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Misleading features of neuroimaging and electroencephalography: insulinoma misdiagnosed as temporal lobe epilepsy

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ABSTRACT – Epilepsy is a common disorder but diagnosis remains largely clinical. Although MRI and EEG significantly aid the diagnosis of epilepsy, these techniques may also be misleading and indicate abnormalities not related to phenomenology. Consequences of erroneous diagnosis of epilepsy may lead to aggressive and escalating pharmacotherapy with potentially serious side effects. Metabolic disorders, which may mimic epilepsy, should always be considered as they are potentially curable and may be fatal if untreated. We report a case of an insulinoma, misdiagnosed as temporal lobe epilepsy. We highlight the risks associated with misinterpretation of neuroimaging and EEG and outline an approach to differentiate between symptoms of insulinoma or neuroglycopenia and temporal epileptic seizures.

Key words: neuroimaging, MRI, EEG, insulinoma, misdiagnosis, temporal lobe epilepsy

Epilepsy is a common disorder and, to date, diagnosis remains largely based on clinical presentation. However, electrophysiological recordings are commonly used to assess interictal abnormalities and, more rarely, to record and characterise seizures. Cerebral imaging, including MRI, is also useful for aetiological purposes in order to identify structural abnormalities when present. This diagnostic approach, however, may lead to the treatment of numerous patients, with the initiation of one or more antiepileptic drugs, without a clear diagnosis of epilepsy. In typical epilepsy referral centres, the rate of misdiagnosis ranges between 25 and 30% for patients who undergo prolonged video-EEG monitoring (Smith *et al*., 1999; Benbadis *et al*., 2004). Moreover, lesions observed on cerebral MRI can potentially be misleading (Alsaadi *et al*., 2003).

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Epileptic seizures may be mimicked by many conditions, including hypoglycaemia and other metabolic disorders. Insulinoma is an uncommon tumour, derived mainly from pancreatic islet cells, which may be misdiagnosed as a primary psychiatric or neurological disorder (Bazil and Pack, 2001; Piccillo *et al*., 2005). We report the case of a patient suffering from an Insulinoma who was initially misdiagnosed with late-onset, focal, temporal lobe epilepsy due to the misinterpretation of MRI and EEG results.

Case report

A 62-year-old woman was referred due to temporal lobe epilepsy. She also suffered from high blood pressure and migraine. Her developmental milestones were normal and she had no previous history of febrile seizures. For the past six months, she had experienced numerous episodes characterised by "*bizarre*" feelings in her entire body, amnesia, occasional speech or reading difficulties, confusion, disorientation, and abnormal behaviour lasting between 10 and 30 minutes. The patient also described an unusual symptom which occurred most often in the morning or several hours after meals, which she described as an "empty head" feeling and anxiety. Neurological and general examination was unremarkable.

Previous brain MRI revealed a right nodular temporal lesion with contrast enhancement compatible with meningioma (*figure 1*). EEG during wakefulness revealed asynchronous, bilateral, temporal spikes and waves. EEG during sleep showed bilateral, independent, delta slow waves. In view of these findings, she was diagnosed with focal temporal lobe seizures. Her medication consisted of levetiracetam at 500 mg bd, despite no clinical benefit.

Four months later, during hospitalisation, EEG was recorded during wakefulness and sleep, showing non-specific abnormalities similar to those previously described (*figure 2*). Repeated low blood glucose levels were noticed (below 0.6 g/L, with a minimum of 0.22 g/L). Insulin and C-peptide were normal. Proinsulin was increased (19.7 pmol/L; *n*=1.2-4.7) compatible with insulinoma. Multiple endocrine neoplasia type 1 (MEN-1) was ruled out based on normal measurements of prolactin, thyroid, parathyroid hormone, and gastrin. Other hormones that may occasionally be secreted by insulinomas, such as adrenocorticotropic hormone (ACTH) and cortisol, were also found to be within the normal range.

Abdominal computed tomography demonstrated a 2-cm-diameter hypervascular nodule in the caudal pancreas with an enhanced central component consistent with insulinoma (*figure 3*). A partial pancreatectomy was performed with good outcome.

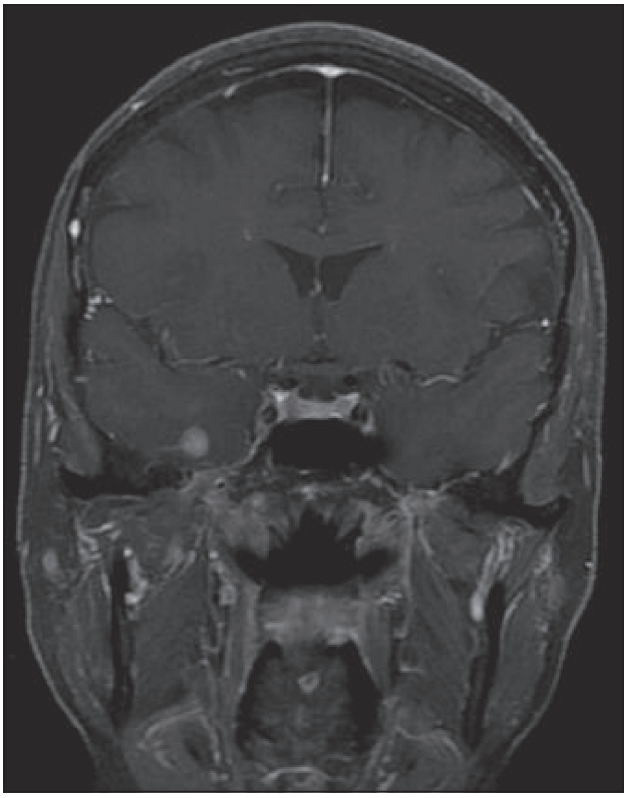

Figure 1. Brain MRI (T1 with gadolinium) coronal slice showing a right nodular temporo-basal lesion with contrast enhancement, compatible with meningioma.

Histopathological investigation confirmed a pancreatic islet cell tumour (insulinoma). We performed a 24-month follow-up. Antiepileptic drugs were stopped, she had no more abnormal episodes, such as those previously described, and EEG was normal.

Discussion

We report the case of an insulinoma observed in a neurological unit, initially misdiagnosed as focal temporal lobe epilepsy. Symptoms of hypoglycaemia, bitemporal spikes and waves on EEG, and the presence of a right temporal lesion compatible with meningioma were clearly misleading. The patient was treated with antiepileptic medication as a consequence of this misdiagnosis, which was rectified after six months.

Insulinomas are the most common hormone-secreting tumour of the gastrointestinal tract. The incidence is estimated at four per million person-years, although this is likely to be an underestimate. The interval between presentation and diagnosis ranges from one month to 30 years (with a median of two years) (Service *et al*., 1991). There is female predominance with a mean age at onset of 50 years (Grant, 2005). Diagnosis

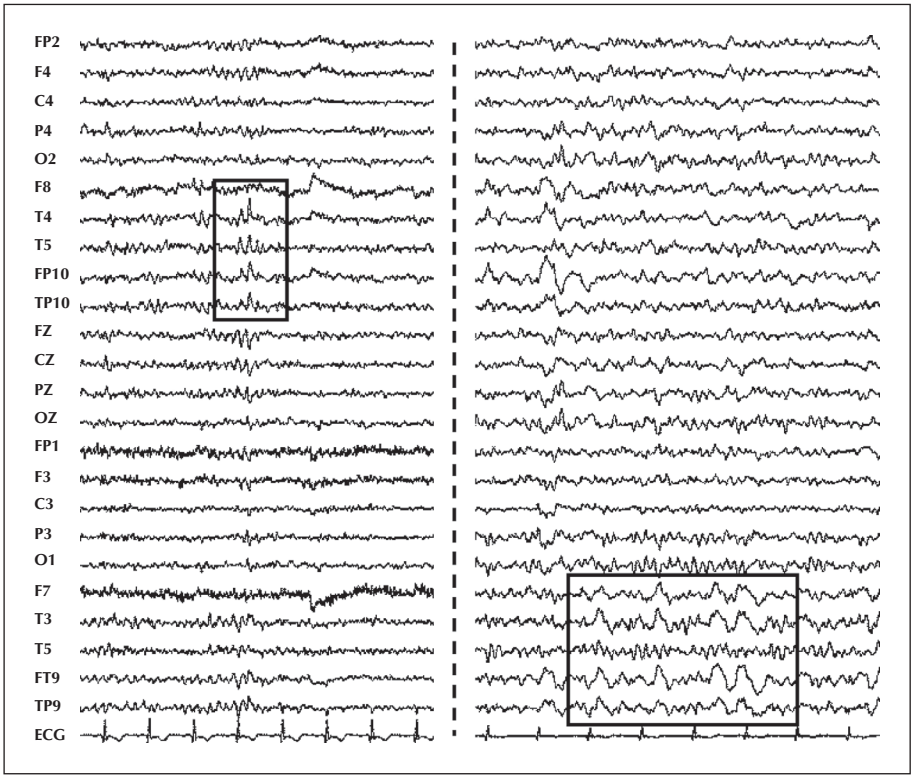

Figure 2. EEG (10/20 system, 20 s, 70 Hz, 0.3 s, monopolar).
Left: EEG during wakefulness with eyes open, showing right temporal spike. Right: EEG during sleep with eyes closed, showing left temporal delta slow waves, preceded by low-amplitude spikes.

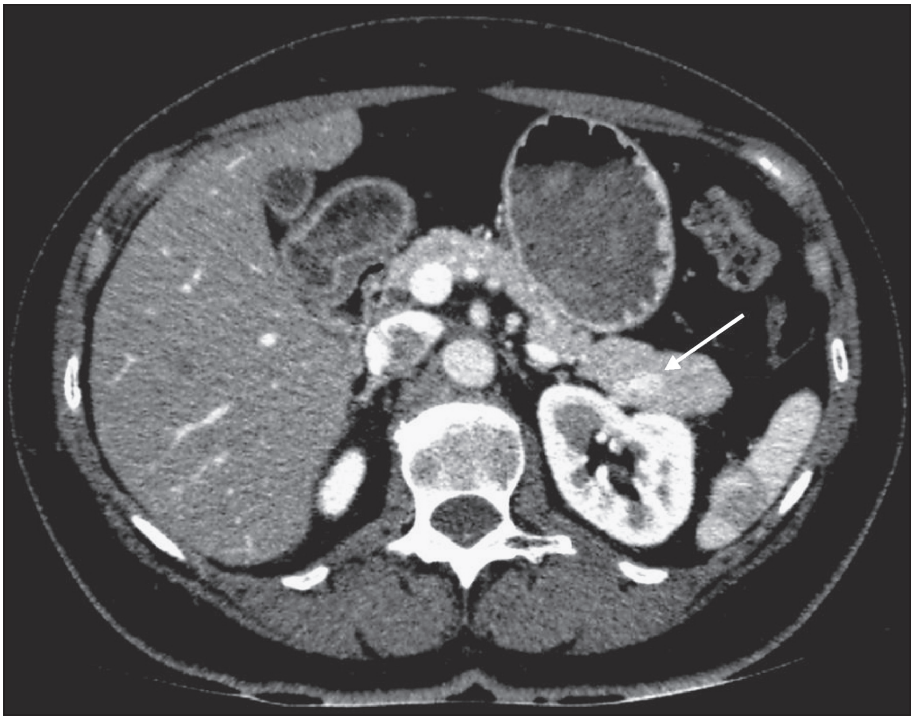

Figure 3. CT of the abdomen with contrast iodine injection demonstrating a 2-cm-diameter hypervascular nodule in the caudal pancreas with an enhancing central component, consistent with insulinoma.

Table 1. Comparison between symptoms of hypoglycaemia and the phenomenology of temporal lobe epilepsy.

Symptoms	Temporal seizures	Hypoglycaemia
Duration	Paroxystic	± Prolonged
Disturbance of consciousness		
Loss of contact	Frequent	Frequent
Confusion	Postictal	Yes
Lethargy-stupor-coma	No	Yes
Vegetative symptoms		
Epigastric feeling	Yes	Yes
Nausea		
Tachy-bradycardia	Yes	Palpitations
Sweating	No	Yes
Neurological deficit		
Amnesia	Yes	Yes
Dysphasia	Yes (major hemisphere)	Possible
Other transitory deficit	Postictal	Yes
Thymic disturbance		
Fear/anxiety	Yes	Yes
Bizarre behaviour	Yes	Yes
Other symptoms		
Déjà-vu	Yes	No
Dreamy-states	Yes	Yes
Weight gain/loss	No	Yes
Relationship with food intake	No	Yes

is based on inappropriate insulin secretion during hypoglycaemia and the presence of a tumour (Marks and Teale, 1991). Presentation is usually insidious as symptoms of hypoglycaemia lack specificity (*table 1*), thus frequently leading to initial misdiagnosis. In a retrospective study by Dizon *et al*. (1999), (58)/59 patients with histologically confirmed tumour islet cells were shown to have had an initial diagnosis of neurological disorders in 64% of cases, including 39% cases of epilepsy, before receiving a diagnosis of insulinoma. Some specific clinical features may aid the diagnosis of insulinoma, including: disturbances occurring mainly in the morning or several hours after meals, relief of symptoms after food intake, abnormal weight gain, atypical phenomenology, and poor response to antiepileptic drugs. A 72-hour monitoring period to measure blood levels of insulin and glucose is recommended to assess inappropriate insulin secretion (Dion *et al*., 2004).

It is well known that hypoglycaemia can affect the EEG, causing, for example, diffuse or focal slowing-down which is enhanced by hyperventilation (Creutzfeldt and Meisch, 1963). Moreover, epileptiform discharges induced by hypoglycaemia are also occasionally found in patients with diabetes (Engel *et al*., 1954; Snogdal *et al*., 2012) as well as genetically predisposed animals with spike-and-wave activity precipitated by low blood glucose (Reid *et al*., 2011). In another case of insulinoma, presenting as adult-onset complex partial seizures, the EEG showed a gradual build-up of bilateral anterior slow-wave activity prior to the seizure (Graves *et al*., 2004). However, these activities are entirely non-specific and can be misleading.

The excessive diagnosis of epilepsy is sometimes based only on the interpretation of an "abnormal" EEG, which can have adverse consequences for the patient (Chadwick, 1990). Bearing in mind that epileptic discharges can also be metabolic in origin, metabolic disorders should always be ruled out. The EEG should always be interpreted in the light of clinical phenomenology. In our case, the presence of a potential meningioma in the same region as abnormal EEG activity was another confounding factor. Similarly, cerebral imaging must be interpreted based on clinical context. To confirm the diagnosis of epilepsy, seizure phenomenology, EEG, and imaging should be concordant. If there is a discrepancy between one or more of these findings, particular caution should be exercised. In this case study, seizure semiology was inconsistent with the imaging data (which implicated the right

temporal lobe), and although anomalies were identified on the EEG, these were rather non-specific. Epileptic seizures can be mimicked by metabolic disorders and a comparison between symptoms of hypoglycaemia and the phenomenology of temporal lobe epilepsy is provided in *table 1*.

Conclusion

Fits, faints and "*funny*" turns are commonly encountered in clinical practice and their accurate characterisation is essential. To confirm the diagnosis of epilepsy, seizure phenomenology, EEG, and imaging data should be concordant. If there is a discrepancy between one or more of these findings, particular caution should be exercised. Hypoglycaemia and insulinoma should always be considered in patients with atypical neurological or psychiatric phenomenology, especially if there is an association between seizures and food intake, symptoms are not stereotyped, and there is a poor response to antiepileptic drugs. Indeed, uncontrolled hypoglycaemia can have serious neurological sequelae and can be fatal, but once suspected, diagnosis is relatively straightforward with 72-hour monitoring of insulin and glucose. The consideration of insulinoma in the differential diagnosis of epilepsy is critical, as insulinoma represents a potentially curable cause of fits, faints, and uncommon behaviour. □

Disclosures.
None of the authors have any conflict of interest to disclose.
A written informed consent for participation in the study was provided by the patient.

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