Advances in Obesity, Endocrinology, and Diabetes
Volume 3 Issue 1 (Jan-June 2026) | ISSN: 3049-0715

Case study: Successful medical treatment of congenital hyperinsulinism with pasireotide in a 12-year-old child

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Keywords: congenital hyperinsulinism; pasireotide; case report

Abstract
Background: Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and children. Prompt diagnosis and treatment is important to avoid long-term neurological damage. In diazoxide-unresponsive cases, somatostatin receptor analogs are used in second line. Pasireotide, which has a higher affinity for the somatostatin receptor 5 than first-generation somatostatin analogs, was trialed in a pediatric patient with hyperinsulinism.

Case description: The patient presented at the age of 8 years with recurrent episodes of non-fasting hypoglycemia and neuroglycopenic symptoms. A diagnosis of autonomous insulin secretion was biochemically confirmed by elevated levels of insulin (22.9 µUI/mL > 3 µUI/mL) and C-peptide (3.43 ng/mL > 0.6 ng/mL) during hypoglycemia (glucose 2.03 mmol/L). Glucose infusion rate to maintain euglycemia was 7 (mg/kg/min). The patient was initially treated by frequent feeding with carbohydrate-enriched formula and diazoxide 10 mg/kg/day. At the age of 12 years treatment with subcutaneous injections of octreotide was added because of recurrent hypoglycemia. Six months later and with parental consent, long acting pasireotide 40 mg every 28 days was initiated. Common side effects associated with pasireotide were carefully monitored, but did not occur. The patient was normoglycemic with a good growth rate, normal weight gain, and excellent neurodevelopment.
Conclusion: This case study adds to findings reported previously suggesting that pasireotide may be a valuable option in second-line treatment of hyperinsulinism.

Introduction

Congenital hyperinsulinism (CHI) is a relatively rare condition characterized by severe and often refractory hypoglycemia in infants and young children, due to dysfunctional or excessive insulin secretion from pancreatic b-cells (1). Untreated, it can result in profound hypoglycemia, causing brain injury and adversely affecting neurodevelopment (1,2). According to a recent analysis, the prevalence of hyperinsulinism in European-ancestry populations is 3.5 per 100,000 births, but this may vary considerably based on local consanguinity patterns (3). Different etiologies of hyperinsulinism have different impacts, thus early diagnosis and prompt treatment is crucial to prevent long term neurodisability (4). In healthy individuals, insulin production is regulated by blood glucose via ATP-sensitive K+ channels in pancreatic β-cells. This regulation is lost in CHI, leading to uncontrolled insulin production. While CHI is considered to be genetic, causative mutations are found in only 50% of cases (4).

Only diazoxide has been approved to treat CHI in childhood (5). However, if there are mutations in the K-ATP channel, diazoxide is unlikely to be effective (4). Somatostatin receptor analogs (SRAs) are routinely used in second line as they are potent inhibitors of insulin and glucagon secretion by activating SSTR, mainly SSTR2 (4,5). Pasireotide is a second-generation SRA. It binds with a higher affinity to SSTR1, SSTR3, and SSTR5, and with the same affinity to SST2 when compared with octreotide; and with higher affinity to SSTR1, SSTR3, and SSTR5, but with the same affinity to SST2R compared with lanreotide (5). Pasireotide has been shown to increase hyperglycemia by decreasing insulin secretion and incretin hormone responses without changes in hepatic or peripheral insulin sensitivity (6). Given this pharmacological profile, off-label pasireotide has been attempted in a handful of cases to manage treatment-resistant hypoglycemia. Current CHI guidelines acknowledge pasireotide use in difficult cases. However, based on limited evidence showing modest efficacy (7), guidelines recommend using it only in research settings (1). The following report describes a case of a pediatric patient with CHI successfully managed with long-acting release (LAR) pasireotide following failure of a conventional treatment regimen (8).

Case description

An 8-year-old patient presented with recurrent non-fasting hypoglycemia and neuroglycopenic symptoms.

A diagnosis of autonomous insulin secretion was biochemically confirmed by identifying an elevated insulin level of 22.9 µUI/mL > 3 µUI/mL and C-peptide was elevated (3.43 ng/mL > 0.6 ng/mL) measured during hypoglycemia (glucose 2.03 mmol/L) (Table 1).

Insulin level (µUI/mL)	22.9	> 3
C-peptide (ng/mL)	3.43	>0.6
Glucose level (mmol/L)	2.03	≥ 3

Table 1: Biological parameters

The glucose infusion rate to maintain euglycemia was 7 (mg/kg/min). Abdominal ultrasound, computed tomography and magnetic resonance imaging (MRI) did not identify any pancreatic abnormalities. Endoscopic ultrasound and octreotide receptor scintigraphy revealed no pathological findings.

The patient was initially treated with frequent feeding with carbohydrate-enriched formula and diazoxide 10 mg/kg/day. At the age of 12 years treatment with subcutaneous (SC) injections of octreotide was added because of recurrent hypoglycemia.

At the age of 12 years 6 months and after parental consent, therapy with the long-acting somatostatin analog, pasireotide was initiated, at a dose of 40 mg every 28 days. The common and expected side effects of pasireotide - elevated liver enzymes, hypothyroidism, and adrenal insufficiency - were closely monitored but did not occur.

After initiating pasireotide treatment, continuous glucose monitoring (CGM) was performed. Figure 1 shows the 24-hour glucose profile, demonstrating stable glycemic values with minimal fluctuations within the target range. The average sensor glucose (SG) was 70 ± 11 mg/dL, with a significant reduction in hypoglycemic episodes compared with baseline.

On this therapy, the patient was normoglycemic with a good growth rate, normal weight gain, and excellent neurodevelopment.

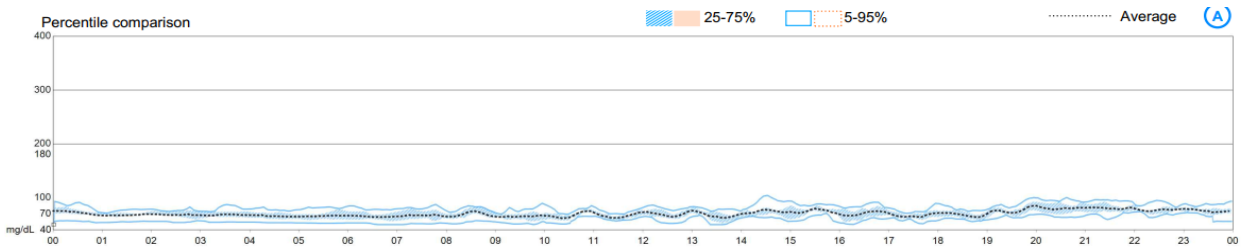

Figure 1: Continuous glucose monitoring (CGM) profile after pasireotide initiation

The graph illustrates the 24-hour glucose profile obtained from CGM following pasireotide treatment. The dotted line represents the average glucose levels, while the shaded areas indicate the 25th–75th percentile (light blue) and 5th–95th percentile (dotted blue). The data demonstrate stable glucose levels with reduced fluctuations and minimal hypoglycemic episodes. The average sensor glucose (SG) was 70 ± 11 mg/dL.

Discussion

This case adds to the evidence supporting pasireotide LAR in treatment-resistant hyperinsulinism. In this case in a child with CHI, the transition to pasireotide, a newer somatostatin analog with enhanced affinity for somatostatin receptor 5, resulted in sustained normoglycemia. This outcome suggests that pasireotide might offer advantages over traditional somatostatin analogs in select cases. A number of case studies have explored this possibility (Table 2). The recent CHI guidelines caution against the use of pasireotide in this indication, but this recommendation is based on a single case study. The present study, in addition to a number of very recent case studies, adds weight to the supposition that pasireotide may be more efficacious than first-generation SRAs in specific, difficult-to-treat cases than previously thought.

Table 2. Available literature reports of use of pasireotide for the treatment of hypoglycemia

Author, date	Patient details	Treatment with pasireotide	Outcomes
Tirosh 2016[9]	72-year-old male with malignant insulinoma, hypoglycemia not controlled by octreotide and lanreotide	LAR 20 mg raised to 40 mg monthly	Hypoglycemic events completely resolved.
Schwetz 2016[10]	46-year-old female with nesidioblastosis failed on steroids and somatostatin analogs	0.6 mg bid	Successful treatment for 3 years with marked improvement in QoL.
Hendren 2018[11]	53-year-old female with malignant insulinoma; diazoxide was discontinued due to intolerance; octreotide ineffective	SC LAR 60 mg every 28 days	Excellent response and near resolution of hypoglycemic events.
Dauriz 2019[12]	63-year-old female with nesidioblastosis experiencing hypoglycemic events despite diazoxide and octreotide	SC 0.6 mg bid	Continuing hypoglycemia, pasireotide discontinued.
Mooij 2021[7]	Male neonate with CHI who failed on diazoxide and octreotide and lanreotide	SC 0.3 mg 4 times daily; LAR 10-40 mg	Pasireotide slightly improved glycemic control without side effects.
Rouland 2021[13]	56-year-old female with nesidioblastosis, failure of diazoxide and octreotide	LAR 40 mg every 4 weeks	Rapid resolution of hypoglycemia. Response sustained for 2 years.
Koneshamoorthy 2022[14]	22-year-old male, hyperinsulinemic; hypoglycemia despite diazoxide	900 mcg SC bid	Improvement in hypoglycemia
Telehuz 2024[15]	Twin male infants	1070 µg/m^2/day for one infant and 1200 µg/m^2/day for the other; switched to 20 mg every 4 weeks	Normal growth and milestones at 3 years.

This case presents several noteworthy aspects in the management of CHI. First, the patient's age at presentation (8 years) differs from typical CHI cases, which are usually diagnosed in the neonatal period (1). Despite the late presentation, the patient exhibited classical biochemical findings, with an insulin level of 22.9 µUI/mL and C-peptide of 3.43 ng/mL during documented hypoglycemia (glucose 2.03 mmol/L). This reinforces the importance of considering CHI in the differential diagnosis of hypoglycemia even in older children, particularly when biochemical evidence shows inappropriate insulin secretion (4).
The negative findings on multiple imaging modalities (ultrasound, CT, MRI, endoscopic ultrasound, and octreotide receptor scintigraphy) in our case highlight the diagnostic challenges in CHI. Despite clear biochemical evidence of hyperinsulinism, demonstrated by a glucose infusion rate of 7 mg/kg/min to maintain euglycemia, the absence of identifiable pancreatic lesions suggests a diffuse form of the disease (16). This underscores the limitations of current imaging techniques and raises questions about the optimal diagnostic algorithm for CHI (1,17).

The CGM data following pasireotide treatment indicate a significant improvement in glycemic control, with fewer fluctuations and reduced hypoglycemia. These findings support the efficacy of pasireotide in stabilizing blood glucose levels in congenital hyperinsulinism. Of particular interest is the favorable safety profile observed with pasireotide in our patient. Despite known risks of elevated liver enzymes, thyroid abnormalities, and adrenal insufficiency (18), our patient showed no evidence of these complications during treatment. Furthermore, the achievement of normal growth rate and weight gain, along with excellent neurodevelopment, provides encouraging data about the long-term tolerability of pasireotide in pediatric patients.

The patient's positive outcome with pasireotide suggests a potential role for this medication in the treatment algorithm for CHI, particularly in cases presenting beyond the neonatal period.

This case demonstrates successful long-term glycemic control with pasireotide in a pediatric CHI patient presenting after the typical neonatal period. The favorable efficacy and safety profile suggest that pasireotide warrants further investigation as a second-line treatment option for CHI, particularly in cases refractory to conventional therapy.

Data availability statement
All relevant and available clinical data is included in the manuscript.

Ethics statement
This case report was conducted in accordance with ethical standards. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. As this is a single case report and not a clinical study, formal approval from an ethics committee was not required per institutional guidelines.

Author contributions
IBN: Conceptualization, Investigation, Project administration, Supervision, Visualization, Writing– original draft, Writing– review & editing.
FK: Investigation; Writing– review & editing.
SM: Investigation; Writing– review & editing.
SE: Investigation; Writing– review & editing.
RL: Investigation; Writing– review & editing.
NM: Investigation; Writing– review & editing.
KK: Investigation; Writing– review & editing.
IR: Investigation; Writing– review & editing.

Funding
No funding was received.

Acknowledgments
The authors would like to express their gratitude to the nursing staff at the Charles Nicolle Hospital who helped with the management of this patient. The authors are grateful to Recordati Rare Diseases for the provision of editorial assistance and to Guy Ramsay who edited the manuscript.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement
The author(s) declare that no Generative AI was used in the creation of this manuscript.

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