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Literature Review

Neurological Manifestations of Hyperosmolar Hyperglycemic State: A Case Report and A Review of the Literature

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Abstract

Hyperosmolar hyperglycemic state (HHS), a life-threatening complication of diabetes mellitus, may initially manifest with a broad spectrum of neurological symptoms. These include encephalopathy, coma, chorea-hemiballismus and epileptic activity. Focal motor seizures are among the most common manifestations whilst aphasia has rarely been described so far. Based on a recent experience from our hospital, we herein report a rare case of a patient with non-ketotic hyperglycemia-induced global aphasia, followed by focal motor seizures and attempt a comprehensive review of the literature with regards to the various neurological syndromes through which, undiagnosed diabetes and HHS may present. Neurological aspects of HHS are not so well-documented and are certainly under-represented in the literature.

Keywords: *epilepsy, global aphasia, focal seizures, hyperglycemia, diabetes mellitus, hemichorea-hemiballismus, coma*

1. Introduction

Hyperosmolar hyperglycemic state (HHS), the most serious hyperglycemic emergency in patients with diabetes mellitus, is a syndrome characterized by severe hyperglycemia, hyperosmolarity, and dehydration in the absence of significant ketoacidosis. Hyperglycemia causes osmotic diuresis with hyperosmolarity leading to an osmotic shift of water into the intravascular compartment. As a result, severe intracellular dehydration occurs in the absence of ketosis due to the presence of basal insulin secretion sufficient to prevent ketogenesis but insufficient to reduce blood glucose.[1] The association between HHS with neurological symptoms is well-known. However, apart from several case reports and small series, there are no publications discussing the whole spectrum of CNS involvement as well as the events that could drive the process in the cellular level. Among the neurological manifestations of HHS are encephalopathy, coma, chorea-hemiballismus, and of course epileptic seizures. Focal motor seizures are probably the most common and well-documented type of seizures caused by HHS. The association between HHS and focal motor seizures was first reported in 1965.[2] On the other hand, symptoms such as aphasia or hemianopia are seen less frequently.[3] In the next section we report a rare case of a patient with HHS-induced global aphasia and complex focal motor seizures who recovered gradually with blood glucose management and anticonvulsant treatment followed by a comprehensive review of the literature with regards to the whole spectrum of neurological complications of HHS.

2. Case Study

A 61-year-old, right-handed male patient was admitted to our hospital with language disturbance for five days. His relatives reported gradually worsening episodes of incoherent speech and poor comprehension of spoken language. They also mentioned two attacks of jerking of his right arm the day of the admission and a weight loss of 10kg over 12 months. The patient had an unremarkable medical history, although he had no health examination recently.

Upon admission to the emergency room, he was drowsy and uncooperative, thus language impairment could not be assessed. Minutes after presentation, a tonic deviation of the head to the right and clonic seizures affecting the right jaw, hand and leg lasting about 30 seconds were observed every 5 minutes, lasted for 20 minutes, and were followed by Todd's palsy.

Laboratory data showed serum glucose 600 mg/dL, osmolality 326 mOsm/L, and HbA1c 19%, without significant ketonuria or systemic acidosis. Venous blood gases showed a serum pH of 7.38 and serum creatinine was 2.8 mg/dL. Cranial computerized tomography (CT) scan at the time of admission and 48 hours later did not reveal any vascular or structural abnormality besides cortical atrophy (Figure 1). Carotid ultrasound was also normal. Electroencephalography (EEG) was not available on admission and was performed 72 hours later. It showed a focal abnormality over the left hemisphere, with a small amount of alpha waves and an excessive amount of low voltage, fast and theta activity. No epileptiform activity was detected (Figure 2A).

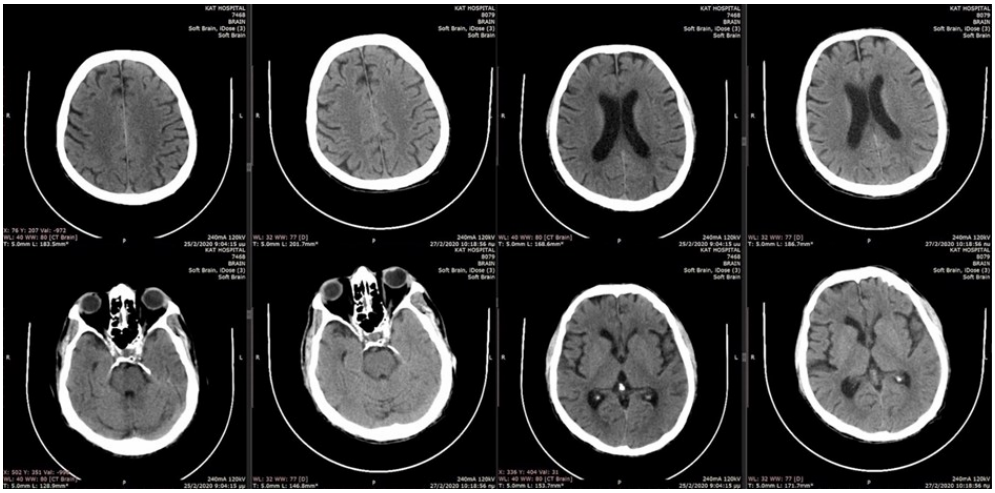

Fig. 1: *CT scans performed on presentation and 48 hours later. No vascular or structural abnormalities were observed.*

Intensive intravenous insulin therapy was administered along with massive fluid replacement to control blood glucose levels and relieve dehydration. Levetiracetam and lacosamide were administered as antiepileptic therapy. Focal motor seizures resolved within the first hour of treatment whilst aphasia persisted. Blood glucose management over a week of hospitalization gradually led to language recovery. Global aphasia initially shifted to Broca's aphasia and then resolved completely. No motor seizures or language alterations were observed within the next week and the patient was discharged.

In the present case, aphasia was the primary symptom followed by complex focal motor seizures. Insulin therapy and rehydration for hyperglycemia control, as well as the administration of antiepileptic treatment including levetiracetam and lacosamide, led to focal seizures' control within the first hour after admission to the emergency room. Global aphasia resolved gradually over a week of hospitalization with blood glucose management. Although no epileptiform discharges were observed in the EEG (performed 72 hours after presentation), laboratory findings as well as the lack of vascular or structural abnormalities in both CT scans performed on presentation and 48 hours later confirmed the diagnosis of HHS-induced global aphasia followed by complex focal motor seizures. The EEG performed two months later, showed significant improvement of the asymmetry. The background activity over the left hemisphere was better organized. (Figure 2B).

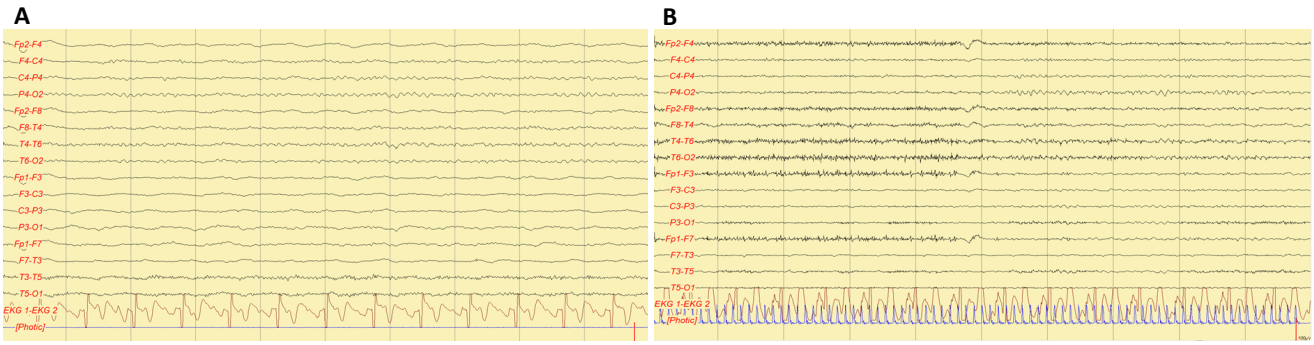

Fig. 2: A. *Electroencephalography (EEG), performed 72 hours after admission, showing a focal abnormality over the left hemisphere, with small amount of alpha waves and excessive amount of low voltage, fast and theta activity. No epileptiform activity was detected.* ***B.*** *EEG performed two months later, showing significant improvement of the asymmetry. The background activity over the left hemisphere is better organized.*

3. Neurological Manifestations of Hyperosmolar-Hyperglycemic State

3.1 Epileptic Seizures

Seizures can be found in 25% of nonketotic hyperglycemic patients and can be the first symptom of HHS in 50% of patients. They include simple or complex focal motor seizures, aphasic, and occipital seizures (table 1). In our literature review, we found that focal motor seizures (simple or complex) were after altered mental status, the most common neurological complication of HHS. We identified 23 cases that manifested primarily as focal motor seizures. Most of them had normal brain scans except for four of them who had focal signal changes. All of them had excellent recovery and did not acquire disability as a result of HHS. Clinically, they manifested with unilateral facial, upper or lower limb jerking followed in some cases by Todd's palsy. Epilepsia partialis continua was also observed approximately in half of the cases.

On the other hand, ten cases which manifested predominantly with aphasic seizures were identified. They all had normal brain scans and had excellent prognosis as well. Interestingly, when aphasic seizures co-existed with focal motor seizures, language disturbance preceded motor seizures. Symptoms included impaired fluency, naming, repetition, and comprehension depending on the affected area. However, most of the cases were characterized by global aphasia since HHS leads to a generalized reduced cerebral perfusion and does not affect a single brain region. EEG abnormalities of aphasic seizures included epileptiform discharges, periodic lateralized epileptiform discharges and slow waves in left frontal, temporal, and parietal cortex.

Finally, ten cases of occipital seizures have been documented as a consequence of HHS. Remarkably, visual symptoms included blurred vision, transient visual field deficits, visual field episodic flashing or even hallucinations. In all cases symptoms were transient and they could reflect an equivalent of Todd's palsy following occipital seizures. In terms of electroencephalography, Wang et al described focal spikes at onset, decrease of voltage and slowing in the affected area which is consistent with other case reports as well.[15-16]

Table 1. Types of epileptic seizures, imaging features and serum glucose levels in patients with HHS.

Publication	Case #	Neurological Syndrome	Serum Glucose	Imaging	Outcome
Askenasy et al [3]	1.	Focal motor seizures + aphasic seizure	320 mg/dL	Normal	Complete recovery
	2.	Focal seizures	360 mg/dL	Normal	Complete recovery
Henis et al [4]	1.	Focal motor seizures + aphasic seizures	991 mg/dL	Normal	Complete recovery
	2.	Focal seizures	320 mg/dL	(R) side perisylvian atrophy	Complete recovery
	3.	Focal motor seizures	623 mg/dL	-	Complete recovery
	4.	Focal motor seizures	617 mg/dL	(R) fronto-parietal infract	Complete recovery
	5.	Focal motor seizures	758 mg/dL	-	Complete recovery
	6.	Focal motor seizures	508 mg/dL	-	Complete recovery
	7.	Focal motor seizures + aphasic seizures	234 mg/dL	Normal	Complete recovery
Grant et al [5]	1.	Focal motor seizures	838 mg/dL	Normal	Complete recovery
	2.	Focal motor seizures	595 mg/dL	Normal	Complete recovery
	3.	Focal motor seizures	441 mg/dL	Cortical atrophy	Complete recovery
	4.	Aphasic + focal motor seizures	432 mg/dL	Normal	Complete recovery
	5.	Focal motor seizures	258 mg/dL	Normal	Complete recovery
Kodama et al [6]	1.	Focal motor seizures	371 mg/dL	Reversible T2 hypointense lesion – (R) frontal operculum	Complete recovery

Table Continued….

Batista et al [7]	1.	Aphasic + focal motor seizures	455 mg /dL	Normal	Complete recovery
Moien-Afshari et al [8]	1.	Occipital seizures + focal motor seizures	639 mg/dL	Normal	Complete recovery
Oh et al [9]	1.	Encephalopathy + aphasic seizures	518 mg/dL	Normal	Complete recovery
Pro et al [10]	1.	Aphasic seizures	358 mg/dL	Normal	Complete recovery
Huang et al [11]	1.	Aphasic seizures	381 mg/dL	Cortical atrophy	Complete recovery
Lee et al [12]	1.	Aphasic seizures	471 mg/dL	Normal	Complete recovery
Misra et al [13]		Focal motor seizures	329-593 mg/dL	Normal	Complete recovery
	2.	Focal motor seizures	329-593 mg/dL	Bilateral laminar necrosis in motor strip	Incomplete recovery
	3.	Focal motor seizures	329-593 mg/dL	-	Complete recovery
	4.	Focal motor seizures	329-593 mg/dL	Normal	Complete
	5.	Focal motor seizures	329-593mg/dL	FLAIR hyperintensity in cerebellar vermis	Incomplete recovery
Raghavendra et al [14]	1.	Occipital seizures	324 mg/dL	T2W L temporoparietooccipital subcortical WM hypointensities, bilateral striatal T2 hyperintensities	-
Lavin et al [15]	1.	Occipital seizures	502 mg/dL	T2W hypointensity in WM of right occipital lobe	-
	2.	Occipital seizures	427 mg/dL	restricted diffusion of R occipital and part of R parietal lobe	-
	3.	Occipital seizures	486 mg/dL	-	-
Wang et al [16]	1.	Occipital seizures	535mg/dL	T2W and FLAIR subcortical hypointensity and gyri hyperintensity at the left occipital lobe	-
Perez-Saldana et al [17]	1.	Occipital Seizures	569 mg/dL	alteration in R cortical–subcortical occipital diffusion sequence	-
Harden et al [18]	1.	Occipital Seizures	371 mg/dL	Normal	-
	2.	Occipital Seizures	484 mg/dL	old L basal ganglia and occipital lacunar infract	-
Sowa et al [19]	1.	Occipital Seizures	611 mg/dL	Normal	-

3.2 Coma

Altered mental status and coma is a well-known complication of HHS. In a case series it was the most common presenting symptom.[13]. Patients who present with coma, usually have decreased level of consciousness several days before admission to the hospital due to the fact that HHS requires almost a week to develop. Most of them (90-95%) are patients with type 2 diabetes, whilst HHS can occur to individuals without prior history of diabetes (and therefore lead to the diagnosis) or to type 1 diabetic patients. Triggers include infections, vascular conditions such as stroke or poor adherence to treatment. When HHS-associated coma is secondary to one of these factors (especially to stroke) clinical outcome and prognosis tend to be unfavorable. On the other hand, when coma is solely a consequence of HHS, prognosis is most of the times better, following blood glucose management and rehydration. This is consistent to the results reported by the above-mentioned case series, which indicated that only those who had a stroke did not recover completely.[13]

3.3 Hemichorea-hemiballismus

Hemichorea-hemiballismus is a syndrome characterized by spontaneous, irregular, and involuntary jerky movements of one side of the body, often attributed to a focal lesion of the contralateral basal ganglia. Rarely, movement disorders can be the first manifestation of HHS in patients with poorly controlled diabetes. Hemichorea-hemiballismus was first reported by Berkell et all in 1960.[20] Since then, there has been a significant number of cases, reporting it as the initial symptom of HHS. Linn et al described three patients who presented with hemichorea-hemiballismus as a complication of HHS.[21] Two of the three patients had associated signal changes in the contralateral basal ganglia (a lacunar infract and calcification) whilst the third had normal CT. MRI was not available back then. All of them fully recovered following blood glucose management. Another case series by Lai et al investigated the imaging findings in 10 patients with hemichorea-hemiballismus and HHS using CT, MRI and single-photon emission CT (SPECT).[22] CT and MRI showed unilateral or bilateral lesions in the putamen or caudate of all of the patients whilst SPECT showed hypoperfusion in the basal ganglia. Lesions were hyperdense in CT scans and hyperintense in T1-weighted images. Therefore, the authors suggest that these lesions can be attributed to small, petechial hemorrhage. Interestingly, the sequential resolution of hyperintense signal on T1-weighted images and the sequential presence of increased hypointensity on T2-weighted and gradient-echo T2*- weighted sequences in the basal ganglia with continuous resolution of high density on CT scans also imply evolution of petechial hemorrhage with hemosiderin deposition. Finally, a SPECT study in 6 patients with hemichorea-hemiballismus and HHS showed again decreased blood flow in the contralateral basal ganglia and hypometabolism of the respective striatum.[23]

4. Discussion

HHS may present with a variety of neurological symptoms including altered mental status, movement disorders, seizures, and aphasia. Our patient experienced HHS-induced aphasia, followed by complex focal motor seizures as the first manifestation of diabetes mellitus. HHS-associated neurological symptoms completely resolved after a week of hospitalization. Focal seizures associated with non-ketotic hyperglycemia are considered refractory to anticonvulsant treatment, however, they respond well to insulin treatment and rehydration. In our case, focal motor seizures resolved within an hour after blood glucose control and the administration of anti-epileptic drugs. Aphasia resolved gradually with blood glucose management. Our findings are consistent with previous studies on epileptic activity as a result of HHS. In the vast majority of cases, seizures stopped when blood glucose was controlled and most of the patients did not require antiepileptic treatment if they maintained optimal blood glucose control.

The pathogenesis of HHS-induced seizures remains unclear; however, several theories have been proposed. Some authors suggested that pre-existing or acute ischemic cortical lesions, as well as decreased blood flow during hyperglycemia, could lead to HHS-induced seizures by decreasing seizure threshold.[26-27] Another study supported that hyperglycemia may be pro-convulsant per se, even in the absence of organic cortical lesions.[28] During HHS, hyperglycemia increases serum osmolarity, leading to intracellular dehydration. Subsequently, Krebs cycle is inhibited, and GABA metabolism is increased. Depressed GABA levels result in a reduction of seizure threshold through an increase in neuronal excitability induced by high extracellular glucose concentration.[29-31]

Similar theories have been proposed for the pathogenesis of HHS-related hemichorea-hemiballismus. Cellular energy demand shifts towards anaerobic metabolism and causes the brain to metabolize GABA as an alternative source of energy. Absence of ketosis prevents re-synthesis of GABA because of lack of acetoacetate. Therefore, GABA depletion is rapid in patients with HHS and can lead to increased pallidal activity and contralateral hemichorea-hemiballismus. Some authors also suggest that patients with HHS might have pre-existing chronic cerebrovascular disease due to diabetes, which could provide the basis for the acute disruption of the blood-brain barrier.[22] During HHS, there is a global decrease in the cerebral blood flow which affects the basal ganglia significantly, as it has been shown by the SPECT studies.[22-23] Reduced blood flow might lead to reduced GABA levels at the basal ganglia leading to hyperactivity, therefore causing hemichorea-hemiballismus. Similarly, to epileptic activity, hemichorea-hemiballismus tends to subside following blood glucose management and no further therapy is required.

Furthermore, the findings of the imaging study are of great interest as they excluded patients with lacunar infractions or other conditions that could cause hemichorea-hemiballismus and focused solely on those who had HHS-related movement disorder.[22] They showed that HHS caused hyperdense CT lesions and hyperintense T1W MRI lesions in the basal ganglia. The sequential decrease of signal intensity in CT and T1W images along with the increase in the intensity of signal in T2W and gradient echo T2W sequences actually suggest petechial hemorrhage and hemosiderin deposition confirming their theory.

Finally, it is worth mentioning that altered mental status and coma remain the most common and life-threatening manifestations of HHS. It is believed that increased serum osmolarity is associated with worse clinical outcomes. However, this was not confirmed by Misra et al, who showed that coma could occur in patients with lower serum osmolarity as well.[13]

5. Conclusion

In conclusion, physicians (both neurologists and internists) should be aware of the association between HHS, altered mental status, focal seizures, and hemichorea hemiballismus. As suggested by most of the studies, blood glucose management may be adequate to reverse HHS symptoms. Prompt diagnosis and immediate management of hyperglycemia and hyperosmolarity can improve the outcome of HHS patients and avoid unnecessary investigation and inappropriate treatment.

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Conflict of Interest

Dr. Panagiotis Gklinos has no conflict of interest to declare.

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