REVIEW

Hypoglycemia as a paraneoplastic syndrome - current state of knowledge

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Abstract

Objective: To provide a comprehensive overview of current knowledge on paraneoplastic hypoglycemia, with particular focus on non-islet cell tumor hypoglycemia, including its epidemiology, pathophysiology, tumor associations, clinical presentation, diagnostic approach and management.

Methods: A narrative literature review based on a structured literature search was conducted using literature retrieved from PubMed, Google Scholar and SpringerLink. Publications from 2020-2026 were screened using keywords related to non-islet cell tumor hypoglycemia and paraneoplastic hypoglycemia.

Results: Non-islet cell tumor hypoglycemia most commonly arises from mesenchymal tumors, particularly solitary fibrous tumors, but has also been reported in a broad spectrum of other tumor types. Hypoglycemia results from tumor overproduction of insulin-like growth factor two, especially its high-molecular-weight form, which mimics insulin activity. Patients typically present with fasting hypoglycemia, adrenergic and neuroglycopenic symptoms. Diagnosis is supported by a markedly elevated insulin-like growth factor two to insulin-like growth factor one ratio. Surgical tumor resection is the primary treatment; in unresectable cases, glucocorticoids, recombinant growth hormone, radiotherapy, or other emerging therapies may be used.

Conclusions: Early recognition and understanding of the diverse tumors causing non-islet cell tumor hypoglycemia are crucial to prevent hypoglycemia-related complications and support effective management.

Keywords: non-islet cell tumor hypoglycemia, insulin-like growth factor 2, solitary fibrous tumor, fasting hypoglycemia, paraneoplastic hypoglycemia

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Introduction

Hypoglycemia is defined as a plasma glucose concentration below 70 mg/dL; however, clinical symptoms often do not appear until glucose levels fall below 55 mg/dL. Clinical manifestations may include adrenergic symptoms (e.g., hunger, diaphoresis, tremor, elevated heart rate), neuroglycopenic symptoms (e.g., mental confusion, dizziness, seizures, coma) or both simultaneously. Etiologically, hypoglycemia is divided into insulin-dependent mechanisms (such as inappropriate use of insulin or insulinoma) and insulin-independent mechanisms, which include systemic infection, hormonal insufficiency, liver failure and paraneoplastic hypoglycemia, also termed non-islet cell tumor hypoglycemia (NICTH), a condition induced by tumors other than insulinoma [1].

NICTH is a rare but clinically significant paraneoplastic syndrome associated with a variety of tumor types. In most cases, it results from tumor overproduction of insulin-like growth factor 2 (IGF-2), which mimics the action of insulin and leads to fasting hypoglycemia [2].

Due to its uncommon occurrence, atypical presentation and non-specific laboratory findings, NICTH can be difficult to identify and may result in life-threatening complications if not treated promptly. This highlights the importance of early recognition and timely intervention [1,3].

The aim of this narrative literature review is to summarize the current knowledge on paraneoplastic hypoglycemia, with particular emphasis on NICTH, encompassing its epidemiology, pathophysiology, tumor associations, clinical presentation, diagnostic evaluation and management strategies.

Methods

A narrative literature review based on a structured literature search was conducted to summarize current knowledge on paraneoplastic hypoglycemia, with particular focus on non-islet cell tumor hypoglycemia. Relevant literature was identified using the PubMed, Google Scholar and SpringerLink databases. The search covered publications from 2020 to 2026 and included the following keywords: “non-islet cell tumor hypoglycemia,” “NICTH,”

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"paraneoplastic hypoglycemia," "insulin-like growth factor 2," "IGF-2," "solitary fibrous tumor," and "tumor-induced hypoglycemia." English-language papers with full-text availability were considered eligible, including systematic reviews, review articles, case series and case reports. Studies unrelated to paraneoplastic hypoglycemia, duplicate records and papers without full-text access were excluded. After screening titles, abstracts and full texts for relevance, 29 studies were included in the final analysis. The selected literature was analyzed to summarize current evidence regarding the pathophysiology, tumor associations, clinical presentation, diagnostic evaluation and management strategies of NICTH. This approach provided a comprehensive overview of its clinical and pathophysiological aspects.

Current state of knowledge

Definition and epidemiology

Tumoral hypoglycemia may arise from both non-islet cell tumors and islet cell tumors, such as insulinomas. NICTH represents an uncommon paraneoplastic syndrome most commonly driven by tumor-derived IGF-2. For this reason, NICTH has also been described in the literature as IGF-2-oma [4].

Clinically, NICTH has an estimated incidence of approximately one case per million person-years, making it considerably rarer than insulinoma. Its true prevalence remains difficult to determine, partly due to underdiagnosis and limited availability of IGF-1, IGF-2 and pro-IGF-2 testing. NICTH was first described in association with hepatocellular carcinoma in 1929, and since then, a broad spectrum of neoplasms has been implicated [3].

Several tumor types of epithelial, vascular and mesenchymal origin have been associated with NICTH [1]. In a systematic review of 233 reported cases of IGF-2-mediated hypoglycemia, fibrous tumors were the most frequently identified underlying neoplasms, accounting for 53.2% of cases. Less commonly observed were non-fibrous neoplasms, such as liver tumors (9%), hemangiopericytomas (8.5%) and mesotheliomas (4.7%) [3]. Additional case reports have also described NICTH in association with sarcoma [5], pancreatic ductal adenocarcinoma [6], ovarian malignancies including high-grade serous ovarian carcinoma [7], and ovarian carcinosarcoma [8]. Metastatic tumors associated with NICTH include urothelial carcinoma [9], metastatic rectal adenocarcinoma [10], and metastatic salivary myoepithelial carcinoma [11]. Although NICTH is most commonly associated with mesenchymal tumors, reports involving other tumor types suggest that the diagnosis should also be considered in less typical clinical scenarios.

Pathophysiology

The primary mechanism of hypoglycemia in NICTH involves upregulated IGF-2 gene expression in the tumor, leading to the production of incomplete IGF-2 precursors characterized by insulin-like activity. These include pro-insulin-like growth factor 2 (pro-IGF-2) or its incompletely processed, high molecular weight precursor, known as "big" IGF-2 [12]. Although total circulating IGF-2 levels may remain within the normal range, tumor-related overexpression results in disproportionate accumulation of "big" IGF-2. Under normal physiological conditions, pro-IGF-2 is efficiently processed into mature IGF-2. In NICTH, however, abnormal glycosylation and proteolysis impair this maturation process, leading to elevated circulating levels of "big" IGF-2. These high-molecular-weight precursors form unstable complexes with insulin-like growth factor binding proteins (IGFBP), which unbind more readily than normal IGF-2 complexes. As a result, the increased fraction of free, bioavailable "big" IGF-2 can cross the capillary endothelium more efficiently and interact with both IGF and insulin receptors, exerting insulin-like effects [13].

Other mechanisms involved in NICTH comprise tumoral secretion of IGF-1, cytokines (such as TNF-alpha, interleukin 1 and interleukin 6), catecholamines, GLP-1, antibodies to insulin or insulin receptor and ectopic insulin production. In NICTH, hypoglycemia is associated with enhanced glucose uptake in peripheral tissues, particularly skeletal muscle, suppression of hepatic gluconeogenesis and glycogenolysis, inhibition of lipolysis in adipose tissue (resulting in reduced levels of free fatty acids and beta-hydroxybutyrate), and decreased secretion of glucagon and growth hormone. Collectively, these metabolic effects result in fasting hypoglycemia and associated clinical manifestations [1,12]. Additionally, IGF-2 has been reported to play a wider role in solid tumors by participating in autocrine signaling loops that can promote tumor progression [14].

Clinical presentation and diagnosis

Paraneoplastic hypoglycemia typically presents as fasting hypoglycemia with a spectrum of clinical manifestations, encompassing adrenergic symptoms, such as nausea, anxiety, tremor, palpitations, tachycardia, diaphoresis and hunger, as well as neuroglycopenic signs, including confusion, dizziness, memory impairment, mental disturbances, seizures, coma [1,15]. or episodes of falling [16]. The heterogeneous clinical presentation highlights the importance of careful biochemical evaluation to avoid misdiagnosis.

Biochemical evaluation plays a crucial role in distinguishing paraneoplastic hypoglycemia from other causes, such as insulinoma. The diagnosis is established by demonstrating an increased IGF-2/IGF-1 ratio, with IGF-1 levels typically suppressed and IGF-2 levels being increased or within the normal range. A molar IGF-2/IGF-1 ratio greater than 10 strongly supports the diagnosis of NICTH, while hypo-insulinemic hypoglycemia accompanied by low IGF-1 provides additional biochemical evidence for the condition. Laboratory findings can also reveal low levels of C-peptide, insulin, proinsulin, and beta-hydroxybu-

tyrate [15,17,18]. A recent study suggests that circulating microRNA-483 (miR-483), derived from the IGF2 gene and potentially co-expressed with IGF-2, could serve as a potential biomarker for IGF-2-associated NICTH. Serum miR-483-5p demonstrated higher diagnostic accuracy than IGF-2 levels or the IGF-2/IGF-1 ratio and decreased significantly after surgical tumor removal, whereas circulating big IGF-2 became undetectable. However, further studies are needed to determine appropriate cutoff values and to clarify its potential role in the diagnosis and monitoring of NICTH [19].

Management and therapy

Most studies indicate that the most effective treatment for hypoglycemia is surgical removal of the tumor responsible for NICTH [13]. In the acute setting, hypoglycemia is initially managed with oral or intravenous glucose administration. After correction of acute hypoglycemia, glucocorticoids can be introduced to prevent later episodes. Glucocorticoids stimulate glucose production in the liver, reduce glucose uptake by peripheral tissues, stimulate lipolysis [20], and suppress tumor secretion of "big" IGF-2 [13]. Case series suggest that the effectiveness of preoperative therapy with prednisone depends on the tumor type and individual patient characteristics. Among patients with pleural solitary fibrous tumors and neuroendocrine tumors of the palate, prednisone has proven effective as a bridging therapy, controlling hypoglycemia prior to surgery. In contrast, it was ineffective in cases of retroperitoneal myxofibrosarcoma and meningeal hemangiopericytoma [16]. Glucocorticoids are generally considered the most effective conservative treatment strategy for hypoglycemia when surgical intervention is not feasible. Commonly used doses of prednisone range from 30 to 60 mg/day (0.5-1.0 mg/kg/day) [13,21]. Alternative glucocorticoids, including prednisolone, dexamethasone and hydrocortisone, may be administered [13]. In a recent case report, glucocorticoid therapy was also associated with palliative effects, including improved appetite, weight gain and fewer hospital admissions related to recurrent hypoglycemia [22]. In patients with unresectable malignant solitary fibrous tumors, depending on tumor characteristics, supportive therapeutic options may include immunotherapy, antiangiogenics [16], neoadjuvant chemoradiotherapy and arterial embolization [20,23]. When complete surgical resection is not possible, debulking [20,24] or local therapies such as radiotherapy can be considered [21,25].

Beyond standard supportive and surgical approaches, several adjunctive and tumor-targeted therapies have also been investigated in selected cases of NICTH. In addition, the tyrosine kinase inhibitor imatinib has been used in the treatment of gastrointestinal stromal tumors (GISTs), particularly when surgical resection is not possible. In a recent case report of GIST-associated NICTH, treatment with imatinib was accompanied by tumor reduction and improvement of hypoglycemia [26]. Recombinant human growth hormone (rhGH) has also been reported to be beneficial in managing hypoglycemia in NICTH, although its mechanism of action is not fully understood; at supraphysiological doses it may inhibit peripheral glucose uptake, stimulate lipolysis, increase glycogenolysis and gluconeogenesis, but its use raises the theoretical risk of stimulating tumor growth [21,27]. and may be limited by potential adverse effects such as fluid accumulation and postural hypotension, as well as its expense [28].

In recent years, increasing attention has been directed toward emerging targeted therapies for refractory NICTH. A new and promising therapeutic option for the treatment of NICTH is alpelisib; however, only a single case has been reported in the literature, in which a patient with a recurrent solitary fibrous tumor and hypoglycemia promptly achieved normoglycemia following administration of alpelisib at a dose of 300 mg daily. Alpelisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) that blocks downstream AKT phosphorylation, thereby interfering with pro-IGF-2-mediated insulin-IGF-1 receptor signaling. An alternative treatment strategy is the use of the human monoclonal antibody RZ358, which functions as a negative allosteric modulator of the insulin receptor, thereby attenuating receptor activation, with potential to reduce hypoglycemia. Although its clinical efficacy has so far been documented only in a single case of malignant insulinoma, this mechanism may also be theoretically applicable in NICTH, where excessive IGF-2 activates insulin receptors [29]. Additionally, the anti-IGF-1 and anti-IGF-2 neutralizing antibody - KM1468 - has been reported to be effective in treating severe hypoglycemia secondary to diverse tumors, such as bone metastases from prostate cancer, liver metastases from colorectal cancer, multiple myeloma and breast cancer [13]. Emerging therapies, including alpelisib and monoclonal antibodies such as RZ358 and KM1468, represent promising yet still experimental approaches in the management of refractory NICTH. However, current evidence is limited to isolated case reports, with no randomized or prospective clinical studies available. The small number of reported cases and the absence of standardized treatment protocols limit the generalizability of these findings. Therefore, further well-designed studies are required to establish their safety, efficacy, and optimal therapeutic role.

Conclusions

Non-islet cell tumor hypoglycemia is a rare but clinically important cause of hypoglycemia that should be considered in patients with unexplained low glucose levels and underlying malignancy. It is most often associated with mesenchymal tumors and results from tumor-related overproduction of insulin-like growth factor 2. Diagnosis relies on characteristic biochemical findings, particularly an increased IGF-2 to IGF-1 ratio. Surgical resection remains the most effective treatment, while glucocorticoids and other supportive therapies may be used when surgery is

not feasible. Early recognition of NICTH and timely diagnosis and management are essential to reduce the risk of severe hypoglycemic complications and improve patient outcomes.

Authors' contributions

KS (Conceptualization; Methodology; Visualization; Writing - original draft; Investigation)
WK (Conceptualization; Methodology; Visualization; Writing - original draft; Investigation)
MK (Supervision; Writing - review & editing; Investigation)
AK (Writing - review & editing; Investigation)
PK (Writing - review & editing; Investigation)
GS (Writing - review & editing)
JG (Writing - review & editing)
JJ (Writing - review & editing)
KM (Writing - review & editing)
ML (Supervision; Writing - review & editing)
All authors have read and approved the final version of the manuscript.

Conflict of interest

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