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Introduction: Monogenic diabetes results from a mutation in single gene, predominantly inherited and typically affects the young. DNAJC3 acts in attenuating endoplasmic reticulum stress and is found in abundance in pancreatic tissue. **Clinical Case:** We report a homozygous DNAJC3 mutation in two siblings of a consanguineous Saudi family. A 3-year boy presented with short stature and thyroid nodule; lab findings confirmed hypothyroidism, with TSH 27.8 and FT4 6.7 (n: TSH:0.35-4.94 mIU/L, FT4:9.0-19 pmol/L). Subsequently, L-thyroxine was started. GH stimulation test was normal. He was severely short; 80.5 cm (< 1 percentile, -3.79 SD). The patient developed sensorineural hearing loss (SNHL) at 6 years. He had low intellectual function and weak school performance. GH treatment was postponed to age 9 due to strong family history of DM. At that point, the patient developed progressive ataxic gait, for which he had muscle biopsy that excluded mitochondrial disease and workup for multiple sclerosis, which was excluded. Brain and spine MRI showed prominent neurodegeneration in subcortical white matter. At age 11, the patient developed DM, 4 years after GH treatment initiation. DM autoimmune markers were negative on multiple occasions. Lifestyle modification was initiated but soon required basal and bolus insulin therapy. Whole exome sequencing revealed homozygous DNAJC3 mutation, which explained his clinical presentation. At age of 17, adult height was 141 cm (Z-score: -5.87). His older brother had similar history discovered retrospectively but did not develop neurodegeneration or ataxia from the same DNAJC3 mutation. **Literature Review:** Literature review revealed six individuals with homozygous DNAJC3 mutation. All patients developed DM, with onset ranging from 11 to 19 years, highly suggestive of MODY. Other endocrine manifestations included short stature, and hypothyroidism due to primary etiology; in view of elevated TSH levels, vs. being secondary, as suggested by the authors. All patients had mitochondrial disease workups and was excluded. Variable neurodegeneration degrees are described; SNHL, progressive ataxia, sensorimotor neuropathy, and cognitive deficits. MRI findings showed atrophy of cerebellum, brainstem, cervical spinal cord, and hyperintense T2 lesions typical of neurodegeneration. **Conclusion:** Homozygous DNAJC3 gene mutation fits MODY criteria, we propose recognizing it as one of the known MODY gene mutations. Hypothyroidism is due to primary etiology, evident by TSH spikes. Physicians evaluating mitochondrial disease in patients with a constellation of SNHL, DM, hypothyroidism, neurodegeneration, and short stature should suspect DNAJC3 as one differential diagnosis. GH treatment must be initiated cautiously, with close monitoring due to its known diabetogenic effect, especially in DNAJC3 mutations, defective endoplasmic stress attenuation mechanism.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY CASE REPORT

Case Report: Primary Hypothyroidism Caused by Autoimmune Thyroiditis in Infancy Requires Early Intervention

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Background: Primary hypothyroidism due to autoimmune thyroiditis is extremely rare in infants, especially under the age of 3 years. For infants, hypothyroidism is most commonly congenital, originating from thyroid dysgenesis with an absent, ectopic, or hypoplastic thyroid gland (1 in 4,000 live births). If left untreated, it can lead to permanent neurodevelopmental deficits. In this report, we describe a male infant who was diagnosed with Hashimoto thyroiditis at 18 months of life, providing a learning example to aid in recognition of this rare disease and enable timely intervention.

Clinical Case:Patient was a 2,765 gram, appropriate for gestational age, male born at term with hypospadias of the penis (surgical correction at 11 months). Patient passed meconium in the first 24 hours of life. During the first few months of life, patient developed constipation. Patient had amblyopia necessitating eye patching and began to wear eye glasses at 18 months of life. Patient's linear and weight growth were within normal limits. Patient had normal motor development, however had language development delay. No known family history of thyroid disease. Screening labs performed at 17-months of age showed abnormal thyroid function: elevated TSH at 14.86 μIU/mL (ref: 0.45 - 4.50 μIU/mL) and normal free T4 level at 1.24 ng/dL (ref: 0.85-1.75 ng/dL). Repeat testing at 18 months of age continued to show elevated TSH at 6.18 μIU/mL (ref: 0.64 - 4.00 μIU/mL), normal free T4 at 1.07 ng/dL (ref: 0.88 - 2.03 ng/dL), and elevated thyroid peroxidase (TPO) antibodies at 163 IU/ml (ref: <35 IU/ml). At 21 months of age, patient was initiated on L-thyroxine therapy for elevation of TSH (9.570 μIU/mL; ref: 0.64 - 4.00 μIU/mL) and free T4 was normal (1.03ng/dL; ref: 0.88 - 2.03 ng/dL). Notably, the newborn screen for hypothyroidism was within normal limits, suggesting chronic autoimmune thyroiditis instead of congenital thyroid dysgenesis.

Conclusions: This case report provides insights into autoimmune thyroiditis in infancy, which, although especially rare under age 3 years, should be considered in infants who present with autoimmunity or abnormal thyroid testing. In the neonatal period, infants' immune systems are learning to discriminate requirements for self-tolerance versus protection against pathogens and may be more prone to infections. Although autoimmunity in this stage of development is uncommon, there can be breakthroughs in tolerance, as seen in this case. In addition to this patient, two other infants were seen with elevated TPO antibodies, diagnosed at 17 and 31 months old, with similar clinical trends. There remains a need for additional studies providing further insights into autoimmunity in infancy. Importantly, this case illustrates that, when infants have abnormal thyroid levels (with or without other autoimmune

conditions), consideration should be made for anti-thyroid antibody testing.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY CASE REPORT

Challenges in the Diagnosis and Consequential Management of Patients 46, XY DSD

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Background: Disorders of sex development (DSD) are clinical conditions that cause an incongruity between the chromosomal and phenotypic sex of an individual. A high variable group of congenital disorders can arise depending upon the timing and location of defect involved in sex determination and differentiation. 46, XY DSD occurs in 1:20,0000 male births; with external genitalia ranging from ambiguous to normal female. Such conditions can be psychologically stressful for patients and their families and have been historically difficult to diagnose, especially at genetic level. Failure to diagnose exact mutation may make the therapeutic approach, genetic counseling and risk assessment even more challenging. Clinical case: Full term baby is born to non -consanguineous parents after an uneventful pregnancy. Mother denied any history of acne/ hirsutism, hormone or substance use during pregnancy. At birth, external genitalia showed non-rugated labia majora with posterior fusion, absence of labia minora and vaginal opening. Enlarged clitoris/ Penile like structure measuring 1.5 cm with palpable corpora and hypospadias was present. No palpable gonads were appreciated. No other dysmorphic features were present and rest of the physical exam was unremarkable. Cosyntropin stim test on day 4 of life showed appropriate adrenal response. Pelvic ultrasound and MRI showed an elongated structure posterior to the bladder presumably uterus with no identifiable gonads. Chromosome analysis revealed an XY karyotype. FISH for SRY and microarray were unremarkable. Further testing at 4 weeks of life showed sub optimal elevation of Gonadotropins and Testosterone. Female gender was assigned due to parents' preference and endocrine/ Urology recommendations. The 46,XY DSD genetic panel including testing for non-syndromic DSD, steroid abnormalities, skeletal dysplasia syndromes, and multiple malformation syndromes was unremarkable. Conclusion: Although a number of cytogenetic or single-gene defects have been associated with DSD, the true incidence of pathogenic variants has not been established. Many cases of 46, XY DSD remain unexplained likely due to an unidentified pathogenic variant of genes not routinely included in the panel or not yet identified to be associated with DSD. Without a clear diagnosis, genetic counseling and risk assessment is difficult. Parents should be informed about future options regarding sexual development, hormonal therapy and surgical treatments available. The determination of social sex must be made in consideration of underlying possible etiology, phenotypic sex, ethnic traditions, sexual identity and the acceptance of the assigned social sex by the parents. The affected child and his/her family must be followed throughout life to determine the patient's adjustment to his/her social sex.

Pediatric Endocrinology

PEDIATRIC ENDOCRINOLOGY CASE REPORT

Continuous Glucose Monitoring Facilitates Diazoxide Use in the Management of Glut1 Deficiency Syndrome

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Background: Glut1 deficiency syndrome (Glut1DS) is caused by mutations in *SLC2A1* on chromosome 1p34.2, which impairs transmembrane glucose transport across the blood brain barrier resulting in hypoglycorrhachia and decreased glucose availability for brain metabolism. This causes a drug-resistant, metabolic epilepsy due to energy deficiency. Standard treatment for Glut1DS is the ketogenic diet (KD) but treatment options are limited if patients fail the KD. Diazoxide, which inhibits insulin release, was used sparingly in the past for a few Glut1DS patients to increase blood glucose levels and thus intracerebral glucose levels. Unfortunately, their treatment was complicated by unacceptable persistent hyperglycemia with blood glucoses in the 300s to 500s. We investigated the use of a continuous glucose monitor (CGM) to enable titration of diazoxide therapy in a patient with KD-resistant Glut1DS.
Clinical Case: A 14-year-old girl with Glut1DS (c.398_399delGCinsTT:p.Lys133Phe) failed the KD due to severe nausea, vomiting, abdominal pain, and hypertriglyceridemia. Laboratory tests revealed CSF glucose of 36 mg/dL when blood glucose was 93 mg/dL. Over the course of 3 hospitalizations targeting blood glucose levels in the range of 120-180 mg/dL with diazoxide, EEG seizure activity decreased from 3 to 0 absence seizures per hour. CGM placement during the third hospitalization showed an average interstitial glucose of 157 mg/dL with glucose variability of 20.8% on diazoxide dose of 7.3 mg/kg/day. After discharge, CGM has been used to adjust diazoxide doses 2-4 times a week to achieve target interstitial glucoses of 140-180 mg/dL. Repeat laboratory tests revealed CSF glucose of 55 mg/dL when interstitial glucose was 158 mg/dL. Current diazoxide dose is 7.9 mg/kg/day and most recent hemoglobin A1c was 5.4%.
Conclusions: This is the first report demonstrating CGM as a tool facilitating the safe initiation and real-time titration of diazoxide in Glut1DS patients who have failed the KD. Diazoxide addresses neuroglycopenia more physiologically by raising blood glucose levels and subsequently intracerebral glucose levels. CGM allows for more accurate titration of blood glucose with diazoxide while avoiding complications of hyperglycemia and thus introduces the possibility of diazoxide becoming a standard of care for Glut1DS. More broadly, CGM provides a valuable tool for the management of other disorders of glucose transport and carbohydrate metabolism.