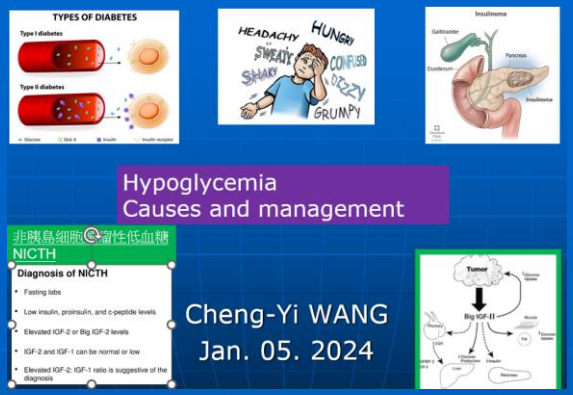


Case discussion Hypoglycemia and Illness Scripts

Hypoglycemia Causes and management

case discussion

Chang-Yi WANG

2024.01.05

Whipple's Triad

- Hypoglycemic symptoms
- Low plasma glucose (<50,<70 DM)
- Relieved by administration of glucose

Differential Diagnosis

	Insulin	C-peptide	Proinsulin	Beta-Hydroxybutyrate
Insulinoma	↑	↑	↑	↓
Autoimmune	↑↑	↑↑	↑↑	↓
Insulin-like Growth Factor (IGF)	↓	↓	↓	↓
Not insulin mediated	↓	↓	↓	↑

Case 1,病史

- 一名 76 歲女性，有 3 年反覆心悸、手震顫和出汗病史，1 個月後這些癥狀加重。癥狀通常伴有饑餓感。在嚴重發作期間，**她有異常行為和意識模糊**。

您在病史上還想知道哪一些狀況呢?

一名 76 歲女性，有 3 年反覆心悸、手震顫和出汗病史，1 個月後這些癥狀加重。癥狀通常伴有饑餓感。在嚴重發作期間，她有異常行為和意識模糊。

您在病史上還想知道哪一些狀況呢?

- 1.有沒有糖尿病,有沒有吃藥降低血糖?-----沒有
- 2.有沒有抽血檢查血糖結果----有
- 3.有沒有心臟病史,有沒有做過心電圖,-曾有高血壓及心絞痛
- 有沒有做過心導管或冠狀動脈攝影相關之檢查(CTA or
- coronary angiography)----有, ECG心房顫動（AF）
- 4.有沒有甲狀腺疾病:甲狀腺機能過高?體重有無變化是否明顯減低.一醫師說不是甲狀腺機能亢進，也沒有.體重減輕
- 5.有沒有中風病史,是否吃阿司匹林預防----沒有吃阿司匹林

一名 76 歲女性，有 3 年反覆心悸、手震顫和出汗病史，1 個月後這些癥狀加重。癥狀通常伴有饑餓感。在嚴重發作期間，她有異常行為和意識模糊。

您在病史上還想知道哪一些狀況呢?

- 如果要做一項檢查來釐清事實,你一定要挑哪一種檢查. Why?
- 1.CBC
- 2.Blood ammonia,
- 3.Blood sugar
- 4. ECG
- 5. Brain CT

- 過去發作時,曾經多次到診所檢查,也抽血檢查血糖
- 發作期間她的靜脈血糖水準為 1.4-2.8 mmol/L
- 偏低。進食或靜脈注射葡萄糖可緩解癥狀。

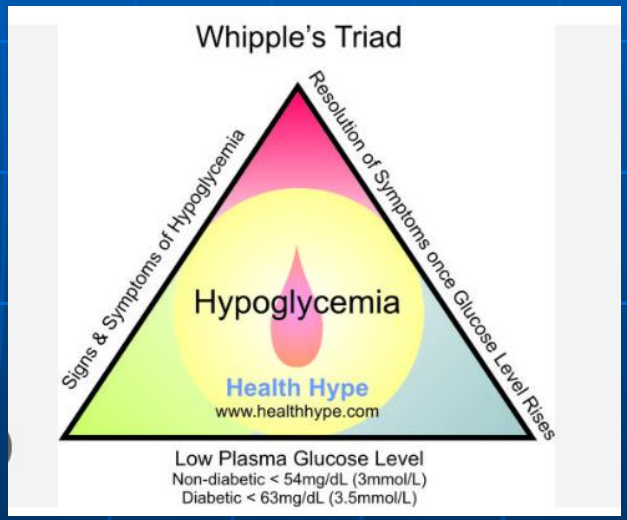
這種情況代表什麼意思?
何謂Whipple's triad ?

3.0 mol/L = 54 mg/dl
1.4 x 18 = 25.2
2.8 x18 = 50.4

低血糖的診斷

- 臨床上，低血糖的診斷有其嚴謹的定義，那就是要符合所謂的『惠普低血糖診斷三要項』Whipple’ s Triad。這個有名的『三要項』是由外科醫師艾倫惠普（Allen Oldfather Whipple）在上個世紀30年代所提出來的。『三要項』的內容包括：
- （1）有低血糖的症狀
- （2）有症狀時測量到的血糖值偏低
- （3）補充糖分之後症狀緩解。

下一步要怎麼辦?



American Association of Endocrine Surgeons 2021.11.,10
https://twitter.com/TheAAES/status/1458434557728989184
(accessed on2023.12.18)

- 病人兩年前曾在一家地區醫院接受檢查。75 g 口服葡萄糖耐量試驗和胰島素-C 肽釋放試驗顯示
- 血清胰島素水準極高，
- 血糖較低，提示內源性高胰島素血症（表1).

表1

口服葡萄糖耐量試驗和胰島素-C 肽釋放試驗的結果。

首次住院			
時間（小時）	葡萄糖（mmol/L）	胰島素[1]（2.6–23 μIU/毫升）	C 肽（1.1–4.4 ng/mL）
0	2.94	> 1000	6.56
1	6.36	> 1000	11.74
2	8.82	> 1000	14.21
3	11.4	> 1000	20.67
4	5.62	> 1000	16.91
5	1.27	> 1000	11.97

第二次住院				
時間（小時）	葡萄糖（mmol/L）	胰島素[1]（μIU/毫升）	胰島素[2]（μIU/毫升）	C肽（ng/mL）
0	5.4	488.1	20.34	6.71
2	11.5	> 1000	100.5	20.6

[1]Insulin tested using the chemiluminescence method
使用化學發光法測試胰島素
[2]Insulin tested after 30% polyethylene glyprecipitation
30%聚乙二醇沉澱后測試胰島素

IAA(-) ,HbA1c:5.7%

- 定性IAA測試（免疫印跡測定;Blot Biotech， Shenzhen，China）呈陰性。抗核抗體譜、免疫球蛋白（IgG、IgM 和 IgA）和補體（C3 和 C4）檢測呈陰性。
- 血紅蛋白A1c水準為5.7%。
- 生長激素、胰島素樣生長因數-1（ insulin-like growth factor-1, ）、甲狀腺激素、生殖激素和皮質醇的水平均在參考範圍內。
- 血液和尿酮體呈陰性。

接下來要怎麼辦?

--- → 找出低血糖的病源

- 增強腹部磁共振成像和正電子發射斷層掃描-計算機斷層（ positronemission tomography-computed tomography s ）掃描未見明顯發現。
- 她有高血壓和冠心病病史，但沒有甲狀腺疾病、惡性腫瘤或糖尿病病史。
- 她從未接觸過**降糖药**或外源性胰島素，她的同居者也沒有。**由於低血糖的原因尚不清楚，她被轉移到另一家醫院。**

Case 1,

- 在第二家醫院，發現她的胰島素水準在低血糖期間顯著升高（245 μIU/mL;化學發光法）。然而，聚乙二醇沉澱后檢測到的遊離胰島素濃度要低得多（表1).定性IAA測試呈陰性。考慮診斷為病因不明的自身免疫性肝炎。

- Follow-up tests revealed a fasting insulin level of 56.72 mIU/mL and a C-peptide level of 3.38 ng/ mL. The hypoglycemia stopped after this treatment. Six months before the current admission, the hypoglycemia recurred, and the insulin and C-peptide levels again increased ·

- 第3次住院： random blood glucose, 2.4 mmol/L; plasma insulin, >300 mIU/mL (1.9–23 mIU/mL); and C peptide, 11.6 ng/mL (1.1–4.4 ng/mL).化學發光試驗（深圳YHLO）顯示非常高的IAA滴度，為61.8·截止指數（cutoff index, COI）：COI<0.9，無反應性; COI ≥ 0.9 至 < 1.1，不確定;和 COI ≥ 1.1，反應性。因此，我們進行了進一步的**IAA亞型分析**，確定為主要亞型IgG1和IgG3。此外，電化學發光用於驗證這一發現，結果非常積極。部研究顯示沒有胰島素瘤的證據。其他相關檢查未見明顯異常。考慮到病史，我們診斷為自身免疫性低血糖(AIH)，並用口服甲潑尼龍治療患者，起始劑量為4mg，每日2次;這種治療降低了低血糖的頻率，並逐漸降低 insulin, C-peptide, and IAA levels

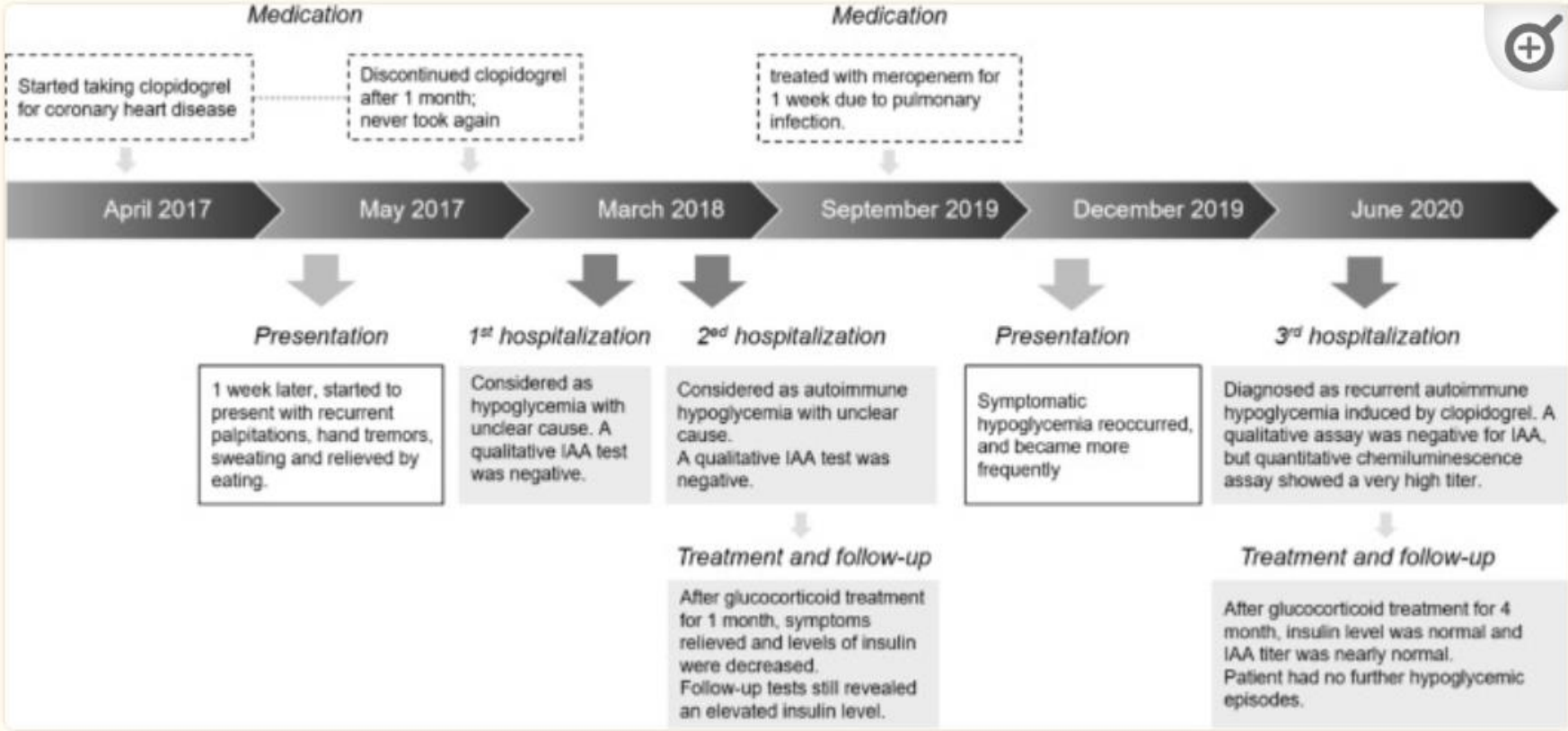
- 詳細的用藥史顯示，3年前，她在首次出現低血糖癥狀前1周,開始服用氯吡格雷
- (Clopidogrel)治療冠心病和心房顫動;這些藥片 在1個月後停葯

A detailed medication history revealed that 3 years ago, she started taking clopidogrel for coronary heart disease and atrial fibrillation 1 week before the first hypoglycemic symptoms; these tablets were discontinued 1 month later. Nine months ago, three months before hypoglycemia recurrence, she was treated with meropenem for 1 week due to an infectious fever .

Its chemical structure is similar to that of imipenem (6), which is known to cause AIH.

Moreover, both drugs contain **sulfhydryl groups**, which can induce hypoglycemia. In addition, after the first course of methylprednisolone, the insulin level decreased but remained high, suggesting that the clopidogrel-induced IAAs were not completely eliminated. Thus, the recurrence might be ascribed to residual IAAs or a meropenem-triggered amplified immune response.

Timeline of Medical Event.



Diagnostic evidence

- 1.Hypoglycemia : 一名非糖尿病患者表現出反覆出現的自主神經興奮癥狀（心悸、手震顫和出汗）、饑餓和神經系統葡萄糖缺乏癥狀（異常行為和意識模糊）。在癥狀階段，她的血糖水準為 <2.8 mmol/L。通過進食或輸注葡萄糖可緩解癥狀，這與Whipple’ s Triad一致，證實了低血糖.
- 2.Roots of hypoglycemuia
- 低血糖期間血漿胰島素和C肽水平顯著升高。
- 胰島素/C 肽摩爾比為 > 1，提示**内源性高胰島素血症**（3）
- 聚乙二醇沉澱后胰島素回收率顯著降低，表明存在胰島素-抗體複合體（3，4）

時間（小時）	葡萄糖（mmol/L）	胰島素[1]（μIU/毫升）	胰島素[2]（μIU/毫升）	C肽（ng/mL）
0	5.4	488.1	20.34	6.71
2	11.5	> 1000	100.5	20.6

[1]Insulin tested using the chemiluminescence method
使用化學發光法測試胰島素
[2]Insulin tested after 30% polyethylene glyprecipitation
30%聚乙二醇沉澱后測試胰島素

The Molar Ratio of Insulin to C-Peptide.

- Lebowitz MR, Blumenthal SA. The Molar Ratio of Insulin to C-Peptide. An Aid to the Diagnosis of Hypoglycemia Due to Surreptitious (or Inadvertent) Insulin Administration. Arch Intern Med (1993) 153(5):650–5.
- 暗中（或無意） **insulin administration-→hypoglycemia**
- After beta-cell stimulation by carbohydrate or other secretagogues, insulin and C-peptide are secreted into the portal vein in a 1:1 molar ratio. A large fraction of endogenous insulin is cleared by the liver, whereas C-peptide, which is cleared primarily by the kidney and has a lower metabolic clearance rate than insulin, traverses the liver with essentially no extraction by hepatocytes. Hence, **the molar ratio of insulin to C-peptide in peripheral venous blood (ICPR) should be less than 1.0 during fasting and feeding**, unless exogenous insulin is introduced into the systemic circulation. Consequently, an ICPR in excess of 1.0 in a hypoglycemic patient argues persuasively for surreptitious or inadvertent insulin administration and against insulinoma (or sulfonylurea ingestion) as the cause of the hypoglycemia.

- 3. IAA: (-)
- IAA 定性檢測結果為陰性，但仍考慮自身免疫性低血糖。
- 糖皮質激素治療緩解了低血糖，並顯著降低了胰島素和C肽值，但未
- 導致胰島素水準正常。
- 4.The third hospitalization
- 住院期間，患者胰島素水平明顯升高，定量試驗顯示IAA滴度升高;自身免疫性低血糖 (AIH)的診斷很明確。
- **她服用了氯吡格雷片劑。誘發了自身免疫性低血糖;**
- 患者在復發前3個月接受了美羅培南治療1周。儘管迄今為止尚未報導美羅培南誘導自身免疫性肝炎的病例，但其化學結構與亞胺培南相似 （6），亞胺培南已知會引起自身免疫性肝炎。此外，這兩種藥物都含有巯基，可誘發低血糖.

- 5.藥物誘導的自身免疫性低血糖的發病時間差異很大，從藥物暴露后數天到數月甚至數年不等（2,7-10）。平均而言，發病時間為 4-6 周 （11， 12）。許多由非降糖藥物引起的自身免疫性低血糖病例是自限性的。平均而言，自發緩解發生在 3-6 個月內 （13）。持續性復發性低血糖可持續 2.1-21.9 年 （14）
- 6.藥物治療包括阿卡波糖、生長抑素類似物、二氮嗪、糖皮質激素、硫唑嘌呤和利妥昔單抗 （2）。潑尼松是最常見的選擇;初始劑量為 30-60 mg/d，逐漸減少，直到 IAA 檢測呈陰性，這可能需要 2 周到 1 年./
- **7.在難治性低血糖的情況下，血漿置換術可能會迅速降低IAA 滴度（18），並且利妥昔單抗也已成功治療以消耗 B 淋巴細胞（19）。**
-

保栓通Clopidogrel

- 8.自身免疫性低血糖是一種與胰島素抗體相關的高胰島素血症性低血糖。其發病機制被認為與自身免疫缺陷或特定藥物誘導的 IAA 有關，具有易感的遺傳背景。一些非降糖葯與自身免疫性低血糖的關係已得到證實。
- 9.在134例病因不明的自身免疫性低血糖病例中，有11例被認為是由氯吡格雷片(Clopidogrel)引起的，因為這些患者中的每一個都有氯吡格雷暴露史或冠心病史或冠狀動脈或頸動脈支架植入史。因此，Clopidogrel引起的自身免疫性低血糖的發生率可能遠高於目前認為的。這可能是由於對非降血糖藥物誘導的自身免疫性低血糖的認識不足所致。
- 氯吡格雷在治療血小板聚集性高引起的心腦血管疾病中起著重要作用。是動脈粥樣硬化性心血管疾病患者的一線選擇。心血管疾病低血糖患者面臨更高的心血管事件風險。因此，照顧使用氯吡格雷的患者的醫療保健提供者應意識到自身免疫性低血糖症的罕見但嚴重的副作用。如果出現此類癥狀，需要及時進行血糖檢測和糖攝入。我們建議將自身免疫性低血糖作為氯吡格雷的一種罕見但嚴重的副作用納入臨床用藥指南

Autoimmune hypoglycemia

- Autoimmune syndromes are a rare cause of hypoglycemia characterized by elevated levels of insulin in the presence of either anti-insulin antibodies (insulin autoimmune syndrome) or anti-insulin receptor antibodies (type B insulin resistance).
- 1. anti-insulin antibodies (insulin autoimmune syndrome)
- 2. anti-insulin receptor antibodies (type B insulin resistance).

Insulin autoimmune syndrome is the third leading cause of hypoglycemia in Japan, but has rarely been described in the non-Asian population.
Two cases of 2 white patients with insulin autoimmune syndrome were reported By Beatrice C Lupsa [1] et al

Beatrice C Lupsa [1], et al **Autoimmune forms of hypoglycemia** Medicine (Baltimore). 2009 May;88(3):141-153

Uchigata Y, Hirata Y. Insulin autoimmune syndrome (IAS, Hirata disease). *Ann Med Interne (Paris)*. 1999;150:245-253.

IAS (Hirata disease)

- **Insulin autoimmune syndrome** or Hirata disease is a rare condition characterized by hyperinsulinemic hypoglycemia associated with high titer of antibodies to endogenous insulin, in the absence of pathologic abnormalities of the pancreatic islets and prior exposure to exogenous insulin.[4]
- The syndrome was first described by Hirata in 1970.[84] In Japan, insulin autoimmune syndrome is the third leading cause of severe hypoglycemia after insulinoma and extrapancreatic neoplasms. The Japanese experience with insulin autoimmune syndrome was summarized by Hirata and Uchigata in 1999.[84]

Patient	Hb_{A1c} (4.8%–6.4%)	Fasting Blood Glucose (70–115 mg/dL)	Fasting Insulin (6–27 µU/mL)	Fasting C-Peptide (0.9–4 ng/mL)	Proinsulin (3–20 pmol/L)	Anti-Insulin Antibodies (0%–2%)	Anti-Insulin Receptor Antibodies	GAD65 Antibodies (0–0.02 nmol/L)	Sulfonylurea Screening
1	7	45	164	34	6200	56	Negative	0.08	Negative
2	5.5	91	18.8	1.9	49	54	NA	0	Negative

Abbreviations: GAD, glutamic acid decarboxylase; Hb, hemoglobin; NA, not available.

*Units and normal ranges for laboratory parameters are given in parentheses.

Baseline Endocrine Characteristics of 2 Patients With Insulin Autoimmune Syndrome, Present Report*

Autoimmune Forms of Hypoglycemia

Medicine88(3):141-153, May 2009.

(L1066)

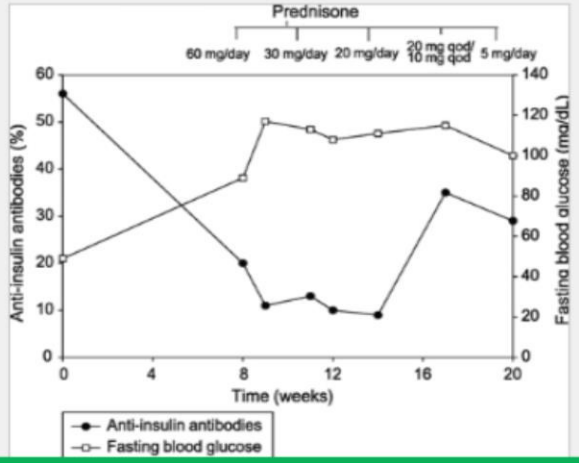


FIGURE 2: Patient 1 (insulin autoimmune syndrome): anti-insulin antibody titers and fasting blood glucose levels during the oral prednisone treatment. Note that there was some increase in the insulin antibody titer as prednisone was tapered, but no hypoglycemia.

Taiwan experience

Case report: hypoglycemia secondary to methimazole-induced insulin autoimmune syndrome in young Taiwanese woman with Graves' disease

Hsuan-Yu Wu, MD[a], I-Hua Chen, MD[b,*], Mei-Yueh Lee, MD, PhD[b,c]

Wu et al. Medicine (2022) 101:25 (L1074, L1075)

In conclusion, this case highlights the significance of life threatening MTZ-induced IAS.(insulin autoimmune syndrome)

In patients with spontaneous hypoglycemia, clinicians should always consider IAS, especially in those with underlying Graves' disease who are receiving MTZ and present with hyperinsulinism

- 一名患有 Graves 病的 27 歲女性在服用抗甲狀腺藥物 MTZ（methimazole, 10 mg，每日兩次）6 wks 后出現冷汗和頭暈。她是是當地一家醫院的病房護士，當出現癥狀時，她檢查手指血糖，發現低血糖，血糖水準低至 42 mg/dL。

MTZ 治療后6 周,低血糖事件發生了 。癥狀可能在飯後加重。她否認服用過任何形式的抗糖尿病藥物，但她報告了**糖尿病家族**史。

甲狀腺功能顯示甲狀腺功能亢進過度矯正，伴有促甲狀腺激素（TSH）升高、遊離甲狀腺素（遊離T4）降低和TSH受體抗體（Ab-TSH R）陽性.因此，MTZ的劑量逐漸減量至5mg，每日兩次。檢查糖化血紅蛋白 （HbA1c） 以排除糖尿病，肝腎功能檢查排除器官衰竭引起的低血糖。**50g口服葡萄糖耐量試驗顯示3小時后出現嚴重餐后低血糖**（表).此外，放射免疫測定顯示皮質醇水準正常，胰島素水準升高（表).安排入院進行 72 小時空腹試驗和影像學檢查，以排除胰島素瘤或腎上腺皮質增生等腹部病變。

Hb A1c : 5.1 %

Table 1

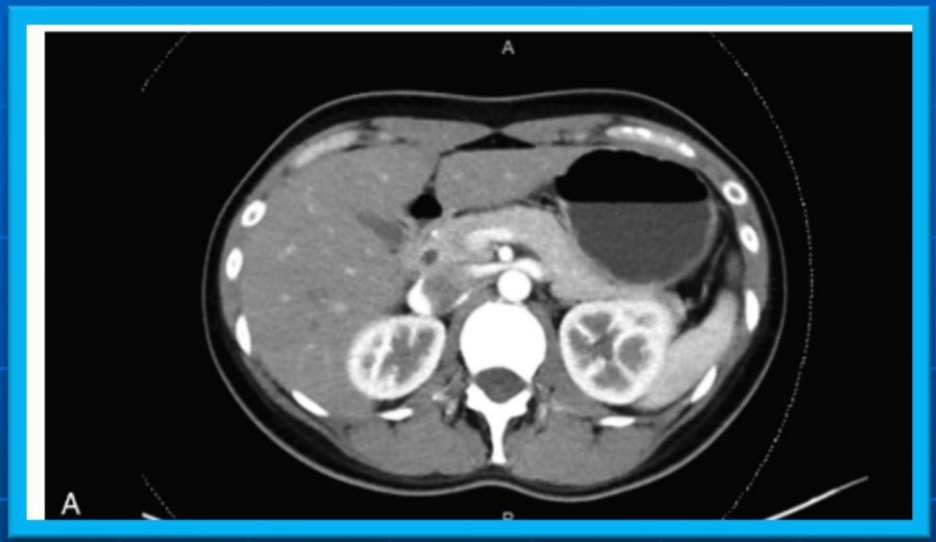
Laboratory data during first visit and admission.

Laboratory data	First visit	During admission	After discharged	Normal range
HbA1c (%)	5.1			4–6
Insulin (μIU/mL)	35.52	38.17	14.72	2–17
C-peptide (ng/mL)		2.71		1.77–4.68
Cortisol (μg/dL)	11.90	9.17		4.7–23.3 (8–10 AM)
TSH (μIU/mL)	8.88			0.25–4
Free T4 (ng/dL)	<0.24			0.7–1.8
Ab-TSH R (U/L)	24.99			<1.5
Thyroglobulin Ab (IU/mL)	176			<40
Microsomal Ab (IU/mL)	117			<35
GPT (IU/L)	18			10–40
Uric acid (mg/dL)	7.0			2.6–8.0
BUN (mg/dL)		13.5		8–20
Creatinine (mg/dL)	0.69	0.68		0.44–1.03
Oral glucose tolerance test (OGTT)				
Glucose (AC) (mg/dL)	93	97		65–109
Glucose (120 min) (mg/dL)	86			<155
Glucose (180 min) (mg/dL)	33			<140

72-h fasting test	First day	Second day	
Glucose (mg/dL)	105 (06:03) 85 (12:08) 86 (17:17)	82 (00:13) 74 (06:02)	65–109

Ab = antibody, Ab-TSH R = thyroid stimulating hormone receptor antibody, AC = ante-cibum (before meals), BUN = blood urea nitrogen, FT4 = thyroxine, free, GPT = glutamic pyruvic transaminase, HbA1c = glycated hemoglobin, TSH = thyroid stimulating hormone.

腹部計算機斷層掃描（CT）和磁共振成像（MRI）未顯示胰腺腫瘤或腎上腺皮質增生的證據（圖1



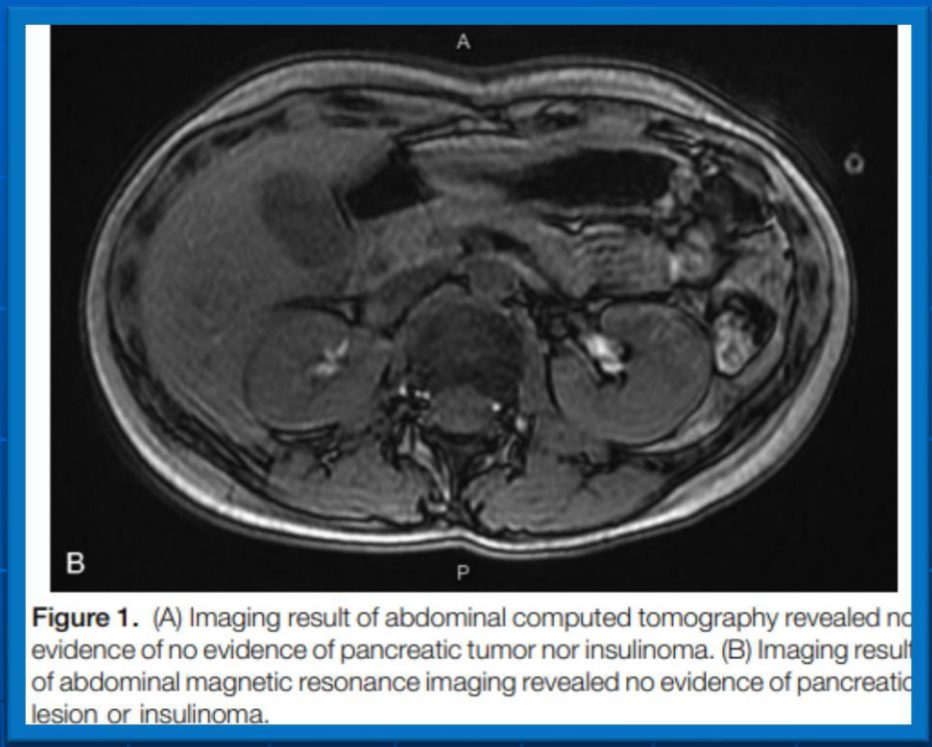


Figure 1. (A) Imaging result of abdominal computed tomography revealed no evidence of no evidence of pancreatic tumor nor insulinoma. (B) Imaging result of abdominal magnetic resonance imaging revealed no evidence of pancreatic lesion or insulinoma.

MTZ-→IAS

- 在第3天將MTZ(Methimazole)改為丙基硫氧嘧啶，之後沒有發現不適或低血糖發作。因此，在排除了低血糖的其他原因后，我們對MTZ誘導的IAS做出了最終診斷。在門診隨訪期間複查胰島素水平，發現在正常範圍內。
- MTZ was shifted to propylthiouracil on day 3 due to possible drug side effects causing IAS, after which no discomfort or hypoglycemia episodes were noted. Thus, after excluding other causes of hypoglycemia, we made our final diagnosis of MTZ-induced IAS. Her insulin level was rechecked during outpatient department follow-up visits, and found to be within normal range

Table 2

Insulin autoimmune syndrome (IAS) triggers.

Methimazole	Carbomazole
Propylthiouracil	Diltiazem
Alfa-mercaptopropionyl glycine	Alpha-lipoic acid
Glutathione	Methionine
Captopril	Hydralazine
Steroids	Penicillamine
Penicillin G	Imipenem
Pantoprazole	Clopidogrel

@@@ In approximately 80% of patients, IAS is self-limiting and quickly resolves after stopping the drug that has induced hypoglycemia. Therefore, the key to IAS treatment is to urgently identify the medication and not re-introduce it. On the other hand, patients with hypoglycemia are told to take small frequent meals with a reduced Amount of carbohydrates to avoid sudden increases in plasma glucose leading to the over secretion of insulin.

For refractory cases

- If hypoglycemia persists, steroids as immunosuppressive therapy, azathioprine or 6-mercaptopurine combined with plasmapheresis can also serve as an alternative therapy.
- For refractory cases, rituximab, an anti-CD20 monoclonal antibody, can be tried to suppress an over-reactive immune system.
- In our case, the patient improved one day after MTZ had been withdrawn.

Case 3,

- 一名 80 歲女性，有短暫的反覆發作意識模糊病史，實驗室確診為低血糖，空腹時血漿葡萄糖為 2.7 mmol/L，符合 Whipple 三聯癥。
- 就診時病因的診斷線索包括空腹低血糖、低鉀血症, 無體重增加。禁食 72 小時結果顯示早期低血糖和血清胰島素、C 肽和胰島素原抑制。未檢測到血清胰島素抗體。
- 隨後測量的**血清 IGF2：IGF1 比值升高至 22.3**，與 IGF-2 介導的低血糖一致

請說明IGF2：IGF1 比值的臨床意義之後要怎麼辦?

Mairead T Crowley [1] et al (Ireland) **IGF-2 mediated hypoglycemia and the paradox of an apparently benign lesion: a case report & revi Literature.** BMC Endocr Disord. 2022 Oct 27;22(1):262. (L1078)

類胰島素生長因子（IGFs)

- **類胰島素生長因子**（insulin-like growth factors，簡稱**IGFs**）為一種與胰島素序列高度相似的蛋白質激素。可以調控生理環境的複雜系，
- 該系統由兩種細胞表面受體（IGF1R及IGF2R）以及兩種配體（IGF-1、IGF-2）構成。

IGF-2

- IGF受體
- 胰島素樣生長因子會與多種受體相結合，如胰島素樣生長因子1（IGF-1）受體、胰島素受體、胰島素樣生長因子2（IGF-2）受體、胰島素受體等相關受體等其他受體。**IGF-1的受體與該因子的親和力遠比胰島素受體與它的親和力高**。正如胰島素受體一樣，IGF-1受體是一種受體酪氨酸激酶，即這種受體是通過在特定的酪氨酸分子上磷酸化來發出信號。**而IGF-2受體只會與IGF-2相結合併形成「清除受體」，這意味著它們不會引發細胞內信號通路，只會起到IGF-2螯合劑的作用並阻斷 IGF-2 的信號傳遞。**
- What does high IGF2 mean?
- An increased amount of insulin-like growth factor 2 may stimulate the growth the growth of tumor cells and prevent damaged cells from being destroyed. destroyed. Loss of imprinting of the IGF2 gene has been identified in several several types of cancer.2
- IGF 2:IGF 1　normal < 10

IGF-1

- 類胰島素生長因子-1(Insulin-like growth factor-1)具有 70 個胺基酸, 分子量為 7.6kDa,是一個內含 3 個雙硫鍵的單一多 鏈(polypeptide),結 構上與 Insulin 及 IGF-2 同源。在人體的血液中,IGF-1 必須要和 IGF-1 結合蛋白(IGF binding protein)以及易酸敗次分子(acid labile subunit)形 成三度結構的大分子,才能穩定存在。在人體內, IGF-1 的生成受到生長 激素(Growth hormone)與營養獲取的刺激調控。 在人體的血液中, IGF-1 的濃度在出生時期幾近於零。隨著幼兒時 期逐漸增加,在青春時期到達濃度高峰,直到 40 歲以後才逐漸下降。在生 長異常疾病的診斷分面,測量血液中 IGF-1 的濃度是一個很好的生長激 素分泌指標。

在臨床和生長激素分泌有關的疾病,例 如:肢端肥大症患者 (Acromegly)是生長激素過多,IGF-1 的濃度也較正常人偏高。成人生長激 素缺乏症患者(Adult GH deficiency), IGF-1 及 IGF-1 結合蛋白(IGFBP-3) 的濃度較正常人偏低。而矮小症患者(Laron dwardism),是因為生長激素 受體的基因缺陷(genetic defects of the growth factor hormone receptor)造成,IGF-1 的濃度也較正常人偏低。

- 單位:ng/mL

成人的 IGF-1 濃度參考值

Age	Median	Central 95% Range
21-25	203	116-358
26-30	196	117-329
31-35	188	115-307
36-40	176	109-284
41-45	164	101-267
46-50	154	94-252
51-55	144	87-238
56-60	135	81-225
61-65	126	75-212
66-70	118	69-200
71-75	110	64-188
76-80	102	59-177
81-85	95	55-166

Siemens DPC IMMULITEr 2000

- Routine admission biochemical investigation demonstrated mild hypokalaemia of 3.0mmol/l with otherwise normal electrolytes and liver function tests. A synacthen test was normal with a rise in serum cortisol to 554nmol/L and 697nmol/L at 30 and 60minutes respectively. Similarly, anterior pituitary hormone profle was normal including T4 14.4pmol/L (reference range 9.0– 19.1), TSH 3.54 mIU/L (0.35–4.94). Prolactin 341mU/L (110–562). LH 13.5IU/L, FSH 32.0IU/L and oestradiol 58pmol/L were consistent with post-menopausal status.
- **IGF1 level was low 4.4nmol/L (4.4–21.8)** as was a random growth hormone of 0.26µg/L. All hormones were measured using Abbott Architect assays except for GH and IGF1 which were measured on the IDS-iSYS analyser. Routine clinical chemistry was performed using the Beckman Coulter AU5800 instrument

- Cross-sectional CT imaging with contrast was performed to investigate for underlying malignancy and revealed a pelvic mass of 13 cm maximal diameter (see Fig. 1). Tis prompted a follow up fuorodeoxyglucose PET-CT scan which demonstrated mild to moderate uptake of fuorodeoxyglucose by this mass (see Fig. 2)

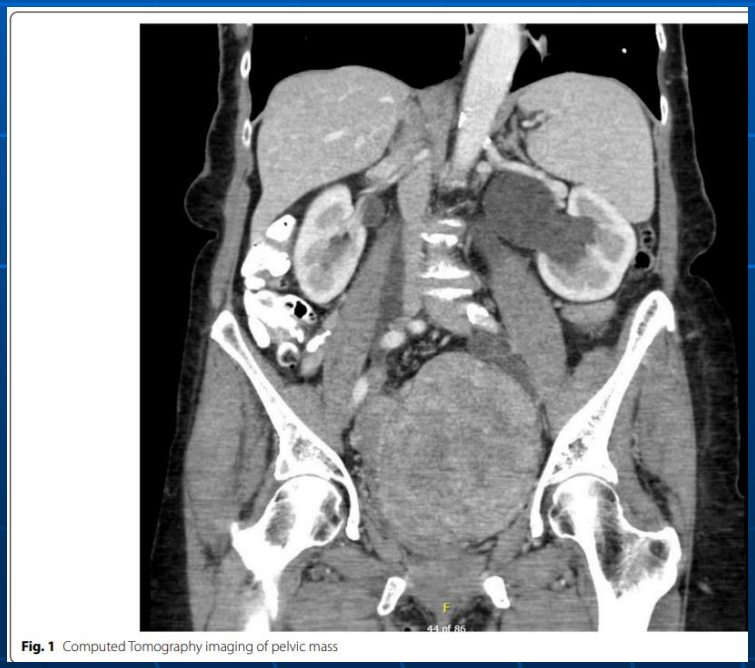


Fig. 1 Computed Tomography imaging of pelvic mass

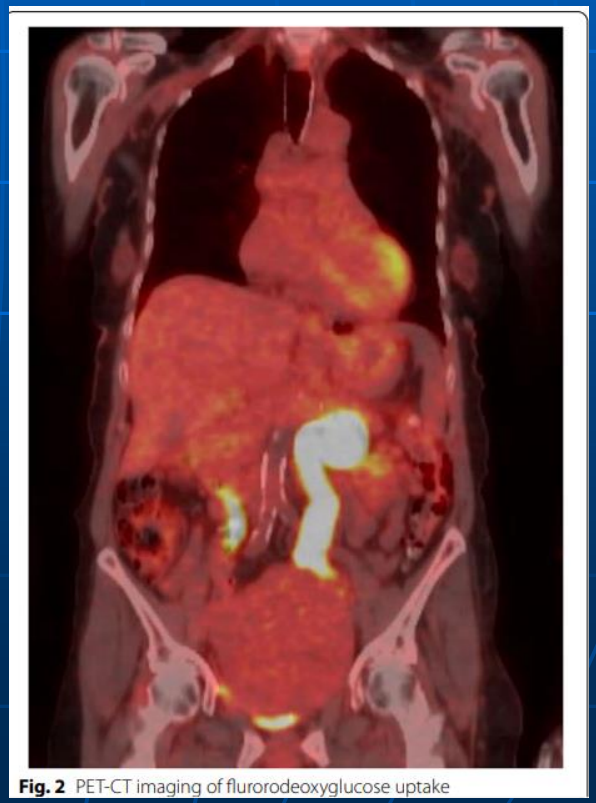


Fig. 2 PET-CT imaging of flurorodeoxyglucose uptake

	Pre-op
IGF1 (nmol/l)	3.5
IGF2 (nmol/l)	78.2
IGF2:IGF1	22.3
IGFBP3 (mg/l)	0.8

serum was analysed for both IGF-2 and IGF-1 and the IGF2:IGF1 ratio was calculated. IGF2 was analysed by radioimmunoassay and IGF1 was measured using the Mercordia immunoassay. Results showed a serum IGF-2 of 78.2nmol/L, IGF-1 of 3.5nmol/L (4.4–21.8) and an IGF-2:IGF-1 ratio of 22.3 which is consistent with IGF-2 mediated hypoglycemia

- Gynaecolological Oncology service proceeded to have a total abdominal hysterectomy and bilateral salpingooophorectomy. Intra-operative findings included a 15 cm solid mass arising from the left uterine wall and extending into the broad ligament and left pelvic side wall. The tumour shows classical "pattern-less pattern" SFT spindle cell morphology, without cytological atypia or necrosis. Mitotic count was low ·

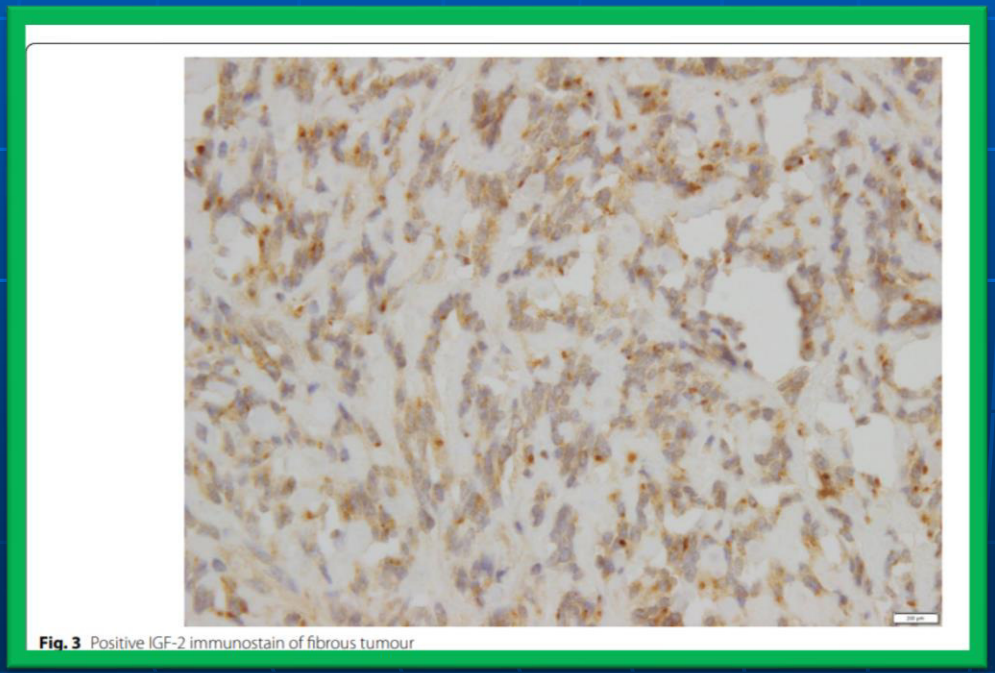


Fig. 3 Positive IGF-2 immunostain of fibrous tumour

Immunohistochemistry demonstrated diffuse positivity for STAT6 in tumour cells, consistent with a diagnosis of an SFT. Immunohistochemistry demonstrated that tumour cells were positive for IGF-2 as depicted in Fig. 3 (Anti-IGF2 monoclonal antibody, Merek Millipore, clone S1F2).

SFT: **solitary fibrous tumour**

Table 2 IGF2 serology profile

	Pre-op	Day 4 post-op	3 months post-op	Reference range
IGF1 (nmol/l)	3.5	5.4	12.6	4.4–21.8
IGF2 (nmol/l)	78.2	57.6	41.7	
IGF2:IGF1	22.3	10.7	3.3	< 10
IGFBP3 (mg/l)	0.8	1.7	3.0	2.0–5.5

At review 3 months post-operatively, our patient reported full symptom resolution. Follow up serology (detailed in Table 3) is indicative of biochemical cure with normalisation of the serum IGF2:IGF1 ratio

- 影像學檢查顯示盆腔腫塊。飲食干預和口服潑尼松龍可減輕手術前的低血糖。
- 最終，低血糖症在手術干預后得到解決，類固醇治療被成功撤回。
- **組織病理學檢查在雙重腫瘤過程中表現突出，子宮孤立性纖維瘤（ uterine solitary fibrous tumour）SFT）被證實是 IGF-2 免疫組化中 IGF2 分泌過多的來源，另外:右輸卵管菌毛的浸潤性高級別漿液性癌。** high grade serous carcinoma involving the fimbria of the right fallopian tube.

Etiologies of hypoglycemia without Diabetes.

- 對於無基礎糖尿病的患者，低血糖的診斷依據是**Whipple**三聯征的血糖低於**3mmol/L[1,5]**。 這包括與低血糖相關的癥狀或體征、實驗室證實的低血糖以及低血糖治療后臨床狀態的改善**[1]**。一旦滿足標準，應根據《內分泌學會實踐指南》中概述的分類進行低血糖病因調查，詳見表**3.**

Table 3 Classification of the aetiology of hypoglycemia in adults without underlying diabetes [1]

Unwell or medicated individual	Seemingly well individual
1. Drugs	1. Endogenous hyperinsulinism
Insulin or insulin secretagogues	Insulinoma
Alcohol	Functional β-cell disorders (nesidioblastosis)
Glucagon during endoscopy	Insulin autoimmune hypoglycemia
Quinine	Insulin secretagogue
Indomethacin	2. Accidental, surreptitious or malicious hypoglycemia
2. Critical illnesses	
Hepatic, renal or cardiac failure	
Sepsis (including malaria)	
3. Hormone deficiency	
Cortisol	
Glucagon and epinephrine	
4. Non-islet cell tumour	
5. Inborn errors of metabolism	

Table based on Endocrine Society Guideline on Evaluation and Management of Hypoglycemic Disorders [1] and amended to include other causes of hypoglycemia [4]

非糖尿病患者低血糖的評估和處理-1

- 1. 回顧病史、體格檢查結果和所有可用的實驗室數據，以尋找特定疾病（藥物、危重疾病、激素缺乏症、非胰島細胞腫瘤）的線索。
- 當低血糖障礙的病因不明顯時，*即*在看似健康的個體中，在自發性低血糖發作期間測量血漿葡萄糖、胰島素、C 肽、胰島素原和 β-羥基丁酸濃度並篩查口服降糖葯，並觀察血漿葡萄糖對靜脈注射 1.0 mg 胰高血糖素的反應。這些步驟將區分由內源性（或外源性）胰島素引起的低血糖與其他機制引起的低血糖。此外，測量胰島素抗體。
- 當無法觀察到自發性低血糖發作時，正式重現可能發生癥狀性低血糖的情況，*即*在長達 72 小時的禁食期間或混合餐后。血糖濃度低於 55 mg/dl （3.0 mmol/L）、胰島素濃度至少為 3.0 μU/ml （18 pmol/L）、C 肽至少 0.6 ng/ml （0.2 nmol/L） 和胰島素原至少 5.0 pmol/L 的癥狀和/或體征的發現表明內源性高胰島素血症;靜脈注射胰高血糖素后 β-羥基丁酸水準為 2.7 mmol/L 或更低，血漿葡萄糖升高至少 25 mg/dl（1.4 mmol/L），提示胰島素（或 IGF）介導低血糖。

非糖尿病患者低血糖的評估和處理-2

- 2.對於有空腹或餐后內源性高胰島素血症、口服降糖葯篩查陰性且無迴圈胰島素抗體的患者，應進行**胰島素瘤**定位手術。這些可能包括計算機斷層掃描或磁共振成像（MRI）、經腹和內窺鏡超聲檢查，以及必要時選擇性胰動脈鈣注射和肝靜脈胰島素水平測量。

- 3.根據特定的低血糖疾病量身定製治療方案，同時考慮低血糖對患者健康和患者偏好的負擔

non-islet cell tumour hypoglycemia， NICTH

- non-islet cell tumour hypoglycemia， NICTH），包括腫瘤分泌的IGF2（成熟和未完全加工的形式），以及較少見的IGF1、生長抑素和胰高血糖素肽1，它們通過不同的機制刺激葡萄糖消耗。
- 在缺乏低血糖的體液介質的情況下，由於葡萄糖消耗增加、肝臟浸潤和/或垂體或腎上腺破壞而導致的嚴重腫瘤性疾病病例中觀察到腫瘤誘導的低血糖現象。

1988年，Daughaday等報導了第一例IGF2免疫染色陽性腫瘤切除術的NICTH病例，並在組織病理學和血清中檢測到大分子量（大）胰島素樣生長因數2。
在此期間，已經描述了具有各種潛在腫瘤的進一步臨床病例。傳統上，它被認為是比胰島素瘤引起的低血糖更罕見的現象.
1929年IGF-2介導的低血糖的原始病例描述中報導的肝細胞癌[8]是引起NICTH的最普遍腫瘤[3]。
NICTH 幾乎完全繼發於 IGF-2 或激素原 pro-IGF-2 的過度分泌。**位於11號染色體短臂上的IGF-2基因啟動子區域異常激活**，導致IGF2前體產生過多

Case 4,人為性低血糖：一種不應被遺忘的疾病

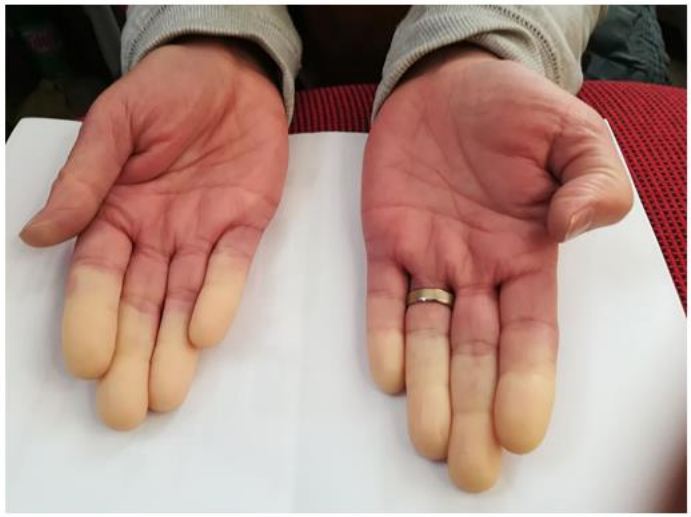


FIGURE 1 | Raynaud's phenomenon during endocrinology appointment.

TABLE 2 | Discrepancy between capillary and venous blood glucose.

	Capillary blood glucose	Plasma blood glucose
First venous blood sample	54 mg/dl	78 mg/dl
Second venous blood sample	24 mg/dl	76 mg/dl

.Sara Amaral et al (葡萄牙) **Case Report: Artifactual Hypoglycemia: A Condition That Should Not Be Forgotten.** Front Endocrinol (Lausanne). 2022 Jul 28: 13:951377

Case 4,

- 一名 46 歲女性患者因疑似低血糖被轉診至內分泌、糖尿病和代謝科。她有血脂異常病史，
- 在 2016 年接受袖狀胃切除術(sleeve gastrectomy)后體重減輕了 50 公斤。她正在接受奧美拉唑 omeprazole 20 mg/天和 simvastatin 20 mg/天的治療。她沒有糖尿病家族史。袖狀胃切除術后約 18 個月，她開始抱怨**lipothymias (syncope)**發作，隨後出現出汗、噁心和頭暈。在其中一次發作中，獲得毛細血管血糖值為 24 mg/dl。
- 在這次發作之後，她多次被送入急診科，在家進行毛細血管測量血糖后被診斷為“低血糖症”。在這種情況下，她多次被送往另一家醫院，以澄清她的臨床表現。

您要如何處理呢?

- 1.Blood tests– Diabetes or hypoglycemia
- 葡萄糖代謝相關的血液檢查報告在表1.其餘的血液檢查沒有顯示任何變化，包括正常血細胞計數、腎功能、肝酶、甲狀腺功能和鈣。

Blood test relative to glucose metabolism.

Blood test	14/08/2019	14/10/2019	29/11/2020
Glucose (mg/dl)	75		
Insulin (RV 3-25 mcUI/ml)	6.2		
Pro-insulin (RV <9.4 mcUI/ml)	<0.6		
C-peptide (ng/ml)	1.98		
72-h fasting test		No evidence of hypoglcyemia	
Oral glucose tolerance test			0′ – 74 mg/dl 60′ – 109 mg/dl 120′ – 61 mg/dl
Anti-GAD			Negative
Anti-insulin			Negative
Anti-ICA			Negative

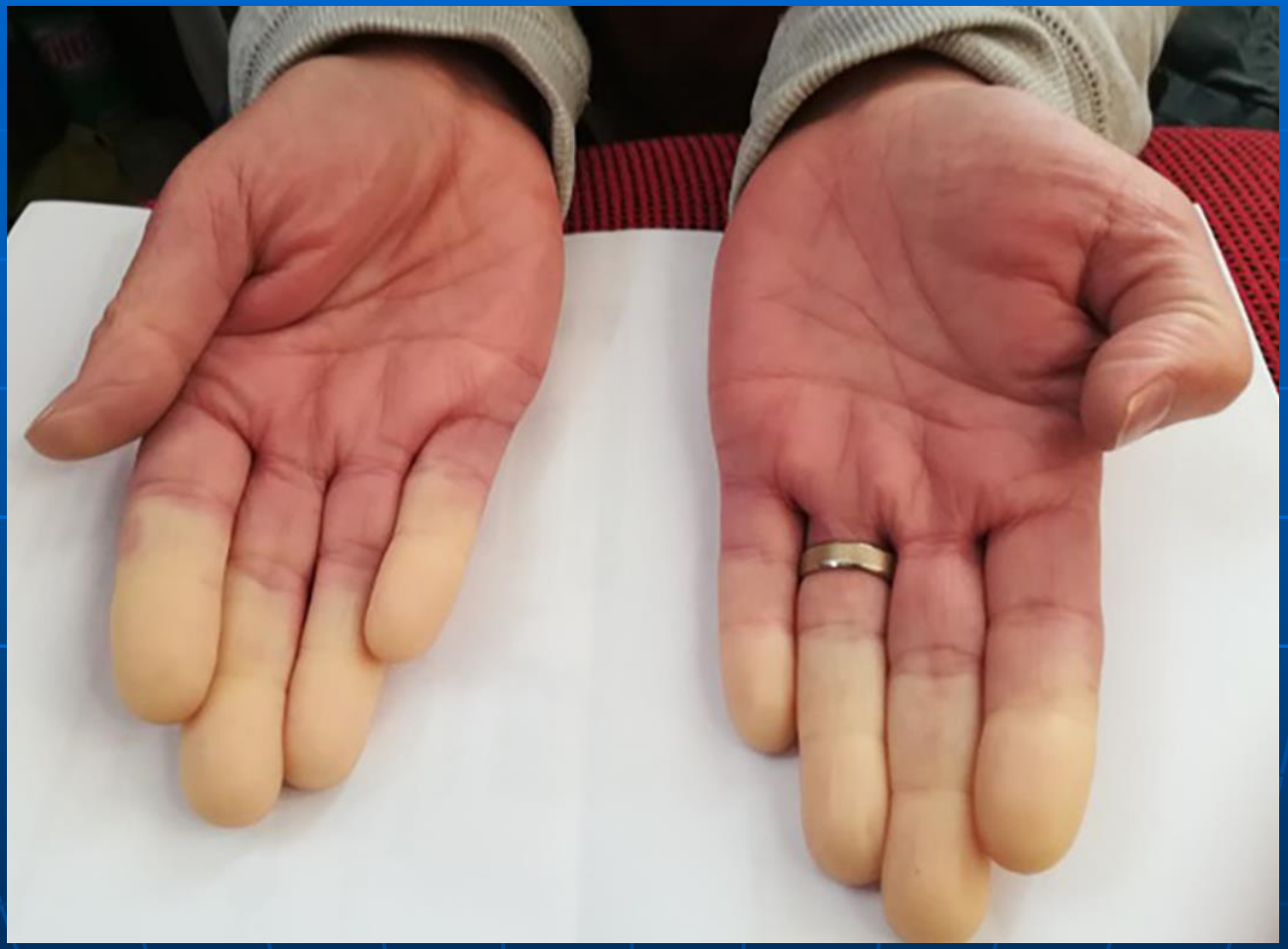
- 2.Medical images :
- abdominal computed tomography (CT), abdominal magnetic resonance (MRI), upper endoscopy, endoscopic ultrasound, fluorodeoxyglucose (FDG)–positron emission tomography (PET), and ^{68}Ga-DOTANOC PET/CT. No changes were found.

→transferred to another hospital.

Dumping syndrome first to be ruled out

- She had the first appointment in our department in December 2020. According to the patient, she needed to eat sugary foods or beverages every 2h during the daytime and twice during nighttime to solve symptoms. She was previously treated with acarbose due to suspected Dumping syndrome with no improvement.
- Her weight increased 6 kg in 1 year. She reported capillary glycemia between 23mg/dl and 45 mg/dl during those episodes.

On examination, the patient was alert and cooperative. Her weight was 82 kg and height was 1.65 m (body mass index of 30.1 kg/m^2). Blood pressure was 147/81 mmHg and heart rate 78 bpm. She reported having had a coffee with sugar 1h before the appointment. A capillary blood glucose was obtained with a value of 54 mg/dl. At the same time, a first venous blood sample was obtained. After 15 min, she started complaining about palpitations, headache, and tremors. Vital signs were measured again with blood pressure 194/130 mmHg, heart rate 84 bpm, and capillary blood glucose 24 mg/dl. A Raynaud's phenomenon (**Figure 1**) was observed. The remaining examination was unremarkable.



Autoimmune Disease appointment

- The patient reported that **Raynaud's phenomenon** was concomitant to the several episodes suggestive of hypoglycemia. She was advised to fractionate meals and to avoid fast-absorbing carbohydrates. An Autoimmune Disease appointment was requested.

- The complementary study on the Autoimmune Disease appointment revealed HLA-B27 positivity and increased Erythrocyte Sedimentation Rate (ESR) 66 mm/h (<16). The remaining investigation was negative for rheumatoid factor, antinuclear (ANA), anti-dsDNA, anti-nucleosome, extractable nuclear antigen (ENA), including SSA, SSB, RNP/Sm, Sm, Jo-1, Scl-70, histones, and ribosomal-P. Anti-centromere B, anti-fibrillarin, anti-NOR 90, anti-TH/To, and anti-citrulline antibodies were also negative. The remaining laboratory results were unremarkable (haemoglobin 12.6 × 10 g/L (12.0–15.0), normal leukocyte count, blood urea nitrogen test 31 mg/dl (15.0–40.0), creatinine 0.74 mg/dl (0.57–1.11), estimated glomerular filtration rate 97 ml/min/1.73 and normal liver enzymes).

- 她還表現為下肢指趾炎。毛細血管鏡檢查顯示繼發性雷諾現象，伴有早期硬皮病。在放射學檢查進行期間，推定診斷為強直性脊柱炎。在最後一次就診（2022 年 2 月）時，她根據需要接受 amlodipine 5 mg/day, salazopyrine 3 g/day, and etoricoxib 90 mg as needed(氨氯地平 5 mg/天、沙拉唑比林 3 g/天和依託考昔 90 mg) 的藥物治療，癥狀有所改善。營養干預后未觀察到低血糖發作。

Artifactual hypoglycemia

- Artifactual hypoglycemia has been described in various conditions including **Raynaud's phenomenon, peripheral arterial disease, Eisenmenger syndrome, acrocyanosis, or hypothermia (4)**. The Raynaud's phenomenon was first described in the 19th century as episodic, symmetrical, and vasospastic disorder, resulting in classic triphasic color change, trophic changes limited to the skin and uncomfortable sensory symptoms of the extremities in the absence of arterial occlusion (5). **In this situation, there is a reduced perfusion of the peripheral microcirculation with decelerated glucose transit and increased glucose uptake into the surrounding tissues** (6). Other conditions such as leukemia could also lead to artifactual hypoglycemia due to increased glycolysis by leukocytes .

L1083, artifactual l hypoglycemia (2016)(Raynaud phenomenon)(2023.12.24)

Table 2

Discrepancy between capillary and venous blood glucose.

	Capillary blood glucose	Plasma blood glucose
First venous blood sample	54 mg/dl	78 mg/dl
Second venous blood sample	24 mg/dl	76 mg/dl

A second venous blood sample was obtained; the results are displayed in **Table 2**. Hypoglycemia was not confirmed and a diagnosis of artifactual hypoglycemia was considered. Plasma-free metanephrines were in the normal range.

Case 5, hypoglycemia and abdominal mass.

- A 76-year-old woman with no major comorbidities presented following an episode of collapse with a blood glucose of 1 mmol/l. She was treated immediately with intravenous (IV) dextrose. She had a firm right upper quadrant mass.

下一步您要怎麼辦?

- She was hypoglycaemic with low insulin :< 6pMol/l(range=12– 150),
- low C-peptide 0.19nmol/l (range=0.34–1.80), low IGF-I 3.8nmol/l (range=4.4–21.8) and a raised IGF-II: IGF-I ratio of 11.0 (normal=<10)
- Normal fasting gut hormone profile, normal biochemistry and slightly deranged liver function tests.

以上的結果您認為**HCC**的低血糖是怎麼引起的**?** 請選擇一項

- 1. HCC with metastases to the pancreas.
- 2. HCC+coexisted with in insulinoma
- 3. Heavy consumption of carbohydrate resulted
- in hypoglycemia
- 4.HCC with insulin-like substance secretion or
- NICTH(IGF-2 secreting)
- 5. Other cause(s)

How to treat him?

Comparisons of different therapies-1

- **1.Glucocorticoids are used in NICTH to raise plasma glucose levels and correct the underlying biochemical abnormalities, but this tends to require high doses, which come with a large, often intolerable, side-effect burden.**
- **2. Recombinant human growth hormone (rhGH) acts to decrease glucose utilisation and has been documented to give good glycaemic control in some cases, especially when combined with glucocorticoids. However, the use of rhGH is limited by the necessity of high doses, side effects of fluid retention and postural hypotension and its cost.**
- Furthermore, rhGH increases the concentration of IGF-II, which may contraindicate its long-term use, and the possibility that it may stimulate tumour growth has not been studied.

Comparisons of different therapies-2

- 3. Somatostatin analogues such as octreotide have been found to improve hypoglycaemia for some and may be a useful steroid sparing agent, but other studies have found limited benefit.There is little analysis of the use of somatostatin analogues in preselected patients found to have avid disease on an octreoscan.
- Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. J Clin Endocrinol Metab 2014; 99: 713–722.
- 4. The risks of a **major operation** outweighed the benefits and the patient did not wish for such a procedure.
- 5. Systemic targeted therapy (Sorefinab) was also considered but was not suitable for this patient following oncology review due to its side-effect profile.
- 6. **Selective internal radiation therapy (SIRT)** was deemed to be the best option, but the finding of a large lung-shunt precluded this option.
- 7. As most treatment options were not suitable, the focus of care became preventing symptomatic hypoglycaemic episodes.

- A nasogastric (NG) tube was used to deliver nocturnal feeds rich in carbohydrate to supplement increased day-time consumption, with initiation of prednisolone 40mg daily. Despite these interventions, hypoglycaemic episodes persisted, particularly nocturnally.
- An IV octreotide infusion was initiated, along with diazoxide, but the diazoxide was soon discontinued due to excess fluid retention. Other authors have reported diazoxide to be poorly tolerated, and it has questionable efficacy as a therapeutic option in NICTH.
- **The addition of octreotide helped stabilise blood sugars.**

- The octreotide infusion was switched to subcutaneous injections of a long-acting somatostatin analogue (Sandostatin 30mg), prednisolone was gradually weaned to 30mg then 20mg and the carbohydrate content of the overnight NG feed was increased to 110g carbohydrate and
- 36g protein in 600ml. During the month-long admission the patient had no further episodes of symptomatic hypoglycaemia.
- The patient was discharged to her family's home after initiating long-acting somatostatin analogue (SSA, Sandostatin LAR 30mg intramuscular depot injection every 28 days) and specialist nurse follow up. Blood sugars were monitored during the day and night and documented in a spreadsheet (Figure 2), with oral glucose therapy if under 5mmol/l

- The combination of nocturnal NG feeding, glucocorticoid (prednisolone 20mg daily) and somatostatin analogue (sandostatin LAR 30mg) was effective in reducing symptomatic hypoglycaemia, allowing the patient to return home for **end-of-life care with her family**. In the first month following discharge, blood glucose was maintained in normal limits, but with more erratic control towards the end of the second month, potentially representing an increased tumour burden, but also coinciding with delays in SSA (+subcutaneous somatostatin analogue) treatment . The patient passed away peacefully at home 3 months after discharge from hospital, having avoided readmission and not suffering the therapeutic side effects.

從這個案例我們得到什麼樣的經驗或心得

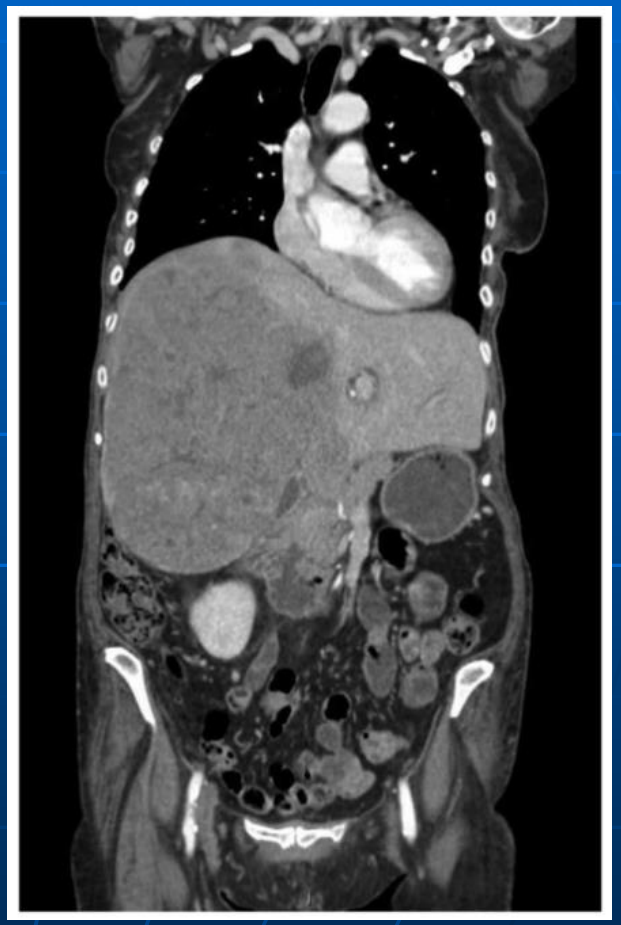
- Nocturnal NG feeding supplemented with prednisolone and a somatostatin analogue were a well-tolerated and effective approach in managing symptomatic NICTH in the palliative setting.
- Anecdotally, glycaemic control worsened when the somatostatin analogue was not given or delayed, and further research is warranted to investigate their role as a steroid sparing agent in patients with positive octreoscans

夜間NG餵食輔以prednisolone, 和生長抑素類似物是緩解姑息治療癥狀性 NICTH 的一種耐受性良好且有效的方法.
當未給予或延遲使用生長抑素類似物時，血糖控制會惡化,這是不可忽略的

- 1. History-問清楚這是第一次發生的呢還是從前就有過?
- 有沒有糖尿病使用低血糖藥物
- 過去半年中有沒有體重明顯的變化
- 有沒有肝病或膽囊疾病? HBV markers ? LFT
- 家族史有沒有糖尿病,有沒有cancer?
- 平常心會狀況是否良好,有心衰竭嗎

如果要挑醫學影像你要選哪一項? 要敘述理由.
Endoscopy
CT,
Abdominal ultrasound
Barium meal/barium enema study

- CT scanning identified a large tumour in the right lobe of the liver (Figure 1), without extrahepatic spread.
- Percutaneous biopsy confirmed this
- as HCC.



Hepatoma與低血糖癥有關係嗎?
病人血糖過低是什麼原因引起的?
下一步要怎麼辦?

Causes and differential diagnosis of hypoglycemia without Diabetes.

Differential Diagnosis

	Insulin	C-peptide	Proinsulin	Beta-Hydroxybutyrate
Insulinoma	↑	↑	↑	↓
Autoimmune	↑↑	↑↑	↑↑	↓
Insulin-like Growth Factor (IGF)	↓	↓	↓	↓
Not insulin mediated	↓	↓	↓	↑

Case 7, insulinoma

- A 55-year-old patient was admitted to our hospital after having had an episode of altered state of consciousness. This state lasted 30 min and had started while she was taking a midday nap.
- Her husband witnessed uncoordinated movements of her arms and legs as well as grunting noises and noticed that his wife did not respond when addressed.

病史上您還想知道哪一些疾病或狀況?

過去有無類似之癥狀,以及發作之頻率
過去有無生病,有無糖尿病,是否有癲癇的病史
過去發作時有沒有檢查過血糖.
過去懷孕狀況是否正常有無大出血
停經是哪一年之後有沒有用特別的藥物
有沒有甲狀腺機能亢進的病史?
平時胃口狀況是否良好體重有沒有變化.

History :frequent attack in the past

- On arrival of the paramedics, her blood sugar level was at 2.1 mmol/L. ---血液中的糖分偏低.
- Her medical history revealed that she had been having similar alterations of consciousness since 2003. 過去有多次發病的病史. These episodes occurred five to seven times a month, including symptoms of feeling generally unwell, weakness, difficulty or inability to speak, sweating, a vacant gaze and partial amnesia without total loss of consciousness.
- The episodes occurred at different times and in different settings. In one case, she reported feeling unwell and having a sensation of stiffness paired with amnesia while cooking lunch and therefore before eating. At other times, they would occur after eating. The patient also described occasional episodes where she would feel chest tightness.

Previous Dx :Epileptic attack ?

- 2. In January 2006—12 years prior to the current hospitalisation—the patient was diagnosed with **epilepsy** and a long-term treatment with lamotrigine was initiated. Eleven years later, neurologists reviewed the electroencephalogram (EEG) from 2006 and deemed there to be no epileptic potentials after all. Antiepileptic medication was discontinued, and the episodes were then reclassified as dissociative episodes.
- 3. Intensifying of psychiatric therapy was recommended. Nearly 2 years prior to hospitalisation at our institution, the patient underwent a 4-day in-hospital video EEG monitoring investigation for her epilepsy. There, an episode lasting a total of 26 min was recorded. The patient reported feeling unwell, had difficulties following instructions as well as giving verbal responses. In her EEG, **severe encephalopathic alteration could be seen**. Blood sugar levels were measured at 2.3 mmol/L**.(Low)**

INVESTIGATIONS

- The patient presented in a good clinical state, had a normal liver and renal function and no history of diabetes mellitus and hence did not take any oral antidiabetic drugs or insulin.
- @@Adrenal insufficiency and autoimmune insulin syndrome were excluded.
- @@Her familial or personal history and laboratory tests (ie, serum calcium and pituitary function) were not indicative of multiple endocrine neoplasia type 1 (MEN-1).
- @@At the emergency room, **endogenous hyperinsulinism was suspected a**nd she was admitted to the medical ward for further investigation.

您是負責醫師要如何逐步安排各項檢查以以找到低血糖的原因或胰島素分泌增加的原因?

1. 72 hour fasting

- 1. The hypoglycaemia was further evaluated using a 72-hour fasting test. Before the presenting symptoms, the patient tolerated glucose levels as **low as 2.5 mmol/L**. Below that, she started to be sleepy and have an altered state of consciousness. During the test, the patient developed neuroglycopenic symptoms after approximately 40 hours of fasting.
- Blood glucose descended to a minimum of 1.6 mmol/L, when the fasting test was terminated

- 2 At that point, plasma insulin, proinsulin, C-peptide and beta-hydroxybutyrate were measured and the insulin–glucose ratio (IGR) was calculated.
- Insulin, proinsulin, C-peptide levels and IGR were clearly elevated.
- The search for sulfonylurea
- in the plasma was negative
- and beta-hydroxybutyrate
- levels were below 2.7 mmol/L,
- indicating a suppressive effect
- of **insulin excess on ketone**
- **body production** (table 1).

Table 1 Values at the end of the fasting test of our patient and criteria for insulinoma

	Values (end of fasting test)	Criteria for insulinoma
Glucose	1.6 mmol/L	<3.1 mmol/L
C-peptide	445 pmol/L	≥200 pmol/L
Insulin	17.6 mU/L	≥3 mU/L
Proinsulin	6.4 pmol/L	≥5 pmol/L
Beta-hydroxybutyrate	1.7 mmol/L	≤2.7 mmol/L
Insulin–glucose ratio	76.4 pmol/L/mmol/L	>32.2 pmol/L/mmol/L
Antibody to insulin	Negative	Negative
Circulating sulfonylurea	Absent	Absent

- 3. Medical imaging.
- MRI (figure 1) showed a large tumour originating from the pancreatic tail without signs of any other intra-abdominal tumours or metastases.

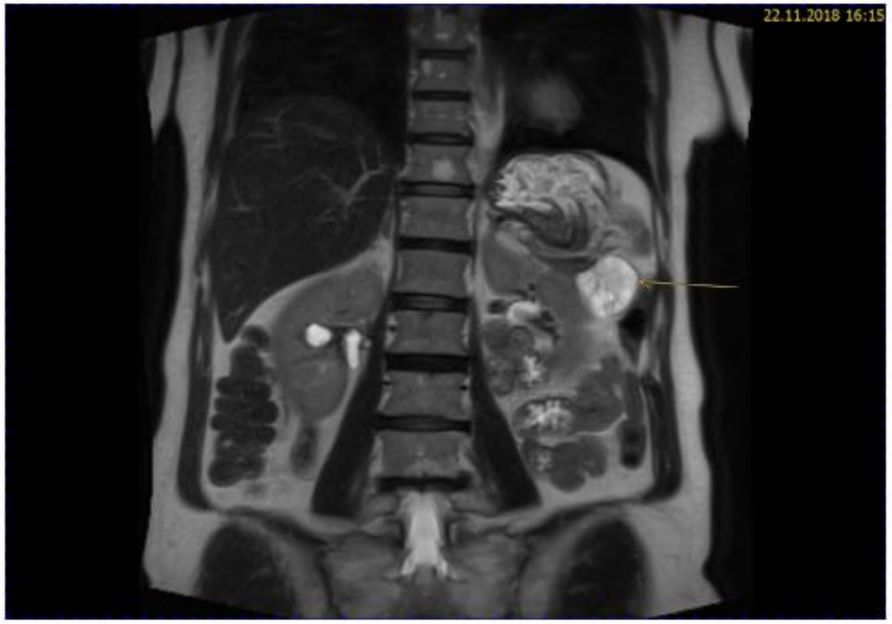


Figure 1 MRI with yellow arrow showing large exophytic mass originating from the pancreas tail (33×47×38 mm).

DIFFERENTIAL DIAGNOSIS

- Major problem: Low blood sugar, symptoms consistent with neuroglycopenia and appeared otherwise healthy.
- (a)She did not have a history of diabetes
- (b) nor did she take hypoglycaemic agents.
- Risk factors that predisposed the patient to hypoglycaemia could be excluded (ie, liver/renal insufficiency, hypocortisolism or autoimmune insulin syndrome).
- **Investigations on insulinoma** and ordered an in-house fasting test to further investigate. During the fasting, the patient demonstrated severe neuroglycopenic symptoms and **a positive Whipple's triad.**
- Laboratory testing confirmed the presence of an endogenous insulin excess. In patients with unexplained hypoglycaemia, one should always think of factitious administration of insulin or sulfonylurea. In our patient, the absence of a suppressed C-peptide level and negative testing for sulfonylureas in the plasma excluded this differential diagnosis.
- Her history revealed no symptoms that could be associated with MEN-1.

Treatment

- Before surgery, the patient was instructed to measure blood sugar levels regularly and to have frequent snacks between meals. With blood sugar levels remaining low, a therapy with diazoxide was installed after which glycaemia remained above 3mmol/L.
- **In December 2018, 15 years after first reporting symptoms, the patient underwent surgery (figure 2) to remove the tumour.**

Histology confirmed a well-differentiated neuroendocrine tumour, grade 1 with a diameter of 4.1 cm and no evidence of spreading into lymph nodes

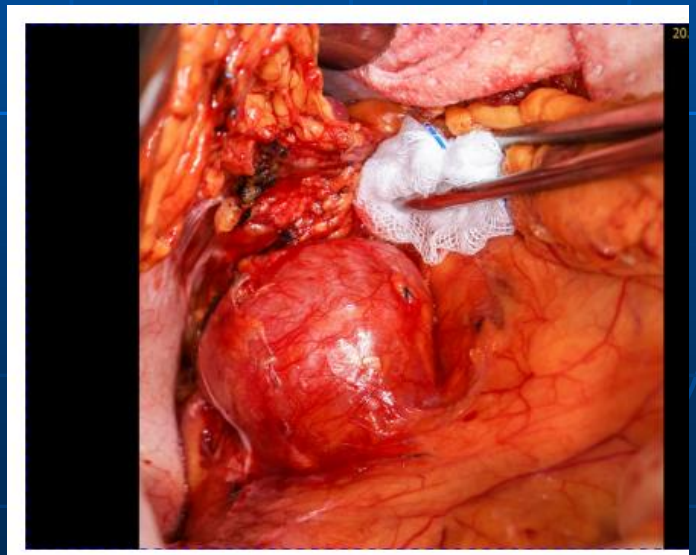


Figure 2 Intraoperative photo of the insulinoma.

OUTCOME

- OUTCOME AND FOLLOW-UP
- The operation was concluded without complications and the patient has not had any symptoms since.

Insulinoma

- Epidemiology : Insulinoma are rare neuroendocrine tumours (incidence 4/1million.), but represent the most common endocrine-active neoplasms of the pancreas.
- The majority are small, unifocal and benign tumours that appear sporadically. Up to 4%–5% of insulinoma are associated with MEN-1.
- Patients with MEN-1 have lesions that are characteristically smaller, often multifocal and sometimes malignant. Insulinomas are usually benign and slow growing tumours causing a variety of clinical signs and symptoms.
- Clinical features :There is a considerable latency from onset of first symptoms to definitive diagnosis.
- Initial misinterpretation of the symptoms as part of a psychiatric or neurological (ie, drug refractory epilepsy) disease is common and well documented in the literature.

Dx evidence

- **1. The gold standard for diagnosing insulinoma still is the 72-hour fasting test.**
- (1)The documentation of neuroglycopenic symptoms and low plasma glucose levels
- (2) inadequately elevated levels of insulin, proinsulin and C-peptide as well as low levels of beta-hydroxybutyrate
- Criteria for insulinoma Glucose 1.6mmol/L 32.2 pmol/L/mmol/L Antibody to insulin Negative Negative Circulating sulfonylurea Absent Absent
- (3) a negative test for circulating sulfonylurea
- (4) No intake of insulin secretagogues (ie, insulin and
- sulfonylurea).

2. Localisation techniques include abdominal CT/MRI, endoscopic ultrasound and selective intra-arterial calcium stimulation. Newer imaging modalities like the **GLP-1-receptor positron emission tomography/CT** usually have better sensitivity to detect small lesions and should be considered in patients with documented insulin excess and a negative CT/MR.

GLP-1-receptor positron emission tomography/CT

- **Interpretation:** (111)In-DTPA-exendin-4 SPECT/CT could provide a good second-line imaging strategy for patients with negative results on initial imaging with CT/MRI.
- L1087.(L1086) Christ E, Wild D, Ederer S,
- Et al eGlucagon-like peptide-1 receptor
- imaging for the localisation of insulinomas
- : a prospective multicentre imaging study.
- Lancet Diabetes Endocrinol 2013;
- 1:115–22

^{111}In-DTPA-exendin-4 SPECT/CT correctly detected the insulinoma in 19 of 20 patients (95% sensitivity, 95% CI 75–100). The technique had four false positive results (two adult nesidioblastosis and two uncharacterised lesions) resulting in a PPV of 83% (95% CI 62–94; table 2). ^{111}In-DTPA-exendin-4 SPECT/CT was more sensitive than CT/MRI (L1086)(L1088)

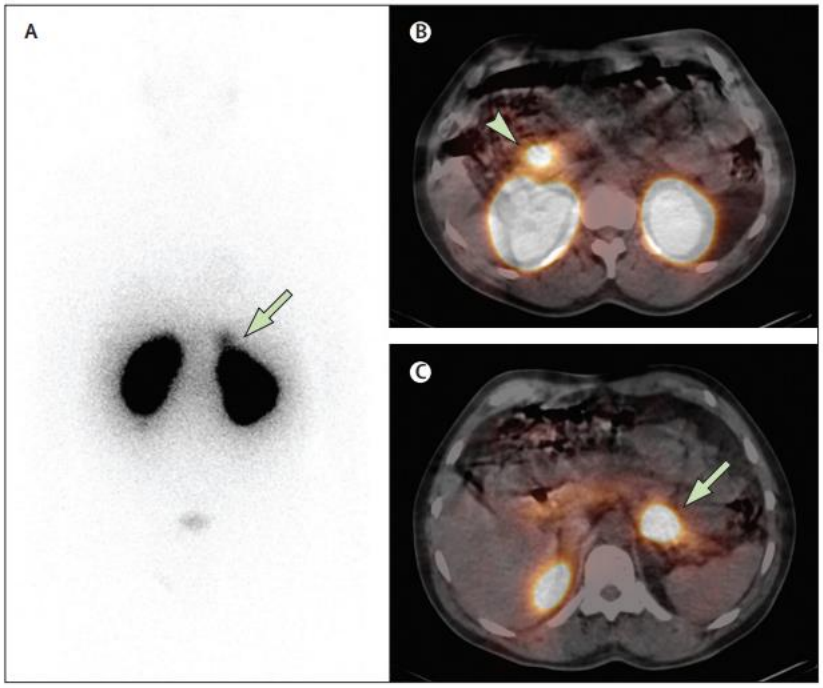


Figure 3: **Whole-body planar image (A) and SPECT/CT images (B and C) from patient 29, 4 h after injection of 108 MBq ^{111}In-DTPA-exendin-4.**
Focal ^{111}In-DTPA-exendin-4 uptake in the head of pancreas (arrowhead) and in the body of the pancreas (arrows). Surgery confirmed an insulinoma in head of pancreas (17 mm) and in the body of pancreas (33 mm). In the tail of pancreas a glucagon-producing neuroendocrine tumour (25 mm) was not detected with GLP-1R imaging. Additional small tumour lesions <10 mm (insulinoma and gastrinomas) were also not detected.
^{111}In-DTPA-exendin-4=^{111}In-[Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-exendin-4.

Case 7-2,

- 一例 16 歲女孩的胰島素瘤病例，表現為癲癇發作。她最初在一家私人診所接受治療，後來在抽搐持續時開始使用卡馬西平。抽搐是全身性的，與頭暈和感覺改變有關，通常在饑餓和體力消耗之前出現，但通過攝入碳酸飲料和果汁可以緩解。

對癲癇病史還要知道一些什麼?
這與一般的癲癇發作有不一樣的地方嗎.

cDavid O Soyoye [1 2], Segun A Atolani [2], Tajudin A Adetunji [1 2], Olusegun I Alatise [3 4]
Insulinoma Presenting as Seizures: Challenges of Managing a Rar Disease in a Resource-challenged Setting
Case Reports JCEM Case Rep. 2023 Dec 19;2(1):luad162. (L1123, L1124)

- The patient is a 16-year-old secondary school female student who was referred to the endocrinology clinic on account of recurrent convulsions and **excessive weight gain of 18 months' duration.**
- The first episode of seizures occurred in school and was said to have been heralded by a prodrome of palpitations and dizziness. Seizures abated after few minutes on intravenous fluid (name unknown) in a private clinic, with marked improvement in clinical status. Subsequent episodes of **seizures typically lasted for a few minutes, were generalized tonic-clonic in nature, were preceded either by hunger or physical exertion, and associated with tremors, palpitations, postictal sleep, and muscle aches. Symptoms were largely preventable by regular consumption** of sugar-containing carbonated drinks. There was no diurnal variation in the symptoms, and there was no preceding history of head injury or delay in the attainment of developmental milestones.

- The patient also has no known family history of seizure disorder.
- @ There has been **progressive weight gain during this period, with recurrent bouts of hunger pangs and hyperphagia.**
- There was no history suggestive of depression or suicidal intent.

- @She was initially managed at a peripheral hospital for seizure disorder and was placed on carbamazepine. She was then referred to the neurology unit of our hospital for expert management on a tentative diagnosis of hypothyroidism from a clinic she later presented due to increasing episodes of seizures and low blood glucose (BG) readings.
- @During evaluation at the neurology clinic, the patient had sweaty spells and palpitations with a random BG of 2.7 mmol/L(48.6 mg/dL). Symptoms promptly resolved with ingestion of a sugar-containing carbonated drink, and she was referred to the endocrinology clinic on suspicion of insulinoma.
- Examination findings at the endocrinology clinic were that of a young woman with a body mass index of 37.1 (body weight 101.1 kg, height 165 cm). There were no striae or easy bruising. Other examination findings were essentially normal

Blood sugar :40 mg/dl

- She was admitted for 72-hour prolonged fast, which was terminated after 12 hours when she developed symptoms of hypoglycemia with BG of 2.2 mmol/L (39.6 mg/dL).
- At termination of fast, serum C-peptide was elevated at 5.85 ng/mL (1.95 nmol/L) (normal reference: 0.5-2.7 ng/mL [0.2-0.9 nmol/L]), and
- **serum insulin was 52.5 μU/**mL(364.6 pmol/L) (normal reference: 2-15 μU/mL [13.9-104.2 pmol/L]).

Diagnosis evidence

1. terminated after 12 hours when she developed symptoms of hypoglycemia with BG of 2.2 mmol/L (39.6 mg/dL) by 72-hour prolonged fast,
2. serum C-peptide was elevated at 5.85 ng/mL
3. **serum insulin was abnormally high, 52.5 μU/**mL.

- Abdominal magnetic resonance imaging scan (MRI) (Fig. 1) showed a tumor at the tail of the pancreas suggestive of insulinoma;

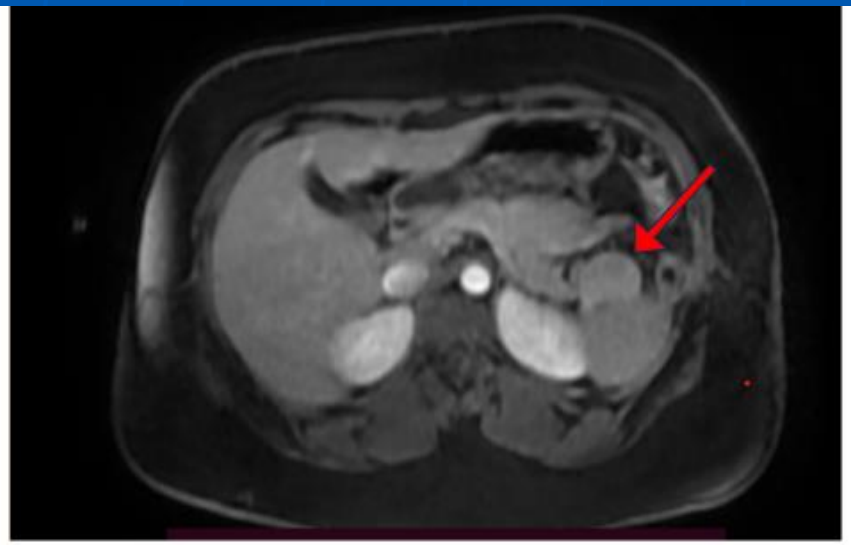
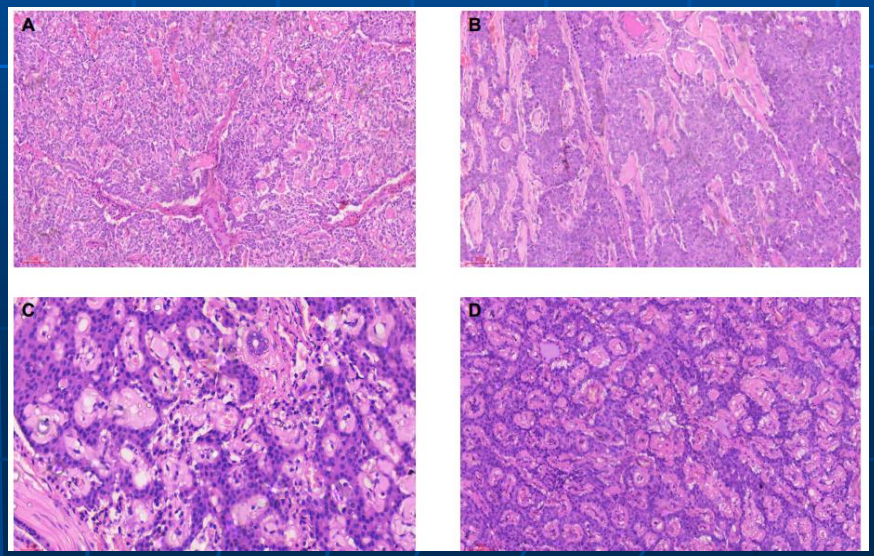


Figure 1. Axial section of the abdominal magnetic resonance imaging scan—an oval-shaped, well-marginated, T1-isointense to splenic parenchymal, T2-hyperintense mass lesion with no restricted diffusion in diffusion-weighted imaging/apparent diffusion coefficient images, measuring 3.64 × 3.72 × 2.63 cm in H × T × AP diameter.

She subsequently had an open distal pancreatectomy performed with complete resolution of symptoms. Histopathologic examination showed a NET, most probably insulinoma (Fig. 2)



- The 72-hour prolonged fast with measurement of blood glucose, serum insulin, C-peptide, and proinsulin levels is a definitive diagnostic test for insulinomas, but may need to be terminated earlier if hypoglycemia sets in, and modified on account of cost and availability of analytes.

Case 8

- 一名 89 歲，49 kg，167 cm 男性（體重指數 [BMI] 為 17.6 kg/m^2）由於存在前列腺增生，計劃進行經尿道前列腺切除術。患者有 7 年的 T2DM 病史和 5 年的腰椎間盤突出症病史。他既往沒有低血糖事件。他的藥物包括沙格列汀，每天口服5毫克。他的血糖控制良好，空腹血糖約為5-11 mmol/L，餐后血糖約為6-15 mmol/L（表1）糖化血紅蛋白: 6.9%

患者在手術前一天停用沙格列汀，並在晚餐后禁食直至手術。手術當天早上8點，空腹血糖為4.7 mmol/L，根據泌尿科醫生醫囑，給予500 mL 5%葡萄糖溶液和5單位胰島素一次，上午10時血糖升高至5.1 mmol/L。12：53 pm 開始麻醉誘導前的基線血糖為 4.0 mmol/L.

術前血壓為 125/77 mm Hg，心率為 73 bpm。患者接受靜脈注射 intravenous etomidate (14 mg), sufentanil (15 μg), and cisatracurium (10 mg) for general anesthesia induction 進行全身麻醉誘導，並用 sevoflurane 七氟醚 （1%-1.5%） 和**remifentani**l瑞芬太尼 （0.04-0.05 μg/kg/min） 維持。放置喉罩氣道進行機械通氣。使用雙頻指數 bispectral index （BIS） 監測麻醉深度。

- Twenty minutes after induction of general anesthesia, the BIS value was approximately 20 to 25. The patient's hemodynamics were stable. Arterial blood sampling showed normal electrolytes and acid-base status but severe hypoglycemia with a blood glucose level of 0.98 mmol/L (Table (Table2).2). Arterial blood gas analysis at the time showed: pH 7.43, $PaCO_2$ 39 mm Hg, PaO_2 214 mm Hg, HCO_{3-} 26 mmol/L, base excess 2 mmol/L, lactate 0.63 mmol/L. Repeat finger stick glucose testing gave a result of 0.96 mmol/L.

40 milliliters of 50% dextrose were administered intravenously followed by an infusion of 5% dextrose. One hour later, the laboratory technologist reported the blood glucose was 0.45 mmol/L. The laboratory test results were as follows: low hemoglobin 8.4 g/L (normal 11–17.2 g/L), mild hypokalemia 3.4 mmol/L (normal 3.5–5.1 mmol/L), and hypoalbuminemia 26.5 g/L

Ten minutes after treatment, the patient's blood glucose was 5.3 mmol/L and the BIS was about 40. Twenty minutes after treatment, the glucose had risen to 10.7 mmol/L while the BIS ranged from 40 to 50. Recovery from anesthesia, extubation, and postoperative recovery were unremarkable.

糖尿病患者低血糖潛在原因

- 糖尿病患者低血糖有多種潛在原因，
- 包括胰島素劑量不當、
- 同時用藥或肝腎功能惡化、
- 腎上腺皮質功能不全
- 其他

@@本例患者在手術前接受了 500 mL 的 5% 葡萄糖溶液和 5 單位胰島素的輸注，並錯過了 2 餐。相對胰島素過量可能在手術過程中引起低血糖。然而，低血糖期間檢查的血清胰島素和C肽水準在正常範圍內。在這種情況下，由於胰島素過量，不太可能發生低血糖症。.
@@皮質醇激素水準正常排除腎上腺皮質功能減退症
@@阿片類藥物是罪魁禍首

阿片類藥物通過各種機制引起低血糖

- 阿片類藥物通過各種機制引起低血糖，
- 包括增加肝細胞和骨骼肌對葡萄糖的利用、
- 促進胰島素釋放以及反調節反應受損。
-]對於阿片類藥物引起的低血糖症，已經提出了幾種假設，但仍然存在爭議。
- 世衛組織發現，阿片類藥物引起的低血糖可能是一種類別(class)效應,
- 另一項回顧性分析顯示，在非糖尿病患者中，低血糖與曲馬多和美沙酮有顯著相關性，但與其他阿片類藥物無關。
- 最近的一項綜述表明，雖然阿片類藥物刺激通常會提高血糖水準，但它可以降低 2 型糖尿病患者的血糖水準。
- 糖尿病似乎是一個危險因素。
- 一份病例報告描述了空腹低血糖伴急性、短暫性、阿片類藥物誘導的繼發性腎上腺功能減退症。[15]

阿片類藥物類效應

- 阿片類藥物誘導的低血糖的比較研究。是阿片類藥物類效應嗎？**Comparative study of hypoglycaemia induced by opioids. Is it a class effect?**
- Basile Chrétien et al :**Expert Opin Drug Saf**.2019 Oct;18(10):987-992

Objective: Drug-induced hypoglycaemia has been described with the use of tramadol and methadone. The authors aimed to determine if drug-induced hypoglycaemia could be a class effect for opioids. **Methods**: The authors performed a disproportionality analysis in VigiBase®, the WHO global individual case safety report database with nine opioids (codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, tramadol, buprenorphine and nalbuphine) using the broad Standardised MedDRA Query for hypoglycaemia. The authors also carried out a descriptive study of opioid-induced hypoglycaemia in the French PharmacoVigilance DataBase (FPVDB) using the MedDRA Preferred Term 'hypoglycaemia'. **Results**: The global adjusted Reporting Odds Ratio (aROR) value for the 9 opioids was 1.53 (95% CI 1.52-1.54). The aROR ranged from 1.09 to 1.97 depending on the opioid, but all were statistically significant. A sex ratio of 0.74 was found for the reports of opioid-induced hypoglycaemia in Vigibase®. The authors also found 133 reports of hypoglycaemia in the FPVDB related to opioids. Among the reports, 55 were glycaemic imbalances in diabetics occurring shortly after the start of opioid treatment. **Conclusion**: This work highlighted a **significant association between all opioids and hypoglycaemia, thereby indicating that opioid-induced hypoglycaemia is probably a class effect.** Women and/or diabetics seem to be more at risk for developing opioid-induced hypoglycaemia

結論

- 將低血糖歸咎於阿片類藥物是我們團隊在排除其他可能性后，根據相關數據和對以往文獻的回顧推斷得出的結論。其次，作為一份病例報告，我們研究結果的普遍性本質上是有限的。該病例的特殊性及其獨特的狀況限制了我們的結果可以推廣到更廣泛的患者群體或情況的程度.
- 在這份報告中，作者強調**暴露於阿片類藥物的患者可能會出現嚴重的低血糖症，尤其是那些接受全身麻醉、禁食時間長、BMI 低、營養狀況差和高齡的糖尿病患者。**在手術期，血糖監測往往更頻繁，特別是對於全身麻醉下的糖尿病患者。

Qin Tian [1] et al **Acute severe hypoglycemia immediately after induction of anesthesia in an elderly patient with type 2 diabetes mellitus: A case report**老年之 2 型糖尿病患者,麻醉誘導后立即發生急性嚴重低血糖：病例報告. Medicine (Baltimore). 2023 Dec 22;102(51):e36683. (L1091, L1-092)