bitemporal dysrhythmias, and according to a neurology consultant, the test was consistent with complex partial seizures. A metabolic workup and CT scan of the head were found to be normal and she was subsequently discharged with a prescription for epival to treat her seizures and with an appointment to follow up with neurology.

**Table 1. Common Causes of Seizures**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
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<tr>
<td>Infection</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Mass Lesions</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Uremia</td>
</tr>
<tr>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Drug Overdose or withdrawal</td>
</tr>
<tr>
<td>Cerebral Ischemia</td>
</tr>
<tr>
<td>Eclampsia</td>
</tr>
<tr>
<td>Porphyria</td>
</tr>
<tr>
<td>Syncope</td>
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</tbody>
</table>

There are multiple causes of seizures (Table 1). A detailed medical history should be obtained from the patient and family members. It is important to inquire about the patient's current habits (e.g. possible substance abuse), a history of seizures, and the presence of risk factors (e.g. head trauma, cerebrovascular disease). Elderly patients can have episodes that mimic seizures but are actually the result of a sleep disorder, or a psychiatric illness. A review of current medications, including over-the-counter drugs, is essential, because some drugs (e.g. narcotic analgesics, bronchodilators) used to treat common geriatric problems may lower the seizure threshold. Physical examination should include a thorough neurologic assessment. Laboratory evaluation of acute symptomatic seizures should include: a complete blood count, electrolytes, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, and glucose levels. When appropriate, serum drug levels and a toxicology screen should be obtained.
Electroencephalography (EEG) can help to classify the seizure type. However, a normal EEG does not necessarily exclude seizure as a diagnosis.

Two days following her discharge, Mrs. S was readmitted to the hospital with ongoing inappropriate behaviour with possible seizure activity. While on the medication, Mrs. S experienced another seizure episode 48 hours following her readmission. Subsequent blood tests revealed repeated episodes of hypoglycemia, which were especially predominant during the early morning hours. These episodes often required IV glucose administration.

Hypoglycemia is characterized by reduced blood glucose concentration. The symptoms of hypoglycemia are often classified as neurogenic (adrenergic) or neuroglycopenic. Neurogenic symptoms, which are due to stimulation of the sympathetic nervous system, include sweating, palpitation, tremulousness, anxiety and hunger. These adrenergic symptoms often precede the neuroglycopenic symptoms and can serve as early warnings for hypoglycemic patients. Neuroglycopenic symptoms – due to decreased cerebral glucose availability – include confusion, concentration difficulties, irritability, hallucination, and focal cerebral impairment. There is a wide differential diagnosis for hypoglycemia (Table 2). Drugs, including diabetes mellitus-controlling medications, and alcohol are considered to be the leading causes of hypoglycemia. Other causes of hypoglycemia include endogenous hyperinsulinism, including insulinoma, critical illness and endocrine deficiencies.

Laboratory results revealed elevated C-peptide level (1450 pmol/L; normal: 300-900 pmol/L), low random serum glucose level (1.9 mmol/L; normal: 4.0-7.8 mmol/L) and serum insulin level present at the high end of normal (177 pmol/L; normal: 14-179 pmol/L). Mrs. S was discharged on diazoxide (to inhibit tumor insulin production) thirteen days following her second hospitalization with instructions to follow up with neurology and internal medicine services as well as her diagnostic imaging appointment.

CT scan with IV and oral contrast revealed an early enhancing mass (2 cm) in the body/tail region of the pancreas (Figure 1). In concordance with the clinical presentation, the diagnosis of insulinoma of the pancreatic body/tail region with no evidence of metastasis was made.

**Clinical Diagnosis**

Insulinoma presenting with hypoglycemia and seizure activity.

**Seizures**

**Epidemiology and Etiology**

According to population-based studies, seizure disorders increase in incidence and prevalence after the age of 60 years. In the United States, the annual incidence of seizures is close to 100 per 100,000 persons over 60 years of age. Epilepsy, a chronic condition characterized by recurrent seizures, affects 1.5 to 3 million people in the United States. Each year 1 in 2,000 Canadians is diagnosed with epilepsy; this is an average of 14,000 new cases every year.

There are various causes of seizure activity in the elderly population. Epidemiologic studies have defined acute symptomatic seizures as those that occur in the context of an acute insult to the central nervous system or during an acute metabolic disturbance. Subdural hematoma, stroke, and infection are common CNS insults that are associated with seizures. Systemic metabolic conditions such as hyperglycemia, hypoglycemia, hyponatremia, uremia and alcohol withdrawal can also precipitate seizure activities.

A study of patients with a first seizure after 60 years of age found that 32% of the seizures were caused by strokes and 14% by brain tumors, including meningiomas, malignant gliomas, and brain metastases. A cohort study reported that among patients with a first stroke, the risk of having a seizure was 2% at stroke onset.
and 11% in the first five years after the stroke. Seizure recurrences are common after hemorrhagic or severe ischemic strokes with cortical (particularly occipital) involvement and late onset of the first seizure.

Degenerative disorders, such as Alzheimer’s dementia and amyloid angiopathy are major major risk factors for seizures. For example, Alzheimer’s disease has been strongly associated with new-onset generalized tonic-clonic seizures in older adults. The incidence of status epilepticus also increases significantly after 60 years of age. Status epilepticus is defined as a single generalized seizure lasting more than five minutes or a series of seizures lasting longer than 30 minutes without the patient regaining consciousness. A study of patients with status epilepticus who had their first seizure after 60 years of age found that cerebrovascular disease was the leading cause, followed by head trauma. Status epilepticus can also be associated with hypoxia, hyperglycemia, intracranial infection, brain tumors, and drug intoxication or withdrawal.

Classification and Clinical Features

Seizures are classified by their clinical symptoms and signs. The clinical manifestations of a seizure depend on the parts of the cerebral cortex that are involved, the functions of the cortical areas where the seizure originates, and the subsequent pattern of spread within the brain.

There are two main types of seizures: generalized and partial/local.

Generalized seizures involve the cerebral hemispheres bilaterally and symmetrically at the time of onset. They are subdivided mainly on the basis of the presence or absence and character of motor manifestations. In generalized tonic-clonic (grand mal) seizures, there is often an abrupt loss of consciousness with bilateral tonic extension of the trunk and limbs (tonic phase), followed by bilaterally synchronous muscle jerking (clonic phase). Urinary incontinence is common; however, fecal incontinence is rare. The ictus (convulsion) usually lasts no more than 90 seconds. The post-ictal phase is characterized by transient deep stupor, lethargy, and confusion. Many patients also complain of headache, muscle soreness, lack of energy, mental dulling and mood changes. Another type of generalized seizures, absence (petit mal) seizures, occurs mainly in children. They are marked by sudden, momentary lapses in awareness, staring, rhythmic blinking, and often, a few small clonic jerks of arms or hands. There is no post-ictal period and usually no recollection of the incidence. The duration of most petit mal seizures is less than 10 seconds.

A partial seizure originates in a specific region or focal area of the cerebral cortex. It is the most common type of epilepsy in the elderly. Consciousness is not impaired in simple partial seizures, whereas impaired consciousness is characteristic of complex partial seizures. Motor signs of simple partial seizures include clonic or tonic movements of a discrete body part. Muscles of the face and hand are often involved. A seizure discharge can begin in the primary motor cortex and spread to the rest of the precentral gyrus, causing clonic movements that progress in an orderly sequence (Jacksonian march) reflecting the homunculus representation (e.g., thumb to fingers to face to leg). Simple partial seizures are often preceded by auras (i.e., subjective sensory and psychological phenomena), which can include visual and olfactory changes, a sense of déjà vu, lip smacking and abdominal symptoms. Complex partial seizures impair consciousness and produce unresponsiveness. Seventy to 80% of complex partial seizures arise from the temporal lobe. The remaining cases arise from the frontal lobe, with smaller percentages originating in parietal and occipital lobes. Many complex partial seizures evolve from simple partial seizures; consciousness becomes impaired as the seizure progresses.

Treatment

Seizures with a reversible precipitant usually do not require drug therapy. Instead, the underlying cause should be treated. In general, all anticonvulsant drugs have significant drug interactions, and may cause cognitive side effects. Therefore, it is important to determine whether medication is absolutely necessary. Candidates for anticonvulsant drug therapy include those patients with recurrent seizures; experiencing onset of epilepsy presenting as status epilepticus; or those with a clear structural predisposition for seizures.

In general, it is advisable to "start low and go slow" with one anticonvulsant agent. A study on the effects of age on epilepsy and its treatment indicate that compared with younger adults, older adults appear to be more responsive to anticonvulsant drug therapy. However, older adults are also more likely to experience side effects at lower serum anticonvulsant drug concentrations. As a consequence, older adults usually require lower dosages and longer dosing intervals. Patients should be monitored closely for adverse effects, drug interactions, poor seizure control, and toxicity.

After the decision to treat is made, one has to decide on whether to prescribe a standard (older) anticonvulsant drug or one of the newer agents. The older anticonvulsant drugs, which include phenytoin (Dilantin), valproic acid (Depakene), and carbamazepine (Tegretol), are less expensive than the newer agents and are considered appropriate selections for the initial treatment of seizures in older adults. Newer antiepileptic drugs that are appropriate as first-line treatment in the elderly include oxcarbazepine (Trileptal), gabapentin (Neurontin), and lamotrigine (Lamictal). These agents have fewer drug interactions and better side effect profiles than the standard antiepileptic drugs.

Insulinoma

Insulinoma is the most common cause of hypoglycemia due to endogenous hyperinsulinism. Wilder was the first to associate hyperinsulinism with functional islet cell tumor in 1927, and Graham performed the first surgical treatment of islet cell adenoma in 1929. Surgical resection has remained the main choice of treatment, and currently has a cure rate of about 90%.

Etiology/Epidemiology

Pancreatic endocrine tumors (PET) have been historically thought to originate from the islets of Langerhans. However, recent evidence suggests that rather than a neuroendocrine lineage, these tumors are derived from pluripotent cells in ductal epithelium.
With an annual incidence of 1 in 100,000, PET are collectively uncommon within the general population.\textsuperscript{29-30} Despite its low frequency, insulinoma (a tumor of pancreatic \( \beta \)-cells) is the most common type of pancreatic endocrine tumors with an annual incidence of 1 to 4 per million.\textsuperscript{31} The majority of insulinomas are sporadic, small (90\% ≤2 cm), solitary (90\%) and benign (>90\%). Unlike other PET, insulinomas occur with equal frequency throughout the gland.\textsuperscript{5,33,32} At presentation, 50\% of patients are over 50 years and have had a median duration of symptoms of 18 months. This statistic indicates insulinoma’s subtle presentation and relatively benign history.\textsuperscript{31}

Insulinoma has a female preponderance of 59\% and, at diagnosis, a 5\% rate of malignancy.\textsuperscript{31} About 8\% of insulinoma patients are diagnosed with multiple endocrine neoplasia type 1 (MEN-1), a syndrome characterized by simultaneous or successive cellular proliferation in at least two endocrine organs. The more commonly affected endocrine organs include the pancreas, parathyroid and pituitary.\textsuperscript{3} MEN-1 patients present at a younger age with a median of 25 years.\textsuperscript{31}

Clinical Features

Table 3 lists the common symptoms of hypoglycemia. Insulinomas, however, are primarily associated with neuroglycopenic symptoms, and occasionally sympathoadrenal autonomic symptoms.

<table>
<thead>
<tr>
<th>Neuroglycopenia</th>
<th>Autonomic</th>
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<tbody>
<tr>
<td>Confusion</td>
<td>Sweating</td>
</tr>
<tr>
<td>Lethargy, stupor or coma</td>
<td>Tremor</td>
</tr>
<tr>
<td>Bizarre behaviour</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Personality change</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Amnesia</td>
<td>Weakness</td>
</tr>
<tr>
<td>Decreased motor activity</td>
<td>Visual disturbance</td>
</tr>
<tr>
<td>Transient neurological deficit</td>
<td></td>
</tr>
<tr>
<td>Gradual decline in cognition</td>
<td></td>
</tr>
</tbody>
</table>

Neuroglycopenic symptoms include dizziness, apathy, amnesia, confusion, personality and behavioural changes, diplopia, seizures, and in some cases, stroke and coma.\textsuperscript{32} Twenty to 60\% of insulinoma patients are initially misdiagnosed with neurological disorders, of which 39\% are diagnosed with seizure disorders.\textsuperscript{33,35} Insulin secretion by the tumor is often periodic and can be seen in the episodic nature of the attacks. With time, patients will develop persistent hypoglycemia. It is important to note that no correlation has been found between size or malignancy of insulinomas and severity of symptoms.\textsuperscript{36}

Approximately 17\% of patients experience sympathoadrenal reactions including tachycardia, chest pain, palpitations and diaphoresis.\textsuperscript{33,35} Hunger, nausea and vomiting also present in 10\% of patients.\textsuperscript{3} It is often noted that eating relieves symptoms while attacks occur before meals or after awakening. Consequently, a detailed history (specifically, relationship of attacks to meals, presence of atypical attacks and a history of poor response to antiepileptic treatment) aids in the timely diagnosis of insulinoma.

Due to its rarity and vague and broad clinical presentation, suspicion of insulinoma and initiation of biochemical investigation is often delayed by a mean of 3.8 years.\textsuperscript{37}

Diagnosis of insulinoma

Insulinoma is diagnosed biochemically through recognition of abnormalities in insulin regulation with concurrent high serum insulin level and low serum glucose.\textsuperscript{39} Low serum glucose in healthy patients with no coexisting disease should indicate further investigation; however, normal result does not exclude the presence of hypoglycemia.\textsuperscript{39} Plasma glucose level less than 2.5-2.8 mmol/ L (<45-50 mg/dL) is often used to define a hypoglycemic state. However, depending on the clinical settings, manifestation of hypoglycemic symptoms varies widely. Therefore, Whipple’s triad is used as a framework for making the diagnosis of hypoglycemia.\textsuperscript{3,38}

1. Hypoglycemic attacks are experienced while in fasting state
2. Blood glucose level is less than 2 mmol/ L during attacks
3. Symptoms are relieved by glucose administration

In evaluating Whipple’s triad, baseline serum insulin and glucose are measured, a 72-hour fast is initiated, and serum glucose is monitored every two hours. Serum insulin is evaluated at the onset of hypoglycemic symptoms or when glucose level falls below 2.5-2.8 mmol/ L.\textsuperscript{36} This is a relatively sensitive test, with 65\% of patients having serum glucose level below 38 mg/dL within 24 hrs, 93\% of patients diagnosed after 48 hrs and 99\% after 72 hrs.\textsuperscript{40} The diagnosis is confirmed with glucose level less than 2.5 mmol/ L, C-peptide level more than 0.2 nmol/ L and insulin level of more than 36 pmol/ L.\textsuperscript{41} In normal individuals insulin is found to be less than 25 pmol/ L with a C-peptide level of less than 75 pmol/ L.\textsuperscript{30} The ratio of insulin to glucose is also a useful diagnostic indicator with normal individuals having a ratio of 0.4 which decreases with fasting. In patients with insulinoma this ratio approaches 1.0 and increases with fasting.\textsuperscript{42}

Concurrent presence of high insulin and low C-peptide suggests an exogenous source of insulin, especially in patients with access to hypoglycemic medication. This diagnosis can be confirmed by measurements of plasma or urine sulfonylureas.\textsuperscript{3}

A range of proactive tests are also available for clarification or confirmation of diagnosis. Unlike normal individuals, there is no suppression of C-peptide level (secreted in equimolar amounts as insulin) after insulin infusion, over 60 minutes or until manifestation of hypoglycemic symptoms. Patients with insulinoma have persistent hypoglycemia (<2.5-2.8 mmol/ L) and elevated insulin level for 2-3 hrs after administration of tolbutamide (a drug that stimulates synthesis and release of endogenous insulin). This test has 80\% sensitivity for insulinoma.\textsuperscript{43} Glucagon administration causes rapid rise in glucose followed by sever hypoglycemia with persistent hyperinsulinism. This test has 72\% sensitivity for insulinoma and is helpful in differentiating insulinoma from reactive
Insulinoma is a rare disease even at large centres. With its vague and broad clinical presentation, insulinoma can present to any branch of medicine if it continues uncontrolled. Insulinoma has the potential to induce serious neurological complication such as cognitive impairment, peripheral neuropathy and possibly death. Hence, it is important that all physicians be aware of its clinical presentation and diagnosis.

Pathological Discussion
Ninety seven percent of insulinomas are found within the pancreas with the ectopic insulinomas mostly peripancreatic. Forty percent of insulinomas are less than 1 cm in diameter and 90% are less than 2 cm. Only 10% of the tumors are malignant at diagnosis with most of the metastases to the peripancreatic lymph nodes and rare hepatic metastases.

Figures 2 and 3 represent H&E stains of Mrs. S.’s pancreatic insulinoma following surgical excision. Ribbons and nests of islet cells can be seen in the collagenous stroma. In addition, immunohistochemical stain (cytoplasmic staining) was performed for insulin (Figure 4). In Figure 4, a normal islet cell surrounded by exocrine pancreas can be seen on the right hand side of the slide. This can be contrasted to the malignant process observed on the left hand side of the slide.

Pathological Diagnosis
Insulinoma of the pancreas.

Treatment and Subsequent Course
Mrs. S was treated by surgical removal of the superior pancreatic lymph node, body and tail of the pancreas. On annual follow up, CT scan indicated no evidence of recurrence. She was taken off diazoxide and epival. She has also been seizure-free since the surgery.

Imaging Used in Localization of Tumor
Recent studies indicate for localization in re-operation cases. Regarding primary treatment of insulinoma, the opinion is divided. This split stems from the fact that all preoperative imaging studies have lower than 85% sensitivity for diagnosing insulinomas.

The imaging modalities used for insulinoma investigations are:
- Transabdominal ultrasound: readily available, inexpensive, non-invasive with detection rate of 25-65%.
- Endoscopic ultrasound: equipment and expertise are not widely available with a 70% detection rate.
- CT: widely available and non-invasive with a detection rate of 70% when contrast is used.
- MRI, angiography, percutaneous transhepatic portal venous sampling, arterial simulation venous sampling and radionuclide imaging can also be used with sensitivities ranging from 50 to 90%.

CT and MRI have limited value for localization (CT has a detection limit of 7 mm in tumor diameter). However, they provide valuable information about possible metastases of insulinoma as well as detection of larger tumors.

In addition to the preoperative diagnostic imaging techniques, intraoperative ultrasonography has been shown in identify 75-90% of insulinomas without palpation by the surgeon. Sensitivity of palpation without intraoperative ultrasonography has also been found to be within a similar range. Combining the two raises the detection and localization sensitivity level close to 100%. Hence, this may be against the less sensitive preoperative diagnostic techniques. In addition, intraoperative serum glucose level is monitored and a 3 mmol/L increase is used as an indication of surgical success. If no tumor could be localized pre or intra-operatively, blind pancreas resection should not be performed as was historically the case.
Acknowledgements

The authors would like to thank Dr. Peter Kopplin and Dr. Geoffrey Gardiner for generously providing advice and support.

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4. Table 324-1, Harrison Online, Chapter 324, Hypoglycemia.
10. Epilepsy Canada. www.epilepsy.ca