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# Non Islet Cell Hypoglycemia

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## ABSTRACT

Non islet cell hypoglycemia (**NICH**) is a rare cause of hypoglycemia. It is secondary to the overproduction of insulin like growth factor -2 (**IGF-2**) which can activate the insulin receptors and cause hypoglycemia. Overproduction of IGF-2 is primarily seen in epithelial and mesenchymal tumors most commonly hepatocellular carcinoma. Diagnosis is established by finding a low insulin, c peptide, proinsulin and beta hydroxybutyrate in the context of hypoglycemia. Most of these tumors are large and easily detectable on imaging. Treatment consists of surgical excision or palliative debulking of the tumor. Glucocorticoids may be used if surgery is not an option.

## INTRODUCTION

Clinical hypoglycemia is one which causes signs and symptoms, there is no definite threshold of glucose below which this occurs. Rather the documentation of Whipple's triad is essential for the diagnosis of hypoglycemia. Whipple's triad consists of signs and symptoms of hypoglycemia, measured plasma glucose which is low and resolution of the same signs and symptoms after the plasma glucose is normalized [1].

There are several different causes of hypoglycemia, it is most commonly observed in diabetics who are on insulin or insulin secretagogues. Non islet cell hypoglycemia (**NICH**) is due to increased production of insulin like growth factor 2 (**IGF-2**) and pro IGF-2 which can cause by various mechanisms [2,3].

## HISTORY

NICH was first described in 1929, however an understanding of the pathophysiology of this disorder was lacking [4]. Unger et al in 1966 proposed a humoral action of NICH which until then were thought to be secondary to increased consumption of glucose by the tumors [5]. Megyesi et al demonstrated the presence of an insulin like growth factor material (**IGF**) substance in patients with NICH and also its disappearance following excision of the tumor. This material consisted of both IGF-1 and IGF-2 and was known as non-suppressible insulin like activity soluble [6]. Rinderknecht et al in 1978 isolated IGF-1 and IGF-2 [7]. Dughaday et al in 1988 described a patient with NICH secondary to leiomyosarcoma who had a normal IGF-2 level but high pro IGF-2 levels [8].

## PHYSIOLOGY

IGF-2 in adults is expressed in the liver. The IGF-2 gene is located on the short arm of chromosome 11 between the insulin and H19 genes. In most tissues paternal imprinting occurs (only the paternal derived allele is expressed) except in the choroid and the leptomeninges where there is biallelic expression [9-11]. This gene is translated into a pre pro IGF-2 peptide which consists of a 24 amino acid N terminal, 67 amino acid mature IGF-2 and a 89 amino acid C terminal. The pre pro IGF-2 undergoes post translational modification by removal of the N terminal, addition of sialic acid oligosaccharides to the E domain and subsequent proteolysis of the E domain. This gives rise to various pro IGF-2's which are collectively called "Big IGF-2s". Prohormone convertase converts pro IGF-2 to mature IGF-2 [12].

There are six IGF binding proteins (**IGFBP**) which can bind to IGF peptides. About 70-80% of IGF-2 is transported in the form of a 150 k-Da complex consisting of IGF-2, IGFBP-3 and acid labile subunit (**ALS**). IGF-2 is also transported in a 50k-Da binary complex of IGF-2 and IGFBP-3. The 50 k-Da subunits have greater biological activity and also can cross the capillary membranes to interact with insulin receptors [13,14].

## MECHANISM OF HYPOGLYCEMIA

IGF-2 has multiple actions which can contribute to the development of hypoglycemia (Figure 1). Similar to insulin, IGF-2 can inhibit gluconeogenesis, glycogenolysis, ketognesis and activity of glucose 6 phosphatase. These actions are mediated through the action on insulin receptors on the hepatocytes and in the hypothalamus. IGF-2 also increases the uptake of glucose by the muscles and inhibits lipolysis. In addition, growth hormone and IGF-1 levels are suppressed which blunts the response of the counter regulatory hormones to hypoglycemia. Although glucose consumption by the tumors could contribute to hypoglycemia this does not appear to be a significant pathway [3].

Typically in patients with IGF-2 induced hypoglycemia the levels of insulin and IGF-1 are low whereas the level of IGF-2 can be normal or elevated [15]. For a long time the mechanism by which a normal IGF-2 could cause hypoglycemia remained a mystery, till the identification of incompletely processed pro IGF-2 (aka big IGF-2) in 1988 [8]. IGF-2omas can secrete excessive quantities of pro IGF-2 due to loss of imprinting secondary to activation of abnormal promoters. This relative excess of pro IGF-2 may overwhelm the enzymes which normally process pro IGF-2 to mature IGF-2 [15-17].

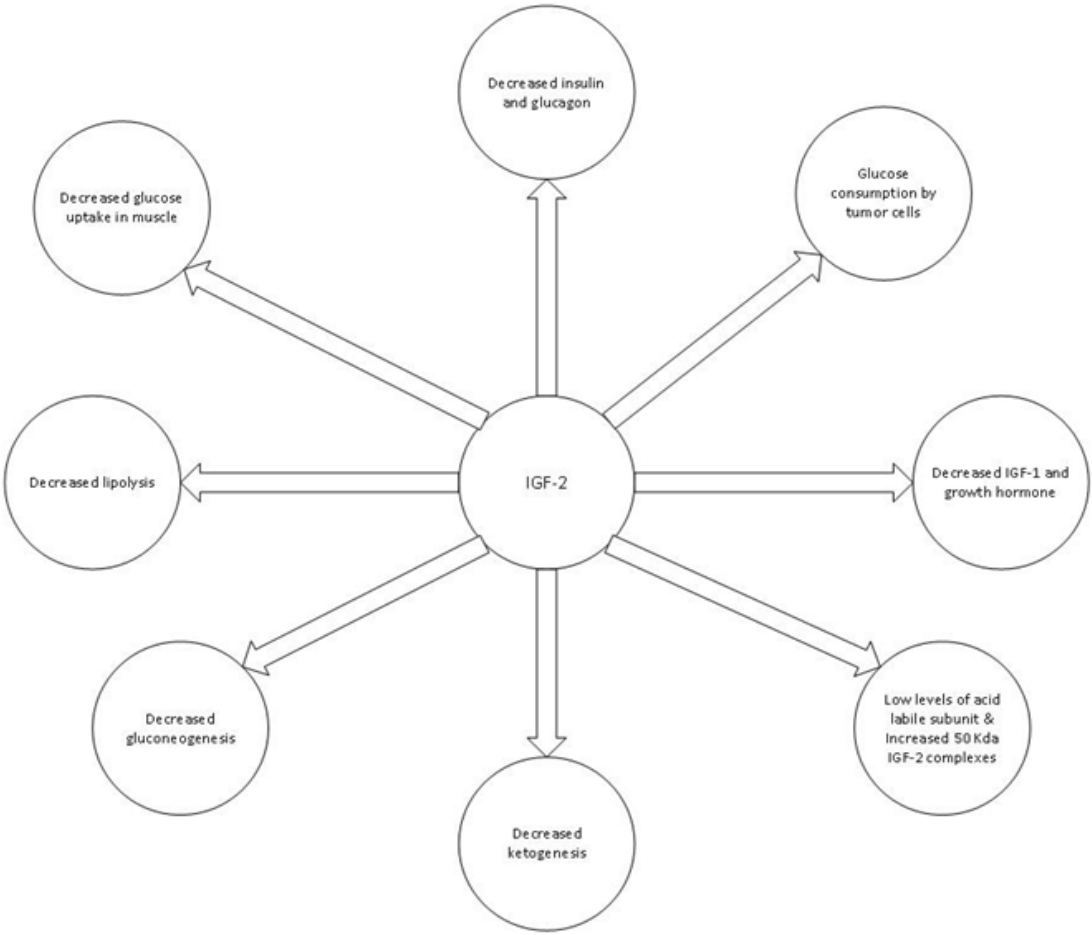


**Figure 1:** IGF-2 has multiple actions which can contribute to the development of hypoglycemia.

Normally IGF-2 exists in two forms a 150 kda form which comprises about 80% of IGF-2 and a 50 kda form which comprises about 20%. IGF-2omas can lead to impaired formation of 150kda fraction of IGF-2 and increased formation of the 50kda fraction. This smaller molecule can easily pass out of the vascular space and interact with insulin receptors causing hypoglycemia. Pro IGF-2 can also form complexes with IGF binding protein 3 and acid labile subunit (**ALS**) which increases the biological half-life [18,19].

## ETIOLOGY

Non islet cell hypoglycemia can be seen secondary to epithelial tumors and mesenchymal tumors. The initial report on this syndrome was done in a case of hepatocellular carcinoma in 1929 [4]. Since then the list of tumors which can cause NICTH has been growing (Table 1). The most common tumors to cause NICTH are hepatocellular carcinoma and fibrosarcoma. Typically these tumors are very large, however occurrence of NICTH does not distinguish between aggressive and benign tumors nor does it have any prognostic significance [3].

**Table 1:** Tumors associated with non-islet cell hypoglycemia.

| | |
|---|---|
| 1. | Hepatocellular carcinoma |
| 2. | Fibrosarcoma |
| 3. | Mesothelioma |
| 4. | Adrenocortical carcinoma |
| 5. | Hemangiopericytoma |
| 6. | Stomach carcinoma |
| 7. | Pancreatic carcinoma |
| 8. | Medullary thyroid carcinoma |
| 9. | Lymphoma/Leukemia |
| 10. | Carcinoid syndrome |

NICTH is likely under diagnosed due to a lack of awareness. Epidemiological data suggests that with an increased prevalence of hepatitis B and hepatitis C an increased incidence of hepatocellular carcinoma can be expected. While this is expected to lead to more cases of NICTH that has not been the case this is likely secondary to under diagnosis of NICH [20].

## CLINICAL PRESENTATION

About 50% patient with NICH present with symptoms and signs of hypoglycemia, in the other 50% they may present with loss of appetite, weight loss, abdominal pain or mass. The latter half of these patients most often have a diagnosis of the tumor before the onset of hypoglycemia.

Typically hypoglycemia is seen in the fasting state. Post prandial hyperglycemia may be observed secondary to the suppression of insulin by IGF-2. Rarely hypokalemia can be observed due to activation of the insulin receptor [21].

Hypoglycemia secondary to IGF-2 differs in that neuroglycopenic symptoms predominate, in fact most patients may present with confusion, psychosis, and amnesia. Lack of judgment is an early sign of neuroglycopenia which can hamper the patient to make decisions in the best interest of their health. The brain is dependent on glucose (first line) or ketones (second line) for its energy needs and therefore is affected the most in cases of NICH. This predominance of neuroglycopenic symptoms is due to the lack of ketogenesis as compared to fasting hypoglycemia [22,23].

This lack of ketogenesis is due to activation of the insulin receptor by IGF-2 which also leads to inhibition of lipolysis, glycogenolysis, and gluconeogenesis. Overproduction of IGF-2 or pro IGF-2 leads to suppression of glucagon and growth hormone which contributes to the hypoglycemia [3].

Acromegaloid changes can be a rare feature of IGF-2 producing tumors secondary to activation of IGF-1 related receptors. Trivedi et al described a woman with acromegaloid features and pelvic clear cell sarcoma which resolved after excision of the tumor. The combination of hypoglycemia and acromegaly can also be seen in multiple endocrine neoplasia 1 (**MEN 1**) which is a triad of pituitary, pancreatic and parathyroid adenomas [24-26].

## DIAGNOSIS

The initial step in the diagnosis of hypoglycemia is to document all steps of the Whipple's triad. The signs and symptoms of hypoglycemia are non-specific therefore care must be taken before ascribing the patient's symptoms to hypoglycemia [2]. False positive low blood sugars may also be noted in hematological disorders like leukemia and polycythemia vera [27]. The next step is to obtain a detailed history and exam needs to rule out systemic diseases and medications which could contribute to hypoglycemia (Table 2) [3].

**Table 2:** Diseases and medications known to cause hypoglycemia.

| |
|---|
| Adrenal insufficiency |
| Sepsis |
| Renal failure |
| Liver failure |
| Starvation |
| Medications (Insulin, sulfonylureas, quinine, alcohol, pentamidine, gatigloxacin) |

If no cause has been found then measurement of plasma insulin, C peptide, proinsulin and beta- hydroxybuytrate in a hypoglycemic state would help differentiate insulinoma, NICH and insulin independent hypoglycemia (Table 3) [2].

**Table 3:** Differential diagnosis of non-islet cell hypoglycemia.

| | Insulin (3 mcu/ml) | C-peptide (0.2mmol/L) | Proinsulin 5 pmol/L | Beta-hydroxybutyrate (2.7 mmol/L) |
|---|---|---|---|---|
| Insulinoma/ Sulfonylurea | High | High | High | Low |
| Exogenous insulin | High | Low | Low | Low |
| Non islet cell hypoglycemia | Low | Low | Low | Low |
| Insulin independent hypoglycemia | Low | Low | Low | High |

Mcu=Microunits; Mmol=Millimole; Pmol=Picomoles; L=Liter; Ml=Milliliter.

Further evaluation of NICH consists of measuring IGF-1 and IGF-2 levels. Typically IGF-1 levels are suppressed and IGF-2 levels are high or normal. The IGF-1 suppression is secondary to the negative feedback mechanism activated by pro IGF-2 [21]. The normal molar ratio of IGF-2: IGF-1 is 3:1. A ratio of >10:1 in the context of recurrent hypoglycemia is diagnostic of NICH [28,29]. Of note the ratio of IGF-1 and IGF-2 may be high in cachexia and sepsis however in both instances levels of IGF-1 and IGF-2 are subnormal [30]. Several radioimmunoassays have been developed to measure pro IGF-2 however none of them are commercially available [31].

# TREATMENT

## Tumor Directed Therapies

The definitive treatment of NICH is to reduce the tumor burden. Surgical excision is the preferred modality Hypoglycemia has been known to immediately resolve after surgery. In instances where complete excision is possible palliative debulking is recommended [32-34]. Neoadjuvant radiation and chemotherapy have also been successful in alleviating hypoglycemia [35].

# MEDICAL THERAPIES

## Glucocorticoids

Glucocorticoids can alleviate hypoglycemia in NICH by counteracting many of the actions of IGF-2. They increase gluconeogenesis, lipolysis and inhibit the peripheral uptake of glucose. Teale et al have also shown that glucocorticoids can suppress pro IGF-2 production secondary to decreased production or increased clearance. Glucocorticoids need to be titrated to achieve euglycemia however this effect lasts only as long as the patient is taking the steroids [32].

# GLUCAGON

Glucagon by increasing glycogenolysis and gluconeogenesis can alleviate hypoglycemia however this best used as an adjunctive therapy. Continuous glucagon infusion have been used as mono therapy with success. A positive glucagon stimulation test predicts increased chances of success. The effect may be blunted as the tumor burden increases [36].

# RECOMBINANT GROWTH HORMONE

Growth hormone by stimulating peripheral glucose uptake, stimulating gluconeogenesis may aid in the treatment of NICH. However it also increases IGF-2., IGF binding protein 3 and acid labile subunit levels. This increases the production of 150 Kda and decreases the production of 50 Kda complexes the former are less efficacious at causing hypoglycemia. There is also concern that growth hormone may promote growth of tumor cells. However octreotide has not been useful in resolving hypoglycemia in NICH [37]. Chung et al did note a reduction in the pro IGF-2 levels with a continuous infusion of somatostatin [38].

## FUTURE THERAPIES

A number of potential therapies to combat IGF-2 mediated hypoglycemia are being investigated. One of the approaches is the development of an antibody to IGF-2 which would prevent its interaction with the insulin receptor. Prince et al have developed a soluble fusion protein which comprises of a human IgG1Fc domain and a modified domain-11of the IGF-2 receptor. A 1 amino acid substitution (IGF-2RE1554k-Fc protein) enhanced the specificity of the antibody [39]. Feng et al have developed an antibody IgG1m610 which has specificity to IGF-2 and pro IGF-2 [40].

Endogenous mannose-6-phosphate/IGF-2R acts as a sink for IGF-2. Overexpression of this receptor can potentially decrease IGF-2 levels. It has also been suggested that mannose-6-phosphate/IGF-2R is a tumor suppressor [2,37].

Another potential approach is to enhance the conversion of pro IGF-2 to mature IGF-2. This can be achieved by upregulating prohormone convertase which cleaves pro IGF-2 to mature IGF-2 or by creating a specific abzyme.

## CONCLUSION

NICH occurs due to the overproduction of IGF-2 and pro IGF-2 which can activate the insulin receptor and cause hypoglycemia. It is seen in association with various tumors most commonly hepatocellular carcinoma. Overproduction of IGF-2 and pro IGF-2 can inhibit glucose production, lipolysis, peripheral uptake of glucose, and secretion of counter regulatory hormones which results in hypoglycemia. Low insulin, proinsulin, c peptide and beta hydroxybutyrate in the context of hypoglycemia would be consistent with NICH. Treatment is aimed at reliving the tumor burden through surgery or radiotherapy. In cases where it is not feasible glucocorticoids may be used. Future potential therapies include development of IGF-2 antibodies, and enhancing conversion of pro IGF-2 to mature IGF-2 by upregulating the activity of prohormone convertase or by creating a specific abzyme.

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