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CASE STUDY

Insulinoma as a Potential Insidious Presenter in Medical Refractory Epilepsy

Malik Ghannam[1], Azizullah Beran[2], Dana Ghazaleh[3], Ryan Lyerla[4], Rami Al-Assadi[1], Tanner Ferderer[1], Bahareh Elahian[5], Thomas Henry[6], Sima Patel[6], Brent Berry[1]

1 Department of Neurology, University of Minnesota, Minneapolis, MN, USA
2 Department of Internal Medicine, the University of Toledo, Toledo, OH, USA
3 Department of Internal Medicine, University of Minnesota, Minneapolis, MN, USA
4 Department of Endocrinology, University of Minnesota, Minneapolis MN, USA
5 Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN, USA
6 Department of Neurology, University of Minnesota Health/MINCEP Epilepsy Care, 5775 Wayzata Blvd, Minneapolis, MN 55416, USA

Correspondence to: Dr. Malik Ghannam
University of Minnesota, MMC 295, 12-181 Phillips Wangensteen Building
516 Delaware St. SE, Minneapolis, MN 55455
TEL.: +1 248 325 4475; E-MAIL: mghannam@umn.edu

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Abstract

BACKGROUND: Insulinoma as a cause of epileptic seizure has been thoroughly described but often not considered in differentials for previously established diagnoses of seizure disorder. Hypoglycemic symptoms can mimic neurological disorders such as epilepsy.
CASE PRESENTATION: A 52-year-old woman presented with a history of epilepsy on anti-epileptic drugs (AEDs) developed repeated episodes consisting of seizures and neuropsychiatric symptoms with no predisposing factors for epilepsy at age 52. She had received full AED treatment before the possibility of hypoglycemia was considered. Following a clinical diagnosis of insulinoma, distal pancreatectomy was performed, and her seizures did not occur again.
CONCLUSION: The early diagnosis of insulinoma requires vigilance, not only for hypoglycemia in patients with neuropsychiatric symptoms, but also for the possible masking effects of a history of epilepsy and preceding AED usage.

INTRODUCTION

There can be multiple possible etiologies for new-onset seizures including metabolic derangement. Basic laboratory assessments for first time seizures are often normal, however this does not preclude metabolic derangement as the driver of seizures. More insidious factors such as endocrine tumors are on the differential, although not often considered, in the evaluation of seizures. Here, we discuss the presentation of a middle-aged patient with minimal co-morbidities who had an insulinoma.

Insulinoma is a rare tumor with an incidence rate of 4 out of 1 million persons per year (Phan *et al.* 1998; Service *et al.* 1991). Insulinoma is a neuro-endocrine tumor that accounts for two-thirds of all neuro-endocrine tumors (Mathur *et al.* 2009). The clinical features of insulinoma can imitate many neurologic diseases, including seizure disorders such as epilepsy syndromes, since they are all-encompassing (Dizon *et al.* 1999). Once epilepsy is found to be the leading diagnosis, it can further obscure the diagnosis of insulinoma considering that patients will likely be on anti-

epileptic drugs (AEDs) early in the diagnostic process (Dizon *et al.* 1999; Murakami *et al.* 2017). AEDs are associated with overlapping symptoms to hypoglycemia, and this may further confuse the clinical picture (Murakami *et al.* 2017).

Hypoglycemic events such as the following are exhibited as part of the Whipple's triad: hypoglycemia, neurologic symptoms (such as encephalopathy or ataxia), and being able to resolve the symptoms with treatment by glucose (Mathur *et al.* 2009; Dizon *et al.* 1999; Shin *et al.* 2010). If a person has persistent seizures, the usual course of action is for that person to see a neurologist (and likely an epileptologist). This evaluation will lead to further testing in all likelihood including a magnetic resonance imaging (MRI) of the brain and a scalp electroencephalogram (EEG). If the seizures persist after initiating the AEDs, then the patient may proceed for phase 1 evaluation consisting of video EEG overnight studies (Berg *et al.* 2010). There are multiple causes for seizures including, but not limited to, hypoxia, metabolic disturbances (e.g., hypoglycemia, uremia, and hepatic encephalopathy), electrolyte imbalance (e.g., hyponatremia, hypernatremia, and hypercalcemia), drug intoxication (e.g., anticonvulsants, antidepressants, antipsychotics, isoniazid, opioids, theophylline, and sympathomimetics), drug withdrawal (e.g., alcohol, barbiturates, and benzodiazepines),trauma, CNS neoplasia, strokes, intracranial hemorrhage (e.g., subarachnoid hemorrhage and intracerebral hemorrhage), and CNS infection (e.g., meningoencephalitis, cerebral abscess, and neurocysticercosis) (Engel 2001). A basic laboratory analysis and imaging can differentiate many of these entities from primary epilepsy, but it is worth noting that, in general, metabolic disturbances are dynamic processes, and in some cases may appear normal on routine daily laboratory tests (Wolf 2003).

We herein report a case of insulinoma with a history of epilepsy in which recurrent seizures had developed. Continuous Glucose Monitor (CGM) was useful for understanding the clinical condition. Our present case highlights the potentially misleading factors in the early diagnosis of insulinoma.

CASE PRESENTATION

The patient was at her baseline-level health until 2013 when she entered menopause. At that time, she began to have nocturnal episodes of involuntary, non-rhythmic movements of her extremities. The patient's episodes worsened in 2018. She was eventually evaluated at an Epilepsy Monitoring Unit (EMU) and was diagnosed with pseudo-seizure. However, due to the worsening symptoms, she was started on levetiracetam. The patient's episodes continued to worsen despite the treatment. In mid-July, the patient began to develop another type of episode: her speech would suddenly slow down, and she would stare into space. She would only be able to respond to her husband by nodding and could not talk or remember what had happened during the episode due to the increasing frequency of these spells. Also, she smacked her lips, had repetitive bouts of cough, and sometimes had urinary incontinence. She initially had a facial droop on the left side, but this hasn't happened since she was put on levetiracetam. She is amnestic of what transpires during such an episode. It takes her up to 30 minutes to recover. After the episode,

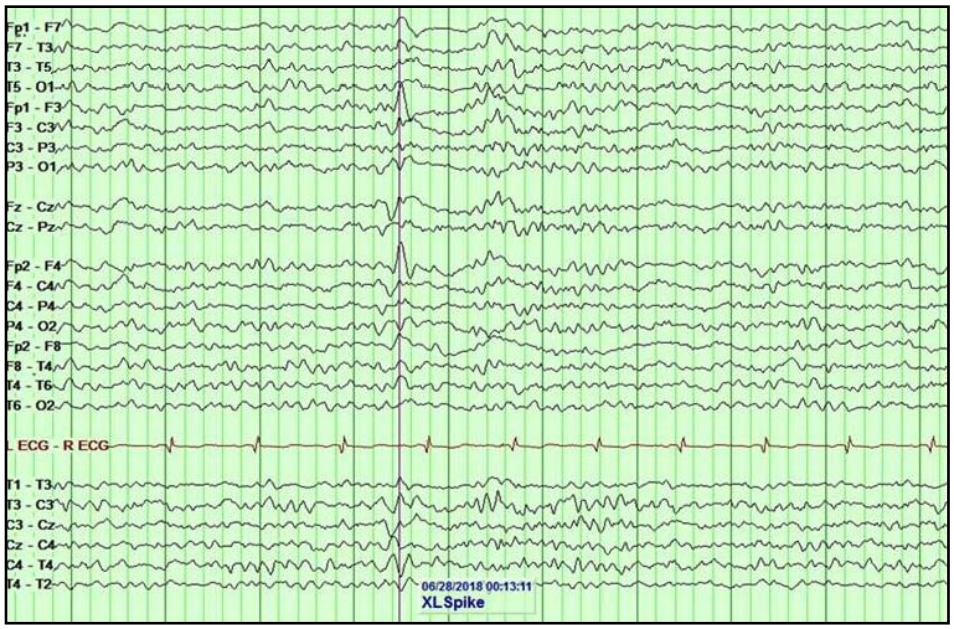

Fig. 1. Presence of intermittent bitemporal delta slowing as well as rare epileptiform discharges which were seen over the left frontotemporal head region during sleep and less frequently over the right temporal head region. Findings are consistent with an irritable structural abnormality over bitemporal head regions and tendency for seizures.

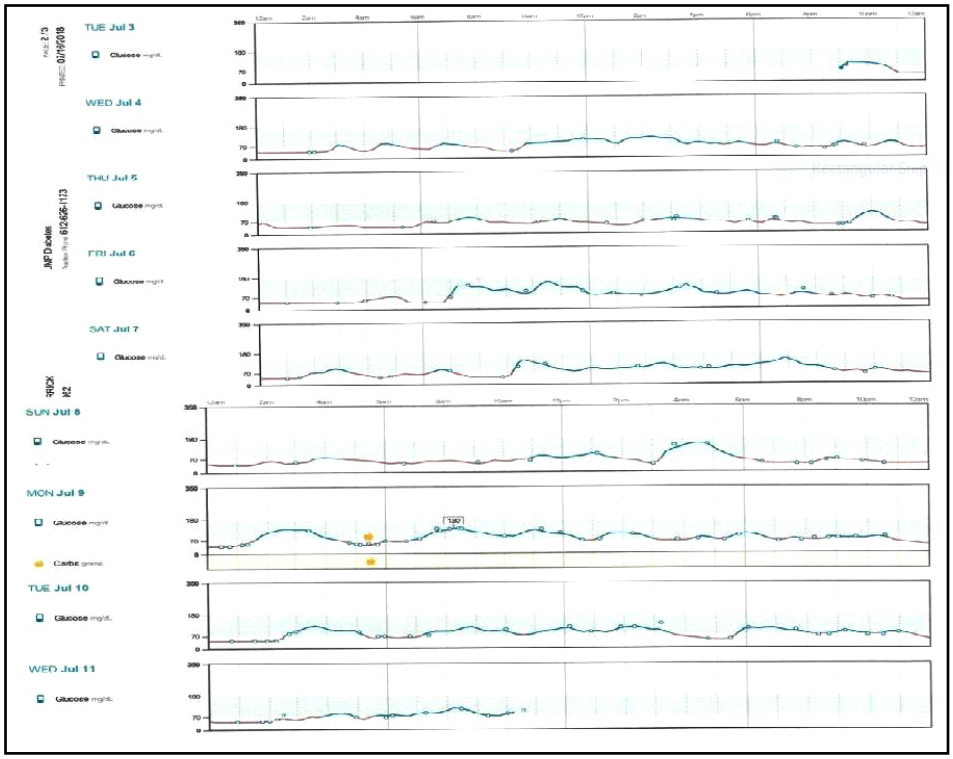

Fig. 2. Representative daily summaries of continuous glucose monitoring (CGM) findings. Prior to the operation before taking diazoxides. Meals are inferred.

she has shakiness, poor balance and slowed speech. She has had approximately 10 such episodes.

The MRI of her brain, both with and without contrast, showed evidence of mild microvascular disease commensurate with her age but was otherwise unremarkable.

Video EEG monitoring was undertaken initially, whereby her ineffective course of levetiracetam was discontinued. On day 9 of the video EEG monitoring, after being off levetiracetam for a few days and having sleep-deprivation, she had a focal onset impaired awareness seizure lasting for approximately 10 minutes out of sleep. During this seizure, she woke up, lifted her head, and looked around. She then made non-purposeful arm movements and some pursed mouth movements. Further, she made repetitive soothing movements with her left hand on the back of her head. Towards the end, she jerked and twitched her body and bilateral extremities in an irregular manner. At the onset, the EEG showed diffuse spike-wave discharges, which appeared to be of a higher amplitude over the right temporal region on the referential montage [Figure 1]. The EEG was obscured by myogenic and movement artifacts during much of the seizure, but at some point, a left temporal rhythmic delta activity could be seen. The patient also had another probable focal onset seizure the day before discharge. When she just woke up and was examined by the nurse, her husband noted that she was slow to respond and follow the commands. The EEG showed that the diffuse spike-wave at the onset was similar to the previous seizure. Her husband believed that these were similar to her habitual nocturnal events.

The patient stated that increasing her dose of levetiracetam helped with her Todd's paralysis, but it didn't seem to help with the frequency of the seizures. The patient eventually was started on 300 mg of oxcarbazepine twice daily and was instructed to gradually increase the dosage to 600 mg twice daily. She tolerated the medication well and denied any occurrence of rash, dizziness, imbalance, or double/blurred vision. She noted that she was not as tired as when she was off levetiracetam during hospitalization. Levetiracetam was restarted and continued while oxcarbazepine was optimized.

In the interim, the epileptologist had been following her in clinic and started her on lacosamide. She is currently on levetiracetam (500 mg in the morning and 1000 mg at night), oxcarbazepine (450 mg in the morning and 1200 mg at night), and lacosamide (100 mg in the morning and 200 mg at night). She has not noticed any significant changes in her seizures since being started on lacosamide. In fact, they seem to have worsened and have been lasting significantly longer. Currently, she is averaging at approximately 1 seizure per night, but it is lasting between 1.5 to 2 hours in the morning. This usually happens between 5 am and 7 am, during which she is described as "hyper-motor" and having bizarre behavior.

Due to the patient's poor response to AEDs, she was brought back 3 months later for another EMU stay to

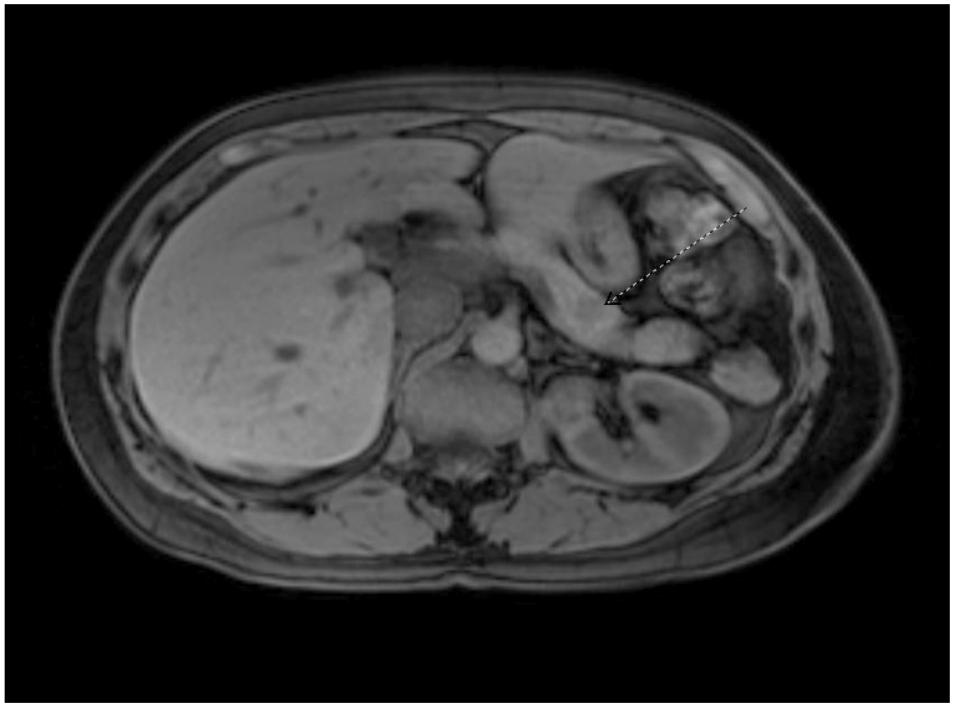

Fig. 3. Pancreatic body lesion of 1.1 cm which demonstrates some arterial enhancement and subsequent washout, possibly reflecting patient's suspected insulinoma.

taper off lacosamide and add phenytoin. The patient tolerated the addition of phenytoin well at admission with some moderate ataxia across 3 days. The EEG was essentially unremarkable, and the patient had only 1 event without EEG correlates on the night of her admission. The patient reiterated that her symptoms largely occurred at night during this hospitalization, and she noticed symptoms during the day only in the last few months after she had begun a diet and exercise weight loss regimen, in which she lost 30 lbs. She had a documented serum glucose of 39 mg/dL during the 2nd night of hospitalization, and the endocrine service was consulted to workup hypoglycemia. An overnight hypoglycemia was noted during the admission. She had no history of diabetes, insulin or secretagogue use, alcohol abuse, adrenal insufficiency, hepatic/renal or cardiac failure, gastric bypass or medications known to cause hypoglycemia. The patient's brain MRI showed a prominent, mildly enlarged pituitary gland but no discrete lesion. The results of a dedicated pituitary MRI proved unremarkable, and no documented imaging of her abdomen was taken. A 72-hour fast was attempted but discontinued in less than 16 hours due to repeated hypoglycemia. Plasma glucose, beta-hydroxybutyrate, insulin, C-peptide, and proinsulin levels were collected. The laboratory testing confirmed an abnormal presence of insulin and C-peptide at blood sugar values less than 40 and high proinsulin levels. Ultimately, a diagnosis of pro-insulinoma was made and she was discharged in a stable condition with a Libre personal continuous glucose monitor (CGM) to help monitor and treat the hypoglycemia [Figure 2].

It was discovered that patient was indeed having night-time hypoglycemia, which matched 3 of her

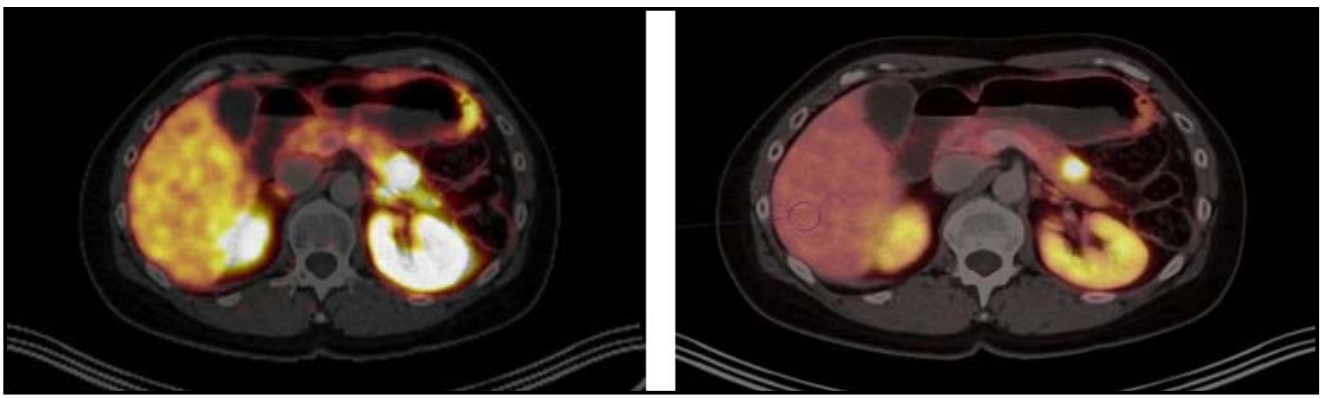

Fig. 4. Hypermetabolic lesion in the body/tail of the pancreas measuring approximately 1.6 x 1.6 cm with a maximum SUV of 41.

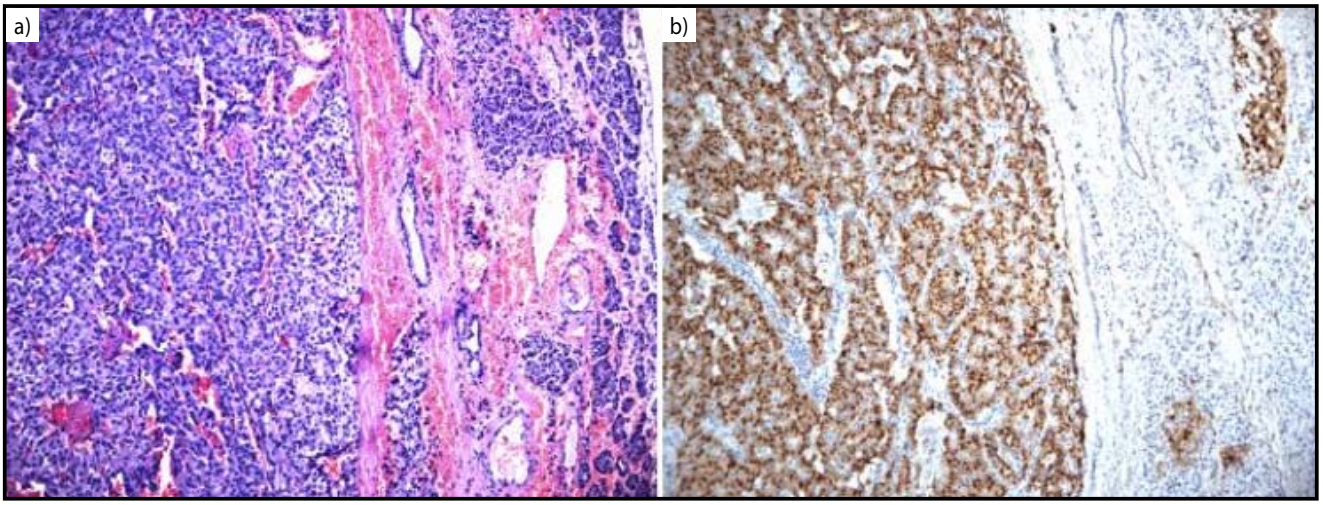

Fig. 5. (a) Insulinoma (left) with prominent trabecular architecture and rosettes; normal pancreatic tissues on the right. (b) Chromogranin A staining showing intense staining consistent with insulinoma.

night-time seizure events. The patient was followed up with an endocrinology referral, and it was decided that she would need an MRI of the abdomen. MRI of the abdomen showed a 1.1 cm pancreatic body lesion with some arterial enhancement and subsequent washout, possibly reflecting the patient's suspected insulinoma. The pancreas was otherwise unremarkable and had no surrounding inflammation. The pancreatic duct was normal in caliber and course with no enlarged lymph nodes [Figure 3]. A follow-up PET scan was undertaken. A 1.6 cm hypermetabolic lesion in the body/tail of the pancreas was found with a maximum Standardized Uptake Value (SUV) of 41, which is consistent with pancreatic neuroendocrine tumors. No evidence was found to suggest metastatic disease [Figure 4].

The patient was admitted to the hospital for surgical resection of the tumor. She was started on Dextrose 10 and diazoxide, as needed for hypoglycemia, and was given a stress dose of hydrocortisone. She underwent the DaVinci assisted distal pancreatectomy and tolerated the procedure well. The diagnosis of insulinoma was confirmed based on the histopathological findings of the pancreatic mass [Figure 5]. She recovered well following the surgery. Her drain amylase was 2434 on postoperative day 1 (POD1) and 252 on POD3. She was followed up with an endocrinologist and completed a steroid taper prior to discharge. She was hyponatremic (up to 127), likely secondary to oxcarbazepine. She resumed the fluid restriction which she followed prior to admission for hyponatremia (which is likely secondary to oxcarbazepine). She was discharged on POD4 with a JP drain in place due to pancreatic fluid leak.

DISCUSSION

We have reported an unusual case of a 55-year-old female with a 3-year history of refractory nocturnal and daytime seizures that were refractory to multiple anti-epileptic drugs, ultimately leading to an underlying diagnosis of insulinoma.

The atypical features of her attacks, which were inconsistent with the complex partial and generalized seizures, combined with her poor response to treatment prompted an inpatient assessment. The hypoglycemia noted on the morning basic metabolic panel raised the possibility of a neuro-hypoglycemic state as the etiology of her symptoms. This case illustrates the significance of considering hypoglycemia in atypical neurological or psychiatric events and highlights the role of phase 1 monitoring of refractory epilepsy.

Despite being a rare tumor, insulinomas are the most common hormone-secreting tumors of the gastrointestinal tract (Correia *et al.* 2012). There is a preponderance of women with onset usually in the middle age; tumors are usually solitary, benign, and sporadic, although 5–10% occur in patients with Multiple Endocrine Neoplasia (MEN-1), 10% are metastatic, and a further 10% are multiple but behave as benign tumors (Correia *et al.* 2012). The only diagnostic feature of malignancy is the presence or subsequent development of metastases (Mathur *et al.* 2009). Insulinomas are found throughout the pancreas and are small (usually 10–20 mm) (Correia *et al.* 2012). Detection relies on inappropriate insulin secretion in the presence of hypoglycemia and subsequent tumor localizations, usually through messages such as imaging (Shin *et al.* 2010). An insulinoma laboratory diagnosis can be made with plasma glucose < 45 mg/dl and symptoms of hypoglycemia, insulin ≥ 6 μU/mL, C peptide ≥ 0.2 nmol/l , proinsulin ≥ 5 pmol/L, an absence of sulfonylurea in the plasma (Shin *et al.* 2010).

The case may play out insidiously with neuroglycopenia and fasting hypoglycemia. As seen in our case, this may lead to a delay in the diagnosis as other neuropsychiatric diagnoses may be considered first (Kuzin *et al.* 1998). The range of onset between the diagnosis

and the onset of symptoms is 1 month to 30 years in the literature, with a median length of time of 24 months (Service *et al.* 1991). The most common neurological presentation of insulinoma is seizure (Dizon *et al.* 1999; Daggett & Nabarro 1984; Schmitt *et al.* 2008). Insulinoma can also present with other neurologic symptoms apart from seizure. Dagget *et al.*, reported that most common presentation of insulinoma in a review of 252 cases of insulinoma were confusion (Daggett & Nabarro 1984). While the second and third most common neurological presentation of insulinoma were coma and seizure, retrospectively (Daggett & Nabarro 1984). Other less common neurologic presentations included headache, visual disturbances, stroke-like paralysis, dysarthria, ataxia and peripheral paresthesia (Daggett & Nabarro 1984). In a prospective study done by Harrington M., two (8%) of 25 patients referred to neurologists with "funny turns" demonstrated hypoglycemia with inappropriately elevated insulin levels and were eventually found to have an insulinoma (Harrington *et al.* 1983).

Misdiagnosis or delay in diagnosis of insulinoma can be potentially life-threatening condition or can lead to significant neurological complications such as cognitive impairment and peripheral neuropathy (Murakami *et al.* 2017; Graves *et al.* 2004). The factors related to delayed diagnosis of insulinoma are summarized in [Table 1]. EEG findings with hypoglycemia consisted of alpha rhythm slowing and the appearance of intermittent theta activity when the glucose level was between 50–80 mg/dl, but when the glucose level below 40 mg/dl, the intermittent rhythmic delta, diffuse delta and theta activity will be demonstrated on the EEG (Faigle *et al.* 2013). In our patient, a serum glucose of 39 mg/d during the 2 nights of hospitalization was documented, which is consistent with severe hypoglycemic EEG findings (Faigle *et al.* 2013).

Neuroglycopenia should be suspected in all patients with funny turns, seizures and/or other neuro-psychiatric symptoms, especially if they do not meet the criteria of seizure disorder or respond to traditional therapies e.g. AEDs (Murakami *et al.* 2017; Graves *et al.* 2004).

Clinical suspicion and obtaining a complete history (such as relationship of episodes to meals, and unsatisfactory response to anti-epileptic drugs) are important to make a diagnosis of insulinoma (Graves *et al.* 2004). Once suspected, the diagnosis of insulinoma can be easily confirmed with a 72-hour fasting test (Graves *et al.* 2004). Insulinoma is considered one of the potentially curable etiologies of seizures (Graves *et al.* 2004).

Tab. 1.

Factors contributing to a delayed diagnosis of insulinoma (4, 5, 17, 18)
Various neuropsychiatric symptomatology that lacks specificity; like seizure, confusion, bizarre behavior, amnesia, dystonia, polyneuropathy, personality change
Falsely normal fasting blood glucose level
Severe hypoglycemia can cause epileptic discharges on EEG
Hypoglycemia can induce neuroglycopenic and autonomic unawareness

CONCLUSION

The early diagnosis of insulinoma requires vigilance, not only for hypoglycemia in patients with neuropsychiatric symptoms, but also for the possible masking effects of a history of epilepsy and preceding AED usage. MG, BB, RL, RA and TF were responsible for the clinical management of the patient. AB, DG and BE participated in drafting of the manuscript and acquisition of data. MG and BB participated in analyzing and interpretation of data. TH and SP participated in critical revision of manuscript for intellectual content. All authors read and approved the final manuscript.

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COMPETING INTEREST

The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

All the data supporting our findings is contained within manuscript.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee approval was not applicable as the information was analyzed in a retrospective manner and had no effect on treatment.

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