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Paraneoplastic hypoglycemia: An overview for optimal clinical guidance

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ABSTRACT

Paraneoplastic hypoglycemia, also known as non-islet cell tumor hypoglycemia (NICTH), is a rare but critical condition occurring in patients with different types of malignancy. This condition is commonly linked to tumors producing insulin-like growth (IGF) factors, particularly IGF-2 and its precursors, which disrupt glucose homeostasis and lead to excessive glucose consumption. The diagnosis typically involves documenting symptomatic hypoglycemia and ruling out other potential causes. Essential diagnostic tools include imaging studies and laboratory tests, specifically measuring IGF-2 levels and the IGF-2:IGF-1 ratio. Treatment strategies for NICTH are multifaceted and may include surgical resection of the tumor if feasible, pharmacological interventions such as corticosteroids to suppress IGF-2 production, or supportive measures to manage acute hypoglycemic episodes. Novel therapeutic approaches targeting IGF-2, such as monoclonal antibodies or siRNA, are also being explored and hold promise for future treatment options. This review aims to enhance understanding of paraneoplastic hypoglycemia, focusing on its pathogenesis and diagnosis, to guide optimal medical treatment.

1. Introduction

Hypoglycemia is conventionally defined as a reduction in serum glucose levels below 70 mg/dL, though clinical signs and symptoms may not manifest until plasma glucose concentrations fall below 55 mg/dL [1]. Individuals experiencing hypoglycemia may present with adrenergic or neuroglycopenic symptoms, or a combination of both. In some instances, symptoms from autonomic nervous system may be present. Adrenergic symptoms include hunger, sweating, nausea, anxiety, tremor, palpitations, and tachycardia. On the other hand, neuroglycopenic symptoms comprise confusion, dizziness, lethargy, seizures, and coma [2]. Since 1938, the clinical diagnosis of symptomatic hypoglycemia has been based on Whipple's triad, which involves the presence of hypoglycemia-related symptoms, plasma glucose concentrations

Abbreviations: AKT2, AKT serine/threonine kinase 2; ALS, Acid-Labile Subunit; BRCA1, Breast Cancer gene 1; cTACE, Conventional Transcatheter Arterial Embolization; DPS, Doege-Potter Syndrome; ERG-1, Early Growth Response Protein 1; FDA, Food and Drug Administration; GH, Growth Hormone; GLP-1, Glucagon-like Peptide 1; GLUT4, Glucose Transporter type 4; IGF, Insulin-like Growth Factor; IGF-1, Insulin-like Growth Factor 1; IGF-1R, insulin-like growth factor-1 receptor; IGF-2, Insulin-like Growth Factor 2; IGFBP-3, IGF Binding Protein 3; IR-1, Insulin Receptors 1; LC-MS/MS, Liquid Chromatography-tandem Mass Spectrometry; NAB2, NGFI-A-binding Protein 2; NICTH, Non-Islet Cell Tumor Hypoglycemia; NIPHS, Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome; PI3K, Phosphatidylinositol 3-Kinase; PIs, Protease Inhibitors; rGH, recombinant Growth Hormone; SFT, Solitary Fibrous Tumor; SiRNA, small interfering RNA; SSTR, Somatostatin Receptors; STAT6, Signal Transducer and Activator of Transcription 6; TACE, Transcatheter Arterial Embolization; TILA-TACE, Targeting Intratumoral Lactic Acidosis Transcatheter Arterial Embolization.

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below 55 mg/dL (3.0 mmol/L), and the alleviation of these symptoms following the correction of hypoglycemia [1].

The etiology of hypoglycemia can be categorized based on its underlying pathophysiological mechanisms into insulin-mediated and non-insulin-mediated processes. Insulin-mediated causes include factitious hypoglycemia resulting from the misuse of insulin or sulfonylureas, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS), and post-bariatric surgery hypoglycemia. Non-insulin-mediated causes encompass critical illnesses such as sepsis and hepatic failure, hormone deficiencies (e.g., cortisol or growth hormone), alcohol abuse, and paraneoplastic hypoglycemia [2,3].

Paraneoplastic hypoglycemia, also known as non-islet cell tumor hypoglycemia (NICTH), refers to hypoglycemia caused by or associated with tumors other than insulinoma. A wide range of epithelial, vascular or mesenchymal-origin neoplasms have been linked with NICTH [4]. NICTH was first described by Nadler et al., in 1929 in a patient with hepatocellular carcinoma, attributed to the liver's inability to mobilize glucose [5]. A year later, Doege and Potter described a case of NICTH associated with a solitary fibrous tumor (SFT), now referred to as Doege-Potter Syndrome (DPS). This syndrome occurs in less than 4 % of these neoplasms [6].

The hypoglycemic symptoms in NICTH do not differ from those of common hypoglycemia, although typically neuroglycopenic symptoms predominate. Most cases of paraneoplastic hypoglycemia are attributed to the tumor's ability to produce insulin-like growth factor 2 (IGF-2) and its precursors, which activate insulin receptors, thereby enhancing glucose utilization [7]. Diagnosing NICTH requires the exclusion of other causes of hypoglycemia, while the determination of the IGF-2: IGF-1 ratio is central in the establishment of the diagnosis [7]. Surgical resection of the underlying tumor remains the gold standard for treatment [7]. However, when surgical intervention is not feasible, symptomatic therapy plays a significant role in managing hypoglycemia. Interestingly, in recent years, novel molecular therapies targeting IGF-2 have emerged, offering promising therapeutic potential for managing paraneoplastic hypoglycemia [7,8].

This narrative review aims to shed light on various aspects of paraneoplastic hypoglycemia, focusing on its primary etiologic causes, underlying pathophysiological mechanisms, clinical presentation, and recommended diagnostic approach. Additionally, we highlight current therapeutic strategies, including alternative treatment approaches for individuals for whom tumor excision is not feasible, and explore potential future treatment options.

2. Etiology

Several types of neoplasms, including epithelial, vascular, and mesenchymal origins, have been associated with NICTH. Among epithelial cancers, hepatocellular carcinomas are the most common, followed by adrenocortical tumors. Vascular tumors like hemangiopericytomas may also be linked to NICTH. In mesenchymal neoplasms, mesotheliomas and fibrosarcomas are the most frequently associated with paraneoplastic hypoglycemia. Various other carcinomas, sarcomas, and lymphomas have also been implicated in causing NICTH [8–10]. Interestingly, Oreggo et al. documented 208 cases of NICTH during their study of a patient with meningeal solitary fibrous tumor (SFT), noting that among these cases, 34 out of 68 SFTs/hemangiopericytomas were malignant. Additionally, they observed cases induced by nine breast phyllodes tumors, nine hepatocellular carcinomas, and nine gastrointestinal stromal tumors [11].

3. Pathophysiology

Paraneoplastic hypoglycemia arises from various pathophysiological mechanisms, prominently due to the overproduction of IGF-2 and its precursor forms. The association between paraneoplastic hypoglycemia and IGF-2 was first established in 1974, with subsequent identification of elevated levels of IGF-2 and its precursor "big" IGF-2 in affected patients. This strong link has prompted some experts to propose renaming NICTH as "IGF-2-oma," aligning with other hormone-producing tumors like insulinoma [12,13].

3.1. The role of IGF-2 in paraneoplastic hypoglycemia

In human adults, IGF-2 is produced by the liver and expressed in tumor cells of both mesenchymal and epithelial tumors. The IGF-2 gene, located on chromosome 11, is translated into the prepro-IGF-2 peptide, which consists of three main domains: the N-terminal peptide, the mature IGF-2, and the C-terminal extension, also known as the E-domain. Post-translational modifications of prepro-IGF-2 occur in the Golgi apparatus, where an intermediate molecule comprising the mature IGF-2 domain combined with part of the E-domain is formed and secreted into circulation in small quantities. This intermediate molecule, referred to as "big" IGF-2, plays a major role in the development of hypoglycemia [14].

The expression of high levels of IGF-2 RNA in such tumors results from a loss of imprinting of parent alleles and abnormal activation of promoter regions of the IGF-2 gene. This leads to the production of large quantities of prepro-IGF-2, which oversaturates the prohormone convertase enzyme responsible for converting prepro-IGF-2 to mature IGF-2. Consequently, there is a significant rise in circulating "big" IGF-2. In addition to the production of "big" IGF-2, patients with NICTH also exhibit high levels of mature IGF-2. The abundance of IGF-2 and its prohormone are critical factors in the development of hypoglycemia in these patients [4,8,14].

3.2. Circulation and bioavailability of IGF-2 in paraneoplastic hypoglycemia

Beyond the increase in total IGF-2 and its prohormone, the actions of these peptides are largely influenced by how they circulate, form complexes, and are made available to tissues. Mature IGF-2 primarily exists in two forms: bound in a 50 kDa binary complex with IGFBP-3 (IGF Binding Protein-3) or in a 150 kDa ternary complex with IGFBP-3 and ALS (Acid-Labile Subunit). In healthy individuals, 80 % of IGF-2 is bound in the ternary complex, while the remaining 20 % circulates in the binary complex [8,15].

Binary complexes, being smaller, can more easily permeate capillary membranes, resulting in higher bioavailability of IGF-2 and a greater potential for hypoglycemic action. In patients with paraneoplastic hypoglycemia, the formation of binary complexes is favored, with ternary complexes comprising only about 20 %. This shift is due to decreased ALS synthesis in the liver and steric hindrance from the large quantities of "big" IGF-2, which cannot form ternary complexes [8,16].

Additionally, "big" IGF-2 competes with both IGF-2 and IGF-1 in forming binary complexes, leading to increased circulating levels of free IGF-2 and IGF-1. The rise in IGF-1 levels suppresses growth hormone (GH) secretion by the pituitary gland, which in turn reduces the production of ALS and IGFBP-3 by the liver. This creates a vicious cycle that further favors the formation of binary complexes. Moreover, increased IGFBP-3 protease activity in these tumors facilitates the formation of binary complexes as well [8,15,16].

3.3. Biological actions of IGF-2 in paraneoplastic hypoglycemia

IGF-2 exerts a wide range of autocrine, paracrine, and endocrine actions by binding to both insulin and IGF-1 receptors, which are present in nearly all human cells. Tumor growth is stimulated by high concentrations of IGF-2 near the tumor cells that express insulin-like growth factor-1 receptors (IGF-1Rs) and insulin receptors (IRs-1) receptors. Most biological effects of IGF-2 mimic those of insulin, with specific receptors showing higher affinity for IGF-2. Even when IGF-2's affinity for IR is lower than that of insulin—35%–40 % for the IR-A

receptor—the elevated levels of IGF-2 and "big" IGF-2 can still cause hypoglycemia comparable to insulin [17,18].

IGF-2 produced by tumor cells binds to IRs in skeletal muscle cells, leading to increased glucose uptake. It also acts on adipose tissue by suppressing the release of free fatty acids through the inhibition of lipolysis and enhancing the esterification of adipocytes. In the liver, IGF-2 suppresses gluconeogenesis, glycogenolysis, ketogenesis, and the activity of glucose-6-phosphatase, thereby blocking hepatic glucose release. This reduction in hepatic glucose output is critical for the development of hypoglycemia, as blocking lipolysis alone did not lead to hypoglycemia in vitro [17,18].

Furthermore, IGF-2 reduces growth hormone secretion from the pituitary gland, indirectly decreasing the liver's production of IGF-1, ALS, and IGFBP-3, and facilitating the formation of binary complexes. Additionally, IGF-2 binds to IGF-1 and IR receptors on pancreatic alpha cells, suppressing glucagon release and exacerbating hypoglycemia. Ultimately, the increased glucose consumption by skeletal muscle combined with the generalized substrate deficiency leads to sustained hypoglycemia, which is difficult to manage through conventional means [17–19]. Fig. 1 depicts the primary hypoglycemic actions of IGF-2.

3.4. Molecular mechanisms in SFTs-Associated hypoglycemia

As previously discussed, there is a clear association between SFTs and paraneoplastic hypoglycemia. These tumors are uniquely characterized by the NAB2-STAT6 fusion gene, a molecular feature not identified in other types of cancer. This chimeric transcription factor promotes carcinogenesis by activating NAB2 target genes and plays a significant role in hypoglycemia by upregulating the expression of early growth response protein 1 (EGR-1). EGR-1, in turn, mediates the transcriptional activation of the IGF-2 gene, leading to hypoglycemia [20].

Besides the distinctive NAB2-STAT6 fusion, there is a solitary case report of an SFT complicated by hypoglycemia linked to a BRCA1 (breast cancer gene 1) mutation [21,22]. Additionally, a different mechanism was described by Alkaissi et al. in a patient with ovarian cancer, where the duplication of the AKT2 gene was associated with the development of hypoglycemia. AKT is a serine/threonine kinase that participates in intracellular signaling pathways, leading to the translocation of glucose transporter type 4 (GLUT4) to the cellular membrane. While the initial step in this process is typically mediated by insulin binding to its membrane receptor, cellular studies have shown that mutant AKT2 can induce hypoglycemia independently of insulin action [23,24].

3.5. Other rare mechanisms of paraneoplastic hypoglycemia

Rarely tumors have been reported to secrete GLP-1, which causes an hyperinsulinemic response, while hypoglycemia due to IGF-1 secretion is even rarer, having been reported only once in a woman with metastasizing large-cell lung carcinoma [25,26]. Finally, two cases of insulin secretion from non-pancreatic tumors, namely a neuroendocrine tumor of the kidney and a small-cell cervical carcinoma should be noted [27,28]. Fig. 2 provides a schematic illustration of the primary molecules and genes involved in the development of paraneoplastic hypoglycemia, including the Doege-Potter Syndrome.

4. Clinical presentation

The emergence of NICTH has been seldom reported immediately after the initial diagnosis of the associated tumor. Kaneko presented a case where hypoglycemia developed 17 years after the diagnosis of an intraabdominal SFT [29]. More recently, Oreggo et al. described a patient who developed hypoglycemia 23 years after the diagnosis of a meningeal solitary fibrous tumor, and 12 years after the detection of extracranial metastatic disease. This discrepancy in timing between tumor diagnosis and hypoglycemia manifestation may stem from late genetic abnormalities within the tumor or the tumor reaching a critical volume necessary to induce hypoglycemia [11].

Clinical symptoms of paraneoplastic hypoglycemia can be categorized into three main groups: those directly caused by the tumor itself, those arising from impaired glucose metabolism, and a minority

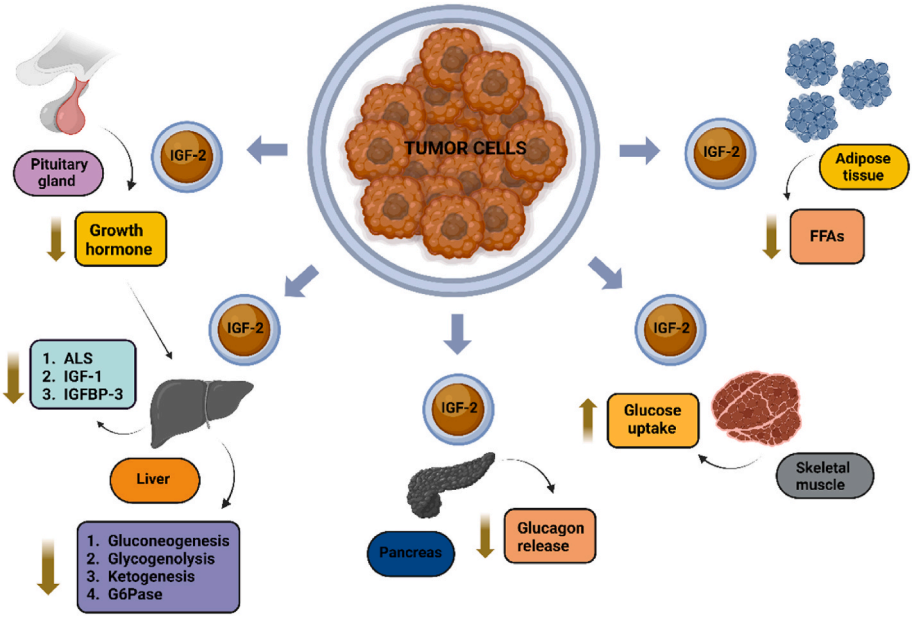

Fig. 1. Primary hypoglycemic actions of IGF-2. As illustrated, IGF-2 exerts its effects on various cells, including skeletal muscle, adipose tissue, liver, and pancreatic alpha cells. In skeletal muscle, IGF-2 increases glucose uptake. In adipose tissue, it inhibits lipolysis and enhances the esterification of adipocytes, suppressing the release of free fatty acids. In the liver, IGF-2 suppresses gluconeogenesis, glycogenolysis, ketogenesis, and the activity of glucose-6-phosphatase, leading to decreased hepatic glucose output. Additionally, IGF-2 suppresses glucagon release from pancreatic alpha cells. Notably, IGF-2 inhibits growth hormone secretion from the pituitary gland, which indirectly lowers the liver's synthesis of IGF-1, ALS, and IGFBP-3, while also encouraging the formation of binary complexes. Together, these actions contribute to the development and maintenance of hypoglycemia. **Abbreviations:** ALS: Acid-Labile Subunit; FFAs: Free Fatty Acids; IGF-1: Insulin-like Growth Factor 1; IGF-2: Insulin-like Growth Factor 2; IGFBP-3: IGF Binding Protein-3. Created with www.BioRender.com. (assessed on July 15, 2024).

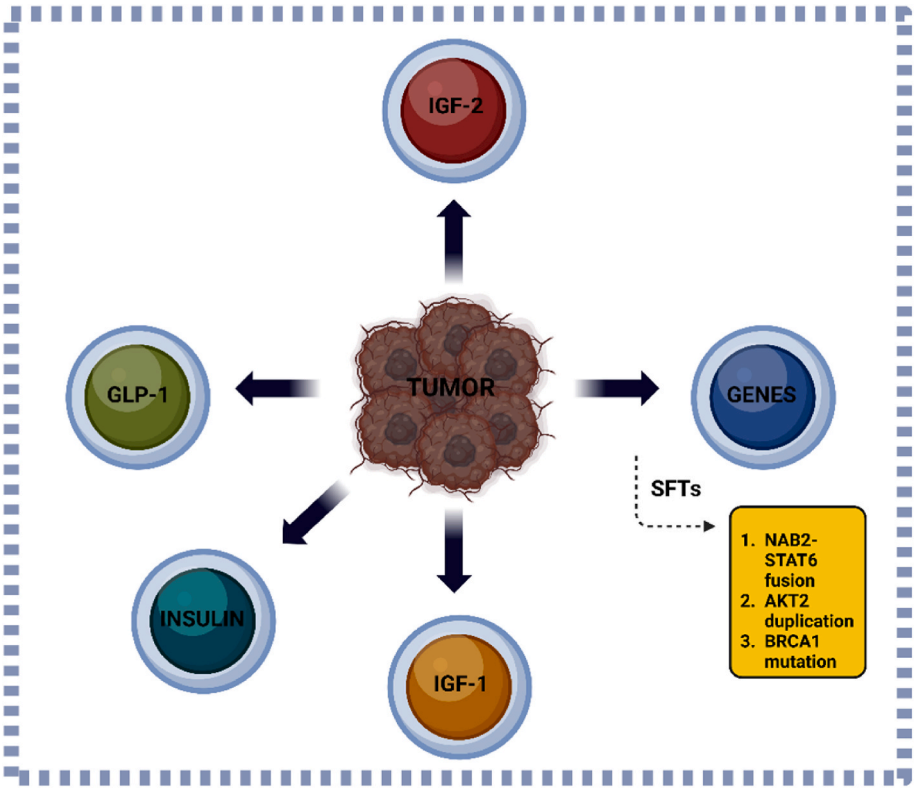

Fig. 2. A schematic presentation of the key molecules and genes involved in the pathogenesis of paraneoplastic hypoglycemia. **Abbreviations:** AKT2: AKT serine/threonine kinase 2; BRCA1: Breast Cancer gene 1; GLP-1: Glucagon-like Peptide 1; IGF-1: Insulin-like Growth Factor 1; IGF-2: Insulin-like Growth Factor 2; NAB2: NGFI-A-binding Protein 2; SFT: Solitary Fibrous Tumor; STAT6: Signal Transducer and Activator of Transcription 6. Created with www.BioRender.com. (assessed on July 15, 2024).

associated with the growth-promoting effects of IGF-2 [8]. Symptoms directly related to the tumor typically include weight loss, abdominal mass, pain, dyspnea, or incidental findings during routine examinations [5,6]. Tumor size and location dictate its physical impact, sometimes presenting as large masses at diagnosis. However, documented cases exist where small, asymptomatic lesions have been linked to the presence of hypoglycemia [30].

In paraneoplastic hypoglycemia, the symptoms predominantly manifest as neuroglycopenic, affecting cognitive function and mental status significantly. On the other hand, in cases of recurrent or gradual-onset hypoglycemia, autonomic symptoms like sweating and tremors may be less noticeable. The spectrum of symptoms can vary widely, encompassing mild cognitive impairment, disorientation, motor symptoms, psychosis, seizures, coma, and, in severe cases, death. Similar to typical hypoglycemia, paraneoplastic hypoglycemia may present with focal neurological deficits that can mimic conditions such as ischemic stroke or brain metastases [4,31,32].

Individuals with NICTH may also experience postprandial hyperglycemia due to IGF-2-mediated suppression of insulin secretion by pancreatic β-cells [4], while up to half of patients may exhibit unexplained hypokalemia [33]. Interestingly, some cases of NICTH have been associated with acromegalic features, as reported by Wang et al., attributed to the activation of multiple insulin and IGF-1-related receptors by tumor-produced IGF-2. These features include acne, prominent forehead, broad nose, and other facial changes, which are uncommon but noteworthy in the context of fibrous tumors [34].

In summary, the clinical presentation and underlying mechanisms of NICTH underscore the complexity and variability of this condition. Timely recognition and thorough evaluation are essential for effective management, emphasizing the need for heightened awareness among clinicians encountering patients with cancer-related hypoglycemia.

5. Diagnostic assessment

5.1. Initial evaluation on admission

The first critical step in diagnosing hypoglycemia is to confirm symptomatic hypoglycemia using Whipple's triad. As mentioned above, this triad requires documenting low blood glucose levels accompanied by hypoglycemic symptoms that resolve upon raising glucose levels to normal or higher [1,2]. Subsequent diagnostic steps depend heavily on the patient's medical history. For instance, in patients with a history of cancer, the cause of hypoglycemia is typically evident from their medical background and physical examination. In such cases, a comprehensive patient history is crucial to rule out other potential causes of hypoglycemia such as alcohol abuse, medications, dietary supplements, prior bariatric surgery, or liver failure [2].

Notably, individuals with malignancies are particularly susceptible to infections, making it essential to rule out sepsis upon admission. Furthermore, symptoms such as orthostasis, hyponatremia, and weight loss may indicate adrenal insufficiency, which can result from the destruction of adrenal glands due to extensive tumor infiltration [35]. Therefore, appropriate diagnostic tests are necessary in those cases. Generally, in cases of NICTH associated with a known tumor type, further investigation for alternative causes of hypoglycemia is generally unnecessary. Conversely, in patients presenting with hypoglycemia without a history of cancer, a thorough evaluation to identify its cause is crucial, although NICTH is less likely to be the underlying issue in such instances.

5.2. Further biochemical investigations

For the accurate differential diagnosis of hypoglycemia, it is crucial to measure serum glucose, proinsulin, insulin, C-peptide, and

β-hydroxybutyrate levels, along with screening for sulfonylurea and meglitinide during hypoglycemic episodes. Elevated insulin levels with low C-peptide levels typically indicate exogenous insulin administration. Conversely, increased insulin concentrations coupled with high C-peptide levels suggest conditions like sulfonylurea or meglitinide use, insulinoma, NIPH, autoimmune hypoglycemia, or post-gastric bypass surgery. Lastly, low insulin and C-peptide levels point to possible hypopituitarism, cortisol deficiency, or paraneoplastic hypoglycemia [36–38]. In cases of NICTH, serum β-hydroxybutyrate levels are also low, consistent with insulin-like activity due to the presence of IGF-2 [36–38]. In this laboratory scenario, the presence of IGF-2 can be confirmed by measuring the plasma glucose response to glucagon administration, which is typically greater than 25 mg/dL, except in cases where low liver glycogen stores result from extensive tumor replacement of hepatic tissue [14,36,37].

5.3. Establishing the diagnosis of paraneoplastic hypoglycemia

When clinical and biochemical findings align with NICTH, further assessment is typically unnecessary. In such cases, physicians should focus on identifying the underlying malignancy by performing cross-sectional imaging of the chest, abdomen, and pelvis. However, if the diagnosis remains uncertain, a definitive diagnosis of paraneoplastic hypoglycemia can be made by measuring IGF-1 and IGF-2 levels, pro-IGF-2 concentrations (if available), and calculating the IGF-2: IGF-1 ratio. A ratio of 10:1 or higher (compared to the normal ratio of around 3:1 in healthy individuals) strongly suggests NICTH [32].

Quantitative analysis of insulin-like growth factors (IGFs) is typically performed using ligand-binding immunoassays or enzymatic digestion liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. However, these methods are not yet approved by the Food and Drug Administration (FDA) and are hindered by time-consuming sample preparation. To address these limitations, new antibody-free LC-MS/MS methods have been developed for the rapid and simple quantification of intact IGF-1 and IGF-2 in human plasma. In adults, normal IGF-2 values typically range between 267 and 616 ng/mL [39,40]. It is important to note that normal IGF-2 levels do not exclude paraneoplastic hypoglycemia, which may be influenced by the presence of "big" IGF-2, a form not commonly measured in commercial assays. Additional markers such as IGFBP-1, IGFBP-2, IGFBP-3, and ALS can support the diagnosis but are not essential for confirmation [4,32].

In summary, hypoglycemia without hyperinsulinemia should prompt consideration of paraneoplastic hypoglycemia, particularly in patients with a history of neoplasia, imaging evidence of cancer, or typical clinical features. Fig. 3 presents the typical biochemical findings in subjects with NICTH.

6. Therapeutic approach

Treatment for paraneoplastic hypoglycemia can be categorized into two main approaches: causative treatment targeting the tumor through surgical or pharmaceutical means, and conservative measures aimed at managing hypoglycemia directly. Causative treatment involves the surgical removal or pharmaceutical intervention to address the underlying tumor, which is considered primary when feasible, aiming to eliminate the source of abnormal hormone production causing hypoglycemia. In cases where definitive treatment, such as surgery, is not feasible or is pending, conservative methods serve as either a temporary solution or adjunctive therapy. These measures focus on stabilizing blood glucose levels through dietary modifications, glucose infusions, or medications that inhibit insulin release or action, providing necessary management until more definitive tumor-directed therapies can be pursued.

6.1. Causative treatment

6.1.1. Surgical treatment

Surgical tumor resection is the primary treatment for NICTH, despite

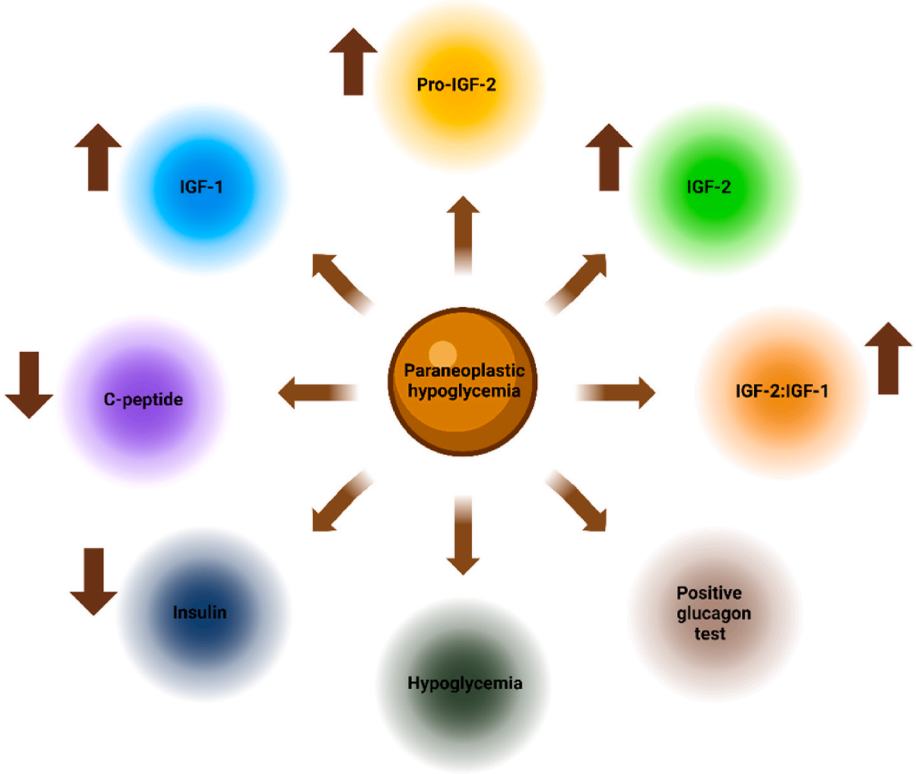

Fig. 3. A schematic illustration of the typical laboratory profile in paraneoplastic hypoglycemia. **Abbreviations:** IGF-1: Insulin-like Growth Factor 1; IGF-2: Insulin-like Growth Factor 2; pro-IGF-2: pro-Insulin-like Growth Factor 2. Created with www.BioRender.com. (assessed on July 15, 2024).

the availability of various medical therapies. Surgical removal of the tumor has been shown to promptly correct hypoglycemia, resulting in a rapid increase in blood glucose levels, a decrease in IGF-2 levels, and normalization of the serum IGF-1 ratio. When complete surgical excision is not feasible, surgical debulking may be considered. There have been cases where subtotal tumor resection resulted in the total resolution of hypoglycemia [13,14]. Given the established correlation between tumor size and IGF-2 production, the main goal of debulking surgery is to reduce the tumor size sufficiently to alleviate hypoglycemia [7].

6.1.2. Alternative treatment options

External radiotherapy has proven effective, in cases where surgical treatment is not feasible. Low-dose radiation treatment (30 Gy) administered over ten days has been shown to effectively treat fasting hypoglycemia. Additionally, a lower dose of 15 Gy in five fractions led to tumor shrinkage and correction of hypoglycemia in a 90-year-old patient with diffuse pigmented synovitis [11,41].

Selective arterial embolization of the tumor's feeding arteries has been used when surgery is not an option. Transcatheter arterial embolization (TACE) has been effective alone or in combination with chemotherapy and radiation therapy, leading to the correction of hypoglycemia in patients with NICTH, including those with metastatic liver SFTs. However, the efficacy of TACE in achieving tumor shrinkage has sometimes fallen short of expectations, necessitating the addition of conventional measures such as continuous dextrose infusion [42].

A novel method described by Jin et al. combines conventional TACE (cTACE) with targeting intratumoral lactic acidosis transcatheter arterial embolization (TILA-TACE) to induce definitive tumor necrosis. cTACE first embolizes blood vessels, creating a low-glucose microenvironment that alters energy metabolism and leads to tumor cell death. However, this effect can be compromised by hypoxia, which can induce transcriptional activation of the IGF-2 gene, increasing pro-IGF-2 production. Tumor cells might also survive by using lactate and protons, potentially resulting in treatment failure. Conversely, TILA-TACE effectively prevents tumor cells from utilizing glucose and accelerates cell death by converting intratumoral lactic acidosis to lactosis using bicarbonate to neutralize the tumor bed. TILA-TACE has proven successful in cases where cTACE was unable to control hypoglycemia [21].

6.1.3. Pharmaceutical tumor-targeted therapy in selected cases

Conventional systemic chemotherapy, such as the FOLFOX regimen (oxaliplatin, 5-fluorouracil, and leucovorin), has been effective in a patient with hepatocellular carcinoma and profound hypoglycemia [43]. Interestingly, imatinib has been successfully used in a patient with severe hypoglycemia attributed to recurrent SFT. Administered at a tolerable dosage, imatinib resulted in increased fasting glucose levels, allowing the cessation of dextrose infusions and corticosteroids after a few weeks. The patient did not exhibit hypoglycemic symptoms during a one-year follow-up [44].

Alpelisib, a phosphatidylinositol 3-kinase (PI3K) inhibitor, has been used to maintain euglycemia in a patient with recurrent lung SFT. The increase in blood glucose caused by Alpelisib is attributed to the decreased phosphorylation of protein kinase B (AKT), a critical step in glucose transfer to muscle cells. In vitro studies have shown that pro-IGF-II increases AKT activation, but Alpelisib effectively counters this action [45]. Furthermore, the combination of dacarbazine and bevacizumab has shown temporary effectiveness in a 44-year-old patient with hypoglycemia associated with remitted intra-abdominal diffuse large B-cell lymphoma. This regimen enabled the discontinuation of dextrose infusions and hospital discharge. However, hypoglycemia recurred, and the patient succumbed to disease progression 135 days after the initial diagnosis [46].

6.2. Symptomatic treatment

Glucocorticoids, particularly prednisone at daily doses of 30–60 mg or hydrocortisone at 40 mg per day, are commonly used to manage hypoglycemia in NICTH. These steroids stimulate lipolysis, reduce peripheral glucose uptake, and enhance hepatic gluconeogenesis. Additionally, they may suppress the production of pro-IGF-2 by tumors. However, their effectiveness requires careful titration, and withdrawal can lead to recurrence of hypoglycemia, limiting their overall efficacy [19,47]. For individuals ineligible for surgery and unresponsive to glucocorticoids, recombinant growth hormone (rGH) has shown promise. rGH promotes gluconeogenesis, diminishes peripheral glucose uptake, and increases levels of IGFBP-3 and ALS, which bind to IGF-2, reducing its bioavailability. Nevertheless, caution is warranted due to the potential for stimulating tumor growth and side effects such as fluid retention and orthostatic hypotension associated with high doses of rGH [41,48].

Somatostatin and its analogs, effective mainly in tumors expressing somatostatin receptors (SSTRs), have generally not been successful in treating NICTH. However, pasireotide, a second-generation somatostatin receptor ligand with increased affinity for SSTR5 and SSTR2 subtypes, has shown some efficacy. Pasireotide can reduce insulin secretion without compromising insulin sensitivity, thereby improving hyperglycemia in selected cases of NICTH [49,50]. Diazoxide is used adjunctively with corticosteroids in the treatment of NICTH to inhibit pancreatic insulin release and stimulate hepatic glycogenolysis. A typical regimen involves 200 mg twice daily, although treatment is discontinued once a more definitive therapy is initiated [11,14]. Glucagon infusions via infusion pump have been employed as a short-term solution for hypoglycemia in NICTH. Glucagon promotes glycogenolysis and gluconeogenesis, providing transient relief and requiring continuous infusion [19]. Fig. 4 presents the main pharmacological agents used in managing paraneoplastic hypoglycemia, along with their underlying mechanisms of action.

6.3. Dietary modifications

Correcting hypoglycemia is the initial step in treating patients with NICTH and is often seen as pivotal for prolonging survival when other treatment options are limited. Immediate correction of hypoglycemia can be achieved by administering glucose orally or intravenously. Patients are advised to consume frequent meals high in concentrated carbohydrates, and 10 % sugar-containing juices can be beneficial. Additionally, uncooked cornstarch taken at night has proven effective in preventing fasting hypoglycemia, similar to its use in glycogen storage disease type I (von Gierke disease). This complex glucose polymer is slowly digested over 2–6 h, maintaining glucose levels effectively even when intravenous infusions are insufficient. When oral intake is not feasible, nutrition can be provided via a nasogastric tube [24,51,52].

6.4. Emerging novel therapies

Future therapies for paraneoplastic hypoglycemia are evolving based on a deeper understanding of the underlying mechanisms involving IGFs and their receptors. One promising approach is the development of high-affinity antibodies targeting IGF-2. For instance, Prince et al. have produced IgG1 m610, an antibody specific for both pro and mature IGF-2 [53]. Feng et al. have also developed antibodies targeting IGF-2, which could potentially block its effects and reduce hypoglycemia by inhibiting its production or action [54].

Another innovative approach involves using *anti*-IGF-2 small interfering RNA (siRNA). This strategy aims to silence the expression of IGF-2 at the genetic level within tumor cells, thereby reducing its secretion and mitigating the hypoglycemic effects associated with NICTH. Additionally, enhancing the activity of prohormone convertase, which regulates the processing of proIGF-2 to its active form, represents another potential therapeutic strategy to lower circulating levels of bioactive IGF-2 [55].

It is important to note that these therapies not only aim to restore

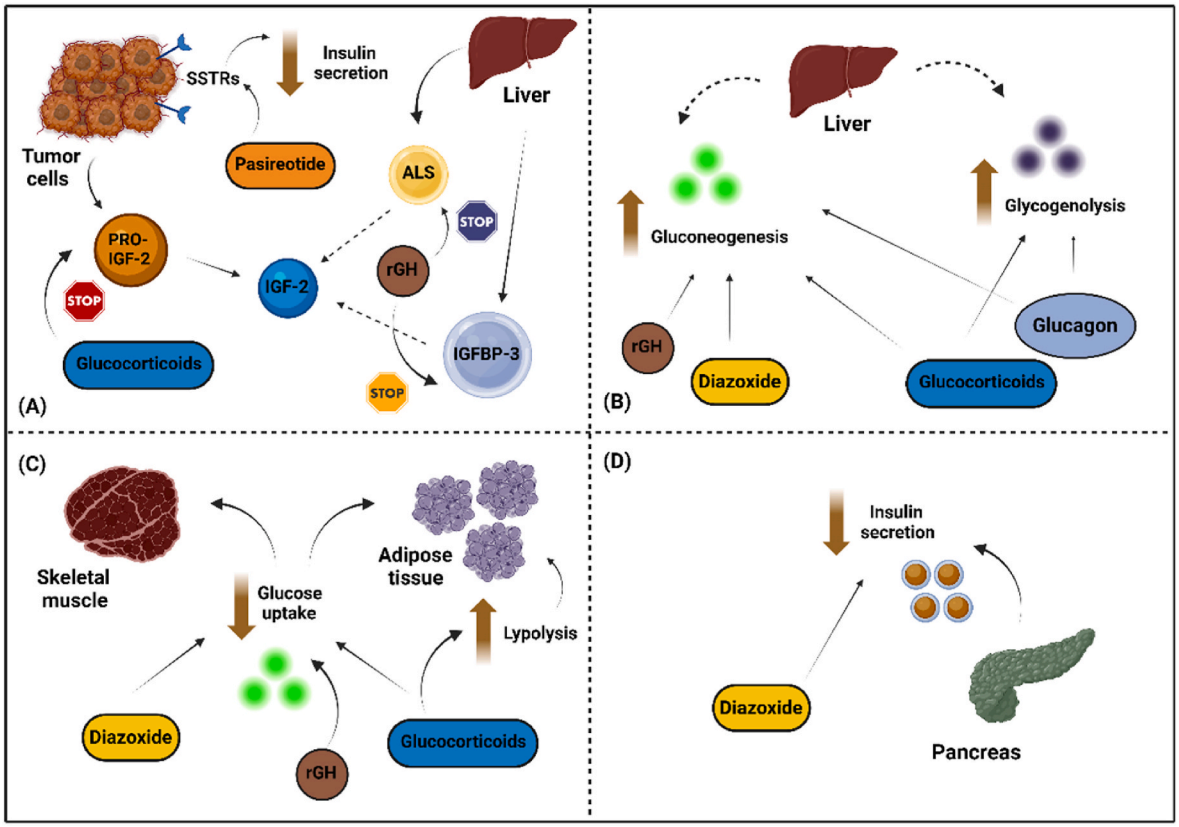

Fig. 4. Conventional symptomatic pharmaceutical treatment in subjects with paraneoplastic hypoglycemia. (**A**). Glucocorticoids reduce pro-IGF-2, the precursor of IGF-2. Notably, IGF-2's bioavailability may be decreased by the administration of rGH, which enhances the hepatic production of IGFBP-3 and ALS, which normally bind to IGF-2. Pasireotide, through its unique mechanism of action, dampens insulin secretion by acting on tumors that express SSTRs, due to its high affinity for these receptors. (**B**). Diazoxide and rGH increase serum glucose concentrations by promoting liver gluconeogenesis. Additionally, glucocorticoids and glucagon enhance hepatic glycogenolysis. (**C**). Glucocorticoids, along with rGH and diazoxide, lead to diminished peripheral glucose uptake. Moreover, glucocorticoids increase lipolysis. (**D**). Diazoxide alleviates insulin release by the pancreas. **Abbreviations:** ALS: acid-labile subunit; IGFBP-3: insulin-like growth factor-binding protein 3; IGF-2: insulin-like growth factor 2; Pro-IGF-2: pro-insulin-like growth factor 2; rGH: recombinant growth hormone; SSTRs: somatostatin receptors. Created with www.BioRender.com. (assessed on July 15, 2024).

normal blood glucose levels but also hold promise in inhibiting tumor growth. Elevated local concentrations of IGF-2 can stimulate tumor growth through autocrine and paracrine mechanisms involving IGF-1R and insulin receptor isoform A (IR-A) expressed on tumor cells. In a more conservative approach, protease inhibitors (PIs) used in the treatment of HIV have shown potential in correcting hyperglycemia associated with NICTH. PIs competitively inhibit GLUT4 membrane proteins, reducing glucose uptake into cells and potentially inducing insulin resistance, which can help mitigate hypoglycemic episodes in some patients [24].

These emerging therapies highlight a shift towards targeted interventions aimed at the molecular pathways involved in NICTH, offering new perspectives for effective management and potentially altering the course of associated malignancies [56–60]. Continued research and clinical trials will be crucial in validating these approaches and optimizing their efficacy and safety profiles for broader clinical use. Fig. 5 illustrates current and potential treatment options for patients with paraneoplastic hypoglycemia.

7. Conclusions

Paraneoplastic hypoglycemia, also known as NICTH, is a rare yet critical condition that clinicians should consider in non-diabetic patients presenting with hypoglycemic symptoms [4,56,61,62]. Hypoglycemia is uncommon outside of diabetes management and requires urgent attention due to its potential to cause significant neurological impairment or even coma. Diagnosing and managing paraneoplastic hypoglycemia in the clinical setting can be challenging, as it may mimic other, more common conditions affecting mental status, such as opioid overdose, brain metastases, or infections [4]. Therefore, a thorough evaluation is crucial, particularly in patients with a known or suspected cancer diagnosis. The definite diagnosis of paraneoplastic hypoglycemia relies on measuring the IGF-2: IGF-1 ratio, a test that is not widely available. Treatment can be difficult even when hypoglycemia is detected, especially when surgery is not an option. In such cases, symptomatic treatment, primarily with glucocorticoids, glucagon infusion, and dietary modifications remains the main therapeutic approach. Additionally, novel therapeutic strategies based on the latest understanding of hypoglycemia mechanisms should be a priority for clinical research to improve patient outcomes.

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Institutional review board statement

Not applicable.

Informed consent statement

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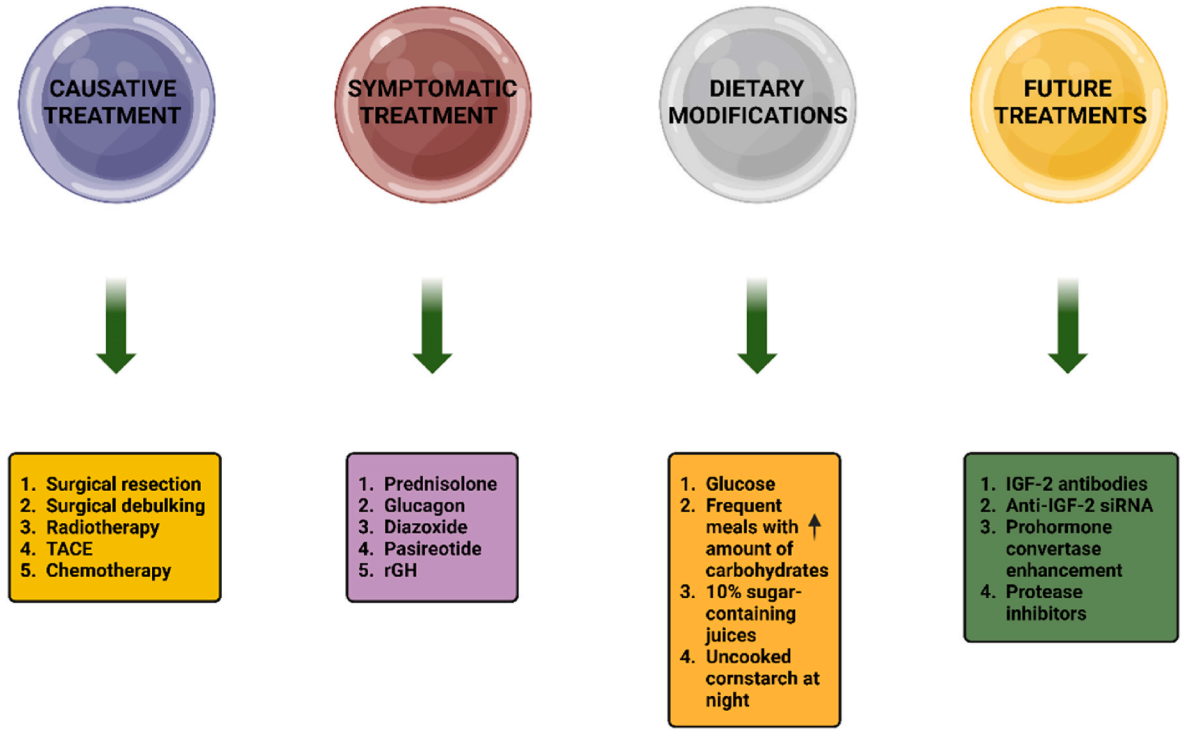

Fig. 5. Main current and potential therapeutic options for the treatment of paraneoplastic hypoglycemia. **Abbreviations:** IGF-2: insulin-like growth factor 2; rGH: recombinant growth hormone; siRNA: small interfering RNA. Created with www.BioRender.com. (assessed on July 15, 2024).

Data availability statement

Not applicable.

CRediT authorship contribution statement

Nikolaos Nektarios Karamanolis: Writing – original draft. **Dimitris Kounatidis:** Writing – review & editing. **Natalia G. Vallianou:** Writing – original draft. **Konstantinos Alexandropoulos:** Writing – original draft. **Eleni Kovlakidi:** Writing – original draft. **Pinelopi Kaparou:** Writing – original draft. **Irene Karampela:** Visualization. **Theodora Stratigou:** Visualization. **Maria Dalamaga:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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