Severe Hyperinsulinemic Hypoglycemia in a Neonate: Response to Sirolimus Therapy

Ünöke Méder, MD, Géza Bokodi, MD, PhD, Lídia Balogh, MD, PhD, Anna Körner, MD, PhD, Miklós Szabó, MD, PhD, Stepanka Pruhova, MD, PhD, Attila J. Szabó, MD, PhD

Hyperinsulinemic hypoglycemia (HH) is one of the most common causes of persistent hypoglycemic episodes in neonates. Current pharmacologic treatment of neonatal HH includes diazoxide and octreotide, whereas for diffuse, unresponsive cases a subtotal pancreatectomy may be the last resort, with questionable efficacy. Here we report a case of congenital diffuse neonatal HH, first suspected when severe hypoglycemia presented with extremely high serum insulin levels immediately after birth. Functional imaging and genetic tests later confirmed the diagnosis. Failure to respond to a sequence of different treatments and to avoid extensive surgery with predictable morbidity prompted us to introduce a recently suggested alternative therapy with sirolimus, a mammalian target of rapamycin inhibitor. Glucose intake could be reduced gradually while euglycemia was maintained, and we were able to achieve exclusively enteral feeding within 6 weeks. Sirolimus was found to be effective and well tolerated, with no major adverse side effects attributable to its administration.

PATIENT PRESENTATION

Our patient, a male infant, was born by normal vaginal delivery during the 37th week of gestation after an uneventful pregnancy. Birth weight was 4400 g, and 1- and 5-minute Apgar scores were 10 and 10. Both parents and the baby’s 2 older siblings had unremarkable medical histories. A right-sided clavicular fracture was noted on first examination, which did not warrant additional intervention. Two hours after delivery, tremor and irritability were observed, with severe hypoglycemia (0.5 mmol/L, 9 mg/dL). High doses of intravenous glucose (up to 20 mg/kg per minute) and occasional glucagon boluses were needed to normalize the persistently low blood glucose levels. The diagnosis of hyperinsulinemic hypoglycemia (HH) was based on the clinical picture and on the laboratory values (glucose, 0.5 mmol/L; concomitant serum insulin, 130.7 μU/mL; growth hormone, 18.3 ng/mL; thyroid-stimulating hormone, 8.2 mU/L; free thyroxine, 20.5 pmol/L; cortisol, 835 nmol/L), and samples were sent for genetic testing.

Diazoxide therapy (with hydrochlorothiazide 1 mg/kg per day) was commenced on day 4 and was gradually increased to a maximum dose of 20 mg/kg per day without any effect. Somatostatin treatment (introduced as intravenous, subsequently modified to subcutaneous) was initiated on week 2 and increased to a maximum dose (35 μg/kg per day), but only a 20% reduction in total glucose requirements was achieved. On week 4 nifedipine was added to the therapeutic regimen, but it was discontinued after a week because of lack of response (Fig 1).
A dose of 0.5 mg/m² per day, with gradual increments controlled by serum levels (aiming for 5–15 ng/mL) checked every 3 to 5 days (see Supplemental Information). During the next 6 weeks the patient’s glucose requirement was significantly reduced for the first time (to 8 mg/kg per minute), and somatostatin could gradually be discontinued, while the patient maintained normoglycemia. During this transitional period, an episode of sepsis with bloody stool developed at week 11, with signs of intestinal pneumatosis on the abdominal radiograph. Bell stage II A necrotizing enterocolitis (NEC) was diagnosed, enteral feed was briefly suspended, and the symptoms resolved with conservative treatment.

Regular blood (complete blood cell count, renal and liver function, lipid levels) and urine samples were collected to monitor for known side effects of sirolimus, but apart from mildly elevated liver function tests and triglyceride and cholesterol levels we could not attribute any significant adverse events to the treatment. Clinical neurologic examinations were unremarkable during the period of treatment apart from the initial tremor witnessed immediately after birth. Neurodevelopmental assessment revealed moderate axial hypotonia, which improved with physiotherapy. A brain MRI scan at 5 months was reported as normal. Weight and head circumference were both above the 98 percentile at birth and remained in this range throughout the period of observation. Although oral intake has remained the primary route for feeding, a percutaneous endoscopic gastrostomy tube was inserted at 6 months to aid supplemental feeding at regular intervals.

Follow-up assessment at the age of 1 year confirmed that the treatment had sustained results. The infant, weighing 13.5 kg, currently receives 1.5 mg sirolimus once a day, which maintains a serum sirolimus level of 9.62 ng/mL. Capillary blood sugar is checked at least ≥4 times every day, with levels ranging between 3.5 and 7.0 mmol/L, and no hypoglycemic episode (serum glucose <2.6 mmol/L) has been reported since discharge. Controlled fasting levels significantly improved from <1 hour at the time of diagnosis to >6 hours at follow-up (insulin levels were 20 µU/mL and 5.52 µU/mL after 4 and 6 hours of fasting, respectively). The liver function tests and serum lipid levels remained mildly elevated (aspartate aminotransferase, 73 U/L; alanine aminotransferase, 65 U/L; cholesterol, 5.9 mmol/L; triglyceride, 3.9 mmol/L) but showed improvement, with the reduction of sirolimus levels, and continue to be closely monitored.

DISCUSSION

HH in neonates, formerly also described as nesidioblastosis or congenital hyperinsulinism, is characterized by unregulated and elevated insulin secretion of the pancreatic islet β cells, resulting in persistent hypoglycemia. This is a rare disease with an incidence of 1 in 50 000 live births, but significant variation has been reported. Early diagnosis and treatment are crucial to the appropriate management of HH. Histologic presentation may be focal or diffuse and very rarely atypical based on the spread of affected regions in the pancreas. Differentiation between these subgroups can be made by using ¹⁸F 3,4-dihydroxyphenylalanine positron emission tomography scans. Several congenital mutations have been described that may have a role, and in ∼50% of the cases the adenosine triphosphate (ATP) sensitive K⁺ channel in pancreatic β cells seems to play a key role in the uncontrolled insulin secretion.皑 KCNJ11 and ABCC8 localized on chromosome 11p15.1 are responsible
for coding the 2 subunits of these K-ATP channels. The primary goal of treatment is to achieve normoglycemia to prevent long-term neurologic damage. The treatment algorithm most widely accepted recommends the K-ATP agonist diazoxide as first-line therapy and the somatostatin analog octreotide as second-line therapy. The calcium channel blocker nifedipine has also been reported as an alternative in unresponsive cases. Focal lesions usually warrant surgical excision, whereas for therapy-resistant diffuse presentations the only treatment option available is subtotal or total pancreatectomy. Definitive success rates are high for the former, but about one-third of patients remain hyperinsulinemic after subtotal pancreatectomy, many develop exocrine pancreatic insufficiency, and nearly all will develop diabetes by adolescence.

A recently published novel treatment option for HH of the newborn has been suggested including the immunosuppressant sirolimus, an mTOR inhibitor. No major adverse reactions were observed during the 1-year follow-up period in the 4 cases reported. This finding is reinforced by the latest case report of another infant. The suggested method of action of sirolimus includes the reduction of β cell proliferation, inhibition of insulin production, and induced peripheral insulin resistance.

Our decision to proceed with this treatment option was prompted by the lack of response to standard therapies, with the aim to avoid the major adverse effects of subtotal pancreatectomy. The desired glycemic control was achieved within 6 weeks of initiating sirolimus treatment. A transient episode of NEC was observed after the introduction of sirolimus, which responded well to conservative treatment and subsequent termination of somatostatin therapy. Based on previously published evidence of somatostatin-related NEC, it was considered most likely that this adverse event was attributable to somatostatin rather than sirolimus. Although the side effects of elevated liver function, hypercholesterolemia, and hypertriglyceridemia were observed, they were mild, and improvement was seen with reduction in sirolimus dosage. Significant renal, hematologic, or pulmonary complications associated with sirolimus reported elsewhere were not experienced. Compliance with dietary and therapeutic recommendations took patience and full engagement with the parents.

CONCLUSIONS
We believe our case report adds to the growing evidence of published cases suggesting that sirolimus could be an effective and safe treatment option in therapy-resistant diffuse HH of the newborn.

ACKNOWLEDGMENTS
Professor Jan Lebl, MD, PhD, of the Department of Pediatrics, 2nd Faculty of Medicine, Charles University in Prague, provided a detailed analysis of the genetic results.

We thank Professor Tivadar Tulassay of the 1st Department of Pediatrics, Semmelweis University Budapest, for his valuable comments and recommendations for this manuscript.

ABBREVIATIONS
ATP: adenosine triphosphate
HH: hyperinsulinemic hypoglycemia
mTOR: mammalian target of rapamycin
NEC: necrotizing enterocolitis

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding was secured for this case report. The molecular genetic analysis was supported by a grant from the Czech Ministry of Health (NT 11402).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES


Severe Hyperinsulinemic Hypoglycemia in a Neonate: Response to Sirolimus Therapy
Ünoke Méder, Géza Bokodi, Lídia Balogh, Anna Körner, Miklós Szabó, Stepanka Pruhoval and Attila J. Szabó
Pediatrics 2015;136:e1369
DOI: 10.1542/peds.2014-4200 originally published online October 26, 2015;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/136/5/e1369

Supplementary Material
Supplementary material can be found at:
http://pediatrics.aappublications.org/content/suppl/2015/10/21/peds.2014-4200.DCSupplemental

References
This article cites 19 articles, 6 of which you can access for free at:
http://pediatrics.aappublications.org/content/136/5/e1369.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Endocrinology
http://classic.pediatrics.aappublications.org/cgi/collection/endocrinology_sub
Fetus/Newborn Infant
http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub
Neonatology
http://classic.pediatrics.aappublications.org/cgi/collection/neonatology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Severe Hyperinsulinemic Hypoglycemia in a Neonate: Response to Sirolimus Therapy
Ünoke Méder, Géza Bokodi, Lídia Balogh, Anna Körner, Miklós Szabó, Stepanka Pruhova and Attila J. Szabó
*Pediatrics* 2015;136;e1369
DOI: 10.1542/peds.2014-4200 originally published online October 26, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/136/5/e1369