

# Insulinoma Treated As Epilepsy; a Case of Misdiagnosis

**Keywords:** Insulinoma; Epilepsy; Seizure; Learning disability

## Abstract

Insulinoma is a rare neuroendocrine tumour. It can occur at any age with nonspecific signs and symptoms. Due to its nonspecific clinical features, insulinoma may be misdiagnosed with other disorders. While evaluating a patient presenting with a seizure, toxic and metabolic causes should always be considered as they are potentially curable and can be fatal if left untreated. We describe a case of hypoglycaemia induced seizures treated as epilepsy in a patient with learning disability.

## Case History

A 49 year old female with learning disability and 2 years history of epilepsy was admitted following a seizure like activity and fall during a routine visit to her GP surgery. She had sustained injury to left knee and x- ray confirmed a distal femur and a patellar fracture. On admission her serum glucose was 2.0 mmol, all other routine blood tests including Full Blood Count, Renal function and Liver function test were normal. Her regular medications included Lamotrigine and Mebeverien. On the ward she had recurrent spontaneous hypoglycaemic episodes requiring regular treatment with glucose infusions. The lowest capillary blood glucose recorded was 1.9 mmol. Due to the learning disability, patient could not describe any symptoms usually experienced at the onset of hypoglycaemia. Glycated Haemoglobin (HbA1c) was 19.0 mmol (Ref range: 20-41 mmol) indicating lower than normal average glucose. Random cortisol and thyroid function test were normal. She underwent left knee exploration and repair of medial retinaculum of quadriceps tendon and excision of patellar fragment. While awaiting results of further investigations, Diazoxide was initiated with good effect. The results of the specific biochemical investigations for her recurrent hypoglycaemia were consistent with endogenous hyperinsulinaemic hypoglycaemia (Table 1).

A CT scan abdomen and pelvis was normal. Endoscopic ultrasound was performed that showed a small 13 x 9 mm well defined lesion with good doppler signals indicating high vascularity raising the possibility of a Neuroendocrine tumour (Image 1). Biopsies taken from the pancreatic lesion (Image 2) showed clusters of ovoid epithelial cells with bland nuclei resembling those of neuroendocrine cells that stained with synaptophysin and chromogranin in addition to BerEP4 consistent with a well-differentiated neuroendocrine tumour.

Patient was referred and discussed with the regional Neuroendocrine centre. The pancreatic lesion was surgically excised with enucleation of the mass resulting in complete resolution of the symptoms.

## Discussion

Spontaneous hypoglycaemia can be difficult to diagnose in



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patients with a learning disability as patient may be unable to describe hypoglycaemia related symptoms. Hypoglycaemia can exhibit various neurogenic and neuroglycopenic symptoms. These can mimic neuropsychiatric symptoms including unconsciousness, confusion, seizure, personality change and bizarre behaviour in most patients [1,2]. Over half of patients with these symptoms are initially misdiagnosed with neuropsychiatric disorders such as epilepsy [1,3]. The seizures can be tonic-clonic, complex partial or absence seizures [4-6]. However, correct diagnosis of epilepsy is also challenging in clinical settings and can lead to inappropriate treatment with anti-epileptic medication. In the setting of an Insulinoma, these symptoms become typically evident after fasting and are often precipitated by physical exercises. However, the median duration of symptoms before diagnosis remains variable and can reach 12-18 months on average or even years in rare cases [7].

An insulinoma is a rare pancreatic endocrine tumour that is typically sporadic, solitary, and usually less than 2 cm in diameter. It is reported in 1-4 people per one million person years<sup>1</sup>. Because of the nonspecific symptoms, insulinoma may be misdiagnosed with other disorders. It can be seen at any age and occurs slightly more frequently in women than in men [8,9]. The clinical clues suggesting insulinoma are based on the clinician's recognition of the presence of hypoglycaemic symptoms included in Whipple's triad [10,11]. This triad includes symptoms of hypoglycaemia induced by fasting or exercise, plasma glucose less than 2.5 mmol and relief of symptoms following the administration of glucose. A previous diagnosis of

**Table 1:** Biochemical investigation indicating endogenous hyperinsulinaemic hypoglycaemia.

Investigation	Results
Serum Glucose	2.2
Insulin	20000 pmol/l
C- Peptide	1160 pmol/l
Insulin Antibodies	Negative
Sulfonyl urea Screen	Negative



Image 1: EUS showing a well-defined hypoechoic lesion on the tail of Pancreas.

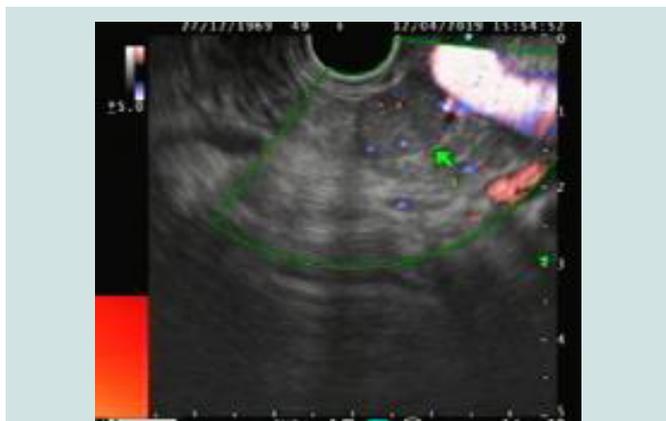


Image 2: EUS with FNA of the pancreatic lesion.

epilepsy and/or a drug history of anti-epileptic drugs can obscure the clinical relationship between patient symptoms and possible hypoglycaemia.

Most insulinomas are benign and are associated with MEN 1 in 5% of patients. It is estimated that 21% of patients with MEN1 develop insulinomas [12,13]. The incidence is 3-10 cases per million people per year. The insulinomas occurring in this autosomal dominant syndrome have a higher risk of relapse [14].

The supervised 72 h fasting test remains the gold standard for biochemical diagnosis with measurement of plasma glucose, insulin, C-peptide, and proinsulin during the onset of hypoglycaemic symptoms. Various preoperative procedures can be used to localize the tumour in order to plan therapeutic strategy. The reported sensitivity of conventional CT and MRI for detection of pancreatic insulinoma ranges respectively from 33-64% and 40-90 % respectively. However, the advent of helical CT scan has enabled detection of approximately 94% of insulinomas [15,16].

Endoscopic Ultrasound (EUS) is now largely considered as the best investigation for preoperative localization of insulinoma with a sensitivity of up to 94 %. It can detect even small tumours of up to 5 mm, and reveal important relation to the bile duct and adjacent blood vessels. In addition EUS allows performing fine-needle aspiration

cytology of suspicious lesions and preoperative marking of tumours to facilitate surgical excision particularly with laparoscopic approach. However, EUS findings largely depend on clinical experience [8,15].

Medical management of insulinoma, used to treat and prevent hypoglycaemia, is generally restricted to un-resectable metastatic tumours, unsuccessful operation with persistent symptoms, inoperable patients, and patients waiting or refusing surgery [3,15]. Moreover, other recent techniques for the management of insulinoma have been reported including injection of octreotide; EUS guided alcohol ablation, radiofrequency ablation [17], or embolization of an insulinoma.

Surgical excision is the treatment of choice for most Insulinomas. Tumour enucleation is the procedure of choice especially in case of small and solitary nodule that is not encroaching on the pancreatic or bile ducts [18]. More recently robotic enucleation of intra-pancreatic Insulinoma has also been reported [11]. Pancreatic resection is indicated for lesions invading or in close proximity to the pancreatic duct or major vessels or suspicious for malignancy [19]. Resection options include distal pancreatectomy (with or without splenectomy), Whipple procedure (pancreaticoduodenectomy), or median pancreatectomy, depending on the site of insulinoma.

Insulinomas are typically reddish-brown, firm, and encapsulated with a clear plane of dissection between the tumour and surrounding soft pancreatic parenchyma [20].

Histologically, insulinomas are epithelial neoplasms associated with strong and diffuse immunohistochemically expression of neuroendocrine markers such as synaptophysin and chromogranin. Mitotic rate (number of mitoses per 10 HPF) and proliferation index (Ki-67 labelling index) are particularly helpful to separate well-differentiated from poorly differentiated tumours [21,22].

## Conclusion

Careful assessment is required to exclude hypoglycaemia as the cause of seizures in all patients in general and particularly in patients with learning disability as it is easily treatable and the underlying cause such as Insulinoma potentially curable.

## Recommendation

We recommend exclusion of hypoglycaemia as a cause in all patients presenting with seizures.

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