Severe Hyperinsulinemic Hypoglycemia in a Neonate: Response to Sirolimus Therapy
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abstract
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).

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and triglyceride and cholesterol levels
we could not attribute any significant
adverse events to the treatment.

Functional imaging with ¹⁸F 3,4-
dihydroxyphenylalanine positron
emission tomography scan performed
on week 6 confirmed diffuse
pancreatic enhancement. Genetic
tests subsequently showed
a compound heterozygote for the
known mutations in the ABCC8 gene:
mutation p.Y512* (c.1536C>A M/n)³
inherited from the unaffected father
and IVS36-13G>A (c.4412-13G>A, p.
M/n)² inherited from the
unaffected mother. Multidisciplinary
discussions, including the parents,
were organized regarding treatment
options, including a subtotal
cystectomy. A recent report³ of
a novel indication of sirolimus,
a mammalian target of rapamycin
(mTOR) inhibitor in similar cases, was
also discussed. After risks and
benefits were considered carefully,
a consensus decision was made to
proceed with this alternative
treatment option. Approval was
sought from Directorate General of
National Institute of Pharmacy,
Hungary, and written consent from
the parents was also obtained.

Sirolimus (Rapamune; Pfizer, Walton
Oaks, Surrey, United Kingdom) was
initiated on week 8, built up from 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 pneumonitis 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.⁴ Early
diagnosis and treatment are crucial to
the appropriate management of HH.
Histologic presentation may be focal
or diffuse⁵ (and very rarely atypical⁶)
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.⁷ 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.⁸

KCNJ11 and ABCC8 localized on
chromosome 11p15.1 are responsible

![FIGURE 1](image_url)

Timeline of parenteral and enteral average glucose intake in relation to the changes in therapy.
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.

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REFERENCES


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