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Congenital Pituitary Gland Abnormalities—A Possible Association With Maternal Hyperglycemia: Two Case Reports

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Introduction

Congenital hypopituitarism (CH) occurs in 1 in 100 000 live births.¹ Genetic factors, hypoperfusion, and environmental changes in utero may play causative roles.² Maternal diabetes mellitus (DM) in relation to other congenital central nervous system abnormalities such as neural tube defects (NTDs) and hydrocephalus have been described, but an association between hyperglycemia in utero and pituitary formation has, to our knowledge, not been reported.³ We present 2 infants with CH, both born to mothers with hyperglycemia in early pregnancy. Both infants' pituitary glands are structurally identical; each has a hypoplastic anterior pituitary, an ectopic posterior pituitary located at the base of the third ventricle, and an absent pituitary stalk.

Case Report

Case 1 (Proband A)

Proband A was a 41-week 4110-gram male delivered by cesarean section to a multiparous mother with a history of gestational DM (GDM). During this pregnancy, an oral glucose tolerance test (OGTT) performed at 25 weeks gestation revealed a 1-hour glucose of 265 mg/dL. Glyburide was started at 29 weeks gestation. Subsequently, fasting glucose ranged from 69 to 105 mg/dL, and 2-hour postprandial glucose levels ranged from 90 to 185 mg/dL.

At birth, Proband A was limp, had poor respiratory effort, and had low-set, posteriorly rotated ears, hypertelorism, a flattened nasal bridge, and normal male genitalia. Echocardiogram demonstrated an interrupted vena cava, bilateral superior venae cavae, and a moderate perimembranous ventricular septal defect. Additional evaluation revealed functional asplenia and intestinal malrotation. Karyotype was 46XY, microarray analysis was normal, fluorescence in situ hybridization for DiGeorge syndrome was negative, and he was diagnosed with heterotaxy syndrome.

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Two months after discharge, Proband A presented to the emergency department with lethargy, seizures, hypothermia, bradycardia, and hypotension and required dopamine for pressor support. Initial laboratory results revealed serum glucose of 36 mg/dL and serum sodium of 124 mEq/L. Further evaluation demonstrated a cortisol of 0.9 µg/dL (normal AM: 3-15), growth hormone of 1.58 ng/ml (normal >5), follicle stimulating hormone (FSH) <0.017 mIU/mL (normal 0.16-4.1), luteinizing hormone (LH) <0.005 mIU/mL (normal 0.02-7.0), testosterone <3.0 ng/dL (normal 60-400 at 20-60 days of age), thyroid stimulating hormone (TSH) of 1.7 µU/mL (normal 0.90-7.7), and a free thyroxine of 0.79 ng/dL (normal 0.90-2.25). He was treated with hydrocortisone, sodium supplementation, and thyroid replacement. He did not receive treatment for hypogonadotropic hypogonadism because of a normally sized phallus. Magnetic resonance imaging (MRI) of the brain with and without contrast revealed a hypoplastic adenohypophysis, an ectopic neurohypophysis located at the base of the third ventricle, and an absent pituitary stalk and cortical atrophy (Figure 1).

Case 2 (Proband B)

Proband B was a 32-week 3020-gram male with prenatally diagnosed left multicystic dysplastic kidney born via cesarean section secondary to a multiparous mother with a 4-year history of type 2 DM and hypertension. Her medications, sitagliptin/metformin and amlodipine, were discontinued at 6 weeks' gestation, a temporary trial of glyburide was started at 9 weeks' gestation, and NPH and lispro insulins were prescribed for the remainder of the pregnancy. The hemoglobin A1c level was 6.4% at 20 weeks' gestation.

At birth, Proband B was hypotonic, had low-set ears, hypertelorism, hypoplastic nipples, a flattened nasal bridge, and a small and narrow phallus (2 cm × 0.75 cm). Apgars were 8 and 9 at 1 and 5 minutes. Serum glucose at 1 hour of life was 17 mg/dL and serum sodium was 124 mEq/L. Bilirubin levels were persistently elevated.

Thyroid function tests demonstrated a TSH of 5.28 µU/mL (normal <8) and a free thyroxine of 0.53 ng/dL (normal 0.90-2.25). Thyroid gland sonogram was normal. Further endocrine evaluation revealed the following: FSH of 0.074 mIU/mL (normal 0.16-4.1), LH of 0.022 mIU/mL (normal 0.02-7.0), testosterone <3.0 ng/dL (normal 75-400 ng/dL), and random growth hormone of 2.55 ng/mL (normal >5.0). Adrenocorticotropin hormone (ACTH) stimulation test (cosyntropin 0.125 mg) revealed a poor cortisol response (prestimulation 0.6 µg/dl; poststimulation 3.9 µg/dL). Karyotype was 46 XY. Proband B was treated with hydrocortisone, thyroid replacement, and testosterone. Nephrostomy and PDA (patent ductus arteriosus) ligation were performed.

MRI of the brain with and without contrast revealed a hypoplastic adenohypophysis, an ectopic neurohypophysis located at the base of the third ventricle, and an absent pituitary stalk (Figure 2).

Discussion

Hypopituitarism is characterized by the reduction in function of two or more pituitary hormones produced by the pituitary gland.² CH can occur secondary to genetic defects or can be associated with midline defect syndromes, such as septo-optic dysplasia.² Though

acquired forms can occur early in life, an absent pituitary stalk is suggestive of a congenital etiology.² Children with CH can present with a spectrum of hormonal deficiencies. A recent report assessed MRI studies of 96 patients with hypopituitarism and found a positive correlation between the degree of abnormality on MRI and the number of deficient pituitary hormones.⁴ Both infants in this report had panhypopituitarism and had structurally identical pituitary abnormalities.

Infants born to pregnancies complicated by preexisting DM have a 2- to 8-fold increased risk of congenital anomalies as do infants born to women with GDM, possibly because some of these women may have had undiagnosed type 2 DM at the time of conception.^{3,5,6} Additionally, women with GDM have an increased risk of developing type 2 DM and/or metabolic syndrome at postpartum follow-up.^{3,7} The mothers of probands A and B were likely to be hyperglycemic during the first trimester. Although the mother of proband A's first trimester hemoglobin A1c was unknown, her OGTT at 25 weeks' gestation suggested a likelihood of pregestational DM. The mother of proband B had a known history of type 2 DM, but did not take her medications from 6 to 9 weeks' gestation.

Fetal organogenesis is completed by 10 weeks gestation, and most birth defects secondary to poor glucose control occur within the first 6 to 8 weeks of gestation.^{5,8} Maternal hemoglobin A1c greater than 5.7% (average plasma glucose 126 mg/dL) at conception is associated with an increased risk of birth defects.⁹ The most common congenital defects associated with hyperglycemia during pregnancy are cardiac anomalies, NTD, and musculoskeletal anomalies.⁵ However, there is also an association between maternal diabetes and less wellstudied congenital anomalies, such as heterotaxy syndrome and multicystic dysplastic kidneys.¹⁰ Both of these anomalies were seen separately in the patients described above. However, to the best of our knowledge, congenital pituitary abnormalities have not been reported in maternal diabetes. Moreover, Brown et al¹¹ described a cluster of 5 infants with CH, in the absence of maternal hyperglycemia (personal communication).¹¹ The similarities between the presented infants led us to suggest that CH may be a newly reported finding that is part of a hyperglycemic-induced syndromic spectrum.

Though the teratogenic effects of a hyperglycemic prenatal environment are not fully understood, several mechanisms leading to the disruption of crucial developmental regulatory processes early in organogenesis have been elucidated.¹² Using streptozotocin-induced diabetic rat models, Li et al¹³ demonstrated an increase in reactive oxidative species leading to *Pax3* down-regulation and subsequent development of NTD in the fetus. Additionally, expression of Glut2 in early embryos creates a hyperglycemic environment that has been shown to dependently halt *Pax3* gene expression in the fetus.¹⁴ *Pax3* inhibition leads to apoptosis of neuroepithelial cells with consequent NTD in embryos of diabetic mice. Apoptosis of the mandible and of the endocardial cushion have also been reported in early rat embryos of diabetic rat mothers.¹⁵ The effects of *Pax3* inhibition on pituitary function has not been reported; however, *Pax3* has been found to be active in the developing brain suggesting a possible role in pituitary development.¹⁶

In the mouse model, the earliest sign of pituitary development occurs at 7.5 days of gestation when the ectoderm thickens within the neural ridge.¹⁷ Key regulatory transcription factors,

cofactors, and morphogenetic signals coordinate to determine both final pituitary gland location within the sella and hormonal cell differentiation. The main transcription factors necessary for early pituitary development are *Hesx1/Rpx*, *Lhx3*, *Lhx4*, *Ptx1*, *Ptx2*, and *Prop1*.¹⁸ Though numerous mouse models have helped characterize the role of transcription factors in pituitary hormone expression, studies are needed to elucidate the effect of a hyperglycemia on pituitary cell migration and differentiation.

There are several limitations to ascribing pituitary abnormalities to maternal hyperglycemia in this case report. Because both mothers reside in New York City, it is possible that there was a common environmental exposure, such as a virus or toxin. However, the infant's gestational periods were 12 weeks apart making an environmental effect less likely. Additionally, to our knowledge, there were no other infants born at our institution with similar pituitary findings within 1 year of these infants' births.

This case report serves to alert physicians caring for both pregnant women and newborn infants of a possible, newly described, association between maternal hyperglycemia during pregnancy and abnormal fetal pituitary development. Larger epidemiologic reports and laboratory workup will help further define the effects of hyperglycemia during pregnancy on pituitary development in utero.

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Figure 1. Proband A

T1 weighted sagittal precontrast image (A) shows a bright spot (arrow) at the anterior third ventricle floor corresponding to an ectopic neurohypophysis. T1 weighted postcontrast image (B) demonstrates no pituitary stalk (white arrow). A small adenohypophysis (black arrow) is seen in the sella turcica. Note the cerebrospinal fluid spaces consistent with atrophy.

Figure 2. Proband B

T1 weighted coronal image (A) of the sella showing a bright signal intensity at the floor of the anterior third ventricle corresponding to an ectopic posterior pituitary (white arrow). T1 weighed postcontrast sagittal image (B) demonstrates an absent pituitary stalk (arrow in the inset image). A small pituitary gland is seen (black arrow).