Insulinoma: pathophysiology, localization and management

Joyce J Shin,
Montefiore Medical Center/Albert Einstein, College of Medicine, Greene Medical Arts, Pavilion 4th Floor, 3400 Bainbridge Avenue, Bronx, NY 10467, USA

Phillip Gorden, and
NIDDK, National Institutes of Health, Building 10-CRC, Room 6-5952, 10 Center Dr., Bethesda, MD, USA, Tel.: +1 301 402 7340, Fax: +1 301 435 5873

Steven K Libutti†
Montefiore-Einstein Center for Cancer Care, NY, USA and Department of Surgery, Montefiore, Medical Center/Albert Einstein College of Medicine, Greene Medical Arts Pavilion, 4th Floor, 3400 Bainbridge Avenue, Bronx, NY 10467, USA, Tel.: +1 718 920 4231, Fax: +1 718 798 0309

Joyce J Shin: jshin@montefiore.org; Phillip Gorden: PhillipG@intra.niddk.nih.gov; Steven K Libutti: slibutti@montefiore.org

Abstract

Insulinoma is a rare neuroendocrine tumor that causes oversecretion of insulin and, as a result, patients present with symptoms of hypoglycemia. Fortunately, insulinomas are usually benign and solitary, and surgical cure rates are highly favorable. Most of these tumors occur sporadically, but they can also be associated with multiple endocrine neoplasia type-1 syndrome. The diagnosis is confirmed by a supervised fast, and early detection is important. Several preoperative and intraoperative techniques with various success rates have been employed in order to localize the lesion. When technically feasible, tumor enucleation is the procedure of choice; however, a more formal resection may be necessary for certain tumors. In the age of laparoscopy, the role of laparoscopic surgery in the management of insulinomas is continuing to attract attention. This review will discuss the historical background, pathogenesis, diagnosis, localization and management of insulinomas.

Keywords
enucleation; insulinoma; laparoscopic; localization; MEN-1 syndrome; metastatic insulinoma

Insulinoma is the most common neuroendocrine tumor of the pancreas with an annual incidence of four in every 1 million persons [1]. Although rare, insulinomas have the potential to produce profound metabolic derangements, necessitating early recognition and treatment. Generally, insulinomas occur sporadically; however, they can be associated with multiple endocrine neoplasia (MEN)-1 syndrome. Patients present with hypoglycemia and
neuroglycopenic symptoms and, historically, the diagnosis has been confirmed by the presence of Whipple’s triad [2]. Once the diagnosis is established, the insulinoma is preoperatively localized by various techniques in order to improve operative success. Owing to the fact that complete surgical excision is the only curative method, accurate preoperative and intraoperative localization of the insulinoma is imperative.

**Historical background**

The pancreatic islet cells were first described by Paul Langerhans in 1869, while still a medical student [2]. In 1922, 53 years later, Frederick Banting and Charles Best discovered insulin from a solution extract from a dog’s pancreas [2,3]. The relationship between hyperinsulinism and a functional pancreatic islet cell tumor was established by William J Mayo, who attempted the first operation for insulinoma in 1927 [4]. Unfortunately, the tumor was malignant and unresectable [5]. However, 2 years later, Roscoe Graham performed the first surgical cure of an islet cell tumor [6].

In 1935, Whipple and Frantz described the diagnostic triad for insulinoma:

- Symptoms of hypoglycemia provoked by fasting
- Circulating glucose level less than 50mg/dl at the time symptoms presented
- Relief of symptoms with administration of glucose [2]

This is the so-called Whipple’s triad, the diagnostic hallmark of insulinomas.

**Pathogenesis**

Insulinomas can occur sporadically or in conjunction with MEN-1 syndrome. Formerly known as Wermer’s syndrome, MEN-1 syndrome is an autosomal dominant disorder associated with mutations in the MEN1 gene mapped to chromosome 11q13 [7,8]. It is characterized by parathyroid hyperplasia, anterior pituitary adenomas and tumors of the endocrine pancreas and duodenum. First proposed by Knudson to describe the tumorigenesis of retinoblastomas, the two-hit hypothesis for tumor suppressor genes also applies to MEN-1 syndrome [9]. In patients affected with MEN-1 syndrome, the presence of MEN1 germline mutations accompanied by loss of heterozygosity at 11q13 is observed [10,11]. This phenomenon has suggested a role of MEN1 as a tumor suppressor gene, requiring inactivation of both alleles for clonal expansion and tumor development [10,11]. In addition, a variety of sporadic endocrine tumors, such as parathyroid adenomas, pancreatic insulinomas and pituitary prolactinomas, have expressed somatic mutations and loss of heterozygosity of the MEN1 alleles, demonstrating that the MEN1 gene may play the same role in nonhereditary endocrine tumors [10–13].

The MEN1 gene consists of ten exons spanning 9 kb of genomic DNA and encodes a 610-amino acid protein product termed menin [14]. Menin is ubiquitously expressed in both endocrine and nonendocrine tissues and does not display significant homology to any known family of proteins [11,14]. Predominantly described as a transcriptional regulator, menin interacts with a wide variety of nuclear and cytosolic proteins, such as JunD, NF-kB, Smad3, FANCD2, RPA2, ASK and others, which suggests that menin may be involved in multiple biological pathways leading to tumor formation [11,15,16]. In mouse models, knockout of both Men1 alleles results in embryonic lethality, whereas the heterozygous phenotype of menin inactivation in mice is remarkably similar to that of the human MEN-1 syndrome [17]. Although the combination of findings from all current research has resulted in a better understanding of menin and its role in the development of the MEN-1 syndrome, the specific mechanisms leading to the endocrine tumorigenesis of MEN-1 syndrome have not been completely elucidated [11,16,17].
Sporadic versus MEN-1 syndrome tumors

Sporadic insulinomas are typically less than 2 cm in size (90% of cases), solitary (90% of cases) and benign (90% of cases) [18–20]. However, insulinomas associated with MEN-1 syndrome (affecting approximately 4–10% of MEN-1-syndrome patients) develop earlier and are frequently multicentric [1,18,21–23]. The risk of recurrence is also greater among patients with MEN-1 syndrome (21% at 10 and 20 years) than in those without the syndrome (0–5% at 10 years and 0–7% at 20 years) [1,24,25]. Owing to these characteristics of MEN-1 syndrome-associated insulinomas, simple enucleation and local resections are less likely to be curative. Subtotal pancreatectomy in addition to enucleation of tumors identified in the head of the pancreas may be required for patients with insulinoma and MEN-1 syndrome [18,22,23].

Multiple endocrine neoplasia type 1 syndrome should be suspected in patients with pathologic changes in two of the three most commonly affected endocrine organs – parathyroid, pituitary and pancreatic/duodenal endocrine tumors [21]. Genetic testing for MEN-1 syndrome can complement the clinical diagnosis and should be offered to patients in whom the diagnosis is being considered. By direct DNA sequencing strategies, the specific MEN1 mutation in the germline DNA can be identified. Other family members at risk can then undergo subsequent analysis by testing selectively for the specific MEN1 mutation of the affected individual [26]. Although genetic testing for MEN1 fails to detect 10–25% of the mutations, it plays an important role in identifying patients with hereditary insulinomas [21,26].

Clinical features & diagnosis

In healthy individuals, euglycemia is maintained within a relatively narrow range (60–100 mg/dl) even after ingestion of food [27]. As described by Whipple’s triad, patients with insulinoma are hypoglycemic and experience neuroglycopenic symptoms that are relieved by the administration of carbohydrate [2,28]. Inappropriately elevated insulin levels cause symptoms of hypoglycemia that have been classified into two major categories: neurologic (neuroglycopenic) and adrenergic (catecholamine response) (TABLE 1) [23,27,29,30]. While symptoms are typically precipitated by fasting or exercise, they can also occur postprandially or can have no relationship to eating [23]. The most prominent and perhaps most reliable symptoms are those of the neurologic type: diplopia, blurred vision, altered mental status, abnormal behavior, amnesia, coma and seizures [5,23,27,29,30]. Symptoms caused by catecholamine response include sweating, anxiety, palpitations, weakness, tremors, hunger, nausea and feeling of warmth [5,23,27,29,30]. Another notable manifestation of insulinoma is weight gain, as patients may eat frequently to avoid symptoms [19,23,30]. Although various combinations of symptoms have been reported, the symptom complex usually follows a stereotypical repeated pattern for each individual [5,27].

One important reason for the delay in the diagnosis of insulinoma is the fact that these symptoms are not unique to hypoglycemia or to this disorder. The mean duration of symptoms prior to diagnosis ranges from several months to more than several decades [1,19,23,27]. Therefore, the diagnosis of insulinoma must be confirmed by documentation of a low glucose level during the time of symptoms. The supervised 72-h fast has been the classic diagnostic test for insulinoma [5,27,31]. The protocol for this test consists of measuring the levels of plasma glucose, insulin, C peptide and proinsulin every 6 h until the plasma glucose level is 60 mg/dl or less, when the interval is reduced to every 1–2 h. The fast is terminated when the plasma glucose level is 45mg/dl or less and the patient has symptoms and signs of hypoglycemia [27]. At this low glucose level, the diagnosis of
insulinoma is established by increased levels of insulin (≥6 μU/ml), C peptide (≥0.2 nmol/l) and proinsulin (≥5 pmol/l), and an absence of sulfonylurea in the plasma (BOX 1) [27,29]. Endogenous insulin is synthesized as a precursor, proinsulin, which undergoes enzymatic cleavage to produce insulin and C peptide in equimolar amounts [29]. Therefore, factitious hypoglycemia produced by exogenous insulin administration demonstrates suppressed C peptide levels. In addition, proinsulin levels are poorly suppressible in insulinoma patients in contrast to noninsulinoma patients [28,32]. In patients with surreptitious use of insulin or an oral hypoglycemic agent, the proinsulin level is either normal or decreased.

**Box 1**

**Common diagnostic criteria for insulinoma**

- Documentation of blood glucose level <50 mg/dl with hypoglycemic symptoms
- Relief of symptoms after eating
- Increased plasma insulin level (≥6 μU/ml)
- Increased C peptide level (≥0.2 nmol/l)
- Increased proinsulin level (≥5 pmol/l)
- Absence of plasma sulfonylurea

For over 80 years, the 72-h monitored fast has been the gold standard for diagnosis of insulinoma. However, recent data have demonstrated that by using the newer assays for insulin and proinsulin, the diagnosis of insulinoma can be achieved in approximately 90–95% of patients undergoing a supervised fast of 48 h, and this is rapidly becoming the new standard [1,22,28,33].

**Localization**

Owing to the fact that insulinomas are potentially cured after complete surgical excision, accurate localization of the lesion is essential. It is appropriate that much attention and investigation have been dedicated to the localization of insulinomas. Although a variety of imaging modalities have been advocated to ensure operative cure, preoperative localization fails 10–27% of the time [5]. At present, there is little consensus regarding the best method or combination of methods for localization, and imaging protocols vary between institutions [34]. Some would suggest that preoperative localization studies are not necessary since nearly all insulinomas can be successfully localized intra-operatively [35,36]. Nevertheless, most institutions continue to apply preoperative imaging to evaluate for evidence of metastatic disease and to better facilitate the extent and type of operation.

Noninvasive localization studies include trans-abdominal ultrasonography, computed tomography (CT) (FIGURE 1) and MRI. While these modalities have the advantages of being readily available and noninvasive, the results are often disappointing, especially in insulinomas less than 2 cm in size [37]. The sensitivities of transabdominal ultrasonography, CT and MRI are 9–67%, 16–73% and 7–45%, respectively [19,20,38–40]. Although CT and MRI are of limited value for localization, these techniques are useful for evaluating the presence or absence of metastatic disease and identifying large malignant tumors, which can aid in appropriate operative planning [20,23]. Since most insulinomas do not express somatostatin receptors, somatostatin receptor scintigraphy is not a useful localizing modality [20].
When preoperative noninvasive studies fail to localize the tumors, invasive studies are utilized, which are often more successful. For many years, selective pancreatic angiography was considered the gold standard for localizing insulinomas with early reports quoting success rates up to 90% [29,41]. However, more recent data are not as promising, reporting sensitivity rates in the range of 29–60% [5,29,40,42,43]. Owing to the low sensitivity and additional disadvantages of angiography, including high cost, invasiveness and technical challenge, it is no longer the first-line localization study for insulinomas.

Transhepatic portal venous sampling (THPVS), such as angiography, is another expensive and invasive study that is technically demanding and only regionalizes the tumor [29]. This procedure involves percutaneous and transhepatic catheterization of a branch of the portal vein followed by advancement of the catheter into the small veins draining the pancreas [19,20]. Plasma insulin levels are sampled from these veins, and an elevated level of insulin determines the location of the tumor. Successful localization rates for THPVS range from 64 to 100% [19,20,23,33]. However, THPVS has been abandoned and replaced by intra-arterial calcium stimulation with hepatic vein catheterization, a procedure derived from the use of intravenous calcium as a secretagogue for the release of insulin from islet cell tumors [42,43]. The gastro-duodenal, proper hepatic, superior mesenteric and splenic arteries are selectively catheterized and then subsequently injected with calcium (0.025 mEq Ca²⁺/kg body weight) [38,42]. Blood samples (5 ml) for insulin determination are obtained from the right and left hepatic veins prior to and 30, 60 and 120 s after calcium infusion. A twofold increase in the insulin concentration from baseline localizes the insulinoma within the anatomic region perfused by the injected artery [42,43]. A response after calcium infusion into the gastroduodenal or superior mesenteric artery localizes the lesion to the head and neck of the pancreas, whereas a response after splenic artery injection localizes the lesion to the body and tail of the pancreas. A response following a hepatic artery injection suggests the presence of liver metastases [42,43]. Intra-arterial calcium stimulation, with a sensitivity of 77–100%, is an effective preoperative test for localizing insulinomas [20,38,40,42,44].

Endoscopic ultrasonography (EUS) is another preoperative localizing modality that has been accepted and utilized in many centers. The sensitivity of this test ranges from 37 to 94%, which is largely dependent on the location of the lesion [39,45–48]. EUS is best at detecting tumors in the head of the pancreas and worst at detecting those in the tail [39,45,47]. Limitations of EUS include poor differentiation between the pancreatic tumor and the peripancreatic lymph nodes, invasiveness, sedation requirement, operator dependency and a lack of universal availability.

One of the most recommended techniques for localizing insulinomas is intraoperative ultrasonography (IOUS) in combination with intraoperative palpation carried out by an experienced surgeon. IOUS, introduced in 1981, is especially useful in discerning the proximity of the lesion to the pancreatic or biliary duct and in guiding the dissection in both palpable and nonpalpable tumors during enucleation [19,29,35,49,50]. With a sensitivity of 75–100%, it has become an essential part of the operative exploration for insulinomas [19,20,34,35,39,40,50,51].

Surgical management

Surgical cure rates in patients with the biochemical diagnosis of insulinoma are favorable and range from 77 to 100% [19,20,34]. At surgical exploration, the abdomen is initially investigated for evidence of metastatic disease. The pancreas is then completely exposed, allowing palpation of the entire pancreas. Intraoperative ultrasonography and palpation can be performed at this time in order to effectively localize and guide in the dissection of the tumor.
Since most insulinomas are benign and solitary, tumor enucleation is the procedure of choice, when technically feasible [5,20,29]. These lesions are usually encapsulated, and the capsule must be completely excised with the tumor in order to prevent local recurrence. Fortunately, a clear dissection plane usually exists between the compact tumor and the normal pancreatic parenchyma [5,29]. For insulinomas that are anatomically unsuitable for enucleation, a segmental resection of the pancreas, distal pancreatectomy or pancreaticoduodenectomy is performed and is associated with lower morbidity when compared with enucleation. These lesions are located deep within the head of the pancreas in close proximity to the pancreatic duct or deep within the last segment of the pancreatic tail, which have a higher risk of pancreatic duct injury and fistula formation after enucleation [24,31]. Formal resection rather than enucleation must also be performed for tumors involving a large portion of the pancreas and lesions suspicious for malignancy, such as those that are hard, infiltrating, create puckering of surrounding tissue or cause pancreatic duct dilatation [5,29].

In the past, blind distal pancreatectomy was the standard surgical therapy for cases in which the insulinoma could not be localized intraoperatively [20,52]. However, because insulinomas are equally distributed among the head, body and tail of the pancreas, distal pancreatectomy does not achieve surgical cure in approximately half of the patients with an occult tumor [29,52]. As a direct result of improved preoperative and intra-operative localizing techniques and increasing surgical experience, blind distal pancreatectomy is not necessary and must be avoided [33,52].

Laparoscopic management of insulinomas has become increasingly popular, and small series of successful laparoscopic enucleation and resection of insulinomas have been reported [39,53–58]. Preoperative localization tests are especially important in minimally invasive surgery because the location of the tumor determines the surgical approach [54,55]. In addition, because the tumor cannot be palpated, laparoscopic intraoperative ultrasonography plays a crucial role in localizing the lesion and determining its anatomical relationship to the pancreatic duct and surrounding blood vessels [53–57]. Laparoscopic exploration using laparoscopic intraoperative ultrasonography is able to detect 86–90% of insulinomas, which is comparable to IOUS during an open exploration [39,55]. Laparoscopic surgery for insulinomas is still an evolving technique, which has the potential to provide shorter duration of hospital stay and faster recovery time [20,54,55,57].

Complications associated with the actual pancreatic procedure include pancreatic fistula, pseudocyst, intra-abdominal abscess, pancreatitis, hemorrhage and diabetes. Morbidity and mortality rates that have been reported range from 10 to 43% and 0 to 4%, respectively [19,23,29,33,35,39,49,50,59]. The complication rates for the laparoscopic approach are comparable to those for open procedures, including pancreatic fistula, the most frequent complication [53–56]. Fortunately, the majority of these fistulas seldom require reoperation; they can be managed conservatively with drainage, parenteral nutrition and somatostatin analogs to decrease the output.

After successful removal of the insulinoma, most patients are cured of their disease. The surgical cure rate is approximately 89–96% and most of these cases are benign solitary lesions [1,19,23,33,34,49,59]. For those patients with benign disease, a normal lifespan can be expected after successful surgical resection [1]. Unfortunately, there are operative failures, and reoperations are more likely associated with metastatic disease, multiple neoplasms and MEN-1 syndrome [23,33,34].
Medical management

Dietary modification and pharmacologic agents play a crucial role in the management of insulinomas in patients who are not candidates for surgical resection or those who are awaiting surgery. Patients who are symptomatic from unresectable metastatic disease or as a result of unsuccessful operations also rely on these therapeutic measures. The goal of dietary therapy is to prevent prolonged periods of fasting by consuming small, frequent meals throughout the day and night.

Diazoxide, a nondiuretic benzothiadiazine derivative, was introduced in the 1950s for the treatment of hypertension. Its ability to induce hyperglycemia has been described, and it is currently the initial drug of choice for patients with insulinoma [60]. Diazoxide directly inhibits insulin release from the $\beta$-cells through stimulation of $\alpha$-adrenergic receptors and also has an extra-hepatic, hyperglycemic effect via enhanced glycogenolysis [61]. The patient can be given diazoxide in a dose of 150–200 mg in two or three divided doses per day, which can be titrated to a maximum dose of 400 mg/day [62]. The benefits of this therapy are observed in approximately 50% of patients [23,63,64]. The main side effects of diazoxide are fluid retention, nausea and hirsutism, which complicate the use of this medication. Fortunately, the side effects are usually mild and well tolerated [63,64].

Since the presence of somatostatin receptors was observed in some insulinomas, treatment with the long-acting somatostatin analog, octreotide acetate (SMS 201–995), has offered a new approach for symptomatic relief in patients with insulinomas [65–68]. By displaying affinity for the somatostatin receptors, sst2 and sst5 [65,67], octreotide lowers plasma insulin levels and alleviates symptoms in approximately 50% of patients [65,66]. Octreotide has a half-life of approximately 100 min and is typically administered in doses of 50 or 100 $\mu$g every 12 h. The most common side effects are pain at the injection site and gastrointestinal disturbances (e.g., nausea, vomiting, heartburn, abdominal pain, constipation and diarrhea) [68–70]. Since octreotide also suppresses the release of glucagon and growth hormone, it can occasionally worsen the hypoglycemia [69–71]. Long-term octreotide treatment can also produce side effects similar to the clinical syndrome observed in patients with somatostatinomas, such as mild diabetes mellitus, cholelithiasis, malabsorption and weight loss [69,72].

Other medications that have modest and variable effects on insulin secretion include verapamil, propanolol, diltiazem and phenytoin [73–77]. Since the published studies on the efficacy of these medications include only a few case reports and small series, their role in the treatment of insulinoma has not been well established and requires further investigation.

Metastatic disease

Insulinomas have a lower malignancy rate than other islet cell tumors, occurring in only 5–15% of all reported cases [1,23,78–80]. Malignant insulinomas are difficult to distinguish histologically and often the diagnosis of malignant disease is only made when metastases occur [78,79]. The evidence of metastatic disease, predominantly in the liver or lymph nodes, is noted at the time of surgery or by imaging studies. Malignant lesions are usually single and have a mean diameter of 6 cm [81]. The median disease-free survival after curative resection is 5 years with a recurrence rate of 63% at a median interval of 2.8 years [81].

Although most insulinomas are benign and cured after surgical resection, malignant metastatic insulinomas have the potential to cause severe and debilitating hypoglycemia even after resection of the tumor. Various therapies, including radical debulking surgery, chemotherapy (e.g., with streptozocin, doxorubicin or 5-fluorouracil), biotherapy, hepatic
embolization, hepatic perfusion, radiofrequency ablation and peptide-receptor radionuclide therapy, have all been utilized to improve the duration and quality of life [78,80,82–87]. Unfortunately, the prognosis remains relatively poor for patients with malignant insulinoma [1,78,87]. Following initial surgical resection, the biology of the tumor, rather than any treatment modality, is the most likely determinant of long-term survival [78].

**Conclusion**

Insulinomas are rare, usually benign, neuroendocrine tumors of the pancreas that can occur sporadically or as a part of the MEN-1 syndrome. The diagnosis is established by the presence of symptomatic hypoglycemia accompanied by inappropriate insulin levels after a period of prolonged fasting. Imaging modalities can then be used preoperatively and/or intraoperatively in order to localize the lesion. Invasive localization studies can also be employed to increase the chance of operative success. In the absence of metastatic disease, patients are cured after complete surgical resection. For unresectable or metastatic insulinomas, pharmacologic agents and nonsurgical therapies are currently available. However, further research is required in order to improve understanding of the pathogenesis and treatment of malignant insulinomas.

**Future perspective**

Owing to the rare nature of insulinomas, our knowledge of this disorder is limited. The etiology of these tumors remains largely unknown. A better understanding of the molecular processes underlying the development and progression of this disease will enhance the management, treatment and prognosis of both benign and malignant insulinomas. Nonetheless, our ability to recognize and manage insulinomas has improved over the years. An earlier and more accurate diagnosis may be feasible with newer and more advanced biochemical assessments. In addition, further improvements in surgical cure rates may be possible with better localization studies. Currently, advances in laparoscopic techniques have led to an increasing number of successful resections reported in the literature. Laparoscopy is emerging as a viable alternative to open procedures.

**Bibliography**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


*Future Oncol. Author manuscript; available in PMC 2012 November 14.*

Future Oncol. Author manuscript; available in PMC 2012 November 14.


### Executive summary

- Insulinoma is the most common neuroendocrine tumor of the pancreas with an annual incidence of four in every 1 million persons.
- Insulinomas occur sporadically or in conjunction with multiple endocrine neoplasia (MEN)-1 syndrome, an autosomal dominant disorder associated with mutations in the *MEN1* gene.
- MEN-1 syndrome-associated insulinomas have different characteristics from sporadic insulinomas and are managed with a different surgical approach.
- Insulinomas cause symptoms of hypoglycemia that have been classified into two major groups: neuroglycopenic and adrenergic symptoms.
- The supervised 72-h fast has been the classic diagnostic test for insulinoma; however, a supervised fast of 48 h is quickly becoming the new standard.
- Once the diagnosis has been confirmed, noninvasive and invasive localization studies with different sensitivity rates are utilized to improve operative success.
- Tumor enucleation is the surgical procedure of choice with low morbidity and mortality and favorable cure rates.
- Laparoscopic localization and resection has the potential to be a safe and feasible surgical approach.
- Dietary modifications and pharmacologic agents play a crucial role in the management of unresectable or metastatic insulinomas.
- Malignant metastatic insulinomas are rare; however, they can cause severe and debilitating symptoms and are associated with poor prognosis.
Figure 1. Insulinoma on contrast-enhanced computed tomography
(A) Axial and (B) coronal images demonstrating a mass in the head of the pancreas with bright contrast enhancement during arterial phase.
Table 1
Features of insulinoma and frequency of clinical symptoms.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuroglycopenic</strong></td>
<td></td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>59</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>80</td>
</tr>
<tr>
<td>Abnormal behavior</td>
<td>36</td>
</tr>
<tr>
<td>Amnesia or coma</td>
<td>47</td>
</tr>
<tr>
<td>Seizures</td>
<td>17</td>
</tr>
<tr>
<td><strong>Adrenergic</strong></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>69</td>
</tr>
<tr>
<td>Palpitations</td>
<td>12</td>
</tr>
<tr>
<td>Weakness</td>
<td>56</td>
</tr>
<tr>
<td>Tremors</td>
<td>24</td>
</tr>
<tr>
<td>Hyperphasia</td>
<td>14</td>
</tr>
<tr>
<td>Obesity</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

Data taken from [23,30].