

## Management of non-malignant hyperinsulinemic hypoglycaemia in resource limited setting: a case report

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### ABSTRACT

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A 37 y.o. Asian male presented with frequent hypoglycaemia in both fasting and post-prandial state. He had elevated blood insulin levels during the hypoglycaemic episodes with normal pancreatic morphology and no extra-pancreatic tumor. Through systematic symptom assessment and the use of simple laboratory examination, non-insulinoma pancreatogenous hypoglycaemia syndrome presented as the most likely diagnosis. Conclusive aetiological diagnosis could not be reached due to the limited availability of diagnostic modalities. Nevertheless, modest symptom control and frequency reduction of hypoglycaemia were achieved with empirical dietary modification and  $\alpha$ -glucosidase inhibitor treatment.

### ABSTRAK

**Keywords:**  
hyperinsulinemic  
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non-insulinoma  
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medical management

Laki – laki ras Asia berusia 37 tahun mengalami hipoglikemia berulang yang terjadi saat puasa maupun setelah makan. Pasien mengalami peningkatan kadar insulin pada saat episode hipoglikemi dengan morfologi pankreas normal serta tanpa tumor ekstra-pankreas. Pendekatan diagnosis berdasarkan analisa sistematis gejala dan pemeriksaan laboratorium sederhana menghasilkan diagnosa kerja *non-insulinoma pancreatogenous hypoglycaemia syndrome*. Diagnosis etiologis yang konklusif tidak dapat dicapai karena keterbatasan modalitas diagnostik. Akan tetapi, perbaikan gejala dan penurunan episode hipoglikemi dapat dicapai melalui terapi empiris modifikasi diet dan obat penghambat  $\alpha$ -glukosidase.

### INTRODUCTION

Adult-onset hyperinsulinemic hypoglycaemia (HH) is uncommon and mostly caused by insulinoma.<sup>1</sup> Non-malignant aetiologies are rare, requiring advanced and costly diagnostic modalities to confirm, which might not be accessible in resource-limited countries.<sup>2</sup> These barriers might result in low awareness among health practitioners, causing underdiagnosis/misdiagnosis and ultimately, inappropriate treatment. In contrast, the treatment approach for this clinical entity can be simple, effective,

and affordable, even without conclusive aetiological diagnosis.<sup>3,4</sup> We presented a 37 y.o. Asian male with non-malignant hyperinsulinemic hypoglycaemia, well-managed with acarbose and diet modification, although no conclusive aetiological diagnosis was reached.

### CASE

A 37 y.o. Asian male presented with frequent hypoglycaemia for the past 3 yr, manifesting as sudden general weakness accompanied by dizziness, sweating, tremor, and palpitation. He

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experienced these symptoms almost daily. These symptoms usually occur with a blood sugar level < 70 mg/dL and improve with starchy food, such as rice and potato consumption. Events of hypoglycaemia occurred in prolonged fasting, after consumption of liquid sugar (most frequent), and after strenuous physical activity. He also experienced significant weight gain of roughly 20 kg in 3 yr due to frequent snacking. He denied other symptoms and was not on any medication. He does not have history of gastric surgery and no history of alcohol consumption. He does not have significant familial history. His physical examination was unremarkable. His abdominal CT scan with contrast was unremarkable, with normal pancreatic dimension. His cranial CT scan with

contrast and chest X-ray were also within normal limits. His initial lab results were within normal limits (TABLE 1). However, his plasma insulin level was elevated during hypoglycaemic episodes (fasting, after strenuous activity) (TABLE 2). He was clinically diagnosed with non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) and empirically treated with acarbose 25 mg t.i.d. He was advised to have frequent, smaller meals low in carbohydrates, which resulted in modest symptom control and less frequent hypoglycaemic episodes. He still experiences weekly symptoms, especially after a huge meal intake and strenuous physical activity. The notable treatment-related side effect in this patient was nausea.

TABLE 1. Initial laboratory results

Parameter	Value	Reference	Parameter	Value	Reference
Fasting blood glucose	77 mg/dL	70-90	Corresponding insulin level (fasting)	10.5 µIU/mL	2.6-24.9
2-hr post-prandial (2-hr PP) blood glucose	127 mg/dL	< 140	Corresponding insulin level (2-hr PP)	89.3 µIU/mL	16-166
Anti-insulin autoantibody	Negative	Negative			
Anti-dsDNA	8.2 U/mL	< 25			
ANA IF	Negative				
Cortisol (morning)	8.9 µg/dL	3.7-19.4			

TABLE 2. Insulin level during hypoglycaemic event

Parameter	Value	Reference
Fasting blood glucose (8 hr fasted)	60 mg/dL	70-90
Corresponding insulin level (8 hr fasted)	149 µIU/mL	2.6-24.9

## DISCUSSION

Hypoglycaemia in seemingly well patients without diabetic medication is uncommon. In such patients, it is helpful to classify hypoglycaemic manifestation as hyperinsulinemic or non-hyperinsulinemic and fasting or post-prandial.<sup>2,5</sup> It is imperative to evaluate insulin levels during an episode of hypoglycaemia to avoid misclassification. In the case of our patient, his insulin levels were normal during normoglycemia but were markedly elevated when evaluated during a hypoglycaemic state. We recorded a hyperinsulinemic state during fasting hypoglycaemia but not during post-prandial evaluation. However, this patient reported frequent hypoglycaemic episodes both during prolonged fasting (> 8 hr) and post-prandial state at home.

The most common aetiology for adult-onset HH is an insulin-secreting tumor, including insulinoma and extra-pancreatic neoplasia.<sup>6</sup> Both were excluded in our patient due to normal cranial, thoracic, and abdominal radiological findings. Non-malignant aetiologies of HH are NIPHS and insulin autoimmune syndrome (IAS)/Hirata's disease. Generally considered a rare disease elsewhere, the incidence of IAS is significantly higher in the Asian population.<sup>2</sup> Hypoglycaemic manifestation of IAS occurs in post-prandial and fasting states and can not be clinically distinguished from other aetiologies of HH.<sup>7</sup> Confirmatory diagnosis of IAS requires the detection of IgG insulin autoantibody, which was negative in our patient. The exclusion of IAS left us with NIPHS as the most likely diagnosis.

Hyperinsulinemia in NIPHS is caused by hypertrophy and sometimes hyperplasia of pancreatic islet cells, which doesn't alter the macroscopic dimension of the pancreas.<sup>8</sup> The etiology of NIPHS is currently unknown and still

under investigation. Hypoglycaemic manifestation of NIPHS mainly occurs post-prandially and occasionally in a fasting state.<sup>9</sup> Confirmatory diagnosis requires a selective arterial calcium stimulation test (SACT) or histopathologic examination of pancreatic tissue.<sup>10</sup> A conclusive diagnosis could not be reached since biopsy was not performed on our patient, and SACT wasn't available in our hospital. NIPHS is challenging to diagnose due to its rarity, non-specific symptoms, and radiological findings.<sup>11</sup> Suggestive patient history, which might lead to suspicion of NIPHS, is usually a history of gastric bypass surgery, which was not present in our patient.<sup>12-14</sup> SACT is the primary diagnostic test, usually performed after other exhaustive radiological examinations have been performed with no significant pathological finding.<sup>15-17</sup> Unfortunately, SACT is an advanced examination requiring skilled interventional radiologists, uncommon in limited-resource hospitals. Nevertheless, effective and safe treatment to prevent episodes of hypoglycaemia was essential.

The general treatment approach for HH is to prevent sudden spikes in blood glucose levels. Patients should be advised to have frequent, smaller meals consisting of low carbohydrates to avoid fasting, the sudden elevation of blood glucose, and, subsequently, insulin level.<sup>18</sup> Slowly digestible carbohydrates such as corn starch can be good carbohydrate sources for these patients, as it is absorbed slowly in the digestive tract, resulting in a steadier blood glucose level. Acarbose (25-100 mg t.i.d, with each main meal), an  $\alpha$ -glucosidase inhibitor, can be prescribed to delay carbohydrate absorption, which helps stabilize post-prandial blood glucose level.<sup>3,19</sup> These approaches can be safely implemented both in IAS and NIPHS.<sup>3,4</sup> Other pharmacological therapy for HH includes diazoxide, a somatostatin analog, and Ca-channel blockers, such

as verapamil, amlodipine, nifedipine, and diltiazem. Diazoxide is the primary pharmacological treatment for HH as it directly inhibits insulin secretion by  $\beta$ -cells which unfortunately wasn't available in our region.<sup>20</sup> Somatostatin analog, such as octreotide, is a less compelling option than diazoxide and is usually reserved in cases unresponsive to diazoxide. It requires parenteral administration and should be used in higher doses to achieve the desirable effect.<sup>21</sup> Calcium-channel blockers may impede calcium-channel at  $\beta$ -cells, inhibiting insulin secretion.<sup>22</sup> Albeit not curative, these approaches can effectively reduce the incidence of hypoglycaemia due to endogenous hyperinsulinemia and should be considered when a conclusive aetiological diagnosis can not be reached.

## CONCLUSION

The most common cause of non-malignant hyperinsulinemic hypoglycaemia includes NIPHS and IAS, which are difficult to differentiate in a resource-limited setting conclusively. Frequent, smaller, and low carbohydrate meals and consumption of acarbose with each main meal present safe, effective, and affordable management in such patients, even without a conclusive aetiological diagnosis.

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