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Initial manifestation of type I diabetes mellitus as an unusual cause of early post-operative seizures

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ABSTRACT – We present a case of an 18-year-old patient who underwent resective epilepsy surgery for intractable epilepsy caused by focal cortical dysplasia. In the early post-surgical period, the patient started experiencing atypical seizures refractory to antiepileptic treatment. In due course, abnormally low levels of blood sodium and extremely high levels of blood glucose were discovered. Significant hyperglycaemia was initially ascribed to steroid-induced diabetes, and antibodies specific to type I diabetes mellitus were subsequently detected, confirming the diagnosis. Following stabilization of glucose and electrolyte levels, the patient became seizure-free. To our knowledge, this is the first report of presentation of type I diabetes as the cause of early post-operative seizures. We discuss less common aetiologies of seizures in the early post-operative period, including metabolic disturbances. Based on our experience, we stress the importance of electrolyte and glucose monitoring in the setting of acute post-operative seizures.

Key words: intractable epilepsy, epilepsy surgery, focal cortical dysplasia, type I diabetes mellitus, acute post-operative seizure

Focal cortical dysplasia (FCD) is the most common aetiology of focal intractable epilepsy in childhood that eventually leads to epilepsy surgery. Often, localization of the epileptogenic zone (EZ) cannot be exactly delineated solely by means of neuroimaging and non-invasive electrophysiological methods, and an intracranial EEG study is necessary to precisely localize the EZ.

Data on the prognostic value of acute post-operative seizures (APOS) are inconclusive in paediatric epilepsy surgery patients. Apart from incomplete EZ removal, potential causes of APOS include various metabolic disturbances and fever (Park *et al.*, 2002). Association between newly diagnosed diabetes mellitus (DM) and epilepsy in young patients is recognized, however, not

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in a post-operative setting. Huang *et al.* (2008) have shown that uncontrolled hyperglycaemia may lead to more frequent seizure recurrence and clustering. Other reports have demonstrated an association between elevated blood levels of anti-GAD antibodies and lower GABA levels in the brain, which may account for an increased propensity to seizures (Stagg *et al.*, 2010).

We present a patient exhibiting atypical APOS caused by hyperglycaemia due to previously undiagnosed type I DM, as eventually confirmed by elevated blood levels of anti-GAD antibodies.

Case study

A 17-year-old male patient with negative family history of epilepsy, no perinatal risks, and normal psychomotor development was evaluated for focal intractable epilepsy. He experienced his first unprovoked seizure at the age of 9 years. Seizure semiology was consistent with type I hypermotor seizures and scalp EEG localized the seizure onset zone to the right frontal lobe; initial MRI was regarded as negative. After years of fluctuating seizure control under multiple AEDs, the family became motivated for the patient to undergo epilepsy surgery. A scalp video-EEG study supported the hypothesis of localization of the EZ within deep structures of the right frontal lobe; high-resolution MRI indicated an area of subtle signal alteration in the right dorsal orbito-frontal cortex, with features consistent with FCD (*figure 1*). Functional neuroimaging tests (FDG-PET and ictal SPECT) delivered normal or equivocal findings; the patient was thus indicated for an intracranial SEEG study. Based on the SEEG results, right orbitofrontal, frontal opercular, and anterior insular regions were resected.

As a standard procedure, MRI was performed on the first post-operative day, revealing no signs of residual dysplastic tissue. Concordance between the extent of resection documented by post-operative high-resolution MRI study and electrophysiological findings during the SEEG study provided reasonable evidence for complete resection of the presumed EZ. The patient was initially clinically stable, fully conscious, with a very mild left-sided hemiparesis.

On the second post-operative day, atypical seizures consisting of sitting up, trunk deviation to the left, clonic twitching of the left oral corner, and salivation appeared, along with a decreased level of consciousness. Due to a large resection area in the high-risk peri-sylvian region, incipient brain oedema was suspected and the patient was started on massive intravenous anti-oedematous and antiepileptic treatment. This led to temporary seizure freedom and stabilization of the neurological status.

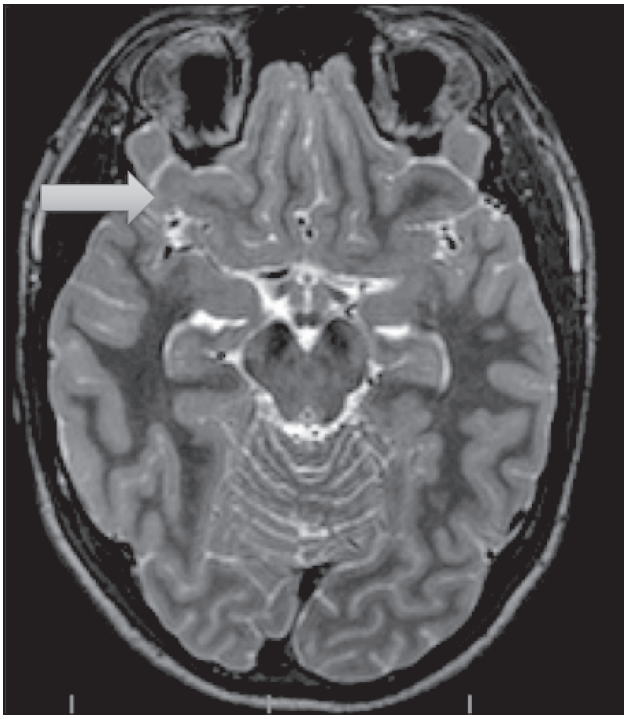

Figure 1. MRI of a presumed epileptogenic lesion showing the area of FCD in the right orbito-frontal operculo-insular cortex. The arrow denotes an area where typical signs of FCD, such as blurring of the grey-white matter interface and hyperintensity in white matter compared to the contralateral side, are visible.

During withdrawal of intravenous AEDs one week later, seizures reappeared and left-sided hemiparesis along with meningeal irritation became more pronounced. Postsurgical EEG showed slow background activity over both hemispheres with no epileptiform discharges. Repeat post-operative MRI revealed enhanced oedema around the surgical cavity and a subtle ischaemic lesion in the right putamen (close to the resection margin). This finding was not regarded causative for the above-described symptomatology.

Complete blood electrolyte evaluation uncovered an abnormally low sodium level (125 mmol/l) and significant hyperglycaemia (up to 46 mmol/l). Electrolyte balance was re-established in the following days and insulin substitution was started. Since pre-surgical blood glucose levels, obtained on the day before surgery, were normal, we suspected steroid-induced DM as a cause of hyperglycaemia. The patient's family history was negative for DM.

Subsequently, obvious association between episodes of hyperglycaemia and seizures was observed. Within 18 days, after his blood glucose levels began to stabilize (*figure 2*), the patient became seizure-free on continuing oral antiepileptic therapy and subcutaneous insulin substitution; his neurological status normalized. In due course, positive serum findings of

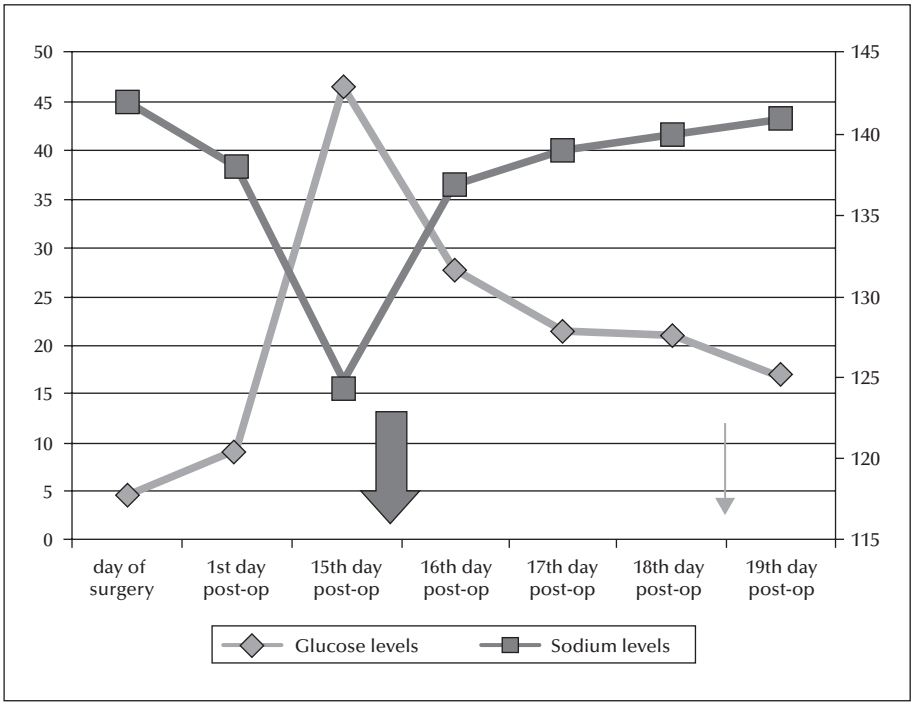

Figure 2. Relationship between maximum blood glucose and sodium levels (as mmol/l) during the post-operative period. Thick arrow denotes the beginning of insulin substitution; thin arrow denotes the last seizure observed.

anti-GAD (11 U/ml) and anti-IA2 (4 U/ml) antibodies confirmed the diagnosis of type 1 DM. Since neither encephalitis nor any other pathology mandating CSF analysis was suspected, no CSF samples were ever obtained from the patient, and we were therefore unable to evaluate the presence of auto-antibodies in the CSF.

Histopathological analysis of a minor portion of resected tissue unexpectedly revealed normal results and we explained this by the use of a resection technique involving an ultrasonic aspirator that most probably resulted in the destruction of a dysplastic portion of the resected tissue.

One year and five months following the surgery, the patient is seizure-free, insulin-dependent, and treatment with one of the prescribed AEDs has already been withdrawn; we continue the process of tapering down the remaining antiepileptic medication.

Discussion

Long-term seizure outcome after epilepsy surgery varies significantly depending on underlying aetiology, completeness of resection, localization of the lesion, age at surgery, *etc*. In larger surgical cohorts of patients with FCD, complete seizure freedom is achieved in ~65% of cases (Krsek *et al*., 2009; Lerner *et al*., 2009; Fauser *et al*., 2015).

APOS are defined as seizures which occur up to one week after epilepsy surgery (Engel *et al*., 1993). Long-term prognosis associated with APOS has not been unequivocally established, however, evidence suggests their appearance might be a negative prognostic factor after paediatric epilepsy surgery (Park *et al*., 2002, Mani *et al*., 2006; Greiner *et al*., 2014).

Various factors, such as seizure semiology, timing, and number of APOS do not appear to influence their overall prognosis (Garcia *et al*., 1991). In the adult population, earlier studies have indicated that patients experiencing APOS similar to their habitual seizures displayed worse long-term prognosis (Malla *et al*., 1998). In contrast, in the paediatric population, occurrence of APOS appeared to be a predictor of an unfavourable outcome, independent of post-operative seizure semiology (Park *et al*., 2002). Other studies have demonstrated that more than one post-operative seizure, similar to seizures before surgery, may suggest a worse prognosis (Malla *et al*., 1998).

The risk of APOS appears to be increased by certain electrophysiological findings, such as multifocal interictal epileptiform EEG abnormality before surgery and the presence of interictal epileptiform activity one week after surgery (Park *et al*., 2002). The same study revealed fever as a statistically significant predictor of the occurrence of APOS.

Multiple factors that possibly account for the occurrence of APOS in patients need to be addressed since the clinical scenario presented in this report remains highly complex. Firstly, we observed a clear tendency of decreasing seizure frequency coincident with stabilization of glucose and electrolyte balance (*figure 2*). Secondly, repeat post-operative MRI revealed no signs of residual epileptogenic tissue.

Moreover, the distinct semiology of APOS, compared to the habitual pre-operative seizures, and the favourable long-term outcome suggest that incomplete resection was not the cause of the patient's post-operative seizures. However, what needs to be taken into consideration is the possible epileptogenicity of the brain tissue surrounding the resection cavity. Due to the effect of perifocal oedema and ischaemia, both rendering the entire region highly prone to seizure formation, this area might have been the "locus minoris resistentiae", where APOS originated even in the absence of dysplastic tissue, in the setting of acute electrolyte disturbance.

The last factor that might have contributed to seizure formation, and the one most difficult to evaluate, is the possible role of anti-GAD-mediated auto-inflammation. Growing evidence supporting the association between increased levels of anti-GAD antibodies and lower GABA levels in the brain, leading to increased propensity to seizures, has been described in the literature (Stagg *et al*, 2010). The pathogenic role of anti-GAD antibodies has been studied in various neurological syndromes (Saiz *et al*., 2008; Ramanathan *et al*., 2014); epilepsy being one of the less prevalent, compared to stiff-man syndrome and cerebellar ataxia (Saiz *et al*., 2008). Neurological syndromes seem to be associated with high levels of anti-GAD antibodies (>1,000 IU/ml) (Ramanathan *et al*., 2014), while our patient manifested with only modest elevation of anti-GAD antibodies, typically observed in type 1 diabetes patients. In addition, our patient also tested positive for anti-IA2 antibodies, supporting the view that inflammation of pancreatic beta cells was the source of anti-GAD antibodies. Given the low serum levels of anti-GAD antibodies, electroclinical picture suggestive of FCD, and lack of any need for further immunomodulatory therapy, we consider autoimmune CNS inflammation less probable. However, since no CSF samples were obtained, the presence of CNS inflammation cannot be ruled out.

The combination of multiple factors therefore seems to be the most plausible explanation of this patient's APOS, and we consider that a concurrent effect of electrolyte imbalance and significant vulnerability of oedematous brain tissue surrounding the resection cavity to seizure formation the most probable cause of our patient's APOS.

An association between DM itself and epilepsy has repeatedly been discussed (Yun and Xuefeng, 2013). Approximately 25% of patients with DM experience various types of seizures. Huang *et al*. (2008) described a strong association between poor glycaemic control in diabetic patients and tendency of seizure recurrence and clustering in the adult population. It is therefore believed that satisfactory treatment of diabetes may lead to complete seizure and antiepileptic drug freedom in this group of patients. Given the pathophysiology of type 1 DM, with continual loss of pancreatic beta cells due to long-lasting autoimmune inflammation and stress-induced strain on glycaemic control, the notion that surgery in our patient was an accelerator of the autoimmune process, and eventually triggered acute decompensation of type 1 DM, is a plausible hypothesis.

In summary, we have demonstrated the importance of blood electrolyte and glucose monitoring in the early post-operative period. Our case also suggests that an understanding of the aetiology of APOS is crucial to ensure optimal prognosis, with acute metabolic disturbance possibly indicating a more favourable outcome. This hypothesis will, however, require further study on a larger patient population. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) What is the most common aetiology of intractable focal epilepsy in children that eventually leads to epilepsy surgery?

(2) What is the definition of acute post-operative seizures?

(3) What less common treatable causes of acute post-operative seizures should be considered in the post-operative period?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".