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Editorial

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Congenital Hyperinsulinism: A Therapeutical Dilemma

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Abstract

Congenital hyperinsulinism in newborns has a prevalence of 1:28000-50000. Syndromic and non-syndromic, as well as nonketotic and ketotic cases were described. Depending on the degree of extension, histologically focal, diffuse and atypical forms are found. The primary diagnostic criterion is detectable insulin and hypoglycemia in the blood. Early onset and late onset forms do exist. A high variability and complexity in patient phenotype and a significant burden of care in families is present in these children. Cure means a mutation repair of the genetic origin. The chromosomal region 11p15 plays a key role in the disease, especially the K+ ATP channel on region 11p15.1 is of upmost importance. The genetic origin is multifactorial with mutations in about 10 different genes, aggravating the chance to find a curative method for these children.

Keywords: Congenital hyperinsulinism; Newborn; Insulin; Child; Treatment

Letter to the Editor

Hyperinsulinism refers to a condition characterized by excessively high levels of insulin in the blood, typically defined by fasting insulin levels above 17 mU/l with a hypoglycemic state more than 48-72 hours in a full-term baby [1,2,4]. This overproduction of insulin can have various causes and often leads to hypoglycemia, an abnormally low blood sugar level, posing significant health risks [3]. Hyperinsulinism can be caused by increased insulin secretion from the pancreas or by a disruption in insulin breakdown [1-18]. The former may be due to peripheral insulin resistance. Tumors like insulinomas can also lead to insulin overproduction. Insulin is produced in the beta cells of the islets of Langerhans in the pancreas and released into the blood. Its main function is to regulate glucose metabolism: insulin promotes the uptake of glucose into cells, thereby lowering blood sugar levels and supporting the storage of glucose as glycogen in the liver. Excessive insulin secretion, as seen in hyperinsulinism, results in a disproportionate decrease in blood sugar levels, leading to hypoglycemia and associated symptoms and complications [1, 5, 9,11,12]. Characteristic laboratory findings include fasting insulin with levels > 17 mU/l are characteristic of hyperinsulinism. Blood sugar levels show often hypoglycemic values (< 70 mg/dl) due to excessive insulin activity. C-peptide elevated levels parallel to insulin were found, indicating endogenous insulin overproduction. Glucose tolerance test shows significant and sustained decrease in blood sugar levels after glucose administration, often accompanied by a disproportionately strong insulin response. Blood ketone levels show decreased levels due to high insulin levels inhibiting lipolysis and ketone body production. Mutations were described in main 10 genes: ABCC8, KCNJ11, GLUD 1, HADH (short chain 3 hydroxyacyl-COA-dehydrogenase), Glukokinase, Hexokinase1, Hepatocyte nuclear factor

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1 Alpha und 4 Alpha (1-18). Moreover MCT 1 (mutations on SLC 16 A1 on chromosome 1) and UCP-2 (dominant loss of function mutation in UCP 2 on chromosome 11q13.4) were found. Congenital insulinism is associated with different syndromes like Wiedemann-Beckwith syndrome, Sotos syndrome, Pearlman and Weaver syndrome (overgrowth syndromes). Moreover CHI was described in Kabuki-, Turner- and Castello syndrome (chromosomal developing syndromes). Diagnostics include following parameters like bedside serum glucose, insulin, c-peptid, reduced levels of ketone bodies, reduced levels of free fatty acids, lactate, liver function tests, acylcarnitine, ammonia, venous blood gas, growth hormone, organic acids and amino acids. Diagnosis is made by molecular analysis.

Therapy is primarily started with diaxozide, a K+ ATP channel agonist. Unresponsive and responsive cases to diaxozide treatment do exist. Unresponsive cases are related to ABCC8, KCNJ11 and GCK gene mutations. Unresponsive cases are related to ABCC8, KCNJ11 and GCK gene mutations. Long treatment is negative influenced by bone marrow suppression, hypertrichosis, hair loss and pulmonary hypertension. Diazoxide is a benzothiadiazine derivative that does not have diuretic effects. It is lipophilic and at physiological pH, only about 10% exists as an anion. It is an orally effective selective potassium channel opener used as a therapeutic agent for hypoglycemia. It causes a rapid and temporary dose-dependent increase in blood sugar levels by inhibiting insulin secretion from the pancreatic islets of Langerhans, generally lasting less than eight hours. Diazoxide is a sulfonylurea receptor 1 (SUR1) agonist. SUR1 and Kir6.2, for example, form the functional ATP-dependent potassium channel K(ATP) in the pancreas. Activation of this channel leads to potassium efflux, which stabilizes the membrane potential. In the pancreas, this inhibits or reduces insulin secretion. Diazoxide binds to SUR1, which acts as a regulatory subunit and likely alters the spatial structure of the receptor, keeping the channel pore, composed of Kir6.2 subunits, open for longer. As more potassium leaves the cell, the resting membrane potential becomes more negative, reducing the likelihood of insulin secretion.

The drug diazoxide is orally administered for hypoglycemia of various origins, such as congenital leucine hypersensitivity, some congenital defects of the KATP channel, nesidioblastosis, pancreatic and extrapancreatic insulin-producing tumors, refractory malignant hypertension in renal insufficiency, and glycogen storage disease. Treatment with diazoxide is contraindicated in cases of hypersensitivity to the active ingredient, allergy to benzothiadiazines, coronary heart disease and heart failure, diabetes mellitus, pheochromocytoma, azo dye and analgesic intolerance. Embryotoxicity was found in animal studies. The drug should not be used during pregnancy unless absolutely necessary. Since it is unknown if diazoxide passes into breast milk and poses a risk of potentially severe side effects for the infant, women who need treatment during breastfeeding should stop breastfeeding. The main adverse effects of diazoxide are sodium and water retention, hyperuricemia, hypertrichosis especially in children, leukopenia and thrombocytopenia, headaches, dizziness. Extrapyramidal symptoms may occur with long-term treatment. Orally administered diazoxide has only a minor effect on blood pressure.

As a second line treatment, octreotide is a synthetic analog of the peptide hormone somatostatin, used as a medication. Octreotide consists of eight amino acids (D-Phe-cyclo[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr(ol)). In Germany, Octreotide is approved for the treatment of acromegaly and certain gastrointestinal tumors (GEP-NET, carcinoids). When coupled to DOTA with 111-Indium or 68-Gallium (Edotreotide, DOTATOC), it is used in somatostatin receptor scintigraphy or positron emission tomography for the detection of these tumors. For therapeutic purposes as a radionuclide, beta emitter such as 90-Yttrium or 177-Lutetium can be used. Octreotide can be used for the treatment of cluster headache attacks and secretory diarrhea in children when other medications are ineffective or contraindicated. In newborns, it will be used as second line treatment for congenital hyperinsulinism. A cAMP-mediated reduction in insulin secretion in the pancreatic beta cell is found, Octreotide is applicated newborns for CHI subcutaneously 15-30 micro /kg/day in three doses. Tachyphylaxis, growth restriction, NEC and gallstones are well known side effects in newborns and older children treated with octreotide.

Recent studies analyzed Dasiglucagon in Diazoxide-unresponsive, nonfocal congenital hyperinsulinism [12,18].

Sirolimus (SRL), also known as Rapamycin, is an immunosuppressant and mTOR inhibitor with a macrolide structure (macrocyclic lactone), which is used to treat congenital hyperinsulinism [19-23]. It is a product of the Streptomyces hygroscopicus bacterium, which was first isolated from the soil of Rapa Nui. Sirolimus and Tacrolimus are related substances that were isolated from different Streptomyces species and have different mechanisms of action. Therapeutically, Sirolimus is used after kidney transplants, usually in combination with Cyclosporine and corticosteroids, to prevent organ rejection. One of the important side effects is impaired wound healing. Unlike Cyclosporine or Tacrolimus, Sirolimus is not nephrotoxic, so it does not contribute to chronic transplant nephropathy. In cardiology, the anti-proliferative effects of Sirolimus are utilized to prevent restenosis (narrowing) caused by intimal hyperplasia after stent implantation in coronary arteries. Stents coated with Sirolimus have shown fewer instances of restenosis compared to conventional metal stents in several studies. However, there is a risk of stent thrombosis due to Sirolimus inhibiting neointima formation, which can lead to platelet accumulation and stent closure over time. Due to its

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anti-proliferative effects on cells, Rapamycin has also been explored in anticancer therapy as it may inhibit the growth and neovascularization of certain tumors. In 2015, the FDA approved Sirolimus for the treatment of the rare lung disease lymphangioleiomyomatosis. Sirolimus is also approved in the EU for the treatment of facial angiofibromas associated with tuberous sclerosis in adults and pediatric patients aged 6 years and older. Furthermore, Sirolimus has shown remarkable efficacy in autoimmune lymphoproliferative syndrome (ALPS) by specifically inhibiting the hyperactive mTOR signaling pathway in CD4-CD8 double-negative T cells (DNT). In biotechnology, Sirolimus is used in chemically induced dimerization of certain fusion proteins. In a 2009 study, the lifespan of mice was extended by 28-38% from the start of treatment, corresponding to a 9-14% increase in maximum lifespan. The treated mice were already 20 months old, equivalent to about 60 human years. The results cannot be directly extrapolated to humans. A 2016 publication reported a 60% extension of lifespan in mice. Sirolimus has a different mechanism of action than Ciclosporin and Tacrolimus, which both inhibit calcineurin. The immunosuppressive effect of Sirolimus occurs by forming a complex with an intracellular cytosolic protein (FKBP12) that binds to a 282 kDa serine/threonine protein kinase called mTOR, inhibiting its activity. This inhibition can suppress various cytokine-mediated signaling pathways that originate from mTOR as part of the protein complexes mTORC1 and mTORC2. As a result, the transcription and translation of various genes, especially those promoting proliferation of T lymphocytes, are prevented. Activation of T cells and progression from the G1 phase to the S phase of the T cell cycle are inhibited. In CHI patients, a reducing insulin secretion was found.

Exendin [9-39] amide, Avexitide, is a glucagon-like peptide-1 (GLP-1) antagonist that competes with endogenous GLP-1 for binding to GLP-1 receptors, thereby antagonizing the effects of excess GLP-1 secretion [24-29]. Exendin [9-39] amide can be used to study postoperative hypoglycemia (PBH). First studies show possible ameliorating effects in congenital hyperinsulinemia [24-29]. Last but not least surgical interventions play an important role, when drug treatment options do not lead to success. Focal forms of CHI were treated surgically by focal lesionectomy or laparoscopic intervention, diffuse forms with subtotal pancreatectomy [30-33]. Diffuse forms are most often autosomal dominant or recessive, compound heterozygous or homozygous. Most often mutations in ABCC8/KCNJ11 were found in diffuse types of CHI. Surgical treatment shows up to 50 per cent relapses with further hypoglycemic states and exocrine pancreas insufficiency, therefore pancreas enzyme supplementation several times a day is necessary [30,32].

In conclusion, the treatment of congenital hyperinsulinism in newborns and childhood is a therapeutical dilemma. Recent research focus on insulin receptor antibodies and chaperones [34,35]. Due to many underlying genetic mutation defects, gene therapy options are in childhood shoes. Further research and drug options have to be evaluated in detail to evaluate new options to treat these pediatric population with an extremely rare disease in childhood.

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