“Riding High on Low Fuel” - Our Experience with Endogenous Hyperinsulinemic Hypoglycemia

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Abstract

Introduction: Endogenous hyperinsulinemic hypoglycemia (EHH) is a condition in which the insulin levels are inappropriately high in the presence of low plasma glucose. Materials and Methods: We did a retrospective analysis of case records of those patients admitted and evaluated for EHH from June 2004 to June 2016 in our center, excluding those that were diagnosed with reactive hypoglycemia. We collected data regarding demographics, clinical presentation, laboratory results, localization techniques, and treatment administered. Results: Sixteen patients who were admitted for evaluation based on history suggestive of repeated hypoglycemic episodes were included in the study. All but one pregnant patient was subjected to a supervised fast in the hospital. All patients developed hypoglycemia (defined using Whipple’s triad) within the first 24 h. Three patients had autoimmune hypoglycemia which differed significantly from insulinoma-mediated hypoglycemia in certain clinical and laboratory parameters. They were older in age with marked fluctuations in the 24 h glucose profile ranging from frank hypoglycemia to frank hyperglycemia. The insulin levels were markedly elevated in this group of patients along with a significantly elevated insulin C peptide molar ratio (ICMR) when compared with patients with insulinoma-mediated hypoglycemia. Conclusions: Although insulinoma is the most common cause of EHH, autoimmune hypoglycemia should be considered as a differential diagnosis, particularly in older individuals with plasma glucose values increasing to the hyperglycemic range. Degree of elevation of insulin levels and ICMR may provide additional clues. Overall, the survival and prognosis of patients with EHH are excellent.

Keywords: Endogenous hyperinsulinemic hypoglycemia, insulin autoimmune syndrome, insulin C peptide molar ratio, insulinoma

INTRODUCTION

Endogenous hyperinsulinemic hypoglycemia (EHH) is a condition in which the insulin levels are inappropriately high in the presence of low plasma glucose.[1] The conditions leading to EHH are broadly classified into congenital and acquired. Among the congenital hypoglycemias, potassium channel mutations leading to unregulated insulin secretion and causing hypoglycemia in the newborn is the most common cause of EHH.[2] However, in adults, insulin secreting tumors of the pancreas or insulinomas comprise the largest etiological group.[3-6] Other etiologies such as autoimmune hypoglycemia, nesidioblastosis, and reactive hypoglycemia may also be encountered occasionally in clinical practice. The estimated incidence of insulinoma is approximately 4 per one million patient-years.[4] They are usually solitary, well-encapsulated benign lesions, with more than 90% of them being small (<2 cm in size).[4] Insulin autoimmune syndrome (IAS) is an uncommon cause of EHH which develops due to antibodies directed against the insulin molecule or the insulin receptor.[7,8] Patients with EHH classically present with symptoms and signs of hypoglycemia and on evaluation will be found to have nonsuppressed insulin levels in the presence of low plasma glucose levels. The present study aims at sharing our experience with EHH that were evaluated and managed in our center.

MATERIALS AND METHODS

We did a retrospective analysis of case records of those patients admitted and evaluated for EHH from June 2004 to June 2016 in our center. We excluded those patients who were diagnosed
to have reactive hypoglycemia based on history, physical examination, and initial biochemical evaluation (extended mixed meal tolerance test). Among the patients who presented with symptoms suggestive of repeated hypoglycemic episodes, confirmation of EHH was done following a supervised fast as per standard protocols. Hypoglycemia was confirmed only in the presence of Whipple’s triad; and samples for biochemical workup including insulin and C-peptide levels were obtained during this episode. EHH was diagnosed if serum insulin levels were $>3 \mu U/ml$ and C peptide levels were $>0.6 \text{ng/ml}$ in the presence of a documented plasma glucose value $<55 \text{mg/dl}$.

Following biochemical confirmation of both hyperinsulinemia and hypoglycemia, all patients were subjected to imaging tests for localization of the tumor. Computed tomography (CT) of the abdomen was the most commonly used imaging modality. Few ($n = 3$) patients underwent initial magnetic resonance imaging (MRI) of the abdomen instead of CT. Endoscopic ultrasonography (EUS) was additionally done in a subset of patients once the modality became available in our center. Insulin antibody titers were done in patients with high clinical suspicion for autoimmune hypoglycemia. IAS was diagnosed in patients with insulin antibody titer level above 10 U/ml. The standard protocol followed in our institute for the workup of EHH is depicted in Figure 1.

Serum insulin levels were measured by commercial chemiluminescence immunoassay (CLIA) using a Cobas 6000 Roche HITACHI analyzer (Roche medical technologies) with a detection sensitivity of 0.5–300 $\mu U/ml$. Serum C-peptide levels were also measured by a commercial CLIA using the IMMULITE2000 analyzer (Siemens Medical Solutions) which has a detection sensitivity of 0.3–7 ng/ml. Measurement of insulin antibody titers were done by enzyme immunoassay using the fully automatic analytic instrument, ALEGRIA (ORGENTEC Diagnostika). The lower limit of detection for this test was 0.5 U/mL. CT scanning was done using a 16 slice GE brightspeed scanner following the standard protocol of triple-phase imaging for abdominal organs. MRI was done using GE 1.5 T HDX (GE Medical systems) scanner. EUS, when done was performed with ALOKA Trivitron Prosound AlphaSSV sonography machine (Hitachi Medical systems).

**Statistical analysis**

Continuous variables have been reported using median and interquartile range as most of our data were not normally distributed. Categorical variables have been reported using numbers and percentages. The continuous variables were compared between two groups using Mann–Whitney $U$-test. Categorical variables were compared between two groups using Chi-square test or Fisher’s exact test as appropriate. All the analyses were done using SPSS version 17 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). All the analyses were considered statistically significant at 5% level ($P < 0.05$).

**Results**

Our study comprised 16 adult patients who were diagnosed with EHH, which included 8 males and 8 females with a median age of 43.6 years (28–65 years). Fifteen (93%) patients who presented with symptoms suggestive of repeated episodes of hypoglycemia were subjected to supervised fast. One patient (6.25%) who was pregnant had repeated spontaneous hypoglycemic episodes and hence did not require the fast. Thirteen out of these 15 patients (86%) developed hypoglycemia within the first 24 h of the supervised fast. Following confirmation of EHH, abdominal imaging was done to localize the tumor. Out of the 16 patients who underwent CT or MRI, 13 were found to have an identifiable lesion suggestive of insulinoma. Nine patients who were evaluated after 2008 underwent additional imaging with EUS; 7 out of these 9 patients were found to have insulinoma. Insulin antibody titers were elevated in 2 out of 16 patients, confirming the diagnosis of IAS.

The remaining one patient who had negative imaging results and negative antibody test was diagnosed as probable IAS based on the clinical picture. The factors supporting IAS were age (75 years), 24 h glucose profile demonstrating fluctuations from hypoglycemic range to hyperglycemic range [depicted in Figure 2] and very high serum insulin levels (217 $\mu U/ml$). She was tentatively treated with steroids. The response to therapy, resolution of hypoglycemia, and recovery of symptoms with a total follow-up period of 3 years were considered as further supportive evidence to autoimmune hypoglycemia being the underlying etiology.

Overall, in our study cohort, 81% ($n = 13$) were found to have insulinoma and 19% were found to have IAS ($n = 3$). Among the patients with insulinoma, one (7.6%) patient was found to have multiple endocrine neoplasm (MEN1), with coexisting hyperparathyroidism. The most common site of insulinoma in our patients was head of the pancreas ($n = 7$), followed by body of pancreas ($n = 3$), tail of pancreas ($n = 2$), and junction between the head and neck ($n = 1$). All 13 identified lesions
whether by CT, MRI, or EUS were <2 cm in size. Both the initial modalities of imaging used (CT or MRI) were equally effective in identifying the offending lesion in all our patients. Among the nine patients who were additionally evaluated with EUS, successful identification of the tumor was possible in all seven patients harboring an insulinoma. The tumor site in this subset followed a similar pattern: 3 in the head of the pancreas, 2 in the tail of the pancreas, and 1 each in the body and the junction between head and neck.

All the patients presented with symptoms suggestive of recurrent episodic hypoglycemia which included sweating, palpitations, increased hunger, tremors, dizziness, and blurring of vision. Four patients had a history of multiple seizures; one patient had presented with syncpe and loss of consciousness. One patient had clinical features suggestive of peripheral neuropathy with marked wasting and weakness of distal muscles attributable to prolonged hypoglycemia. The mean duration of symptoms before diagnosis was longer in patients with insulinoma as compared to those with IAS though this was not significant (1 year vs. 6 months). The patients in the IAS group were also significantly older than the patients in the insulinoma group. No difference was noticed in time taken to achieve hypoglycemia during the supervised fast between the two groups; however, the patients in the IAS group did show fluctuations in the blood glucose levels varying from hypoglycemia to frank hyperglycemia [Figure 2]. The mean serum insulin and C-peptide levels were significantly higher in the IAS group compared to the insulinoma group. The differences between the two groups have been illustrated in Table 1.

All patients with insulinoma were advised surgical excision of the tumor. Medical therapy with diazoxide and/or octreotide was used in a few patients with refractory hypoglycemia before surgical excision. One patient was successfully treated with diazoxide for 6 weeks before surgery (surgery deferred due to personal reasons). Twelve out of 13 patients underwent surgery in our institute; one patient opted to get surgery done elsewhere. Among the 12 patients who underwent surgery, enucleation of the insulinoma alone was successful in nine with complete resolution of the hypoglycemic episodes. Three patients had to undergo more extensive surgery. Distal pancreatectomy along with splenectomy was done in one patient as the insulinoma was in the tail of the pancreas which was in proximity to the splenic hilum; the patient with MEN1 also underwent distal pancreatectomy in view of multiple pancreatic tumors; and the third patient’s intraoperative ultrasonography (USG) failed to identify a lesion forcing the surgeon to perform a distal pancreatectomy. Two out of the three patients who underwent distal pancreatectomy have developed diabetes while on follow-up.

All the three patients with IAS were treated with dietary modification along with steroids for approximately 3 months. All of them are off steroids now with complete resolution of hypoglycemic episodes.

**Discussion**

In this retrospective study, insulinoma was found to be the most common cause for EHH with a prevalence of 81% (13/16 patients). We also found a relatively higher prevalence of IAS (19%; 3/16 patients) in this cohort. IAS has been described as the third most common cause of hypoglycemic attacks from Japan, after insulinoma and extrapancreatic neoplasms;[9] this has been attributed to the high prevalence of specific HLA alleles (mostly DR4) that confer predisposition to developing this syndrome. There are few case reports from India, describing the occurrence of IAS, including one which demonstrated the presence of a high-risk HLA allele.[10] Most of them have been attributed to intake of offending drugs containing the sulfhydryl group;[11,12] however,

![Image](https://example.com/image.png)

**Figure 2:** 24 h glucose profile - insulinoma versus insulin autoimmune syndrome

**Table 1: Comparison of patients with insulinoma and insulin autoimmune syndrome**

| Characteristics                  | Insulinoma (n=13) | IAS (n=3) | P     |
|----------------------------------|-------------------|-----------|-------|
| Age (years)                      | 37* (30.5-46.5)** | 65* (65-75)** | 0.004 |
| Duration of symptoms (years)     | 1 (0.8-3.0)       | 0.5 (0.3-0.5) | 0.060 |
| Sex (male), n (%)                | 7 (53)            | 1 (33)    | 0.52  |
| Autonomic (neurogenic) symptoms, n (%) | 13 (100)    | 3 (100)   | 1     |
| Neuroglycopenic symptoms (severe), n (%) | 4 (30)       | 1 (33)    | 0.70  |
| Onset of hypoglycemia (h)        | 18                | 16        | 0.72  |
| Serum insulin µIU/ml             | 11.2 (8.3-25.16)  | 222.75 (217-600) | 0.004 |
| C peptide ng/ml                  | 2.70 (2.05-3.9)   | 8.61 (7.8-20)  | 0.005 |
| Insulin C-peptide molar ratio    | 0.093             | 0.925     | 0.01  |
| Insulin auto antibodies          | Positive (n=2)    |           |       |

*Median, **Quartiles. IAS: Insulin autoimmune syndrome*
none of the patients in our series had a history of exposure to any known drug that could cause IAS. The reason for a higher proportion of cases with IAS may be attributed to the fact that our center is a tertiary care referral center; hence, EHH cases with no identifiable tumor on imaging are more likely to get referred for further evaluation. Insulinoma, on the other hand, is the leading cause of EHH reported worldwide, with an estimated incidence of 4 per 1 million patient years.\(^{[4]}\)

As depicted in Table 1, the patients with IAS were more likely to be older in age compared to those with insulinoma; and the total duration of hypoglycemic symptoms was also shorter. However, both groups of EHH presented with similar symptoms of hypoglycemia, with all 16 patients giving positive history of autonomic symptoms such as sweating, palpitations, tremors, paresthesias, anxiety, or hunger; around 30% of patients from each group presenting with severe neuroglycopenic symptoms such as seizure or loss of consciousness. The patients with IAS also had significantly higher insulin and C-peptide levels compared to those with insulinoma similar to what has been reported earlier in literature.\(^{[6,13,14]}\) When endogenous insulin is bound to insulin antibodies, there is sequestration of insulin, leading to reduction in amount of bioavailable insulin. In the early postprandial phase, this sequestration of insulin may lead to hyperglycemia, stimulating further insulin secretion from the pancreas.\(^{[11]}\) Subsequently, if the insulin is released from the antibody complex during the late-prandial or fasting state, hypoglycemia ensues. All the three patients with IAS demonstrated this phenomenon of transient hyperglycemia as is depicted in Figure 2.

This is also the explanation for the insulin: C-peptide dissociation seen with IAS. After beta cell stimulation by glucose or other insulin secretagogues, both insulin and C-peptide are released from the pancreas into the portal circulation in a 1:1 molar ratio. However, endogenous insulin undergoes extensive hepatic extraction, significantly reducing its concentration in peripheral circulation. C-peptide, on the other hand, undergoes predominantly renal clearance and passes the liver with zero or negligible hepatic extraction. Hence, the insulin C-peptide molar ratio (ICMR) should always be <1.\(^{[15]}\)

In the past, an increased ICMR (>1) was suggested as evidence of surreptitious or inadvertent exogenous insulin administration. IAS is another condition where the ICMR may be elevated.\(^{[16]}\)

In the current series, the ICMR between the two groups showed a clear differentiation with the IAS group demonstrating a significantly higher ICMR reflecting the dissociation between insulin and C-peptide secretion that occurs in these patients. However, only one patient had a calculated ICMR that was more than 1. The other 2 patients had insulin levels greater than the upper limit of detection for the assay (>300 μIU/ml) along with elevated C-peptide levels, limiting the measured elevation in ICMR. The very high-measured insulin levels during hypoglycemic attacks in IAS may be partly due to assay artifact caused by the antibodies against insulin.\(^{[17]}\)

The supervised 72 h fast is recognized as the gold standard test to rule out endogenous hyperinsulinemia; however, about two-thirds of patients with documented insulinoma develop hypoglycemia within the first 24 h.\(^{[18]}\) A recent study by Anakal \textit{et al.} also found that all patients with insulinoma in their series developed hypoglycemia within the first 24 h of supervised fast, which was similar to our results.\(^{[19]}\)

One patient in our study cohort was found to have insulinoma associated with MEN1, which was suspected based on the multiple pancreatic tumors detected on imaging. He also had coexisting hyperparathyroidism. He was subjected to distal pancreatectomy and neck exploration with removal of all parathyroid glands. Insulinomas may be the first manifestation of MEN1 in 10% of patients, and approximately 4% of patients with insulinomas will have MEN1.\(^{[20]}\)

Regarding the localization studies utilized for insulinomas, all 16 patients were subjected to either CT or MRI as the first imaging modality. Thirteen out of the 16 patients were found to have an identifiable tumor on imaging. Based on previous studies, the sensitivity and specificity of these imaging modalities are comparable and there is no specific advantage of MRI over CT. CT scanning is reported to be able to detect around 70%–80% of insulinomas on imaging, and MRI may detect up to 85%,\(^{[21]}\) EUS, on the other hand, is reported to have much higher sensitivity (>90%)\(^{[22]}\) along with the option of performing a fine-needle aspiration of any detected tumor if desired. However, this is an invasive procedure and also requires trained personnel with technical expertise. These numbers on sensitivity and specificity reflect the experience and expertise with a given modality in a given center and should be interpreted as such.

In our series, conventional imaging (with either CT/MRI) had a sensitivity of 92% and EUS had a sensitivity and specificity of 100% with seven out of nine patients having their tumor identified accurately. Although the overall sensitivity of EUS is placed at >90%, it depends on the location of the tumor. The sensitivity varies from 93% for a tumor in the head to 79% for a tumor located in the body, and these further drops to 40% for tumors located in the tail region.\(^{[23]}\) In our series, out of the seven insulinomas detected by EUS, only two were located in the tail, and both of them were identified during the procedure.

In some cases, where the initial imaging is negative or equivocal, invasive procedures such as selective pancreatic arterial calcium injections may be utilized to rule out insulinoma.\(^{[24]}\) However, this is the procedure of choice for confirming noninsulinoma pancreaticentogenous hypoglycemia and hypoglycemia occurring postgastric bypass surgery as standard imaging will be negative in these conditions. None of our patients required any invasive procedure for conformation. Intraoperative USG is another excellent modality that can be utilized in cases where clinical suspicion of insulinoma is high, but imaging is negative.\(^{[25]}\) Gallium-68-DOTA-TOC is reported to have a sensitivity of about 97% for detecting endocrine tumors\(^{[26]}\) and was found to be useful in detecting a lesion missed by conventional imaging in the study by Manjunath \textit{et al.}
Enucleation of the tumor is the ideal surgical choice if possible as this will achieve resolution of symptoms without increasing risks of pancreatic exocrine and endocrine deficiency in the future. However, if the tumor is not identified intraoperatively or due to location of the tumor in proximity to surrounding anatomical structures, more extensive surgery may sometimes be necessary which confers a higher risk of developing diabetes in the future.[27] IAS is more often a transient condition with spontaneous resolution within 3–6 months in about 80% of the patients.[28] Majority of the patients with mild symptoms will respond to dietary modifications alone like small frequent meals low in simple carbohydrates. In cases with troublesome and refractory hypoglycemia, corticosteroids are a good choice as adjunctive therapy.[28] Any offending drug exposure should be identified and removed. The long-term prognosis for conditions causing EHH is positive with excellent survival rates and good quality of life reported following therapeutic intervention for benign insulinomas and IAS.[14,28]

**Conclusion**

In conclusion, the most common cause of EHH in a seemingly well individual is likely to be an insulin-secreting tumor of the pancreas. However, entities such as IAS, which were previously considered very rare, should also be kept in mind, especially in older individuals exhibiting transient episodes of both hypoglycemia and hyperglycemia. Another clue would be the very high insulin levels measured during the hypoglycemic episode with dissociation of the ICMR. Inclusion of insulin antibody measurement in the workup of hypoglycemia should be considered, especially in those cases with high clinical suspicion. Conventional imaging with either CT or MRI is usually adequate for localization of the tumor; however, as insulinomas are frequently small, a negative imaging does not exclude the diagnosis. EUS is a promising imaging modality with excellent sensitivity and specificity (100% in our series), which, in future may overtake the conventional imaging methods.

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**Conflicts of interest**

There are no conflicts of interest.

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