinism due to HNF4A deficiency (FHI-HNF4A) is a form of diazoxide-sensitive; diffuse hyperinsulinism, characterized by transient or persistent hyperinsulinemic hypoglycemia.
2. Hyperinsulinism may lead to increased levels of circulating androgens, which has been demonstrated in conditions with insulin resistance and consequent hyperinsulinism, such as polycystic ovary syndrome (PCOS).
3. Regulation of HNF4A by many factors indirectly governs hepatic sex hormone-binding globulin (SHBG) synthesis, as HNF4A plays a key role in the regulation of SHBG.
4. The association of elevated insulin levels, insulin resistance, and functional hyperandrogenism has been previously described in youth with benign premature adrenarche (BPA) and PCOS; however, this is the first such report in a patient with FHI-HNF4A.
5. These findings suggest that patients with FFI-HNF4A may be at greater risk for insulin-induced hyperandrogenism, and therefore diazoxide dosage should be titrated to insulin levels, to prevent functional hyperandrogenism and its sequelae.

ABSTRACT.

Background: Familial Hyperinsulinism due to HNF4A deficiency (FHI-HNF4A) is a form of diazoxide-sensitive, diffuse hyperinsulinism, characterized by transient or persistent hyperinsulinemic hypoglycemia, and a propensity to develop Maturity-Onset Diabetes of the Young type 1 (MODY1). The association between FHI-HNF4A deficiency and benign premature adrenarche (BPA) is unknown.

The Case: We report the case of a 5-year-old girl with FHI-HNF4A, controlled on diazoxide, who presented with BPA and Tanner stage III pubic hair associated with body odor and acne. Work-up revealed elevated dehydroepiandrosterone sulfate (DHEAS), elevated free testosterone, and advanced bone age. Insulin levels were elevated in the setting of normal fasting blood glucose. We discuss the possible hormonal underpinnings of hyperandrogenism.

Conclusion: Though the underlying pathophysiology of this phenotype is unclear, a possible synergistic mechanism exists between insulin-induced hyperandrogenism and HNF4A deficiency leading to a transient decrease of SHBG and thus increased free testosterone levels. Further investigation is required to determine the association between HNF4A dysfunction and BPA.

Key Words: Hyperinsulinism; Congenital Hyperinsulinism; Adrenarche; HNF4A; Hyperandrogenism (Source: MeSH-NLM).

INTRODUCTION.

Congenital hyperinsulinism (CHI) is due to a variety of etiologies that result in dysregulated insulin release from pancreatic β-cells. There are two histological variants of CHI, focal and diffuse, which differ in the extent of pancreatic involvement. In the diffuse variant, all of the β-cells are affected, while in the focal form, a localizable lesion is found, affecting only a subset of the β-cells.[1] Insulin secretion uncoupled from glucose metabolism results in hyperinsulinemic hypoglycemia.[2,3] Familial Hyperinsulinism due to HNF4A deficiency (FHI-HNF4A) is a form of diazoxide-sensitive, diffuse hyperinsulinism, characterized by macrosomia, transient or persistent hyperinsulinemic hypoglycemia, and a propensity to develop Maturity-Onset Diabetes of the Young type 1 (MODY1). Patients with FHI-HNF4A are responsive to diazoxide treatment, which activates K_{ATP} channels, leading to increased potassium conductance, cellular membrane hyperpolarization, and inhibition of insulin release.[4,5] Patients with CHI due to other genetic variants, in which the mutation lies within subunits of the K_{ATP} channels themselves, are not responsive to diazoxide treatment.[6] The role of HNF4A in FHI-HNF4A has yet to be fully elucidated, but it is thought to work in combination with other transcription factors, forming a regulatory network of proteins in the pancreatic islet.[7] Mechanistically, HNF4A deficiency can impair the binding of HNF4A with p300, which then prevents HNF4A from binding to the promoter region of HNF1. Interestingly, there is a growing body of evidence that mRNA levels of HNF4A correlate with sex hormone binding globulin (SHBG) mRNA levels. Therefore, HNF4A deficiency may result in decreased SHBG, with subsequent increased levels of free testosterone.[8] The clinical consequence of this process is poorly understood.

Benign premature adrenarche (BPA) is a clinical diagnosis often associated with elevations of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) for chronological age,.[9,10] If phenotypic signs of androgen activity, such as pubic and/or axillary hair, adult-type body odor, oily skin or hair, comedones, or accelerated growth velocity, are detected before the age of 8 in females or 9 in males, premature adrenarche is present.[9] Prior studies have found increased rates of obesity in children with BPA.[9,10] However, other conditions that present similarly must first be excluded before BPA can be diagnosed. These include: central puberty, adrenocortical and gonadal sex-hormone secreting tumors, congenital adrenal hyperplasia, and exposure to exogenous androgens. In some populations, BPA has been associated with low birth weight, insulin resistance, adverse cardiometabolic risk, and progression to polycystic ovary syndrome (PCOS).[11-15] Herein, we report a 5-year-old female patient with FHI-HNF4A who presented with BPA in the setting of elevated insulin level, despite euglycemia on diazoxide therapy. The underlying pathophysiology of this phenotype remains obscure; however, we discuss a possible synergistic mechanism between insulin-induced hyperandrogenism and HNF4A deficiency, leading to transient decrease of SHBG and thus increased free testosterone levels.

THE CASE.

A 5-year-old girl with known FHI-HNF4A, who was first noted by her mother to have new-onset acne and body odor without any associated breast changes, pubic hair, or menses at 4 years of age, presented to the pediatric endocrinology clinic for follow-up. Her pubic hair had progressed to Tanner stage III with increased acne and body odor. No exogenous steroid exposures were reported. Physical exam revealed Tanner stage 1 breasts. Laboratory testing revealed abnormalities in the following: free testosterone 0.6 ng/dL (normal range < 0.04-0.14 ng/dL), and DHEAS 146 mcg/dL (normal range: ≤ 34 mcg/dL). The following were within reference ranges: fasting laboratory testing revealed a HbA1c of 4.0% (normal range: 3.0-5.8%), a fasting blood glucose of 80 mg/dL (normal range: 70-100 mg/dL), anti-Mullerian hormone 1.3 ng/mL, estradiol < 7 pg/mL (normal range: < 7 pg/mL), total testosterone < 7 ng/dL (normal range: <7-20 ng/dL), insulin 11.3 uIU/mL (normal range: 2.0-19.6 uIU/mL), 17-hydroxypregnenolone 177 ng/dL (normal range: ≤ 561 ng/dL), 17-hydoxyprogesterone 35 ng/dL (normal range: ≤ 137 ng/dL), serum androstenedione 18 ng/dL (normal range : ≤ 45 ng/dL and serum DHEA 159 ng/dL (normal range: ≤ 487 ng/dL) (Table 1). A bone age study revealed an advanced bone age of 7.8 years and at this time, the decision was made to monitor the patient serially, without altering diazoxide dosing.

The patient's past medical history was significant for premature delivery at 34 weeks gestation due to premature rupture of membranes. The vaginal delivery was complicated by prolonged labor and fetal distress. Her birth weight was 1870 grams, with an associated length of 43.15 cm, appropriate for gestational age. She had a macrosomic appearance at birth. She was admitted to the neonatal intensive care unit for fifty days, requiring supplemental oxygen for twelve days. She was found to have persistent hypoglycemia, requiring a glucose infusion rate of 18-20 mg/kg/minute She was diagnosed with hyperinsulinemic hypoglycemia on day five of life and was started on diazoxide at 15 mg/kg/day. Subsequent laboratory and genetic testing confirmed her heterozygous HNF4A mutation (NM_00457.4 c.253C>T, p.Arg85tro – PubMed. 2030154, OMIM. 6160266), pathogenic for FHI-HNF4A. By the age of 2, she was taking 100% of her caloric needs orally, requiring gastrostomy tube (G-tube) supplementation only during times of illness. Her blood glucose levels were within the target range 90% of the day based on continuous glucose monitoring data and her HbA1c was 4.5%. Her father was diagnosed with FHI-HNF4A in infancy; at the age of 20, was found to have hyperglycemia consistent with MODY1.

The family was lost to follow up and presented for referral to the pediatric endocrinology clinic for consultation and management of congenital hyperinsulinism when she was 2.5 years old. At this time, she weighed 10.5 kg (< 3rd percentile), with a height of 87.5 cm (10th percentile) and BMI of 13.71 kg/m^2 (< 3rd percentile). On physical exam, she had numerous dysmorphic features including macrosomia, down-turned palpebral fissures, broad midface, low-set ears, and broad, wide-set thumbs. She had diffuse hypertrichosis of the arms, face, back, and abdomen. Her external genitalia was normal for age, with Tanner stage 1 axillary and pubic hair, and breasts with Tanner stage 1 development. At this time, blood glucose levels were being monitored only once daily, and it was recommended that blood glucose checks be increased to 6 times daily to ensure that cryptic hypoglycemia was detected, as HbA1c was < 4.0%. She was placed on an iPro glucose monitor (CGM) to collect continuous glucose levels for 96 hours, which demonstrated hypoglycemia 20% of the time. She was maintained on

diazoxide at 12 mg/kg/day divided three times daily (TID). Due to concern for poor annualized growth velocity of 1.4 cm/year, a bone age was obtained, which showed skeletal age concordant with chronological age.

At a subsequent follow-up at 3.5 years old, her HbA1c was 4.0%, with weight gain and associated increased annualized growth velocity of 6 cm/yr. Continuous glucose monitoring was recommended to detect overnight hypoglycemic episodes, but the patient's family declined this option. She was receiving feeding therapy and her oral intake had improved significantly. Although she no longer utilized G-tube feedings, she was having multiple episodes of hypoglycemia overnight. Her diazoxide dose was increased to 13 mg/kg/day divided TID, with resolution of her overnight hypoglycemia.

DISCUSSION.

We report a unique case of a 5-year-old female with FHI-HNF4A who presented with Tanner 3 pubic hair, acne, body odor, elevated DHEAS and free testosterone, and advanced bone age in the absence of elevated estradiol levels. Her presentation is most consistent with BPA; however, the relationship between FHI-HNF4A and BPA remains poorly understood. Although the BMI percentile of our patient was 18%, prior studies have found an association between BPA and obesity.[9,10] There is a wide differential diagnosis for patients that are found to be persistently hypoglycemic after birth, including hyperinsulinism as in our patient, mutations in enzymes involved in fatty acid metabolism, glycogen storage disorders, counter-regulatory hormone deficiencies.. While the differential is broad, we suspected hyperinsulinemia as the culprit in our patient, given her father's diagnosis of FHI in infancy. Thus, genetic testing was obtained early in her disease course. Many of the etiologies of persistent hypoglycemia in infancy involve a genetic component, highlighting the importance of obtaining a satisfactory family history, as this can help narrow the differential diagnosis, expediting achieving a diagnosis.

Besides HNF4A, other genes have been implicated in hyperinsulinemia, with the two most common being mutations in ABCC8 and KCNJ11. Mutations in these two genetic loci are responsible for both focal and diffuse forms of CHI, leading to vastly different treatments and outcomes. Therefore, genetic analysis becomes important for counseling families on treatment and prognosis, as one study demonstrated that detecting a single paternally derived mutation predicted focal disease 94% of the time.[16]

One possible mechanism to explain the observed association is that our patient was experiencing transient hyperinsulinism resulting in increased adrenal androgen production. Insulin is hypothesized to play a role in the regulation of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes.[17,18] A variety of regulatory mechanisms have been proposed, including altered expression of key enzymes involved in steroidogenesis, increased secretion of gonadotropin-releasing hormone (GnRH), increased amplitude of luteinizing hormone (LH) pulses, potentiation of ACTH-stimulated steroidogenesis, and inhibition of SHBG production.[8] By up-regulating one or both of the HPA and HPG axes, hyperinsulinism may lead to increased levels of circulating androgens. In patients with conditions such as PCOS, which have been associated with BPA, elevated total and free androgens have been demonstrated in the setting of insulin resistance and decreased SHBG.[19,20] However, prior studies have not explored the potential relationship between FHI-HNF4A or other genetic CHI disorders, and BPA. Mechanistically, insulin has been demonstrated to increase mRNA levels of CYP17A1 and 3β-HSD and potentiate ACTH production of intermediates involved in DHEAS synthesis, leading authors to conclude that the hyperandrogenic features observed in PCOS may be due in part to a hyperinsulinemia-derived increase in adrenal androgens.[21,22]

Ibanez *et al.* studied 10 non-obese adolescent females who had experienced BPA, hirsutism, ovarian hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinemia. These females were administered metformin daily for 6 months, which reduced insulin levels, hirsutism, and hyperandrogenism, and attenuated the release of LH in response to GnRH pulses. One of the mechanisms by which metformin improves hyperglycemia in diabetes is through the inhibition of mitochondrial glycerophosphate dehydrogenase, which inhibits gluconeogenesis and increases insulin sensitivity, thereby decreasing insulin requirements. Metformin administration also increases SHBG, leading to decreased serum-free androgens.[23,24] Importantly, the authors

noted that DHEAS decreased with metformin, buttressing the argument that insulin increased adrenal androgen production.[23] In a study contrasting 47 adolescent females with BPA vs 22 healthy female controls, Kaya *et al.* found that females with BPA had higher body mass indexes and insulin concentrations.[10] These females also had hyper-responsiveness to ACTH, leading to increased androstenedione and DHEA levels. This study further elucidates the unique role insulin plays in the regulation of adrenal sex hormone production.

An additional mechanism to consider in this patient is the effect of HNF4A function on SHBG levels. Hammond *et al*. proposed that activation of the SHBG promoter in the liver involves HFN4 binding to a DR1-like cis-element which then stimulates production.[25] Therefore, in HNF4A deficiency, SHBG production would be decreased, with consequent increases in free androgen levels. Winters *et al*. found a strong positive correlation between the level of HNF4A mRNA and SHBG mRNA, with an inverse relationship between insulin resistance/insulin levels, and circulating SHBG and HNF4A mRNA levels.[26] These findings suggest that circulating SHBG levels may be mediated by HNF4A and provide further insight into the mechanism by which HNF4A deficiency could predispose a patient with FHI-HNF4A to BPA. The combination of these two molecular entities could have resulted in the BPA-like phenotype observed in our patient.

This case demonstrates that clinically silent hypoglycemia with concomitant intermittent hyperinsulinemia may have long-term sequelae for the patient. Therefore, even if glycemic control is adequate overall, with HbA1c levels within normal limits, it is important not to ignore either glucose levels or HbA1c levels that are down-trending. Large fluctuations in blood glucose levels should be avoided, with close monitoring of daily glucose checks. In our patient, glucose checks were only being performed once daily; subsequent continuous glucose monitoring demonstrated hypogylcemia 20% of the time. This highlights the importance of more rigorous glucose monitoring in these patients, as they may not present with the normal signs of hypoglycemia (diaphoresis, lightheadedness, tachycardia, etc.) and thus their hypoglycemia may go clinically undetected until more severe sequela develops. This has important treatment implications, as tight medical management becomes paramount. While our patient responded well and tolerated diazoxide, other patients may not respond as well, requiring additional treatment considerations to adequately control glucose, and subsequently, insulin levels.

We believe that our patient may have been experiencing episodes of hypoglycemia, as evidenced by her HbA1C levels on the low end of normal. Episodes of hypoglycemia may have been due to intermittent hyperinsulinemia in spite of diazoxide treatment. We hypothesize these periods of hyperinsulinemia may have been sufficient to increase adrenal steroidogenic activity, and subsequently, increased circulating levels of DHEAS. Furthermore, her HNF4A deficiency may have led to a decrease in SHBG levels resulting in elevated free testosterone. Future studies are needed to 1) investigate the underlying molecular etiology of hyperandrogenism in patients with FHI-HNF4A and BPA, 2) elucidate the optimal dosage of diazoxide treatment in FHI-HNF4A to prevent any long-term sequelae that could occur in the setting of transient hyperinsulinemia, and 3) explore the relationship between HNF4A deficiency and BPA.

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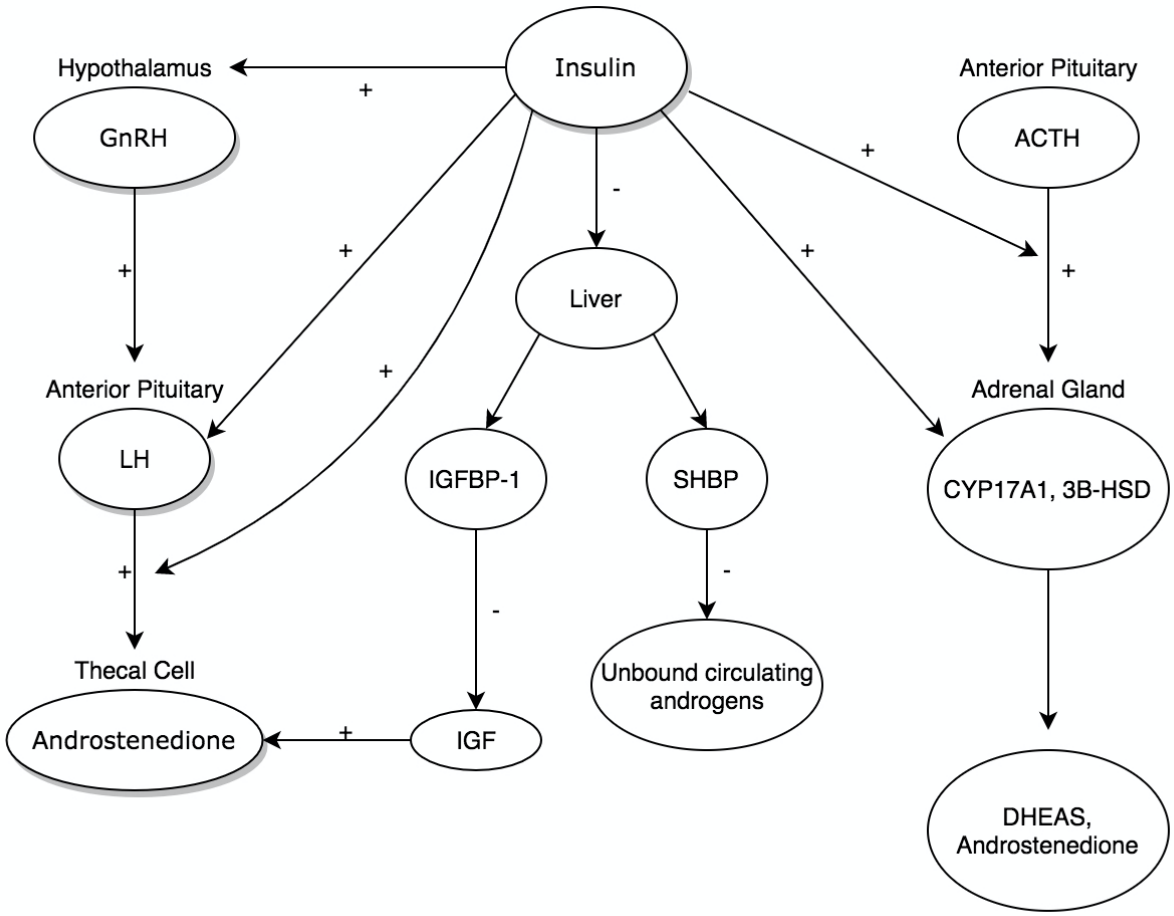
FIGURES AND TABLES.

Figure 1. Proposed mechanisms of insulin regulation of androgen synthesis and circulatory levels. 3B-HSD = 3β-hydroxysteroid dehydrogenase; ACTH = Adrenocorticotropic hormone; CYP17A1 = cytochrome P450 17A1; DHEAS = dehydroepiandrosterone sulfate; GnRH = gonadotropin releasing hormone; IGF = insulin-like growth factor; IGFBP-1 = insulin-like growth factor binding protein 1; LH = luteinizing hormone; SHBP = sex hormone binding protein.



318 **Table 1:** Clinical and laboratory findings at most recent visit
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	Patient Values	Reference Range (if applicable)
Age, years	6.0	
Bone age, years	7.8	
Weight, kg (%ile)	17.3 (15)	
Height (%ile)	110.7 (27)	
BMI (%ile)	14.12 (18)	
Tanner Stage (breast/pubic hair)	1/3	
Glucose, mg/dL	80	60-115
HbA1c	4.3	3.0-6.0
Anti-Mullerian Hormone	1.3	
Estradiol, pg/mL	< 7	<7
Total Testosterone, ng/dL	< 7	< 7
Insulin, uIU/mL	11.3	2.0-19.6
17-hydroxyprogesterone, ng/dL	35	≤ 137
17-hydroxypregnenolone, ng/dL	177	≤ 561
Serum androstenedione, ng/dL	18	≤ 45
DHEA sulfate, mcg/dL	146	≤ 34
DHEA, ng/dL	159	≤ 487

321 BMI = body mass index; DHEA = Dehydroepiandrosterone