

A Case of Non-Islet Cell Tumor Hypoglycemia Due to Gastrointestinal Stromal Tumor in a Patient with Neurofibromatosis.

Gnanathayalan S.W¹, Sivageethan S¹, Bulugahapitiya U¹

¹ National Hospital of Sri Lanka

Abstract

Introduction:

Non-Islet Cell Tumor Hypoglycemia (NICTH) is a rare but serious complication of malignancy leading to recurrent episodes of severe hypoglycemia and impaired quality of life. It is commonly due to mesenchymal and epithelial tumors. The underlying mechanism is overproduction of insulin-like growth factor-2 (IGF-2) and its precursors that activate the insulin receptor. Patients with Neurofibromatosis type 1 (NF-1) have a high incidence of GISTs. GISTs are rare mesenchymal tumors. This case describes a case of NICTH due to GIST with hypoglycemia as the first presentation.

Case Description:

A 57-year-old man with NF-1 was evaluated for frequent severe hypoglycemic episodes including seizures and loss of consciousness. He also reported reduced appetite, weight loss and melena. He denied history of diabetes mellitus, alcohol abuse or illegal drug abuse. Initial biochemical assessment showed anemia with normal liver, renal and thyroid profile with normal cortisol level. Further laboratory assessment during an episode of hypoglycemia with plasma glucose of 35 mg/dL revealed very low levels of insulin, C-peptide and beta-hydroxybutyrate. IGF-1 was suppressed. Unfortunately, IGF-2 level could not be done due to unavailability in Sri Lankan settings. He had a dramatic rise in blood glucose level with glucagon administration, suggesting the presence of insulin like substance. Computed Tomography (CT) of the chest, abdomen and pelvis showed multiple large liver lesions and a large enhancing paraaortic lesion. Biopsy of the liver lesion with immune staining confirmed metastatic GIST. He was started on imatinib. He is treated with prednisolone for NICTH with good response in hypoglycemia.

Conclusion:

In patients with an underlying malignancy, if clinical and biochemical findings are compelling for NICTH, additional assessment with IGF-2 levels is not usually necessary to make the diagnosis. The Glucagon challenge test is a supportive investigation for the diagnosis. Glucocorticoids might be effective to control hypoglycemia and improve quality of life if tumor can't be surgically treated.

Keywords: Non-islet Cell Tumor Hypoglycemia(NICTH), Hypoglycemia, Insulin-like growth factor 2 (IGF-2), Glucocorticoids

Correspondence email: winsgshahini@gmail.com

 <https://orcid.org/0000-0001-6348-6229>

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. (CC BY 4.0)

Introduction

Non-islet tumor hypoglycemia (NICTH) is a rare paraneoplastic manifestation associated with malignancies especially of mesenchymal and epithelial origin^[1]. As it is a rare cause of hypoglycemia, it is seldom encountered by Endocrinologists. It causes recurrent, refractory, and severe episodes of hypoglycemia, so prompt recognition is vital to institute appropriate management. The underlying

mechanism is overproduction of insulin-like growth factor-2 (IGF-2) and its precursors that activate the insulin receptor^[2]. Diagnosis is challenging due to its rarity and lack of availability to do IGF-2 levels in many countries. The most effective mode of management is complete resection of the culprit tumor. In the setting of unresectable burden of tumor especially with metastasis, glucocorticoids may

be used to reduce hypoglycemic episodes and improve quality of life [3].

Gastrointestinal stromal tumors (GISTs) are mesenchymal or sarcomatous tumors of the gastrointestinal tract. The incidence of GISTs is low [4]. Histologically, they show features of smooth muscles and nerve sheath cells. NICTH has been very rarely reported with these tumors [5]. Patients with Neurofibromatosis type 1 (NF-1) have a high incidence of GISTs [6]. Here, we report a rare case of NICTH due to GIST in a patient with NF-1.

Case Presentation

A 57-year-old male patient with NF-1 was evaluated for frequent episodes of severe hypoglycemic events including seizures and loss of consciousness for one month duration. He also reported loss of appetite, loss of weight and melenas for the same period. Hypoglycemia occurred during both fasting and postprandial state, and he had almost daily episodes. During the episodes of hypoglycemia, requiring hospital admissions, he needed multiple vials of 50% dextrose followed by 10 % dextrose infusion to correct hypoglycemia. He denied any history of diabetes mellitus, alcohol abuse or illicit drug use. He had no significant past medical or surgical history except for NF-1. He denied family history of NF, malignancies, or multiple endocrine neoplasia syndromes (MEN). Physical examination was significant for pallor, hepatomegaly, and cutaneous manifestations of neurofibromatosis type 1.

Initial biochemical assessment showed microcytic hypochromic anemia with normal liver, renal, and thyroid profile. Cortisol response was normal during short synacthen test (SST). Further laboratory assessment during a spontaneous episode of hypoglycemia with plasma glucose of 35 mg/dL revealed very low levels of insulin, C-peptide and beta-hydroxybutyrate. IGF-1s and growth hormone levels were suppressed (Table 1). Unfortunately, IGF-2 level could not be done due to unavailability in Sri Lankan settings. He had a dramatic rise in blood glucose level with glucagon administration, suggesting the presence of insulin like substance.

Endoscopic assessment of upper and lower gastrointestinal tract did not reveal anything significant. Ultrasonography of abdomen showed a large hyperechoic liver lesion and two other mass lesions in the celiac region. In further imaging with contrast enhanced computer tomography of abdomen, there were multiple enhancing defined lesions in the liver with the largest one measuring 9.3 cm × 8.8 cm × 8.6 cm. There were also well-defined enhancing lesions on the right side of the aorta. A biopsy of the liver lesion with ultrasound guidance showed tumor tissue composed of nests and sheets of polygonal and spindle cells. Tumor cells showed strong cytoplasmic positivity with CD 117 and vimentin, but negative for Hep par 1, synaptophysin and pan-cytokeratin (Figure 1). The diagnosis of GIST with liver metastasis was made. Serum alpha fetoprotein was normal. Further imaging was not performed to identify the primary tumour in the gastrointestinal tract.

He was initiated on high dose glucocorticoids (prednisolone 40 mg daily) as soon as the diagnosis of NICTH was made, even before the histological confirmation, as he continued to be hypoglycemic.

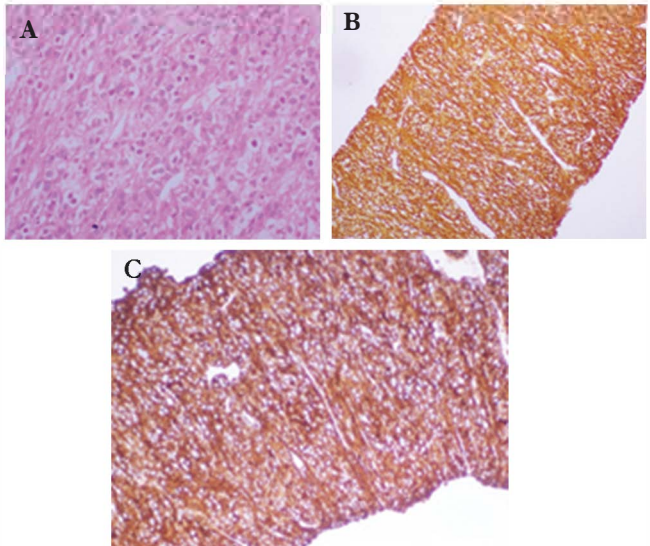


Figure 1: A, Spindle cell neoplasm comprising nests and sheets of fusiform and spindle cells (H&E). B, Positive immunostaining with CD 117. C, Positive staining with vimentin

Table 1: Relevant biochemistry results

Tests	Patient Value	Normal value
Plasma glucose (mg/dl)	35	
C-peptide (ng/ml)	0.14	0.78 – 5.19 [>0.6 during hypoglycemia indicates hyperinsulinism]
Insulin (mU/L)	< 1	2 – 25 [>3 during hypoglycemia indicates hyperinsulinism]
Beta hydroxybutyrate (mmol/L)	Not detected	
IGF-1 (ng/ml)	11	65-222
Growth hormone (ng/ml)	0.2	0.4 - 10
Glucagon challenge test	Dramatic rise of plasma glucose from 50 mg/dl to 86 mg/dl at 30 minutes of glucagon administration	Rise in blood glucose ≥ 25mg/dl within 30 minutes after glucagon is suggestive of the presence of insulin or insulin like substance.

Proper measures were taken to protect the bone and stomach from high dose steroids. He had a good response with a marked reduction in frequency and severity of hypoglycemia. After the histological diagnosis of GIST was made, imatinib was started by the oncology team as he was not a suitable candidate for the surgical removal of the tumor due to the presence of liver metastasis. The patient and his family were explained about the disease state and its bad prognosis. Further investigations were not arranged to identify the site of the primary tumour in the gastrointestinal tract. At the time of writing this report, three months later the initiation of prednisolone, he is free of severe hypoglycemic episodes with improved quality of life, despite persistence of loss of appetite and loss of weight.

Discussion

Hypoglycemia is uncommon in non-diabetic patients. Hypoglycemia should be confirmed with Whipple's triad before evaluating further. Exclusion of the possibilities of drugs, critical illnesses and hormonal deficiencies causing hypoglycemia is essential. In the absence of these causes, endogenous hyperinsulinism is the commonest etiology. Insulinomas, nesidioblastosis, insulin autoimmune syndrome and insulin secretagogues are the main causes of endogenous hyper-insulinemic hypoglycemia. Insulin, C-peptide, and beta hydroxybutyrate should be measured during an episode of hypoglycemia to confirm endogenous hyperinsulinism [7]. NICTH is a rare cause of non-diabetic hypoglycemia due to excessive tumour secretion of precursor IGF-2 molecules. It leads to hypoinsulinemic hypoglycemia. It frequently occurs with mesenchymal and epithelial tumors, with hepatocellular carcinoma as the most common malignancy reported to cause it [1]. Mesenchymal tumors more frequently associated with NICTH are fibrosarcoma and mesothelioma [1]. GIST is a rare mesenchymal tumor. Therefore, NICTH is a rare manifestation of a rare disease. The incidence of GISTs is higher in patients with NF-1 in compared to normal population [6]. The other endocrine conditions known to be associated with NF-1 are pheochromocytomas/paragangliomas, primary hyperparathyroidism, and gasteropancreatic neuroendocrine tumors [8]. Tumors causing NICTH are usually larger with inability to be resected completely. Most of the reported cases of NICTH had been diagnosed after the diagnosis of the primary malignancy unlike our case where hypoglycemia precedes the tumor diagnosis [11].

NICTH occurs mainly due to increased glucose utilization and inhibition of glucose release from the liver due to tumoral secretion of precursor IGF-2 molecules (big IGF-2). IGF-2 is a single chain polypeptide (7.5 kDa). It is expressed in the liver and is present at constant levels in adults [9]. In normal circumstances, 80% of IGF-2 is bound to IGF-binding protein-3 (IGF-BP3) and acid-labile subunit (ALS) forming a large complex (approximately 150 kDa) which due to its large size, cannot cross the capillary membranes and thus has limited biological activity [2,10]. Only a small

proportion is bound to only IGF-BP3 and crosses the membranes to be active biologically in the circulation. In NICTH, abnormal processing of IGF-2 results in high concentrations of big IGF-2 (10-20 kDa) in the plasma [2]. These big IGF-2 molecules are unable to bind to ALS and bound to IGF-BP3 only. This 60 kDa structure readily crosses capillary membranes leading to higher concentrations of biologically active IGF-2 and causes hypoglycemia by exerting insulin like effects. [2,10]. NICTH due to excessive secretion from IGF-1 has been very rarely reported in literature [9].

The measurement of IGF-2 level is commercially not available in many countries and it is very expensive. The diagnosis of NICTH can be made in patients with a large tumor if they have hypo-insulinemic hypoglycemia with suppressed c-peptide level [11]. Suppressed beta hydroxybutyrate should be demonstrated to confirm the presence of insulin like substance [7]. Suppressed levels of IGF-1 and growth hormone levels further support the diagnosis. In the presence of hypo-insulinemic hypoglycemia with suppressed beta hydroxybutyrate level, the glucagon challenge test is a useful adjunct to confirm the diagnosis of NICTH where glucose response to glucagon administration is typically dramatic with more than 25 mg/dl within 30 minutes unless there is low glucagon stores due to extensive tumor infiltration of the liver [12,13]. In the settings where IGF-2 level can be measured, elevated IGF-2/IGF-1 ratio is used to confirm the diagnosis. [11]

The most effective management of NICTH is surgical removal of the tumor. Unfortunately, most tumors causing NICTH are larger and unable to be removed completely. In surgically incurable patients, glucocorticoids at higher doses have been effective in improving hypoglycemia and improving the quality of life [3]. Frequently, prednisolone 30 to 60 mg daily or the equivalent doses of other steroid preparations have been used. The beneficial effect of glucocorticoids is thought to be due to reduction of IGF-2 secretion by the tumor and increase in the clearance of it. But the exact mechanisms are not known [3]. The usual medical therapies used in other forms of non-diabetic hypoglycemia such as diazoxide and octreotide as well as the systemic chemotherapy had been ineffective in the reported cases [11].

Conclusion

NICTH is a rare but life-threatening paraneoplastic phenomenon due to excessive secretion of precursor IGF-2 molecules. In patients with an underlying malignancy, if clinical and biochemical findings are compelling for NICTH, additional assessment with IGF-2 levels is not usually necessary to make the diagnosis. Glucocorticoids might be effective to control hypoglycemia and improve quality of life if tumor can't be surgically treated.

Abbreviations

NICTH	non-islet cell tumor hypoglycemia
GIST	Gastrointestinal stromal tumor
IGF	Insulin like growth factor

References

1. de Groot JWB, Rikhof B, van Doorn J, et al. Non-islet cell tumor-induced hypoglycemia: a review of the literature including two new cases. *Endocr Relat Cancer*. 2007;**14**(4):979-993.
2. Dynkevich Y, Rother KI, Whitford I, et al. Tumors, IGF-2, and hypo-glycemia: insights from the clinic, the laboratory, and the historical archive. *Endocr Rev*. 2013;**34**(6):798-826.
3. Kimberly Voon, Aaron Simpson, Peter Gerard Fegan, John P Walsh, Three Cases of Non-islet Cell Tumor Hypoglycemia Highlighting Efficacy of Glucocorticoid Treatment, *JCEM Case Reports*, Volume 1, Issue 4, July 2023, luad045, <https://doi.org/10.1210/jcemcr/luad045>
4. Saeed Z, Taleb S, Evans-Molina C. A case of extragastrointestinal stromal tumor complicated by severe hypoglycemia: a unique presentation of a rare tumor. *BMC Cancer*. 2016;**16**(1):930. Published 2016 Dec 1. doi:10.1186/s12885-016-2968-8
5. Guiteau J, Fanucchi M, Folpe A, Staley CA 3rd, Kooby DA. Hypoglycemia in the setting of advanced gastrointestinal stromal tumor. *Am Surg*. 2006;**72**(12):1225-1230. doi:10.1177/000313480607201216
6. Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. *Am J Surg Pathol*. 2006;**30**(1):90-96. doi:10.1097/01.pas.0000176433.81079.bd
7. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;**94**(3):709-728. doi:10.1210/jc.2008-1410
8. Alshahrani A, Abuoliat Z, Alshahrani AS, Al Balwi MA. Prevalence of Associated Endocrine Diseases in Patients with Neurofibromatosis Type 1. *Ancenna J Med*. 2022;**12**(1):16-20. Published 2022 Feb 18. doi:10.1055/s-0041-1742197
9. Iglesias P, Diez JJ. Management of endocrine disease: a clinical update on tumor-induced hypoglycemia. *Eur J Endocrinol*. 2014;**170**(4):R147-R157. Published 2014 Mar 14. doi:10.1530/EJE-13-1012
10. Livingstone C, Borai A. Insulin-like growth factor-II: its role in metabolic and endocrine disease. *Clin Endocrinol (Oxf)*. 2014;**80**(6):773-781. doi:10.1111/cen.12446
11. Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. *J Clin Endocrinol Metab*. 2014;**99**(3):713-722. doi:10.1210/jc.2013-3382
12. Placzkowski KA, Vella A, Thompson GB, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. *J Clin Endocrinol Metab*. 2009;**94**(4):1069-1073. doi:10.1210/jc.2008-2031
13. O'Brien T, O'Brien PC, Service FJ. Insulin surrogates in insulinoma. *J Clin Endocrinol Metab*. 1993;**77**(2):448-451. doi:10.1210/jcem.77.2.8345050