

Case report

A multimodal approach using somatosensory evoked potentials for prognostication in hypoglycemic encephalopathy

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ABSTRACT

Objectives: We present a case of a patient with hypoglycemic encephalopathy with loss of median nerve N20 somatosensory evoked potentials (SSEPs) and describe our multimodal approach to prognostication in hypoglycemic encephalopathy.

Case: The patient was a 67-year-old woman with type 2 diabetes and stage 5 chronic kidney disease hospitalized for hypoglycemic encephalopathy. SSEPs showed bilateral absence of the median nerve N20 response. She ultimately suffered a poor outcome.

Discussion: There are no high-quality evidence-based clinical, neurophysiologic, or imaging studies available to aid in neurologic outcome prediction in hypoglycemic encephalopathy. In our practice we use a multimodal approach to neurologic prognostication, similar to that used in coma after cardiac arrest that includes SSEPs, EEG, and brain MRI, which enables an estimate of the severity of brain injury. As the literature is largely based on small studies or case reports, and is extrapolated from the cardiac arrest literature, we caution against early prognostication and disposition including the withdrawal of care, to avoid a self-fulfilling prophecy.

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1. Introduction

Hypoglycemia is associated with neurological complications ranging from inattention and impaired memory to coma (Languren et al., 2013). Hypoglycemic encephalopathy is defined as altered sensorium from sustained reduction in serum glucose below 50 mg/dL. While this has been a long-time concern, there are few reports on prognosis in hypoglycemic encephalopathy (Witsch et al., 2012; Barbara et al., 2017; Ikeda et al., 2013). Somatosensory evoked potentials (SSEPs) are an important part of the multimodal approach to prognostication in the anoxic/ischemic coma that follows cardio-respiratory arrest (CRA), because the absence of a cortical N20 response almost invariably heralds poor outcome (Rossetti et al., 2016). The value of SSEPs in prognostication of coma due to other states of global metabolic compromise is largely unknown. In this article, we present the case of a patient with hypoglycemic encephalopathy, in which SSEPs were used as part of a multimodal approach to prognostication.

2. Case presentation

A 67-year-old woman with a complicated past medical history including type 2 diabetes and stage 5 chronic kidney disease was noted by her family to be confused for several hours and later was found unresponsive for which she was brought to the hospital. In route to the hospital she had an undetectably low blood glucose level. Despite intravenous administration of 50% dextrose solution in the ambulance and maintenance of normal blood sugar, she was unresponsive to noxious stimulation with a GCS of 6: she did not open her eyes spontaneously, had roving eye movements, reactive pupils, and intact corneal reflexes. EEG done within 24 h of arrival to the hospital showed generalized background slowing in the theta and delta range and was without reactivity to noxious stimuli. EEG was repeated two days later and showed a burst suppression pattern. The patient had not been on sedation prior to or during either study. MRI on day four showed T2 hyperintensity and restricted diffusion affecting bilateral cerebral cortex as well as the left basal ganglia (Fig. 1). The patient's neurological exam remained the same, so SSEPs were performed on day four for prognostication and showed bilateral absence of the median nerve N20 response (Fig. 2). She had a complicated medical course including acute kidney injury with a blood urea nitrogen (BUN) peaking at 113 mmol/L. Fig. 3 shows a timeline of events plotted against her

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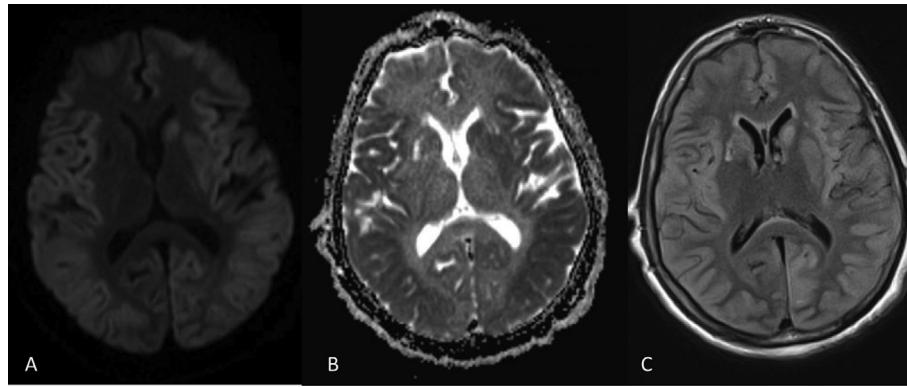


Fig. 1. MRI showing cytotoxic edema (DWI in panel A and ADC in panel B) in the left caudate head and putamen as well as throughout the cerebral cortex; FLAIR hyperintensity is seen in these areas as well (panel C).

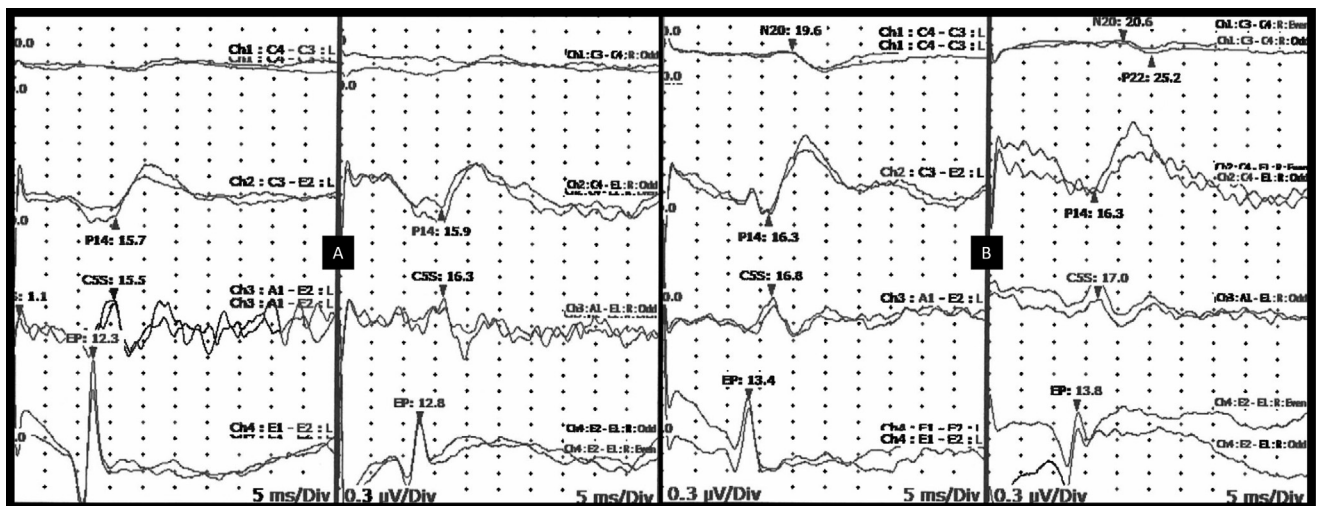


Fig. 2. Median nerve N20 somatosensory evoked potentials on day 4 (panel A) and day 13 (panel B) showing bilateral absence of the N20 response (channel 1). Of note, there is a low amplitude, reproducible N20 on day 13 (C4–C3 derivation in panel B). Vertical gain: $0.3 \mu\text{V/div.}$, high frequency filter: 10 kHz, low frequency filter: 10 Hz, Number of averaged responses: 500/limb, patient height: 68 in. *Montages:* Left median stimulation Channel 1 – Cp4 (contralateral sensory cortex) referenced to Cp3 (ipsilateral sensory cortex) Channel 2 – Cp3 (ipsilateral sensory cortex) referenced to E2 (right Erb's) Channel 3 – CSS (C5 – 5th cervical spinous process) referenced to E2 (right Erb's) Channel 4 – E1 (left Erb's) referenced to E2 (right Erb's) Right median stimulation Channel 1 – Cp3 (contralateral sensory cortex) referenced to Cp4 (ipsilateral sensory cortex) Channel 2 – Cp4 (ipsilateral sensory cortex) referenced to E1 (left Erb's) Channel 3 – CSS (C5 – 5th cervical spinous process) referenced to E1 (left Erb's) Channel 4 – E2 (right Erb's) referenced to E1 (left Erb's).

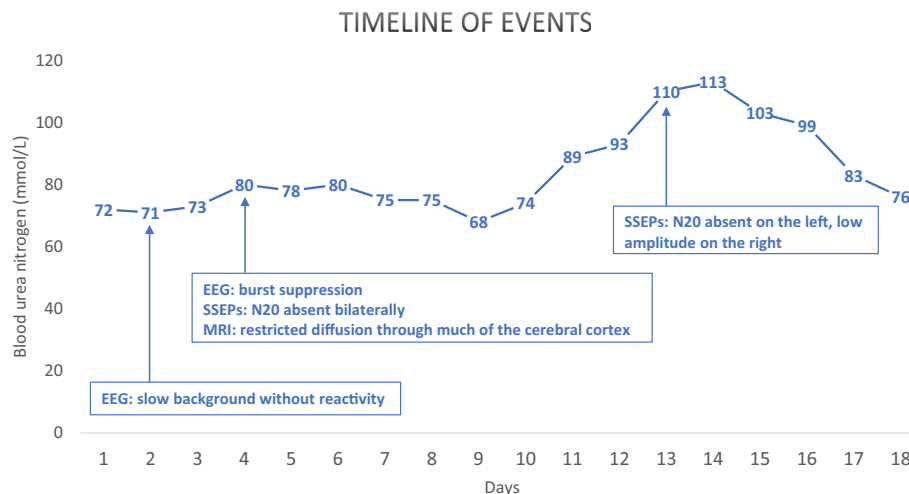


Fig. 3. Timeline of events during the patient's hospitalization. The patient's mental status improved modestly despite worsening uremia. The patient was discharged to an inpatient hospice facility on day #18.

BUN. Over the next few days, there was modest improvement in uremia and severity of encephalopathy: at best, her GCS was 11, she had spontaneous eye opening, grimaced and moaned incomprehensibly to pain, had roving eye movements, reactive pupils, and a positive corneal reflex; however, she did not follow simple commands and did not show any signs of meaningful awareness of the environment. Due to improving mental status, SSEPs were repeated on day 13: the N20 was absent on the left and there was a low amplitude, reproducible N20 on the right. After a discussion of the goals of care, she was transferred to comfort care, but unfortunately died several days later, presumably due to complications from acute kidney injury, as her last serum potassium was 7.0 mmol/L.

3. Discussion

Hypoglycemic encephalopathy may present in varying severities and is not uniformly associated with poor outcome. In a retrospective study of 165 patients, 77% had a good outcome (i.e., Glasgow outcome score of 5) (Ikeda et al., 2013). Table 1 lists clinical and imaging parameters associated with outcomes in case series and small retrospective studies. Unfortunately, there are no high-quality evidence-based clinical, neurophysiologic, or imaging variables available to aid in neurologic outcome prediction. In our practice we use a multimodal approach to neurologic prognostication in hypoglycemic encephalopathy, similar to that used in coma after cardiac arrest that includes SSEPs, EEG, and brain MRI.

The basis for using SSEPs is largely extrapolated from the CRA literature. In coma after CRA, bilateral absence of the median nerve N20 cortical response is reportedly associated with a false positive rate (FPR) for poor outcome of 0.5% (Rossetti et al., 2016). Should practitioners extrapolate the prognostic significance of bilateral N20 loss to non-hypoxic encephalopathies? Given the parallels in pathophysiology between hypoglycemic and hypoxic encephalopathy, this might seem reasonable as hypoglycemic encephalopathy has several parallels with anoxic brain injury including sudden onset of cerebral energy failure, overlapping anatomical distribution of brain injury, coma, and frequently, a poor outcome (Languren et al., 2013; Witsch et al., 2012; Barbara et al., 2017; Ikeda et al., 2013). At autopsy, patients with prolonged coma from

severe hypoglycemia had extensive necrosis of cerebral cortex (Kalimo and Olsson, 1980; Auer and Siesjö, 1988). Similarly, comatose survivors of cardiac arrest with bilaterally absent N20s also had extensive necrosis of cerebral cortex at autopsy whereas those with N20s that were present, did not (Rothstein, 2000). In the absence of stronger outcome data in hypoglycemic encephalopathy, we are left to extrapolate based on these principles.

There is one other case report describing the use of SSEPs in hypoglycemic encephalopathy (Appoloni et al., 2003). Appoloni et al. report a diabetic patient who developed status epilepticus from hypoglycemia. She remained comatose once seizures resolved and nine days later, was found to have bilateral absence of the N20 responses. The patient gradually recovered consciousness and the study was repeated one month later and showed a unilateral presence of the N20 response.

We include routine EEG and brain MRI in our multimodal approach to prognostication in hypoglycemic encephalopathy. With regard to EEG, there are no studies that correlate specific EEG patterns with clinical outcome in hypoglycemic encephalopathy; however, in a cohort study of 262 patients with acute nonhypoxic encephalopathy (including those with metabolic encephalopathy), nonreactive EEG background was an independent predictor of death (Sutter and Kaplan, 2016). EEG can identify periodic patterns or seizures which, if successfully treated may have an impact on outcome. In this patient, the lack of background reactivity and burst suppression pattern provide additional evidence that the outcome is likely to be poor. Brain MRI is an increasingly used modality for prognostication in coma after CRA. A recent review concluded that diffusion restriction (i.e., cytotoxic edema) affecting >10% of the cerebral cortex is associated with poor outcome (Keijzer et al., 2018). Anoxic brain injury and hypoglycemic encephalopathy may both cause diffusion restriction in the cerebral cortex, cerebral white matter tracts, and basal ganglia (Johkura et al., 2012; Ma et al., 2009; Kang et al., 2010). Although there are no quantitative studies, case series describe poor outcomes in patients with widespread cortical and/or white matter injury in hypoglycemic encephalopathy (Table 1). For this reason, we feel that a brain MRI with extensive burden of cytotoxic edema, as in this patient's case, likely portends a poor prognosis, if this were to be extrapolated from the CRA literature.

Prognostication in hypoglycemic encephalopathy warrants gathering relevant clinical data as outlined in Table 1, which with the results of brain MRI, SSEPs, and routine EEG enables an estimate of the severity of brain injury. As the literature is largely based on small studies or case reports, and is extrapolated from the CRA literature, we caution against prognostication and disposition including the withdrawal of care, to avoid a self-fulfilling prophecy.

4. Conclusions

Data from small studies indicate a wide variability in outcomes in hypoglycemic encephalopathy. Some patients recover with little or no residual impairment while others die or remain in a vegetative state. We recommend a multimodal approach that includes brain MRI, EEG, and SSEPs for prognostication in hypoglycemic encephalopathy. Further study of the contribution of various clinical, serum, brain imaging, and electrophysiological parameters on outcome in hypoglycemic encephalopathy are needed to improve prognostic accuracy.

Declaration of Competing Interest

Dr. Gugger, none; Dr. Geocadin reports receiving funding from the NIH for studies on brain injury after cardiac arrest; Dr. Kaplan

Table 1
Variables to consider in prognostication of hypoglycemic encephalopathy.

Parameter associated with poor prognosis	Source of data
History of diabetes	Series of 49 patients with hypoglycemic encephalopathy (Barbara et al., 2017)
Any level of baseline disability (modified Rankin scale score of ≥ 1)	
Severity of hypoglycemia	Series of 49 (Barbara et al., 2017) and 165 (Ikeda et al., 2013) patients with hypoglycemic encephalopathy, respectively
Duration of hypoglycemia (i.e., several hours)	
Normal temperature and lactic acid value	Series of 165 patients with hypoglycemic encephalopathy (Ikeda et al., 2013)
Abnormal brain imaging, in particular widespread DWI lesions affecting cerebral cortex and/or hemispheric white matter	Three small studies in hypoglycemic encephalopathy including 15 (Ma et al., 2009), 20 (Barbara et al., 2017), and 23 (Johkura et al., 2012) patients, respectively
Unreactive EEG	Series of 262 patients with non-hypoxic encephalopathy (Sutter and Kaplan, 2016) and cardiac arrest literature (Rossetti et al., 2016)
Bilateral absence of N20	Cardiac arrest literature (Rossetti et al., 2016)

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