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Congenital hyperinsulinism

CLINICAL REVIEW

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This clinical review will give doctors who work with children and neonates an introduction to the diagnosis and treatment of congenital hyperinsulinism, the most common cause of persistent neonatal hypoglycaemia. The condition is a rare monogenic disorder characterised by elevated

insulin secretion and is a result of mutations in genes that regulate insulin secretion from pancreatic beta cells. The anabolic effect of insulin induces systemic glucose uptake and inhibits gluconeogenesis, glycogenolysis, ketogenesis and lipolysis. Low levels of glucose and ketone bodies in the blood are harmful to the central nervous system and can lead to brain damage or death. Early diagnosis and treatment of congenital hyperinsulinism are therefore crucial for a good prognosis.

About 15 % of full-term infants will develop hypoglycaemia within 48 hours of birth (1). Initial treatment involves the administration of carbohydrates, either in the form of glucose, breast milk or formula milk. This can be given orally, buccally with glucose gel, or as a glucose infusion to stabilise blood glucose levels. If hypoglycaemia persists beyond 48–72 hours without a clear cause (e.g. prematurity, growth restriction, small or large for gestational age) in a full-term infant, there is reason to suspect congenital hyperinsulinism (2).

In Western populations, the reported prevalence is 1:28,000–50,000 (3). Over the last decade, the National Treatment Service of Diagnostics and Treatment of Congenital Hyperinsulinism at Haukeland University Hospital has received 1–7 new referrals annually, and over 70 % have resulted in a diagnosis of congenital hyperinsulinism. Congenital hyperinsulinism is a clinically and genetically heterogeneous disease (4). In the most severe cases, both patient and family face considerable strain due to complex treatment that requires continuous monitoring throughout childhood (3).

The purpose of this article is to provide information on clinical findings, diagnostics, and treatment of congenital hyperinsulinism. The content is based on the authors' clinical experience and subjectively selected material from a literature search.

Clinical presentation

Congenital hyperinsulinism typically presents in the neonatal period, but in around 10 % of cases, onset is not until childhood or adolescence (5). Symptom-onset with hypoglycaemia usually occurs shortly after birth, and symptoms can range from non-specific and subtle (pallor, hypotonia, lethargy) to severe and neurological (apnoea, reduced consciousness, jitteriness, seizures, unconsciousness, death) (4, 6). Elevated birth weight can be an indication of congenital hyperinsulinism, but normal or low birth weight does not rule out the condition (4).

Diagnostics

Central to the diagnosis is a detailed medical history to uncover information that may indicate congenital hyperinsulinism (elevated birth weight, parental consanguinity, family history of diabetes and symptoms of hypoglycaemia) or other causes of

hypoglycaemia (intrauterine growth restriction, gestational diabetes, prematurity, asphyxia) (4).

It is important to identify the presence of ketotic or non-ketotic hypoglycaemia at an early stage of investigations. Ketone bodies can be measured in serum and/or urine, and testing should be performed during hypoglycaemia (< 2.6 mmol/L). Many of the differential diagnoses are metabolic disorders (gluconeogenesis disorders, glycogen storage diseases, organic acidurias, mitochondrial disorders, cortisol or growth hormone deficiency) and can be ruled out by reduced levels of ketone bodies or through the Newborn screening programme in Norway. Hyperinsulinism presents as non-ketotic hypoglycaemia. Persistent non-ketotic hypoglycaemia without hyperinsulinaemia raises suspicion of fatty acid oxidation disorders. Several syndromes are associated with hyperinsulinism and these need to be ruled out (e.g. Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, Turner syndrome, etc.) (7). Midline anomalies or small genitalia may be due to pituitary diseases and need to be ruled out (8).

General investigations for persistent neonatal hypoglycaemia are summarised in international guidelines (9) and the Norwegian Paediatric Association's Neonatal Guidelines (2). Investigations of congenital hyperinsulinism are carried out in hospitals, and early contact with an expert treatment centre is recommended. The primary diagnostic criterion for congenital hyperinsulinism is detectable insulin in the serum concurrent with hypoglycaemia. Hypoglycaemia is triggered by fasting and can be particularly harmful to brain development (10). Glucose levels therefore need to be monitored with a continuous glucose sensor or frequent capillary blood tests.

When blood glucose drops below 2.6 mmol/L, a venous blood sample is taken to measure serum glucose, insulin and C-peptide. Three sets of samples should be collected at different times, as a single measurement can yield false low insulin levels due to the pulsatile nature of insulin secretion. Haemolysis could also potentially affect the sample. C-peptide is used as a supplement to the insulin measurement, as C-peptide is more stable and is typically elevated in hyperinsulinism (2). If serum insulin is detectable at blood glucose levels below 2.6 mmol/L, clinically verified hyperinsulinism is present. When initially testing for reduced levels of ketone bodies (beta-hydroxybutyrate), reduced levels of free fatty acids (EDTA plasma) should also be checked in connection with the sample sets to verify the insulin measurement, as the anabolic effect of insulin inhibits ketogenesis and lipolysis. The glucagon response must also be examined. Patients with hyperinsulinism typically show an increase in blood glucose following a glucagon injection (0.03 mg/kg). An increased carbohydrate need further supports the diagnosis (> 8 mg/kg/min, reference range 4–6). Elevated ammonia levels can reveal a subtype of congenital hyperinsulinism that involves mutations in the *GLUD1* gene (11).

If insulin is detected simultaneously with blood glucose levels below 2.6 mmol/L, genetic testing should be initiated. Genotype is important for a precise diagnosis, further investigations, and treatment. Therefore, both parents should also be genetically tested. Mutations in at least 15 genes can cause congenital hyperinsulinism, and the majority of the mutations are recessive (see Table 1 at tidsskriftet.no) (4, 6). The mutations result in altered function of corresponding protein products in beta cells and can be classified as disruptions of ion channels (channelopathies), metabolic enzymes (metabolopathies), or transcription factors (transcriptionopathies) (Figure 1). Ion

channel disruptions typically cause the most severe phenotype. However, a large Finnish cohort study on patients with congenital hyperinsulinism shows that around 30 % of patients have an unknown genetic aetiology (12). In cases of unexplained severe hypoglycaemia with or without syndromic features, a genomic copy number analysis is recommended.

Table 1

Overview of the main genes that can cause congenital hyperinsulinism when mutated (4, 6).

Affected process in the beta cells	Gene	Protein	Mechanism of action
Transport of ions across the plasma membrane (channelopathies)	*ABCC8*	Sulfonylurea receptor-1 (SUR1)	SUR1 and Kir6.2 are subunits of the beta cells' ATP-dependent potassium channel. Inactivating mutations cause the channel to close, leading to depolarisation of the plasma membrane and influx of calcium into the cell. As a result, insulin is released when the energy level in the cells is low.
	KCNJ11	Inward-rectifier potassium channel 6.2 (Kir6.2)	
Enzymatic reaction in cell metabolism (metabolopathies)	*GLUD1*	Glutamate dehydrogenase (GDH)	GDH catalyses the conversion of glutamate to alpha-ketoglutarate, which can be used for energy production in the tricarboxylic acid cycle. Mutations cause overactive GDH. The energy level in the beta cells becomes too high, even at low glucose levels, and excess insulin is released.
	HADH	Short chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD)	The SCHAD protein inhibits the activity of GDH. Mutations disrupt SCHAD, indirectly causing overactive GDH.
	GCK	Glucokinase (GK)	GK phosphorylates glucose after its enter into the beta cells and subsequently activates energy production. Mutations lead to overactive GK. Consequently, the energy level in the beta cells becomes too high, resulting in the excessive release of insulin.
	HK1	Hexokinase 1 (HK1)	HK1 phosphorylates glucose after entering into the beta cells. The protein functions at low glucose levels and should be silenced in the beta cells. Mutations cause HK1 to remain expressed in beta cells, leading to insulin secretion at low glucose levels.

Affected process in the beta cells	Gene	Protein	Mechanism of action
Maturation and differentiation of the cells (transcriptionopathies)	*HNF1A*	Hepatocyte nuclear factor-1α (HNF-1α)	HNF-1α and HNF-4α are transcription factors that are crucial for giving beta cells their identity and, consequently, the right properties. Mutations cause alterations in HNF-1α/HNF-4α, indirectly disrupting the insulin secretion of beta cells.
	HNF4A	Hepatocyte nuclear factor-4α (HNF-4α)	

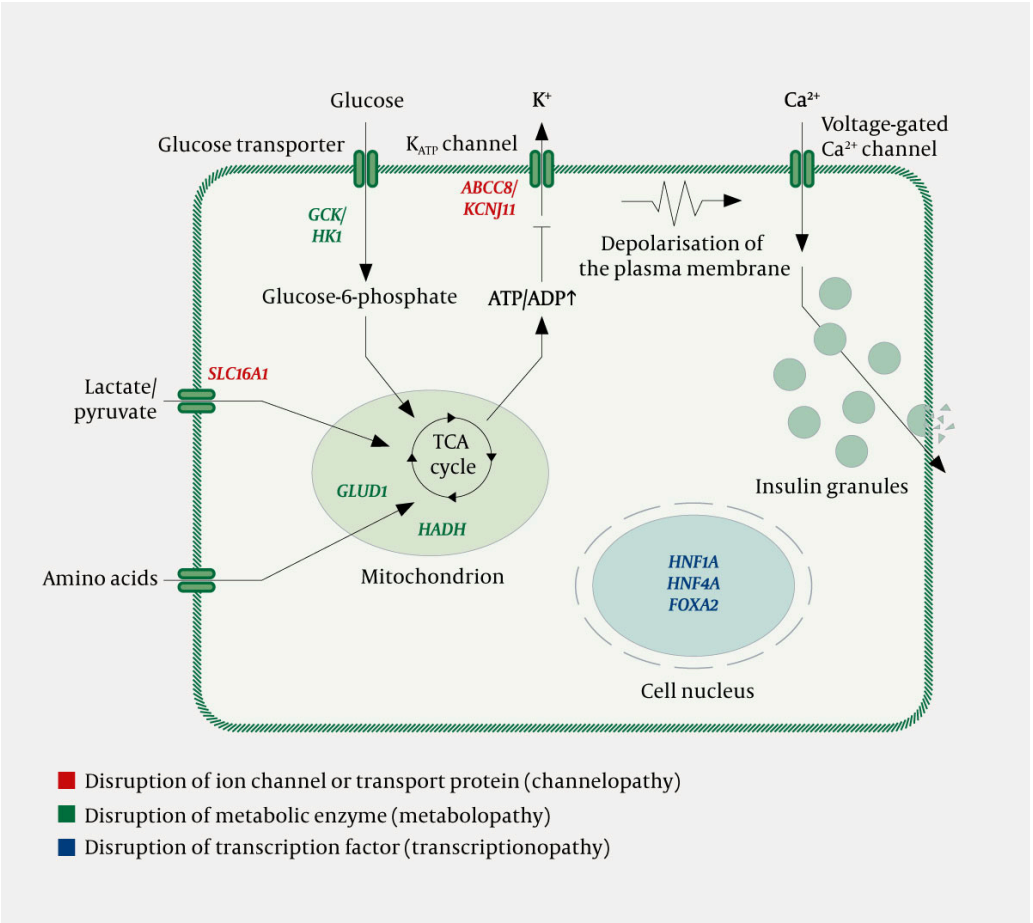

Figure 1 Beta cell. The figure illustrates glucose- and amino acid-induced insulin secretion and the most common disease-causing genes of congenital hyperinsulinism (6). The beta cell absorbs glucose and amino acids, which enter the TCA cycle. This increases the ATP/ADP ratio in the cytoplasm, which in turn closes the KATP channel and depolarises the plasma membrane. As a result, calcium flows into the cell, insulin granules fuse with the plasma membrane, and insulin is released into the bloodstream.

Histologically, all pancreatic beta cells (diffuse form) or a defined area with beta cells (focal form) can be affected, depending on the genotype (Figure 2 (13)) (14). ^{18}F-DOPA positron emission tomography (PET) can differentiate between diffuse and focal involvement of the beta cells (15). The PET result will determine the choice of treatment (4).

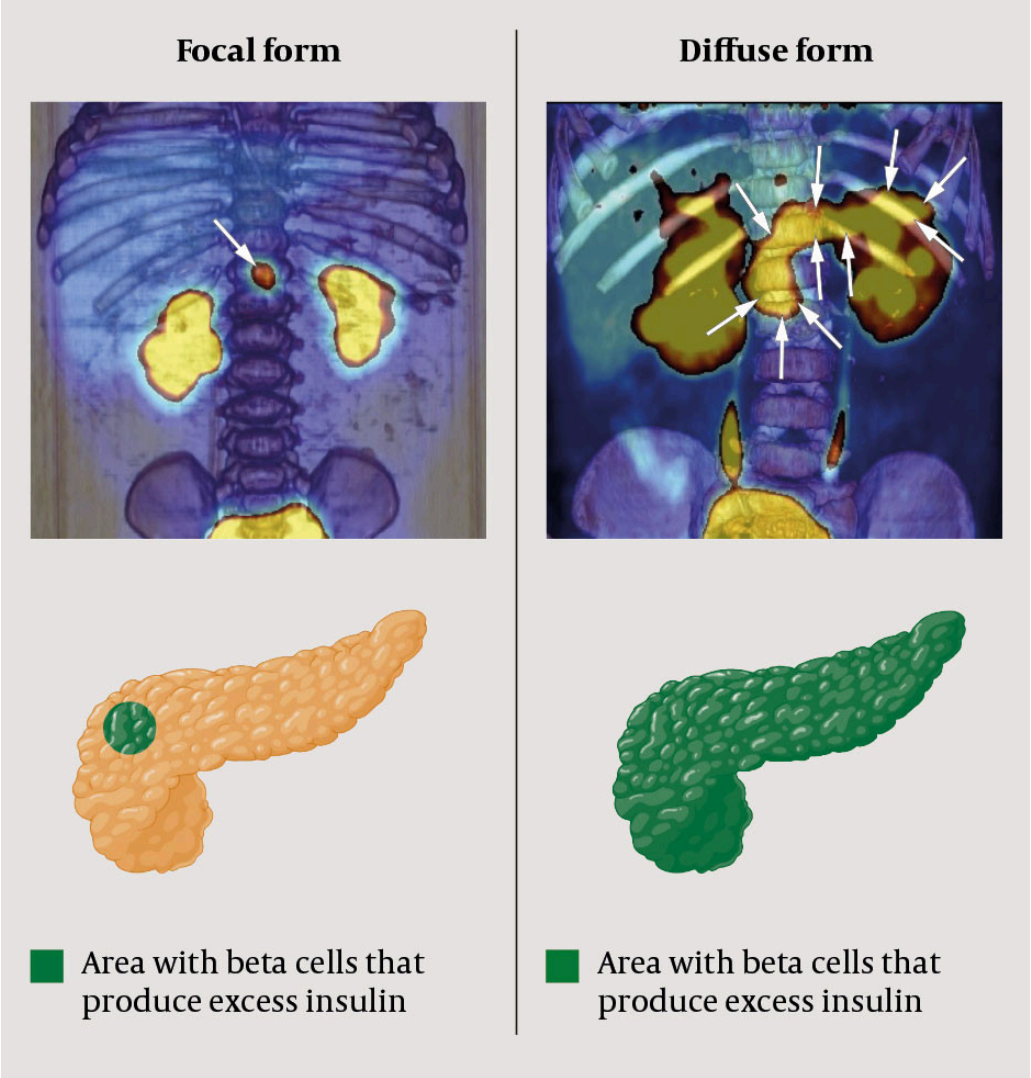

Figure 2 18F-DOPA-PET scan of diffuse and focal form of congenital hyperinsulinism. In the focal form (left), only parts of the pancreas are affected, and this can be cured by surgical resection of the focal lesion. The focal form is caused by a paternally inherited, recessive ABCC8 or KCNJ11 mutation in combination with a somatic loss of a chromosomal region on the maternal allele in a limited area of the pancreas. If the entire pancreas produces an excess of insulin, the diffuse form is present (right). The two upper panels are reproduced from Haldorsen et al. (13) with the permission of Springer Nature (copyright: Pål Rasmus Njølstad).

Treatment

The severity of congenital hyperinsulinism varies considerably. The overall goal of treatment is to prevent severe hypoglycaemia, achieve near-normal blood glucose levels and prevent obesity and eating disorders. For children at risk, the objective of treatment is to maintain blood glucose levels at ≥ 2.6 mmol/L for neonates less than 48 hours of age, and ≥ 3.0 mmol/L for those more than 48 hours of age (2).

Acute treatment

The goal of acute treatment is to stabilise acute onset of hypoglycaemia. This is carried out in the patient's home following parental training, or in hospital by administering carbohydrates in the form of, for example, milk, glucose gel, tablets or carbohydrate-enriched food. If the child is unable to ingest the necessary amount, the carbohydrates

must be administered through a gastrostomy tube or in hospital intravenously. High doses of glucose may be required to stabilise to normoglycaemia (up to 25 mg/kg/min of continuous intravenous glucose infusion) (16). Administering glucose in repetitive boluses is advised against as this can trigger insulin secretion and exacerbate the situation (16).

In cases where carbohydrate supplements are insufficient to stabilise blood glucose, glucagon can be administered. This activates gluconeogenesis, glycogenolysis and lipolysis, leading to an immediate elevation of blood glucose. In hospital, glucagon can be given as an infusion (5–20 µg/kg/h) concurrently with glucose in lower doses (2). The patient's family can be given a prescription for subcutaneous/intramuscular glucagon injections (0.5–1 mg) for use when hypoglycaemia occurs outside the hospital setting. In the event of a poor response, the family should seek immediate help. Doses in excess of 1 mg must be avoided, as this paradoxically may increase insulin levels (4). Glucagon in the form of a nasal spray is an alternative for children over two years of age.

Episodes of hypoglycaemia must also be prophylactically prevented. There are three forms of treatment: diet, pharmacotherapy and surgery (see Figure 3 at tidsskriftet.no) (6). Diet is generally preferred over pharmacotherapy, and pharmacotherapy is preferred over surgery. The exception is the focal form, where the goal of surgery is curative (Figure 2) (17).

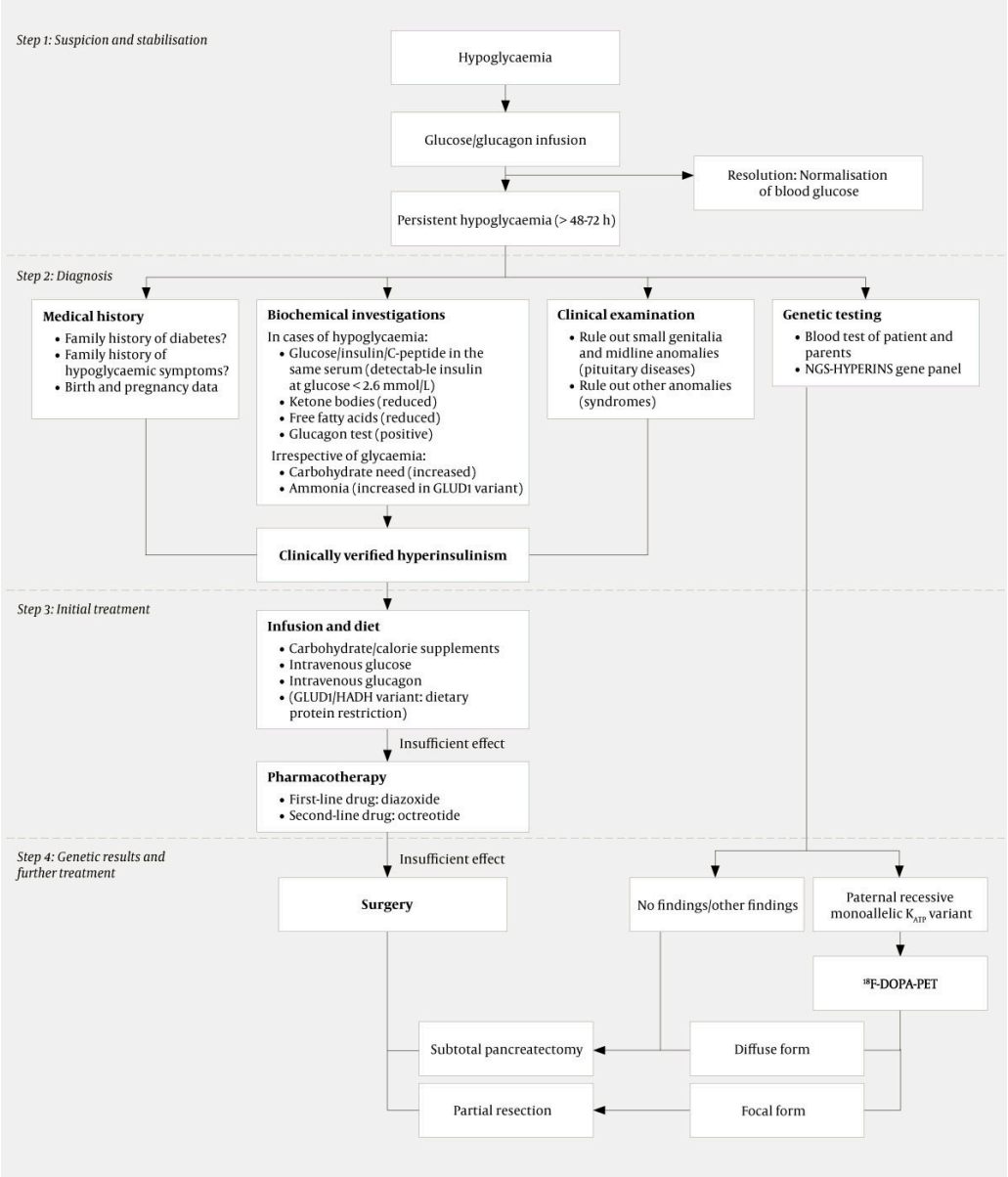

Figure 3 Diagnostic and treatment algorithm for patients with congenital hyperinsulinism from the National Treatment Service of Diagnostics and Treatment of Congenital Hyperinsulinism.

Diet

Nutrition is central to the treatment of congenital hyperinsulinism. The goal is to find a balance where the patient has normal weight development. For patients with a mild phenotype, frequent carbohydrate-rich meals (every 2 - 3 hours), possibly with the addition of slow-release carbohydrates, may be sufficient. Gastrostomy is indicated for children who require a large supply of carbohydrates and who become satiated and nauseated from the required amount of oral nutrition (3, 16). Gastrostomy is also useful in cases of acute-onset hypoglycaemia. If genetic testing reveals a mutation in the *GLUD1* or *HADH* genes, it may be necessary to introduce a dietary protein restriction, as these patients are particularly sensitive to protein-triggered insulin secretion (4).

Pharmacotherapy

The first-line drug for the treatment of congenital hyperinsulinism is diazoxide, a K_{ATP} channel agonist. The K_{ATP} channel is encoded by the genes *ABCC8* and *KCNJ11* and closes with increased energy levels in the beta cell. This results in depolarisation of the cell's plasma membrane, ultimately leading to insulin secretion. However, diazoxide

efficacy is poor in patients with mutations in the genes encoding the K_{ATP} channel, which applies to 30–50 % of patients (4, 12, 18). Initially, 5–10 mg/kg/day is administered in three oral doses. The dose can be increased to a maximum of 15–20 mg/kg/day. The medication can cause fluid retention and must be taken with a diuretic (hydrochlorothiazide).

With long-term treatment, the antidiuretic effect of diazoxide decreases, and diuretics can be gradually discontinued. Other adverse effects include hypertrichosis, poor appetite, bone marrow suppression and, in rare cases, pulmonary hypertension or heart failure (4, 16). Echocardiography is therefore recommended before initiating diazoxide. However, normal findings do not rule out the onset of potentially adverse side effects.

Octreotide is a short-acting somatostatin analogue that is used in patients where diet and diazoxide are not sufficient to control hypoglycaemia (19). Octreotide is administered subcutaneously with an initial dose of 15 µg/kg/day divided into three doses. The dose can be increased to a maximum of 30 µg/kg/day (16). Tachyphylaxis, growth restriction, necrotising enterocolitis and gallstones are rare, but reported adverse side effects (20). After the age of two, it is common to switch to a long-acting somatostatin analogue (lanreotide), which can be administered subcutaneously every six weeks.

Sirolimus and exendin-(9–39) are emerging drugs with potential for future use. Sirolimus inhibits the mTOR pathway, which is crucial for beta cell growth, thereby reducing insulin secretion (21). However, there are some concerns about prolonged exposure (22). Exendin-(9–39) is a GLP-1 receptor antagonist (23).

Surgery

On indication of a focal form in a PET scan, the patient is assessed for surgical resection of the affected lesion (partial resection). Partial resection of patients with a focal form is curative. Subtotal pancreatectomy can be performed on patients with a diffuse form and involves removing 95–98 % of the pancreas (6). Unfortunately, all patients undergoing such surgery develop diabetes at some point, and many also experience exocrine pancreatic insufficiency (4, 24). Consequently, subtotal pancreatectomy is rarely performed.

Follow-up

The initial assessment and initiation of treatment usually take place in the nearest hospital's neonatal ward. The emergency services or an accident and emergency department (A&E) should be contacted for infants exhibiting severe symptoms of hypoglycaemia after discharge from the maternity ward. They are then referred to or admitted to the nearest paediatric ward. When hyperinsulinism is confirmed, patients should be referred to an expert treatment centre for treatment optimisation, potentially including a PET scan or further aetiological investigation. An 'open return' is recommended for newly diagnosed patients, and parents should be advised to contact the hospital or A&E in the event of hypoglycaemia that does not resolve after carbohydrate supplementation and a glucagon injection.

Children with congenital hyperinsulinism should receive regular check-ups by an expert. Over time, many patients will improve and cease to need medication, while some will eventually develop diabetes (25). During follow-up, the effect of treatment on blood glucose is checked in relation to fluctuations and frequency of hypoglycaemic episodes. Any adverse effects are monitored and treated. Primary healthcare providers must pay special attention to complications in these children when they have infections. Gastroenteritis can induce severe hypoglycaemia, often necessitating hospitalisation, especially the first few times it occurs. Other intercurrent infections and physical stress can lead to elevated blood glucose levels. It is therefore important that parents and the local treatment team are trained in blood glucose control.

Summary

Congenital hyperinsulinism is a rare and severe monogenic disease that often manifests shortly after birth. Early contact with an expert treatment centre is recommended to discuss diagnostics and treatment.

The article has been peer-reviewed.

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