Molecular Syndromology

Novel Insights from Clinical Practice

Mol Syndromol 2020;11:223–227
DOI: 10.1159/000509837

Received: February 24, 2020
Accepted: June 14, 2020
Published online: September 2, 2020

Intrauterine Growth Restriction and Hypertrophic Cardiomyopathy as Prenatal Ultrasound Findings in a Case of Leprechaunism

Kevin Perge[a, b] Mona Massoud[c, d] Hélène Gauthier-Moulinier[e] Olivier Lascols[f] Nicolas Pangaud[g] Carine Villanueva[a, b] Linda Pons[h]

[a]Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service d'endocrinologie pédiatrique, Bron, France; [b]Université Claude Bernard, Lyon 1, Lyon, France; [c]Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service de gynécologie-obstétrique, Bron, France; [d]Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Centre pluridisciplinaire de diagnostic prénatal, Bron, France; [e]Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service de néonatologie, Bron, France; [f]Hôpital Saint-Antoine, Laboratoire commun de biologie et génétique moléculaires, Paris, France; [g]Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service de cardiologie pédiatrique, Bron, France; [h]Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service de génétique, Bron, France

Established Facts

- Donohue syndrome is a rare and often lethal autosomal recessive disease caused by mutations in the INSR gene and characterized by severe insulin resistance (hyperinsulinemia, fasting hypoglycemia, and postprandial hyperglycemia), severe intrauterine growth restriction, postnatal growth failure, organomegaly including hypertrophic cardiomyopathy, hypotonia, developmental delay, and facial dysmorphism.
- Recombinant human insulin-like growth factor-I has been postulated as a potential therapeutic option in Donohue syndrome in order to improve glycemia, promote linear growth, and prolong survival.

Novel Insights

- To our knowledge, this is the first case of Donohue syndrome being revealed by intrauterine growth restriction and hypertrophic cardiomyopathy during the prenatal period with precise ultrasound description.
- Clinicians should keep in mind that the association of intrauterine growth restriction with hypertrophic cardiomyopathy could indicate Donohue syndrome.
- A prenatal diagnosis is essential to allow early neonatal management.
- Specific early neonatal management could be proposed, in particular with recombinant human insulin-like growth factor-I.

Keywords
Donohue syndrome · Hyperinsulinism · Hypertrophic cardiomyopathy · Insulin resistance · Intrauterine growth restriction · Leprechaunism

Abstract
Donohue syndrome (leprechaunism; OMIM *246200) is a rare and often lethal autosomal recessive disease caused by mutations in the *INSR* gene. We report the case of a 29-year-

karger@karger.com
www.karger.com/msy

Karger

Kevin Perge
Service d'endocrinologie Pédiatrique, Hôpital Femme Mère Enfant
Hospices Civils de Lyon 59, boulevard Pinel
FR–69677 Bron cedex (France)
kevin.perge@chu-lyon.fr

old pregnant woman, primigravida, who was referred at 33 weeks of gestation for severe intrauterine growth restriction (IUGR). Ultrasound examination found severe IUGR associated with an obstructive hypertrophic cardiomyopathy (HCM), confirmed postnatally. The newborn's blood glucose level fluctuated from fasting hypoglycemia to postprandial hyperglycemia. The infant was found to be homozygous for a novel missense pathogenic variant, c.632C>T (p.T211I), in exon 2 of the *INSR* gene, predicted to result in an abnormal insulin receptor. To our knowledge, this is the first report of leprechaunism being revealed by IUGR and HCM during the prenatal period. Clinicians should keep in mind that the association of these prenatal signs could indicate leprechaunism and specific early neonatal management could be proposed, in particular with recombinant human insulin-like growth factor-I.

Introduction

Donohue syndrome (DS, leprechaunism; OMIM *246200) is a rare, often lethal autosomal recessive disease caused by mutations in the *INSR* gene that leads to nonfunctional insulin receptor (IR) and insulin resistance [Ben Harouch et al., 2019]. DS, the most severe phenotype of *INSR*-related disorders, is characterized by hyperinsulinemia with fasting hypoglycemia and postprandial hyperglycemia, severe intrauterine growth restriction (IUGR), postnatal growth failure, organomegaly including hypertrophic cardiomyopathy (HCM), hypotonia, developmental delay, and facial dysmorphism [Ben Harouch et al., 2019]. Death usually occurs during the first years of life because of intercurrent upper airway infections and heart failure [Ben Harouch et al., 2019]. We report herein a case of DS revealed by IUGR and HCM in the third trimester of pregnancy.

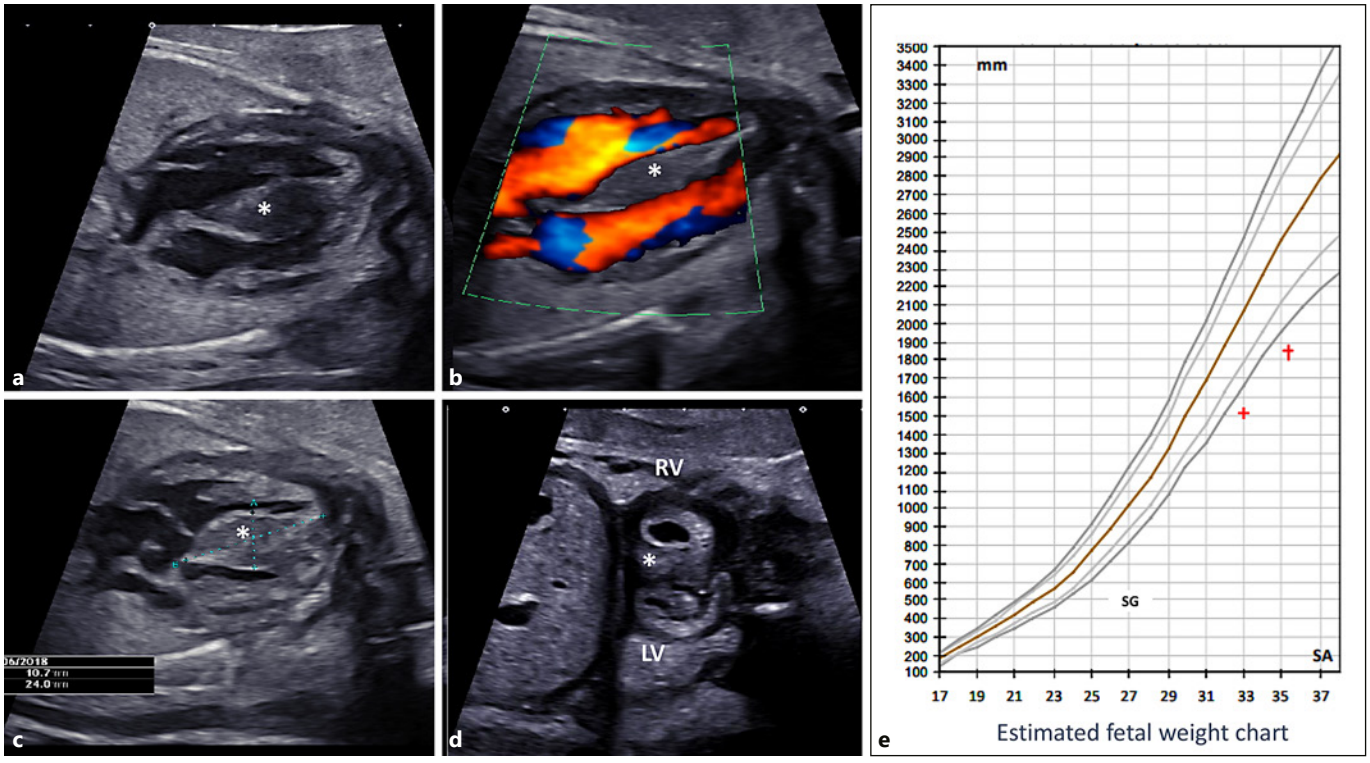

Fig. 1. Patient referred at 33 weeks of gestation (WG) for severe intrauterine growth restriction (IUGR). Examination of the fetal heart. On the axial 4-chamber views of the heart with 2D standard ultrasound (**a**) and using the color Doppler ultrasound (**b**), severe septal hypertrophy (*) 10.7 × 24 mm on the axial view (**c**) and 8.7 mm on the short axial view, with a mild hypoplastic left ventricle (**d**) were found. This was suggestive of an obstructive hypertrophic cardiomyopathy. LV, left ventricle; RV, right ventricle. The estimated fetal weight at 33 and 35 WG <–2 SD on the French National charts (**e**) confirmed severe IUGR.

Mol Syndromol 2020;11:223–227
DOI: 10.1159/000509837

Case Report

A 29-year-old woman, primigravida, was referred to our prenatal diagnosis center at 33 weeks of gestation (WG) for IUGR. The couple is consanguineous (first cousins). The risk of Down syndrome was at 1/1,517 (increased nuchal translucency [3.03 mm; larger than +2 SD] for crown-rump length of 75.11 mm, PAPP-A 1.74 MoM, and β-hCG 0.86 MoM). Estimated fetal weight was on the −1 SD curve during the second trimester without structural anomalies. At 31 WG, severe IUGR was diagnosed (<−2 SD) with normal Doppler ultrasound. Ultrasound examination performed in our center at 33 WG confirmed severe IUGR (<−2 SD) and revealed obstructive HCM. Echocardiography confirmed septal hypertrophy (8.7 mm during diastole; normal <3.6 mm) and showed obstruction with aortic flow acceleration (2.4 m/s), pericardial effusion, and mild hypoplastic but normally contractile left ventricle (LV; Fig. 1). Screening for cytomegalovirus infection, diabetes mellitus, and pregnancy-related vascular disorders were negative. Amniocentesis for chromosomal analysis was refused. Labor was induced at 35 WG due to the IUGR. A boy with a birth weight of 1,800 g (<−3 SD), length of 41.5 cm (<−3 SD), and a head circumference of 31 cm (−2 SD) was delivered vaginally. Placenta analysis was normal. The newborn had slight dysmorphic features including proptosis, infraorbital folds, large low-set posteriorly rotated ears, and hypertrichosis. He presented with respiratory distress requiring noninvasive ventilation. Postnatal echocardiography confirmed severe obstructive HCM with LV obstruction (peak systolic gradient: 55 mm Hg) but normal cardiac function (Fig. 2). Interventricular septal thickness during diastole was 7 mm (*Z* score larger than +3), and LV posterior wall thickness during diastole was 5 mm [*Z* score +3; severe HCM is defined as *Z* score larger than +2 by Pettersen et al. [2008]. High-dose propranolol was gradually increased to 6.5 mg/kg/day. Extensive metabolic screening was normal. Moreover, the boy's blood glucose level fluctuated from fasting hypoglycemia to postprandial hyperglycemia. Carbohydrate intake increased to 15 mg/kg/day with glycemia between 3 and 8 mmol/L. At day 15, he presented with ulcerative necrotizing enterocolitis that was medically treated. He had chronic hypoalbuminemia and hematological abnormalities (anemia, thrombocytopenia, and a prothrombin time 50% with low factor VII). Etiological assessment found severe hyperinsulinemia with extremely high levels of insulin (1,190 mIU/L) and C-peptide (15.1 μg/L). DS was diagnosed by Sanger sequencing identifying a novel homozygous missense pathogenic variant c.632C>T in exon 2 of the *INSR* gene that results in a nonsynonymous substitution (p.T211I). The *INSR* variant is absent from all public databases (ExAC/gnomAD, EVS, GME; a total of 150,058 subjects sequenced) and has never been reported before. The p.T211I mutation is located in the extracellular domain of INSR, predicted to be damaging by in silico prediction programs (POLYPHEN-2/SIFT/PROVEAN/CADD/UMD predictor) and classified pathogenic according to the American College of Medical Genetics and Genomics and Association for Molecular Pathology (ACMG; online suppl. Table 1; for online suppl. material, see www.karger.com/doi/10.1159/509837). Each parent was found to be heterozygous. These data were submitted to the Clin-

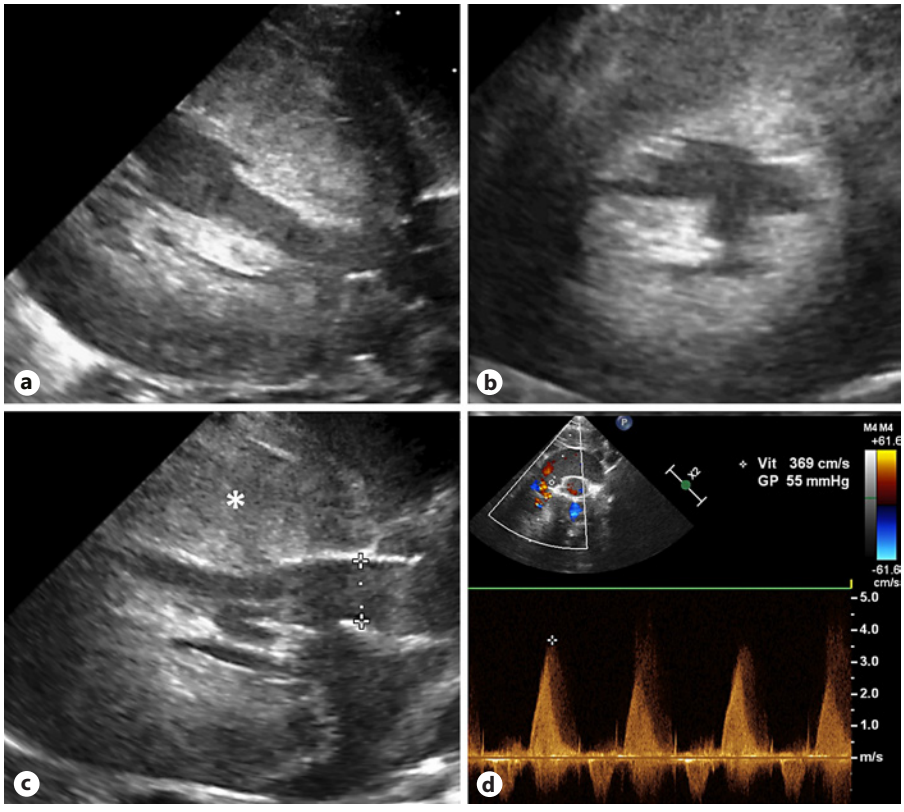

Fig. 2. Postnatal echocardiography. Long axis view of the heart (**a**) and parasternal minor axis view (**b**) showing severe concentric left ventricular hypertrophy. Parasternal long-axis view showing left ventricular outflow tract and a thickened ventricular septum* (**c**). Pulsed Doppler flow of the ascending aorta showing left ventricular obstruction with peak systolic gradient of 55 mm Hg (**d**).

Var public database (variation ID: SCV001245465). Mecasermin, a recombinant human insulin-like growth factor-I (rhIGF-I), was introduced at day 35 and increased to 161 μg/kg/day, using continuous subcutaneous infusion. Glycemic balance was good allowing a decrease of carbohydrate intake to 11 mg/kg/day. Severe HCM was persistent, but the LV gradient decreased to 20 mm Hg at 2 months of age. Progressive cardiorespiratory degradation with increased cardiac obstruction during sepsis provoked death at day 70 despite high-dose propranolol and rhIGF-I, which was still increasing.

Discussion

Herein, we report a case of DS revealed by IUGR and HCM in the third trimester of pregnancy. Diagnosis was made during the neonatal period because of hyperinsulinism associated with extreme glycemic fluctuations, facial dysmorphism, intestinal fragility, and hematological abnormalities.

The physiopathological mechanism leading to IUGR and HCM in DS, 2 prenatal signs of this syndrome, is related to structural homology between insulin and IGF-I receptors and use of common post-receptor signaling pathways [Dupont and LeRoith, 2001]. IGF-I and IGF-II, the main endocrine regulators of prenatal growth along with insulin, mediate their effects via both the IR and IGF-I receptor [Kido et al., 2001], and therefore, the absence of a fully functioning IR leads to IUGR observed in DS [Lamothe et al., 1998; Semple et al., 2011; Ben Harouch et al., 2019]. In parallel, the IGF-I receptor compensates at least partially for the defective IR function [Lamothe et al., 1998; McDonald et al., 2007]; the hyperinsulinism resulting from the absence of IR, acting through the IGF-I receptor, can therefore cause pseudoacromegalic growth in soft tissues, particularly in the heart and result in HCM [Ren et al., 1999; Deosch and Muslin, 2008]. The latter is present in 30% of DS infants and leads to death in 85% of these patients [Termote et al., 2016; Ben Harouch et al., 2019]; prenatal diagnosis is therefore essential to allow early neonatal management. Another characteristic of DS seen in prenatal ultrasound is virilization in girls because pseudoacromegalic growth affects in particular sex hormone-dependent tissues (insulin increases the effects of gonadotropins synergistically) and hyperinsulinism also promotes hyperandrogenism [Nestler, 1997; Semple et al., 2011]. For instance, prenatal clitoral hypertrophy has been reported once, in the only prenatal description of DS published to our knowledge, in a case of recurrence in siblings; this was associated with IUGR, facial dysmorphism, but not HCM [Bouzid et al., 2015]. The other characteristic manifestations in DS due to this effect of insulin on sex hormone-dependent tissues are in particular hypertrichosis and hypertrophic nipples, only the former was present in the patient presented herein [Nestler, 1997; Semple et al., 2011].

rhIGF-I has been postulated as a potential therapeutic option in DS by stimulating peripheral glucose use and suppressing hepatic glucose production in order to reduce hyperinsulinemia and pseudoacromegalic characteristics [McDonald et al., 2007; Plamper et al., 2018]. The long-term aim is to improve glycemia, promote linear growth, and prolong survival [McDonald et al., 2007]. There is no standard protocol, and only 6 case reports, reviewed by Plamper et al. [2018], describe successful long-term use of rhIGF-I in patients with leprechaunism. Early treatment and continuous administration of rhIGF-I seem to be more beneficial [Nakae et al., 1998; Weber et al., 2014]. Used doses range from 80 to 1,120 μg/kg/day [Plamper et al., 2018]. In most treated children, levels of blood glucose, insulin, and glycosylated hemoglobin decreased, growth parameters improved, sometimes HCM also improved, and survival was prolonged [Nakae et al., 1998; McDonald et al., 2007; Plamper et al., 2018; Ben Harouch et al., 2019].

The present report highlights that DS can be revealed by prenatal IUGR and HCM. Clinicians should keep in mind that the association of these prenatal signs could indicate DS and specific early neonatal management could be proposed, in particular with rhIGF-I.

Statement of Ethics

The paper is exempt from ethical committee approval because it is a retrospective case report. The parents of the index case have given their written informed consent to publish their case including the accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

There is no grant or funding support associated with this article.

Author Contributions

Kevin Perge performed the literature search, prepared figures, collected, analyzed and interpreted data, and wrote the initial draft of the manuscript. Hélène Gauthier-Moulinier and Nicolas Pangaud prepared figures and interpreted data. Olivier Lascols interpreted data. Linda Pons, Carine Villanueva and Mona Massoud initiated the study and proposed the study design, performed the literature search, prepared the figures, performed data collection, analysis and interpretation, and wrote the first draft. All authors reviewed the final manuscript, and endorsed the findings and the scientific content.

References

Ben Harouch S, Klar A, Falik Zaccai TC. INSR-related severe syndromic insulin resistance. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, et al., (eds). GeneReviews® [Internet] Seattle (WA): University of Washington, Seattle; 1993–2020. http://www.ncbi.nlm.nih.gov/books/NBK476444/. Initial posting: January 25, 2018; last update: January 23, 2019.

Bouzid A, Ayachi A, Khammessi I, Chelli I, Mourali M. Antenatal diagnosis of a recurrent case of leprechaunism (in French). Gynecol Obstet Fertil. 2015;43(7-8):556–9.

DeBosch BJ, Muslin AJ. Insulin signaling pathways and cardiac growth. J Mol Cell Cardiol. 2008;44(5):855–64.

Dupont J, LeRoith D. Insulin and insulin-like growth factor I receptors: similarities and differences in signal transduction. Horm Res. 2001;55(Suppl 2):22–6.

Kido Y, Nakae J, Accili D. Clinical review 125: The insulin receptor and its cellular targets. J Clin Endocrinol Metab. 2001;86(3):972–9.

Lamothe B, Baudry A, Christoffersen CT, De Meyts P, Jami J, Bucchini D, et al. Insulin receptor-deficient cells as a new tool for dissecting complex interplay in insulin and insulin-like growth factors. FEBS Lett. 1998;426(3):381–5.

McDonald A, Williams RM, Regan FM, Semple RK, Dunger DB. IGF-I treatment of insulin resistance. Eur J Endocrinol. 2007;157(Suppl 1):S51–6.

Nakae J, Kato M, Murashita M, Shinohara N, Tajima T, Fujieda K. Long-term effect of recombinant human insulin-like growth factor I on metabolic and growth control in a patient with leprechaunism, J Clin Endocrinol Metab. 1998;83(2):542–9.

Nestler JE. Insulin regulation of human ovarian androgens. Hum Reprod. 1997;12(Suppl 1):53–62.

Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of Z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr. 2008;21(8):922–34.

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;19(5).

Ren J, Samson WK, Sowers JR. Insulin-like growth factor I as a cardiac hormone: physiological and pathophysiological implications in heart disease. J Mol Cell Cardiol. 1999;31(11):2049–61.

Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. Endocr Rev. 2011;32(4):498–514.

Termote JU, Breur J, de Vroede MA Hypertrophic cardiomyopathy in Donohue syndrome. Cardiol Young 2016;26(4):815–818. .

Weber DR, Stanescu DE, Semple R, Holland C, Magge SN. Continuous subcutaneous IGF-1 therapy via insulin pump in a patient with Donohue syndrome. J Pediatr Endocrinol Metab. 2014;27(11-12):1237–41.