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Genetics Corner: Donohue Syndrome in a Small for Gestational Age Infant with Hyperinsulinemia

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Abstract:

Donohue syndrome, previously (but no longer) described as Leprechaunism, is a rare autosomal recessive trait. The primary defect in the insulin receptor causes extreme insulin resistance and failure to thrive with hyperinsulinemia, intermittent preprandial hypoglycemia, and persistent postprandial hyperglycemia. Impaired glucose metabolism causes prenatal and postnatal growth deficiency, dysmorphic facial features, visceromegaly, and lipoatrophy. A preterm male was born following an uneventful prenatal course with a birth weight of 1450 g, length of 40.5 cm, and head circumference of 32 cm. Apgar scores were 9 at one and 9 at five minutes. His postnatal course was complicated by recurrent episodes of abdominal distension and emesis with appropriate stooling, intermittent fasting hypoglycemia, and persistent postprandial hyperglycemia despite daily titrations in total parenteral nutrition. Glycemic fluctuations (20-230 mg/dl) were wide. The maximum serum insulin level was 1388 uIU/ml. With time, his dysmorphic features became more prominent. Echocardiogram identified a moderate ostium secundum atrial septal defect, mild dilation of the right ventricle, mild hypertrophy of the right ventricle, and mild pulmonary stenosis with doming. Gene testing for INSR identified two novel variants of uncertain significance.

Keywords: Donohue syndrome, Hyperinsulinemia, *INSR*, Preterm infant, Insulin resistance

"Donohue syndrome (DS), originally known as Leprechaunism, is an autosomal recessive disorder caused by biallelic pathogenic variants in the gene that encodes the insulin receptor, INSR, located on the short arm of chromosome 19 at 19p13.3. (1)"

Introduction:

Donohue syndrome (DS), originally known as Leprechaunism, is an autosomal recessive disorder caused by biallelic pathogenic variants in the gene that encodes the insulin receptor, *INSR*, located on the short arm of chromosome 19 at 19p13.3. (1) In this condition, loss of insulin receptor function causes severe impairments in glucose metabolism and other endocrine abnormalities that restrict neonatal growth and development. The characteristic pattern of findings in DS is distinctive, which helps narrow the differential diagnosis. Intrauterine growth restriction (IUGR) is accompanied by hyperinsulinemia, preprandial hypoglycemia, postprandial hyperglycemia, visceromegaly, lipoatrophy, and distinctive dysmorphic coarse facial features, alveolar thickening, prominent nipples, rectal prolapse, nephrocalcinosis, and other classic features. (2) With an incidence of less than one in one million live births worldwide, only a few dozen cases of Donohue syndrome have been reported in the literature. Given the rarity of this syndrome, experience with management is limited. We present our experience of diagnosis and management of a preterm infant with DS followed from birth and discuss its unique presentations, management challenges, and future considerations.

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Case Summary:

A 36 week and 5-day gestation male was delivered to a G3P1 33-year-old woman. This pregnancy was complicated by an IUGR fetus and diet-controlled gestational diabetes that required an insulin drip prior to delivery. Antenatal steroid therapy was completed. The mother was Rubella immune and negative for Hepatitis B surface antigen, Venereal disease research laboratory (VDRL), Human immunodeficiency virus, Group B streptococcus, and COVID-19 at delivery. Labor progressed, and the infant was delivered by spontaneous vaginal delivery without complications. Birthweight was 1450 grams (<3rd %ile, Z-3.48), length was 40.5 cm (<3rd %ile, Z-3.09), and head circumference was 32 cm (21st %ile, Z-0.77). Assisted Apgar scores of 9 were assigned at one and five minutes. The infant was admitted to the Neonatal intensive care unit (NICU) for small size and early gestational age.

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The infant was given expressed breast milk (EBM) ad lib q3 hours. He subsequently developed increased abdominal distention and was made NPO. A kidney-ureter-bladder (KUB) radiograph was unremarkable. Trophic feeds with EBM and peripheral Total Parenteral Nutrition (TPN) were restarted the following day. He had recurrent episodes of intermittent abdominal distention with KUBs demonstrating increased bowel gas without distended abdominal loops. Although glycerin enemas were highly effective in relieving distention, oral feedings were intermittent secondary to recurrent episodes of abdominal distention. His feedings were advanced when possible, with caloric density titrated to his gestational age. Preprandial hypoglycemia and postprandial hyperglycemia did not respond to daily adjustments in TPN. Glycemic fluctuations were wide: 20-230 mg/dL. The maximum serum insulin level was 1388 uIU/ml, and the C-peptide level was 135 uIU/ml. To stabilize his blood glucose levels above 70 mg/dL, he was treated with Diuril 20 mg/kg/day PO q12hr and Diazoxide at 10 mg/kg/day PO q8hr. An excrescence on the umbilical stump persisted despite silver nitrite applications. At 46 days of age, he was transferred to a regional children's hospital for a higher level of care. An ACTH challenge test showed a normal cortisol response.

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Dysmorphic features became increasingly apparent with time. He was emaciated and hypotonic with decreased subcutaneous fat, a coarse facial appearance, upturned nose, thick alveolar ridges, soft, distended abdomen, thin extremities, large scrotum, and prolapsed rectum. Testicular ultrasound confirmed moderate bilateral hydroceles. Abdominal ultrasound demonstrated echogenic medullary pyramids in the kidneys, suggesting early medullary nephrocalcinosis, a persistent urachus with bowel peristalsis, and grossly unremarkable urinary bladder. An echocardiogram revealed an ostium secundum atrial septal defect (5.3 mm), mild right ventricular dilation and hypertrophy, and mild pulmonary valve stenosis with doming. Following ultrasound confirmation, the omphalomesenteric remnant was surgically removed. Molecular gene testing of a panel of genes associated with hyperinsulinemia was negative. A genetics consultation was requested at 48 days of age, and the diagnosis of Donohue syndrome was made on clinical grounds.

An echocardiogram on day 79 showed progressive cardiomyopathy with moderate concentric left ventricular hypertrophy. There was no evidence of elevated pulmonary artery pressure. At 86 days of age, his weight was 2.35 kg. He required 2 LPM of nasal flow up to 30% O2. He nippled 23% of his feedings with subcostal retractions. He had an oral diet that was lipid fortified with PE30 and expressed breast milk with MCT, Cod Liver, and beneprotein at total fluids of 160cc/kg/day. Random glucose was >200 mg/dL. He had cholestasis with elevated total and direct bilirubin. Recombinant human IGF1 (rhIGF-1) was proposed as an investigational therapy to the family. His care team includes endocrinology, nutrition, nephrology, cardiology, genetics, and palliative care.

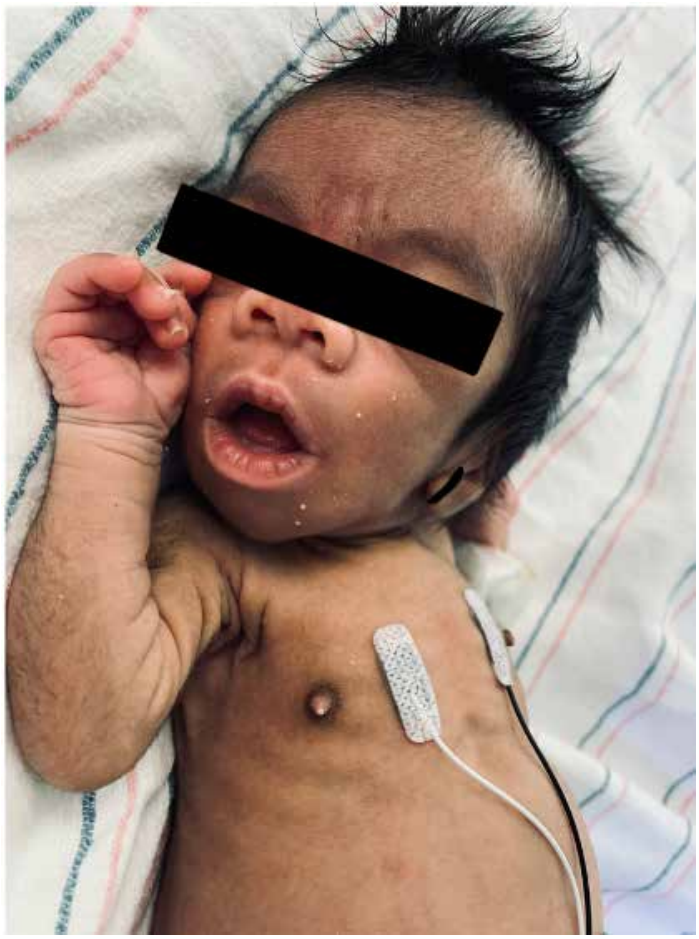

Figure 1a. This 51-day old infant of Chinese ethnicity (4 weeks corrected) has typical features of Donohue syndrome: coarse facial features, prominent eyes, infraorbital creases, and a short upturned nose. Note darkly pigmented skin, hypertrichosis on the arms, and prominent nipples.

Figure 1b. The infant has a prominent abdomen and little subcutaneous tissue. His umbilical stump healed well after surgery.

Family history:

Both parents are of Chinese ancestry. Mother is 33, and the father is 38 years old. Both are healthy. They have a healthy 4-year-old son. They deny consanguinity.

Laboratory studies:

Gene analysis of *INSR* identified 2 novel variants: c.3792_3793dup and c.344_348delinsCCTTG. These two variants were classified as variants of uncertain significance (VUS) because they had not been previously identified as either pathogenic or benign. The first variant, located near an intron-exon boundary, is predicted to result in a frameshift in exon 21. This frameshift is predicted to introduce a premature stop codon in the last exon and result in a truncated protein. It would disrupt the original protein's last 117 amino acids (8.5%). This variant is absent from general population databases. Computational predictions for this protein change show that it is expected to occur with a higher frequency than it is observed (Expected 66.799 vs. Observed 21), which implies a deleterious effect. The second variant is predicted to cause an in-frame complex insertion/deletion in *INSR*. This variant is absent from the general population (The Broad Institute gnomeAD database). Parental testing for these variants is in process to confirm biallelic variants in this child. The laboratory is reviewing clinical information on the patient and may reclassify the variants as pathogenic or likely pathogenic if they are confirmed to be biallelic.

"Donohue syndrome (DS, OMIM 24620) is a rare cause of insulin resistance in the newborn, but it has a distinctive phenotype that aids in the diagnosis. (1) DS has also been referred to as Leprechaunism, which is not the preferred name."

Discussion:

Donohue syndrome (DS, OMIM 24620) is a rare cause of insulin resistance in the newborn, but it has a distinctive phenotype that aids in the diagnosis. (1) DS has also been referred to as Leprechaunism, which is not the preferred name. The characteristic pattern of anomalies in DS includes small size at birth with preserved head circumference, poor postnatal growth, hyperinsulinemia, preprandial hypoglycemia, postprandial hyperglycemia, coarse facial features, thick alveolar ridges, prominent nipples, rectal prolapse, nephrocalcinosis, and cardiomyopathy. This child has the classic appearance of this condition. Typically, the mothers of children with DS have gestational diabetes, as did our patient. In retrospect, the affected fetus with IUGR in this family may have been similarly affected with Donohue syndrome and a chromosome anomaly.

A milder phenotype associated with biallelic variants in *INSR* has been described as Rabson-Mendenhall syndrome (RMS). In the first year of life, it is not easy to distinguish between DS and RMS.

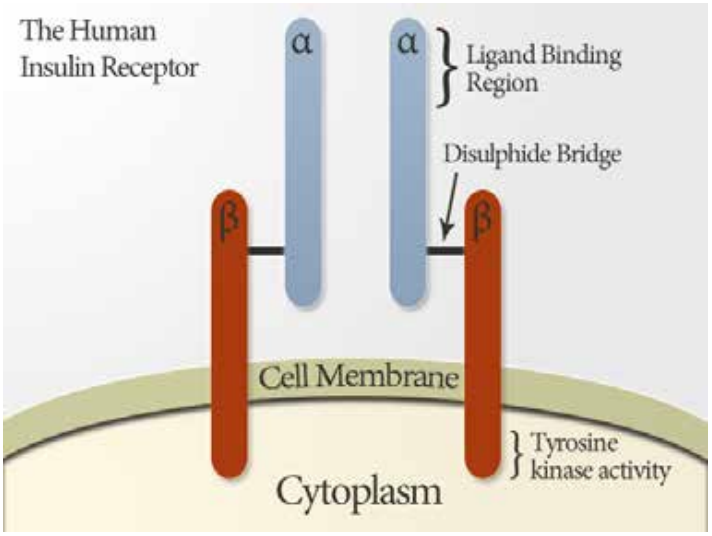

Figure 2. The tetrameric insulin receptor consists of two alpha, and two beta subunits joined by disulfide bridges. These two subunits are encoded by the same gene: INSR. Source for illustration: https://vetsci.co.uk/2011/04/22/development-of-insulin-resistance/

Children who survive beyond the first year of life with normal psychomotor development may have RMS. Heterozygous pathogenic variants in *INSR* can cause insulin-resistant diabetes mellitus with acanthosis nigricans (OMIM 610549) and autosomal dominant familial hyperinsulinemic hypoglycemia 5 (OMIM 609969), including neonatal hyperinsulinemic hypoglycemia. (2)

Donohue syndrome is life-limiting, and most affected children die by two years of age, often due to infection. Progressive cardiomyopathy, a frequent cause of death in DS, can be seen prenatally. (3,4) There is no effective treatment for insulin resistance in DS. Recombinant human IGF-1 is being studied in severe insulin resistance syndromes, but there is no standard protocol regarding its use.

Homozygous or compound heterozygous pathogenic variants cause DS in the insulin receptor gene (*INSR*; OMIM 147670) on chromosome 19p13. The insulin receptor is a tetramer of 2 alpha and two beta subunits, both coded by this single gene. Disulfide bonds join these alpha and beta subunits (Figure 2). The gene has 22 exons, of which 11 encode the alpha subunit and 11 encode the beta subunit. The alpha chains carry the insulin-binding region, while the beta chains carry the kinase domain. Defects in the alpha subunit could affect ligand binding, while defects in the beta subunit could affect membrane binding or signal transduction. This child has one variant in the first 11 exons that could affect the alpha subunit and one in the last 11 exons that could disable the beta subunit. A tetramer with two normal alpha and two normal beta subunits would be expected to represent 1/16th of the total number of insulin receptors produced. The other 15/16^{ths} would be expected to have some combination that included at least one abnormal alpha or beta subunit.

Insulin has pleiotropic functions that extend well beyond its role in carbohydrate metabolism. Insulin receptor substrates are phosphorylated and interact with the PI3K-AKT/PKB pathway, which is responsible for most of the metabolic actions of insulin, and the Ras-MAPK pathway, which regulates the expression of some genes and cooperates with the PI3K pathway to control cell growth and differentiation. This is why the absence of a functional insulin receptor has such widespread and devastating consequences for growth and organ function. In addition to binding insulin, the insulin receptor can bind insulin-like growth factors (IGFI and IGFII). Recombinant human IGF1 (rhIGF-1) has been shown to improve metabolic control in DS, although it may not alter the lethal outcome of DS, (5) which was the basis for offering rhIGF-1 as palliative therapy in our patient.

Practical Applications:

1. Please pay attention to uncommon features: the more rare the feature, the more discriminating it can be in narrowing the differential diagnosis. Thick alveolar ridges, prolapsed rectum, and nephrocalcinosis are rare findings in the newborn but common features in Donohue syndrome.
2. Consider a genetic etiology early in treatment when neonatal hypoglycemia does not respond to standard therapy or when dysmorphic features accompany hypoglycemia and small size. Although genetic disorders may be rare, genetic disorders are often undiagnosed in the NICU.
3. Recognize that heterozygous variants in *INSR* are more commonly encountered in patients than biallelic variants. Consider *INSR* gene analysis in infants with neonatal hypoglycemia with hyperinsulinemia even when they do not have the severe presentation of Donohue syndrome.

References:

1. *Ben Harouch S, Klar A, Falik Zaccai TC. INSR-Related Severe Syndromic Insulin Resistance. 2018 Jan 25. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Mirzaa GM, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022. PMID: 29369573.IGF1-like factors in Donohue syndrome*
2. *Sethi A, Foulds N, Ehtisham S, Ahmed SH, Houghton J, Colclough K, Didi M, Flanagan SE, Senniappan S. Heterozygous Insulin Receptor (INSR) Mutation Associated with Neonatal Hyperinsulinemic Hypoglycaemia and Familial Diabetes Mellitus: Case Series. J Clin Res Pediatr Endocrinol. 2020 Nov 25;12(4):420-426. doi: 10.4274/jcrpe.galenos.2019.2019.0106. Epub 2020 Jan 28. Erratum in: J Clin Res Pediatr Endocrinol. 2021 Jun 2;13(2):249. PMID: 31989990; PMCID: PMC7711633*
3. *Rojek A, Wikiera B, Noczynska A, Niedziela M. Syndrome*

of Congenital Insulin Resistance Caused by a Novel INSR Gene Mutation. J Clin Res Pediatr Endocrinol. 2021 Dec 30. doi: 10.4274/jcrpe.galenos.2021.2021.0256. Epub ahead of print. PMID: 34965699

4. *Perge K, Massoud M, Gauthier-Moulinier H, Lascols O, Pangaud N, Villanueva C, Pons L. Intrauterine Growth Restriction and Hypertrophic Cardiomyopathy as Prenatal Ultrasound Findings in a Case of Leprechaunism. Mol Syndromol. 2020 Nov;11(4):223-227. doi: 10.1159/000509837. Epub 2020 Sep 2. PMID: 33224016; PMCID: PMC7675228*
5. *Plamper M, Gohlke B, Schreiner F, Woelfle J. Mecasermin in Insulin Receptor-Related Severe Insulin Resistance Syndromes: Case Report and Review of the Literature. Int J Mol Sci. 2018 Apr 24;19(5):1268. doi: 10.3390/ijms19051268. PMID: 29695048; PMCID: PMC5983765*

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