Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome

Chander Mohan Batra, Sundeep Singh Saluja, Rajeev Bajaj, Usha Rajshekar, Vineeta Thakur, Vimal Gupta

Abstract

We present the case of a 55 yr female who had recurrent severe hypoglycemic attacks with neuroglycopenic symptoms and altered sensorium including coma. The hypoglycemic episodes were not related to fasting. The hypoglycemia was hyperinsulinemic but all imaging modalities for insulinoma were negative. Selective arterial calcium stimulation test localized the lesion to splenic artery territory and distal pancreatectomy left to the splenic vein was done. The histopathology was consistent with nesidioblastosis and gradient guided pancreatectomy relieved the hypoglycemic episodes.

Introduction

Non insulinoma pancreatogenous hypoglycemia syndrome was first described by Service et al. They described 5 adults with neuroglycopenic episodes from hyperinsulinemic hypoglycemia within 4 hours of meal ingestion and negative 72 hour fast, negative trans-abdominal ultrasound, spiral CECT (contrast enhanced computerized tomography) and coeliac axis angiography of the pancreas but positive selective arterial calcium stimulation test indicative of beta cell hyperfunction. At pancreatic exploration, no insulinoma was detected by complete mobilization, palpation and intraoperative ultrasonography.

Resected pancreata showed islet hypertrophy and nesidioblastosis but no insulinoma and gradient guided partial pancreatectomy relieved the hypoglycemic episodes. This is a rare disorder with 75 published cases so far, none from India. We present one patient who has all the features of this rare syndrome.

Case Report

A 55 yr female, non diabetic with no family history of diabetes had recurrent severe hypoglycemic attacks with neuroglycopenic
Table 1: This table shows the results of selective intra-arterial calcium stimulation and hepatic venous sampling. The splenic artery territory shows doubling of serum insulin levels

<table>
<thead>
<tr>
<th>Artery</th>
<th>0sec</th>
<th>30sec</th>
<th>60sec</th>
<th>90sec</th>
<th>120sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenic Insulin UIU/l</td>
<td>19.5</td>
<td>50</td>
<td>38.7</td>
<td>30.3</td>
<td>25.4</td>
</tr>
<tr>
<td>C-pep ng/dl</td>
<td>3.18</td>
<td>5.5</td>
<td>4.54</td>
<td>4.37</td>
<td>4.16</td>
</tr>
<tr>
<td>Gastroduodenal Insulin</td>
<td>15.6</td>
<td>24.0</td>
<td>20.6</td>
<td>17.1</td>
<td>16.3</td>
</tr>
<tr>
<td>Superior Mesenteric Insulin</td>
<td>21.8</td>
<td>24.2</td>
<td>25.9</td>
<td>27.6</td>
<td>25.5</td>
</tr>
<tr>
<td>Mesenteric C-pep</td>
<td>3.15</td>
<td>2.42</td>
<td>3.92</td>
<td>3.92</td>
<td>3.92</td>
</tr>
</tbody>
</table>

Table 2: This table shows the results of oral glucose tolerance test done 10 days after surgery. The patient has now become diabetic, there is no reactive hypoglycemia

<table>
<thead>
<tr>
<th>Blood Sugar (mg/dl)</th>
<th>Serum insulin level (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hour</td>
<td>124</td>
</tr>
<tr>
<td>1 hour</td>
<td>232</td>
</tr>
<tr>
<td>2 hour</td>
<td>240</td>
</tr>
<tr>
<td>3 hour</td>
<td>152</td>
</tr>
<tr>
<td>4 hour</td>
<td>138</td>
</tr>
<tr>
<td>5 hour</td>
<td>113</td>
</tr>
</tbody>
</table>

symptoms and altered sensorium including coma, since 2002. The hypoglycemic episodes were not related to fasting. She was admitted five times to various tertiary care hospitals of Delhi relieved each time within minutes with iv glucose.

She was fully investigated for insulinoma. She was put on a 72 hours fast 4 times but each time hypoglycemia could not be provoked. Triple phase spiral contrast enhanced computed tomography (CECT) scan, magnetic resonance imaging (MRI) abdomen, endoscopic ultrasonography, magnetic resonance imaging (MRI) sella, liver function tests, urea, creatinine and cortisol were repeatedly normal. Insulin auto-antibodies were not detected. Extended OGTT showed reactive hypoglycemia with the 3 hour value of 40mg/dl. Positron enhanced tomography (PET) scan and somatostatin receptor scintigraphy showed a small focus in middle of body of pancreas. The patient was diagnosed reactive hypoglycemia and discharged on small frequent meals and acarbose thrice daily on all 5 occasions.

She was admitted in our hospital on 25.4.08 at 3.26am five and a half hours after dinner with complaints of restlessness for 2 days, loss of consciousness for one hour. Blood sugar was 26mg/dl and 100 cc 50% dextrose was given immediately. She regained consciousness within minutes. There were no positive findings on examination, no focal neurological deficit.

A 10% dextrose drip at a rate of 50 cc/hour was given continuously. At 10 am blood sugar became 40mg/dl in spite of dextrose infusion. At that time serum insulin was 33micro units/ml and C-peptide=16ng/dl. A hypoglycemic attack occurred again at 5 pm with blood sugar of 36 mg/dl, at that time serum insulin was 16microunits/ml and C-peptide19ng/dl. The patient was investigated again CECT abdomen, LFT, urea, creatinine cortisol were normal and a 72 hours fast did not provoke hypoglycemia. Selective intra-arterial calcium injection and hepatic venous sampling was done by our cardiologist.

Materials and Methods

Selective Intra-arterial Calcium Stimulation of Pancreatic Arteries and Right Hepatic Vein Sampling by method of Doppman 3.

Right hepatic vein was canaled through femoral vein puncture. Splenic, gastroduodenal and superior mesenteric artery were canaled in turn with a gap of 15 minutes each and 0.025 meq/kg body wt (1.0mg/kg) of calcium was injected rapidly. Samples for serum insulin and c-peptide were taken at 0, 30, 60, 90, 120 secs after calcium injection. Samples were stored on ice and assayed within 1 hour.

The splenic artery was selectively stimulated by intraarterial calcium injection with a doubling of serum insulin levels and a significant increase in the serum C-peptide after 30 secs of injection of calcium. The other arteries were not stimulated (Table1).

Surgery

Mobilization and palpation of pancreas was negative for insulinoma.

Distal pancreatectomy to right of superior mesenteric vein was done along with splenectomy. Postoperative period was uneventful No hypoglycemic attack has occurred in the last 2 years. Post op OGTT 10 days after surgery was done revealed that the patient had become mildly diabetic but she was euglycemic on diet therapy alone and did not require insulin or oral hypoglycemic agents (Table 2).

Histopathological report Dr Ricardo V Lloyd, Mayo Clinic USA, Dr Usha, Batra Hospital

The H&E sections show pancreatic tissue with rare hypertrophic islets forming ductuloinsular complexes associated with small pancreatic ducts. A mixture different types of islet cell hormone producing cells associated with acinar cells. The findings are consistent with but not diagnostic of mild nesidioblastosis. The photographs of...
the slides which were stained at Mayo clinic USA are shown in figure 1 and the H/E staining (Fig. 2).

**Discussion**

There are some discoveries that change the way we think, change age old principles and laws that were supposed to be with such a solid foundation that it is blasphemy to question their authenticity.

In the workup of cases of spontaneous hypoglycemia the first principle was that hypoglycemia in the fasting state is important and should be seriously investigated but hypoglycemia occurring after a meal does not have a serious cause, is reactive and can be ignored. The second principle was that if a patient does not have symptomatic hypoglycemia after a 72 hours supervised fast, he cannot have a serious problem. Post prandial hyper-insulinemic hypoglycemia even if severe and life threatening was labelled as reactive hypoglycemia and prescribed frequent low carbohydrate meals and acarbose. The third principle is that only children have nesidioblastosis and adults have insulinomas.

Service et al described a new syndrome “Non insulinoma pancreatogenous hypoglycemia syndrome (NIPHS)" and the discovery that nesidioblastosis is the cause in 4% of adults presenting with serious hypoglycemic episodes, have taught us that the previously described principles for evaluation of hypoglycemia were incorrect.

Hypertrophic islets, beta cells with pleomorphic nuclei and ductulo-insular complexes are the key features of nesidioblastosis on histopathology.

Selective pancreatic artery calcium stimulation causes abnormal beta cells to hyperstimulate insulin production. Normal beta cells are not hyperstimulated by calcium. Increase of serum insulin to greater than double the baseline value localizes the lesion to the territory supplied by that artery. Hyperstimulation of insulin in the splenic artery territory localizes the lesion to body and tail of pancreas, gastroduodenal to the head and uncinate process, superior mesenteric to the uncinate process and head. Gradient guided distal pancreatectomy is done to the right of superior mesenteric vein if the splenic artery territory is involved and to the left if superior mesenteric or gastroduodenal artery territory is involved. Gradient guided distal pancreatectomy usually relieves the hypoglycemia.

Hypertrophic islets, beta cells with pleomorphic nuclei and ductulo-insular complexes are the key features of nesidioblastosis on histopathology. All features of noninsulinoma pancreatogenous hypoglycemia syndrome were present in this patient.

Neuro-glycopenic patients with hyperinsulinemic hypoglycemia, fasting or postprandial. should not be labelled as reactive hypoglycemia even if a 72 hours fast is negative.

**Acknowledgement**

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**References**


