Persistent Diabetes Mellitus Postadrenalectomy in Neonatal McCune-Albright Syndrome

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Background

McCune-Albright syndrome (MAS) is caused by a somatic-activating mutation in GNAS1, which encodes the stimulatory α subunit of G-protein, leading to constitutive activation of downstream signaling pathways in a variety of cells. One of the main manifestations is excess hormone.1 Neonatal MAS is a rare presentation, with severe clinical manifestations. Although neonatal hyperglycemia has been observed in association with neonatal Cushing syndrome in MAS, persistent diabetes mellitus after treatment of Cushing syndrome has never been reported.

Here, we describe a case of neonatal MAS with hyperthyroidism, precocious puberty, polyostotic fibrous dysplasia (PFD), neonatal cholestasis, nephrocalcinosis, and Cushing syndrome with persistent diabetes mellitus, even after bilateral adrenalectomy.

Case Presentation

A Hispanic woman delivered at 33 weeks via cesarean delivery at a rural hospital. The infant was microcephalic and small for gestational age (birth weight 1162 g). She had café-au-lait macules with irregular borders on her left anterior chest and upper back. In the first week of life, she developed hypertension, hypercalcemia (with hypercalciuria and hyperphosphaturia), hypokalemia, and hyperglycemia requiring insulin treatment (blood glucose: 206 mg/dL; insulin: 14 µIU/mL). The patient had supraventricular tachycardia at 11 days of age and was treated with adenosine. She was transferred to our facility for further evaluation and care.

A workup revealed hypercortisolism, hyperthyroidism, and PFD, prompting a clinical diagnosis of MAS. Within the first few months of life, the patient developed peripheral precocious puberty, nephrocalcinosis, severe osteopenia with multiple fractures, and neonatal cholestasis, eventually dying from multiple organ failure at 8 months of age.

The patient’s serum cortisol levels ranged from 80 to 130 µg/dL, with undetectable adrenocorticotropic hormone. A high-dose dexamethasone test failed to suppress both 8-AM cortisol (90 µg/dL) and 24-hour urinary free cortisol excretion (29 µg). The adrenals were homogeneously enlarged on magnetic resonance imaging. She developed malignant hypertension (up to 210/150 mm Hg) requiring angiotensin-converting-enzyme inhibitor, calcium channel blocker, β-blocker, and diuretics. Bilateral adrenalectomy at 2 months of age improved her hypertension, but insulin-dependent diabetes mellitus persisted until her death.

The workup for diabetes mellitus included a normal ultrasound of the pancreas, normal islet autoantibody titers (glutamic acid decarboxylase-65, insulin, and islet cell autoantigens-512 autoantibodies), and hypoinsulinemic hyperglycemia (insulin: 1.2 µIU/mL; blood glucose: 196 mg/dL). A pancreatic biopsy was entertained, but never performed because of the patient’s unstable medical status and concerns of pancreatitis. The patient’s family

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refused an autopsy after her death; thus, no pancreatic tissue was available for study.

The patient was hyperthyroid (thyroid stimulating hormone: <0.004 µIU/mL; free thyroxine [free T4]: 5 ng/dL) with negative thyroid stimulating immunoglobulin. She was treated with propylthiouracil and eventually underwent total thyroidectomy and levothyroxine replacement because of progressive conjugated hyperbilirubinemia and liver enzyme elevation. Her progressive neonatal cholestasis prompted a liver biopsy, which revealed a nearly complete absence of portal tracts, with only a single poorly formed bile duct.

The patient developed peripheral precocious puberty with vaginal bleeding and breast tissue at 6 months of age (estradiol: 56 pg/mL; follicle stimulating hormone: <0.3 mIU/mL; and luteinizing hormone: <0.1 mIU/mL) with complex bilateral ovarian cysts on ultrasound. She did not have excess growth hormone or hyperprolactinemia. The patient also had multifocal bony involvement with mixed scoliotic and lytic lesions. At 6 months of age, she developed profound osteopenia with multiple fractures. The patient had hyperphosphaturia, hypercalciuria, and nephrocalcinosis. She was treated with phosphate and calcitriol and received 1 cycle of intravenous pamidronate, with no appreciable improvement.

Sequencing of GNAS1 from peripheral leukocytes, adrenal2 and thyroid tissue samples revealed the arginine to histidine (R201H) mutation, confirming the diagnosis of MAS. The whole genome expression profile of the patient’s adrenal glands was described previously in another article.3

Discussion
This case exemplifies the complexities of medical management in a population of patients with health disparities and describes the experience of a patient at a tertiary care hospital where multiple teams were involved. We report a novel finding of persistent neonatal diabetes mellitus in association with neonatal MAS. To the best of our knowledge, hyperglycemia has not been reported previously in the setting of neonatal MAS without concomitant Cushing’s syndrome. Hyperglycemia in Cushing’s syndrome in neonates with MAS universally resolves after treatment with metyrapone4 or bilateral adrenalectomy.5,6 In our case, neonatal diabetes mellitus with hypoinsulinemia persisted until the child’s death. Our initial thought was that the hyperglycemia was steroid induced, resulting from suppression of insulin secretion and severe peripheral/hepatic insulin resistance. However, the persistence of hyperglycemia and hypoinsulinemia postadrenalectomy suggested a primary islet defect. But autoimmune processes and pancreatic agenesis were excluded in the workup.

Our patient developed almost all the known complications of MAS at a very early age. This severe presentation with extensive tissue involvement indicates that the mutation occurred very early in embryological development and affected multiple tissues, potentially including the pancreas. Given the early presentation and extent of the disease, a possible explanation for postadrenalectomy-persistent diabetes mellitus with pancreatic insufficiency in our case could be that it was secondary to G-protein involvement in islet cell development and/or function.

GNAS1 expression has been shown in pancreatic tissue,7 and abnormalities in the pancreatic tissue architecture8 have been reported in MAS. Thus, potential deviations from normal pancreatic tissue and islet cell development may have impaired the optimal insulin production in response to glucose levels. However, definitive proof is lacking in our case because of the inability to obtain pancreatic tissue.

The direct β-cell effect of hypercortisolism in utero may have contributed via abnormal islet development/function through epigenetic changes or β-cell exhaustion from prolonged exposure to high-dose glucocorticoids. However, in other reports, hyperglycemia resolved after the treatment of Cushing’s syndrome4,6 despite a similar exposure. Furthermore, prenatal dexamethasone treatment to prevent virilization in female fetuses with congenital adrenal hyperplasia does not lead to diabetes mellitus in infancy.9

As practicing physicians, we need to understand and think about a case like this and why this is different from the reported cases of Cushing’s disease when there is recovery of β-cells. As treating doctors, we do not have all the answers, and there is uncertainty about our conclusions. We can argue that the lack of recovery of pancreatic β-cells may still be secondary to the exposure of steroids at a critical time of development. Alternatively, silencing of the β-cell secondary to the G-protein in this case is very possible. In addition, it is imperative that physicians in community hospitals recognize the severity of the patient’s condition at an early stage and seek appropriate interventions.

In conclusion, further studies are warranted to identify the exact pathophysiology of persistent diabetes in neonatal MAS, including the involvement of glucocorticoids in turning off β-cells.

Author Contributions
MT: Contributed to acquisition, analysis, and interpretation; drafted manuscript; gave final approval; agrees to be...
accountable for all aspects of work ensuring integrity and accuracy.

MTC: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SWP: Contributed to interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of Conflicting Interests

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