TITLE PAGE

A difficult case: Atypical status epilepticus with hippocampal involvement in Hyperosmolar Hyperglycemic State

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KEY POINTS

- Diabetes mellitus may abruptly precipitate a hyperosmolar hyperglycemic state.
- Generalised brain dysfunction may occur, leading to coma, which reverses after normalisation of metabolism
- Very rarely, an insidious status epilepticus can occur, impairing vigilance despite the recovery of metabolic parameters.
- Epilepsy and hippocampal sclerosis may develop in the long term.
- Monitor EEG in people with HHS whose alertness is not fully restored after the correction of metabolic parameters.

DETAILS PAGE

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ABSTRACT

Diabetes mellitus may arise abruptly with sudden decompensation leading to a hyperglycemic hyperosmolar state. Coma often ensues, which usually reverses after metabolic parameters are restored. In conscious individuals, acute symptomatic seizures can also occur, ceasing after osmolarity and glycemia normalised.

We describe an individual who failed to regain vigilance despite prompt treatment. We describe how we identified the culprit in an unusual nonconvulsive status epilepticus arising from the mesial temporal lobe and promoting a progressive and selective hippocampal involvement. We also ascertained epilepsy onset and hippocampal sclerosis development during follow-up, attaining seizure freedom by antiseizure medications.

Subclinical epileptiform discharges should be suspected in an unresponsive person with a hyperglycemic hyperosmolar state. Possible permanent brain damage and the development of epilepsy in the long term should be monitored.

CASE

We saw an 81-year-old female found in a confusional state at home and brought to the Emergency Department. She had a florid medical history, including long-standing hypothyroidism (on hormone replacement), permanent atrial fibrillation (on edoxaban), an anxiety disorder and Chronic Obstructive Pulmonary Disease (COPD).

Over the previous month, she used oral steroids to treat a COPD exacerbation. She also overused steroid inhalers with tens of puffs daily. Increasing polydipsia and polyuria were reported.

On arrival to Casualty, her alertness had decreased (GCS=6; no eye-opening either verbal response, flexion to pain). She appeared pale and sweaty, with no signs of meningism or fever. She had a convulsion during the examination.

Brain Computed Tomography (CT) scan did not show remarkable findings. EEG showed generalised slowing of background activity. Laboratory analysis suggested a nonketotic hyperglycemic hyperosmolar state (plasma glucose level 1430 mg/dl, pH=7.33, effective osmolality 355 mOsm/kg, no urinary ketones) and respiratory acidosis (pCO2 50 mmHg, normal serum bicarbonate). Of note, undiagnosed diabetes mellitus (DM) was identified (HbA1c 104 mmol/mol), She required general anaesthetic (propofol infusion 1.5 mg/kg/h), noradrenaline vasopressor support, intubation and mechanical ventilation in the intensive care unit. Intravenous insulin supplementation was introduced.

On day 2, despite propofol discontinuation and correction of metabolic parameters, vigilance appeared to wax and wane, and she seemed to be unresponsive. We organised a prolonged EEG recording which showed rapidly recurring left frontotemporal seizures. A diagnosis of a focal onset nonconvulsive status epilepticus (NCSE) was made (Figure 1). Intravenous lacosamide (bolus dose: 200 mg iv, repeated once) successfully stopped the seizures and prompted a gradual recovery of consciousness. On day 3, her neurological examination had normalised.

A 1.5T MRI showed hippocampal hyperintensity on T2W and Diffusion-Weighted Images (DWI), with no restricted diffusion on ADC map and no gadolinium enhancement. The temporal lobe white matter returned a normal sign. Over other brain regions, no cortical or subcortical signal abnormalities were seen except a mild degree of subcortical chronic microvascular lesions-(Fig. 2 A,B).

She was discharged on lacosamide 200 mg b.i.d. and metformin 500 mg b.i.d.

At six months follow-up, no seizures recurred, and the glycemic control was restored (HbA1c 58 mmol/mol). Episodic memory deficits ensued, yet global cognitive performance was within normal

values (MMSE=27/30). A brain MRI showed left hippocampal sclerosis with increased T2W signal over the hippocampal head and body (Figure 2 C,D). The EEG was normal.
Given the abrupt clinical course with temporal lobe involvement, we re-assessed the case by dosing glutamic acid decarboxylase (GAD) serum antibodies showed in mildly elevated (42.3 IU/ml, ELISA immunoassay; normal values $\leq$5 IU/ml)
Two months later, she discontinued lacosamide of her own volition due to dizziness. Soon after medication withdrawal, she started to have almost daily focal impaired-awareness seizures preceded by an epigastric aura. We reintroduced Antiseizure treatment (eslicarbazepine 800 mg/day). At 12 months follow-up, no further episodes have occurred.

DISCUSSION

Diabetes mellitus may precipitate life-threatening medical emergencies: diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Such complications may arise *de novo* at DM onset, triggered by an unbalance between insulin effect and counter-regulatory hormones (i.e. glucagon, catecholamines, cortisol, growth hormone). This is often associated with intercurrent factors such as infectious disorders or steroids intake. In DKA, absolute or relative insulin deficiency prevents cellular glucose intake, promotes gluconeogenesis and activates lipolysis releasing glycerol and free fatty acid from adipose tissue. Hyperglycemia worsens, while free fatty acids are oxidised to ketone bodies, acetoacetate and 3-hydroxybutyrate, leading to metabolic acidosis and elevated keto-uremia within 1-2 days. Seizures are infrequent in DK, probably due to the anti-epileptogenic effect of ketones. Insulin deficiency in HHS is milder, and free fatty acids, cortisol, growth hormone and glucagon levels are lower. This leads to a slower and progressive metabolic derangement with hyperglycemia and dehydration.

The metabolic derangement of HHS provokes a generalised brain dysfunction, even leading to a state of coma, which, however, reverses after metabolic parameters are restored.

In conscious individuals, hemichorea/hemiballism and acute symptomatic seizures have been reported. Focal seizures develop in up to 40% of cases, mainly as epilepsia partialis continua (EPC), i.e. recurrent and unrelenting hemiclonic seizures originated by the peri-rolandic cortex [2]. More rarely, seizures exhibit non-motor semiology, namely visual/disperceptive and aphasic. Visual/disperceptive seizures have been reported as short-lasting simple or complex visual phenomena which may yield reversible hemianopia [3]. Aphasic seizures are infrequent and prolonged, rarely establishing an NCSE as pure alexia [4] and as rapidly recurring aphasic seizures [5]. All these seizures types have, however, only been reported in alert individuals. Typical MRI hallmarks have been described to occur over the brain regions from which seizures originate:

cortical T2W hyperintensity, restricted diffusion and faint enhancement, subcortical T2W hypointensity with 'negative shine through' effect [2,6].

Our case demonstrates that people with HHS may develop subtle persisting seizures leading to an unusual NCSE. This peculiar condition should be suspected in people with HHS who remain unresponsive after restoring metabolic parameters. Of note, the associated neuroimaging pattern appears to be different from the HHS classical findings and instead recall those commonly encountered in temporal lobe onset NCSE: a continuum of hippocampal cytotoxic oedema (increased DWI and decreased ADC signal; alteration of the neuronal osmotic balance; acute phase), vasogenic oedema (increased DWI and T2W signal without decreased ADC signal; localised disruption of the blood-brain barrier; subacute phase) and hippocampal sclerosis (T2W hyperintensity and atrophy; chronic phase) [7].

Interestingly, acute hippocampal vasogenic oedema followed by long-term sclerosis was never reported in HHS but described in the only reported case of NCSE in DKA. This person had moderate hyperglycemia (269 mg/dl), normal osmolality (279.3 mOsm/kg), ketosis, normal GAD antibodies and ongoing recurring seizures from the right middle-posterior temporal region [8]. Hence the hippocampus could also be targeted by hyperglycemia even at lower values and in the presence of anti-epileptogenic ketone bodies.

During follow-up, we found mildly elevated GAD serum antibodies (42.3 IU/ml). Antibodies targeting GAD may cause autoimmune neurological disorders such as stiff-person syndrome, cerebellar ataxia, limbic encephalitis and sporadic drug-resistant temporal lobe epilepsy. DM can accompany all. Our case shares some similarities with GAD-related limbic encephalitis. Vigilance can be altered, seizures arise abruptly from the mesial temporal lobe, the hippocampus undergoes first "swelling" and then atrophy/sclerosis.

We ruled this diagnosis out as titers of antibodies are much higher in GAD-related encephalitis than in our case (> 1000 IU/ml vs 42.3 IU/ml). It may be argued that we only ascertained antibodies at a 6-month follow-up. Yet, higher titers at onset are extremely unlikely as spontaneous decreases are seldom reported, particularly in the absence of immunomodulatory treatment. She has become seizure-free despite hippocampal sclerosis, whilst the long-term prognosis of GAD-associated temporal lobe epilepsy is usually poor without immunotherapy. Seizure may even persist in those who have a temporal lobectomy after multiple unsuccessful immunological treatments [9,10].

Low titers of GAD antibodies can be found in healthy subjects and are common in DM [10].

The presence of low-titer GAD antibodies in our subject may suggest a predisposition to DM, likely triggered by steroid treatment resulting in HHS, unusual NCSE and hippocampal sclerosis.

In conclusion, we suggest monitoring EEG in people with HHS whose alertness is restored after correcting metabolic parameters. New-onset NCSE arising from the mesial temporal lobe, albeit rare, can occur and may result in hippocampal sclerosis requiring acute treatment of NCSE and then long-term antiseizure medications.

FIGURE LEGEND

Figure 1. NCSE depicted by EEG monitoring

EEG 10-20 International System Bipolar Montage, 40-sec epoch page. Sensitivity: 100 microV/cm; high-frequency filter: 30 Hz; low-frequency filter 1.6 Hz.

Individual unresponsive, no clinical manifestation. Low-voltage background activity at 5-6 Hz. Enduring electrographic focal seizure displayed by left frontotemporal rapid activity evolving to sharply countered theta-delta waves intermixed with spikes (arrow; note phase opposition on F7).

Figure 2. Progressive hippocampal abnormalities shown by brain MRI.

1.5 T MR scan, Baseline day-2 FLAIR coronal (A) and axial (B) views; 6-month follow up coronal (C) and axial view (D).

Day-3: hyperintensity of hippocampal head (arrowhead in A) and body (arrow in B) with vasogenic hippocampal edema (not shown).

Month-6: hippocampal sclerosis highlighted by hyperintensity and atrophy of hippocampal head (arrowhead in A) and hyperintensity of hippocampal body (arrow in B).

REFERENCES

1. Umpierrez G, Korytkowski M. Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016;12:222–232.

2. Tiamkao S, Pratipanawatr T, Tiamkao S, Nitinavakarn B, Chotmongkol V, Jitpimolmard S. Seizures in nonketotic hyperglycaemia. Seizure. 2003;12:409–410.

3. Moien-Afshari F, Téllez-Zenteno JF. Occipital seizures induced by hyperglycemia: A case report and review of literature. Seizure. 2009;18:382–385.

4. Kutluay E, Pakoz B, Yuksel A, Beydoun A. Nonconvulsive status epilepticus manifesting as pure alexia (alexia without agraphia). Epilepsy & Behavior. 2007;10:626–628.

5. Pro S, Randi F, Pulitano P, Vicenzini E, Mecarelli O. Nonconvulsive status epilepticus characterised exclusively by a language disorder induced by non-ketotic hyperglycaemia. Epileptic Disorders. 2011;13:193–196.

6. Urbach H, Berger B, Solymosi L, Zimmermann J. "Negative T2 shine through" in patients with hyperglycemia and seizures: a frequently overlooked MRI pattern. Neuroradiology [online serial]. Epub 2020 Mar 26. Accessed at: http://link.springer.com/10.1007/s00234-020-02408-w. Accessed March 31, 2020.

7. Giovannini G, Kuchukhidze G, McCoy MR, Meletti S, Trinka E. Neuroimaging alterations related to status epilepticus in an adult population: Definition of MRI findings and clinical-EEG correlation. Epilepsia. 2018;59:120–127.

8. Martínez-Fernández R, Gelabert A, Pablo MJ, Carmona O, Molins A. Status epilepticus with visual seizures in ketotic hyperglycemia. Epilepsy & Behavior. 2009;16:660–662.

9. Malter MP, Frisch C, Zeitler H, et al. Treatment of immune-mediated temporal lobe epilepsy with GAD antibodies. Seizure. 2015;30:57–63.

10. Graus F, Saiz A, Dalmau J. GAD antibodies in neurological disorders — insights and challenges. Nat Rev Neurol. 2020;16:353–365.