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Causes of hypoglycemia

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ABSTRACT:

Introduction: Hypoglycemia is metabolic state of ogranism characterized by abnormally low blood glucose level. Due to International Hypoglycemia Study Group (2017) and following Polish Diabetes Association Guidelines is recognized with serum glucose below 70mg/dl – with or without accompanying symptoms, such as tremor or altered mental status or even hypoglycemic coma. Symptoms mentioned above may have huge impact on personal or social functioning of the patient.

Purpose: To present a list of known causes of hypoglycemic state.

Summary: Hypoglycemia is quite unpleasant and dangerous metabolic state that may be caused by multiple etiological factors. The most common cause of this condition is useing too much insulin in treatment of diabetes mellitus. Other diabetic drugs, such us for example sulphonylureas may result in hypoglycemia. Chemicals containing sulfhydryl group in their structure may result in severe hypoglycemia in progress of Insulin Autoimmune Syndrome (IAS).

Organic basis of hypoglycemia due to increased amount of producing insulin may be recognized, in progress of pancreatic secreting tumor, called insulinoma. From the other hand functional abnormality of carbohydrate metabolism may be found. It's called functional hypoglycemia and may develop due to presence of hyperinsulism and insulin resistance secondary to incorrect lifestyle and diet. Partly organic and functional cause of hypogycemia may be recognized after bariatric surgery.

Fairy seldom hypoglycemia with low blood insulin level may be found. The example of this state constitutes Dodge-Potter Syndrome, when tumor is able to produce insulin-growth factor 2 (IGF-2) stimulating insulin receptor, what results in serum glucose reduction.

Hypoglycemia, as very adverse state for human organism, should be closely diagnose and efficiently treated.

Keywords: hypoglycemia; drug-induced hypoglycemia; insulinoma; Non-Islet cell tumors hypoglycemia; Dodge-Potter Syndrome; post-bariatric hypoglycemia

Introduction

Hypoglycemia is metabolic state of ogranism characterized by abnormally low (due to Polish Diabetes Association Guidelines under 70mg/dl) serum glucose level. Standard it manifest itself with symptoms specific for adrenergic system activation such as anxiety, sweats, violent hunger or with neuroglycopenic syndromes, for example tremor, altered mental status or extremely with coma and death. It does not remain, that this state has a huge impact on everyday functioning of entity and developing complete risk of cardiovascular complications – especially in those with type 2 diabetes. Alexandra K. Lee and others were published quite interesting work, proving, that severe hypoglycemia in patients with type 2 diabetes was associated with coronary heart disease, cardiovascular mortalit, cancer mortality and all-cause mortality, but wasn't associated with stroke, heart failure, atrial fibrillation, or noncardiovascular and noncancer death[1]. Zougas S. and collaborators confirmed increased cardiovascular risk in patients, who experience hypoglycemia and demonstrated the relations of featured state with nonvascular outcomes, such as respiratory, digestive, and skin conditions[2].

State of knowledge

DRUGS-INDUCED HYPOGLYCEMIA

Considering the huge possible negative impact of hypoglycemia on human organism, proper prevention and treatment of the state seems to be crucial. As mentioned above, drug-induced hypoglycemia is the most common. In simple way patients treated with insulin, are most exposed to decrease of blood glucose level: administration of excessive dose of insulin relative to current blood glucose level and to consumed meal, or taking unplanned physical activity may result in hypoglycemia. Also other groups of medication, such as sulphonylureas may result in rapid fall of blood sugar level. Popularly used glimepiride or gliclazide, as receptor's SUR-1 agonists, stimulate secreting of insulin. Besides drugs used in diabetes treatment, there are some interesting reports about others chemicals resulting in hypoglycemia, for example tigecycline - glycylcycline-class antibiotic, with a broad-spectrum activity[3]. Sometimes the cause of it is evolution is unknown. Astounding is fact of developing Insulin Autoimmune Syndrome (IAS) due to usage of certain drugs. Decreased level of blood glucose, increased molar ratio of insulin to C-peptide, and elevated autoantibodies to insulin are noted. Well known is occurrence of this state when drugs containing a sulfhydryl group are used, for example carbimazole[4] or thiamazole. Interestingly, there have been appeared reports of developing IAS due to treatment with another groups of drugs, for example clopidogrel – antiplatelet agent, that does not have a sulfhydryl group, but its active metabolite does[5] or sertraline -a selective serotonin reuptake inhibitor.[6]

Murad and others in 2009 have presented systematical review of the literature for drugs reported to cause hypoglycemia, detailing quinolones, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme agents, and IGF as the most commonly affecting drugs[7]. Salem and others in 2011 were published also valuable summary of drugs, listing NSAIDs, analgesics, antibacterials, antimalarials, antiarrhythmics, antidepressants and other miscellaneous agents as potent indicators of decrease of blood glucose level. [8]

INSULINOMA

The diagnosis of insulinoma is established due to biochemical confirmation of hypoglycemia and concomitant endogenous hyperinsulinemia secondary to pancreatic betacells tumor. Interestingly approximately 1% of patients an extra-pancreatic location is possible[9]. To establish the diagnose, 72-hour fasting test should be performed and Noninsulinoma Pancreatogenous Hyperinsulinemia Syndrome (NIPHS) need to be excluded. Insulinoma is a very rare tumor, with an approximated incidence of 4 per 1 million person years.[10]

Insulinomas are mainly benign. They are usually single, whereas in about 10% of patients diagnosis of multiple malignancies will be established, sometimes in progress of multiple endocrine neoplasia

type 1 (MEN1). According to management guidelines recommended by the Polish Network of Neuroendocrine Tumours Prognosis, prognosis in benign tumours is very good – over 95% of such patients will be cured after surgical treatment. In patients with distant metastases, mean survival time unfortunately is less than two years[9].

NONINSULINOMA PANCREATOGENOUS HYPOGLYCEMIA SYNDROME (NIPHS)

As we mentioned above, during the diagnostic procedure on insulinoma, noninsulinoma pancreatogenous hypoglycemia syndrome should be excluded. It's the state, that has been sometimes called „nesidioblastosis". It affects mainly children, but some extremely rare cases has been reported also in adults. The pathogenesis of described state is correlated with pancreatic beta-cell dysregulation and producing too high amount of insulin with no presence of insulinoma[11 12].

POST-BARIATRIC HYPOGLYCEMIA

Hypoglycemia, often diagnosed because of its neuroglucopenic symptoms may develop due to Roux-en-Y gastric bypass (RYGB) surgery, after sleeve gastrectomy and fundoplication by-pass surgery. The pathogenesis of above aphenomenom is complicated and not fully understood. Repeating for Salehi and others, secretion of insulin after meal is tightly regulated by meal-induced gut factors – incretins.

RYGB-mediated bypass of the pylorus and proximal intestine results in earlier and greater peak of level of blood glucose, furthermore strengthened secretion of insulin and GLP-1 after bariatric surgery, what in simple way may result in hypoglycemia[13].

NON-ISLET CELL TUMORS HYPOGLYCEMIA (NICTH)

Non-islet cell tumor hypoglycemia (NICTH) is very uncommon paraneoplastic syndrome, in which a tumor produces and secretes big-IGF-II. High molecular weight IGF-II is able to cause hypoglycemia due to stimulation of insulin receptors. NICTH, also known as Doege-Potter syndrome (DPS) is secondary to solitary fibrous tumor which may be intrapleural or extrapleural in origin[14]. The best way of treatment of this kind of hypoinsulin hypoglycemia is excision or decreasing the mass of secreting tumor. Another ways of treatment consist glucose or dextrose infusion, whereas it's often insufficient to resolve the problem of low blood glucose level. In some cases, glucocorticoids are used in treatment, alone or in combination with growth hormone. Experienced clinicians may also consider continuous glucagon infusion or even parenteral nutrition. Citing Bodnar and others, diazoxide and octreotide seem to have no role in NICTH treatment[15].

It’s worth to mention, that special hormonal deficiencies may result in decreased level of serum glucose. Perfect instance of this constitute in adrenal insufficiency due to the lack or decreased level of endogenous glucorticosteroids. Hypoglycemia may also developed due to weakened gluconeogenesis, liver glucagon diminution and intensified glucose utilization in progress of sepsis.

Concludes, hypoglycemia is quite common and dangerous metabolic state, that may results in serious complications. Authors of this article has had an intention of revealing variety of possible causes of decreased serum glucose level. We hope that this short review turn out motivating for further exploration of above topic.

Table 1. Special causes of hypoglycemia

SPECIAL CAUSES OF HYPOGLYCEMIA
drugs-induced hypoglycemia: 1. hypoglycemic drugs: insulin, sulphonylureas; 2. due to Insulin Autoimmune Syndrome (AIS): quinolones, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme agents, IGF[7]
Insulinoma
Noininsulinoma Panctreatogenous Hypoglycemia Syndrome (NIPHS)
Post-bariatric hypoglycemia
Non-Islet cell tumors hypoglycemia (NICTH), Doege-Potter Syndrome
Adrenal insufficiency
Sepsis

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