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## Case Report

# Metabolic Encephalopathy vs Seizures: Distinguishing between Triphasic Waves and Epileptiform Discharges - Ⓜ

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## ABSTRACT

Continuous Video EEG (cVEEG) monitoring is often utilized in the evaluation of impaired consciousness. Non convulsive seizures may be distinguished from encephalopathies in this manner. However, Triphasic Waves (TWs), commonly associated with metabolic dysfunction, may assume a pattern concerning for epileptiform activity, calling into question the presence of electrographic seizures, and thus requiring further assessment for elucidation. The following case describes the transient resolution of quasiperiodic TWs after acute administration of glucose in a patient with hypoglycemic encephalopathy.

**Keywords:** Triphasic Waves; Encephalopathy; Seizures; EEG; Hypoglycemia

## ABBREVIATIONS

cVEEG: Continuous Video EEG; NCSE: Non Convulsive Status Epilepticus; TWS: Triphasic Waves

## INTRODUCTION

Continuous Video EEG (cVEEG) monitoring is often utilized in the evaluation of impaired consciousness. Non convulsive seizures may be distinguished from encephalopathies in this manner. However, Triphasic Waves (TWs), commonly associated with metabolic dysfunction, may assume a pattern concerning for epileptiform activity, calling into question the presence of electrographic seizures, and thus requiring further assessment for elucidation. The following case describes the transient resolution of quasiperiodic TWs after acute administration of glucose in a patient with hypoglycemic encephalopathy.

## CASE

A 66 year old woman with type 1 diabetes mellitus presented with decreased responsiveness after being found at home by a friend. She was subsequently intubated upon arrival of emergency medical services. She was stuporous. Cranial nerves were intact. All four extremities withdrew to noxious stimulation. Plantar responses were flexor. In the hospital, MRI brain exhibited leptomeningeal enhancement consistent with meningitis. Serum blood glucose was 392 mg/dL, with a corresponding CSF glucose of 16mg/dL. Studies from CSF were positive for *Streptococcus pneumoniae*, and the patient was treated with penicillin G for a total of 14 days after initially receiving empiric treatment with vancomycin, ampicillin and cefepime for 2 days. Three weeks after hospital admission and one week status post completion of antibiotics, her mental status fully returned to baseline. However, during recovery, she developed sudden onset stupor. A CT head was negative for acute pathology, as was subsequent MRI brain, which no longer demonstrated leptomeningeal enhancement. Laboratory evaluation was significant for low blood glucose (50 mg/dL) (Figure 1). She underwent cVEEG monitoring. The EEG showed generalized, polymorphic delta/theta slowing intermixed with TWs that demonstrated a quasiperiodic pattern (Figure 2). During cVEEG, TW activity fluctuated, with the emergence of increasing frequencies, coinciding with worsening hypoglycemia, and a blood glucose nadir of 14mg/dL (Figure 3). Electrographic activity was not induced or exacerbated by tactile or auditory stimulation. Administration of 50 ml of D50 (25 g D - glucose) at bedside resulted in transient resolution of TWs within minutes, which corresponded to a blood glucose of 64 mg/dL (Figure 4). However, background slowing remained on cVEEG, with gradual re-emergence of infrequently occurring TWs despite normoglycemia (Figure 5). Mental status returned to baseline approximately 72 hours after blood glucose stabilization. This was associated on cVEEG with gradual resolution of TWs and an increase in background frequencies.

## DISCUSSION

Triphasic Waves (TWs) have been described as early as the 1950s [1], and are commonly associated with metabolic encephalopathy [2]. The waveform is characterized by three phases: 1. an initial low amplitude negative deflection; 2. a dominant, high amplitude, steeply declining positive phase; and 3. a broad, slow rising component. Though greater than a half century of literature exists on TWs, controversies remain as to their definition, distinction from visually similar EEG activity, and significance. This leads to a diagnostic dilemma frequently encountered in the clinical setting: does the presence of TWs merely imply encephalopathy, or do they represent an ictal phenomenon such as Non Convulsive Status Epilepticus

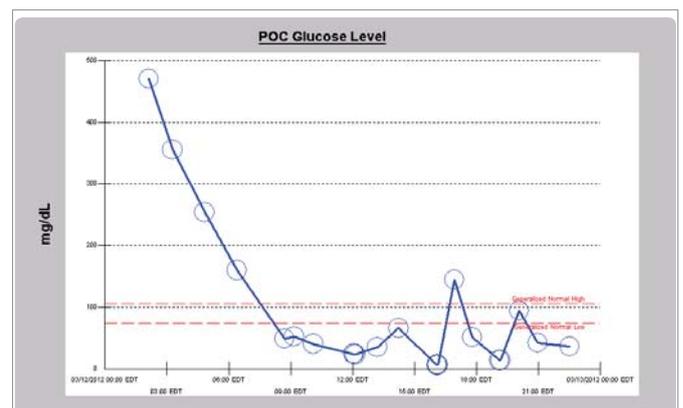


Figure 1: Blood glucose plot.

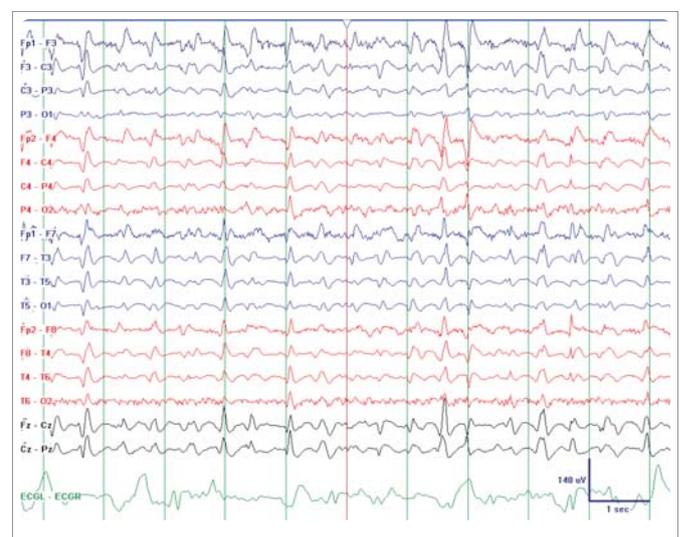


Figure 2: Initial EEG prior to administration of 25 g D - glucose.

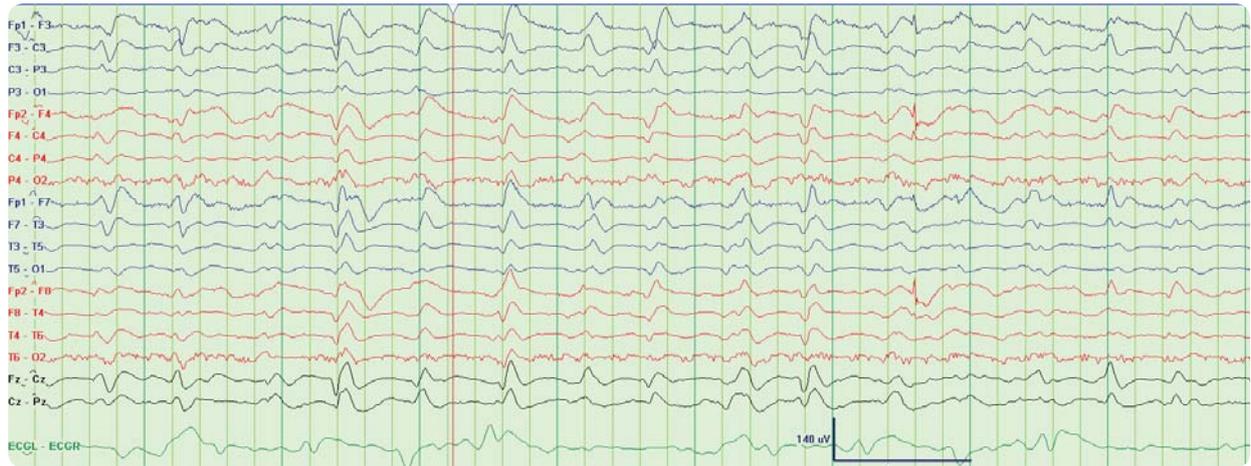


Figure 3: EEG at blood glucose nadir of 14 mg/dL.

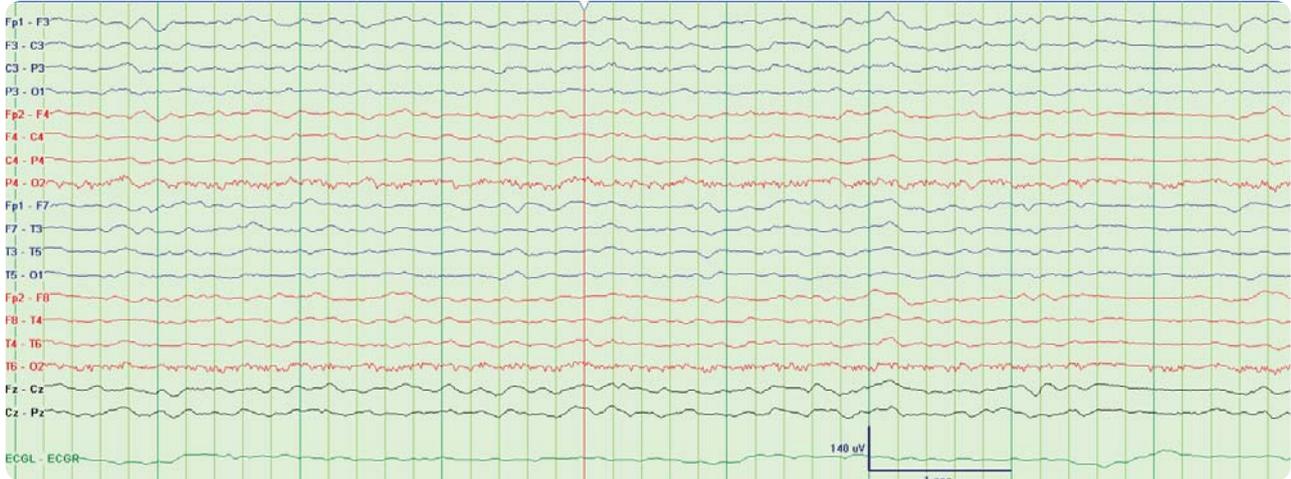


Figure 4: EEG with transient resolution of Triphasic waves after administration of 25 g D-glucose, with consequent normalization of blood glucose to 64 mg/dL.



Figure 5: EEG demonstrating occasionally re-emergent triphasic waves during normoglycemic periods. Blood glucose = 84 mg/dL.

(NCSE)?. Several attempts have been made to distinguish TWs from epileptiform activity. While an anterior-posterior lag has been classically described, this is not a reliable feature [3]. In a series of 87 EEGs from 71 patients, noxious or auditory stimulation increased the TWs in 51% of those with metabolic encephalopathy, while there was no effect in patients with NCSE [4]. Kaplan and Schlattman studied the EEG of a patient with genetic epilepsy with generalized frontocentral spike waves who simultaneously developed TWs due to hepatic failure [5]. In using the patient’s prior and current EEGs as a comparative control, objective criteria were posited to distinguish TWs from generalized epileptiform discharges. Based on their analysis, generalized spike waves were more narrow-angled, briefer and front polar dominant, while TWs were characterized by longer duration, a frontocentral predominance, and blunting of morphology with stimuli. More recently, in 2012, the American Clinical Neurophysiology Society published recommendations for standardization of EEG patterns encountered in the critical care setting [6]. Though primarily targeted for research use, this introduced greater objectivity into EEG interpretation. In this context, the term “Triphasic waves” was replaced with “continuous 2/s generalized



periodic discharges (with Triphasic morphology).” Criteria for identifying EEG patterns based on location, rhythmicity, periodicity, sharpness and baseline crossings, among other features, were established. In addition, the presence of unequivocal electrographic seizures and equivocal EEG patterns was acknowledged. While helpful in terms of defining clear criteria for electrographic seizures, the identification that an EEG pattern is equivocal leaves a clinician with the same diagnostic dilemma as previously mentioned. In the case described, this was the exact scenario that presented itself: altered mental status in a patient with quasiperiodic TWs (or continuous 2/s generalized quasiperiodic discharges with Triphasic morphology) on EEG. With the limitations of EEG interpretation as discussed above, the management of this equivocal EEG pattern required clinical intervention to elucidate its significance. Response to a benzodiazepine, which broadly suppresses EEG activity, would not electrographically distinguish whether this activity was an ictal or interictal phenomenon. Administration of a loading dose of an antiepileptic drug may have clarified the significance of EEG findings. However, electroencephalographic resolution would be delayed due to the time required for a drug’s pharmacologic actions to take effect. On the other hand, if hypoglycemia was the cause of the patient’s clinical condition and EEG activity, correction of the metabolic disturbance might be expected to ameliorate the quasiperiodic TWs, which it did, and in an immediate manner, thus avoiding unnecessary additional procedures or medications. Certain antibiotics, including *cephalosporins* and *penicillins*, have also been associated with TWs, encephalopathy and seizures [7]. As the patient had completed antibiotics one week prior to presentation with altered mental status, and as *cephalosporin’s* had last been administered for 2 days 3 weeks beforehand, antibiotic related encephalopathy was unlikely. Hypoglycemia does not necessarily result in TWs. TWs are a nonspecific phenomenon associated with multiple medical conditions, including but not limited to uremia, sepsis, hypercalcemia, hepatic failure, dementia, post anoxia, and toxic exposure (i.e., lithium) [3,8]. In hypoglycemia, many EEG patterns have been described in addition to TWs, and individual EEG patterns can vary widely without consistent correlation to blood glucose levels. Alpha frequencies may slow to the theta range at 50-80 mg/dL, and below 40 mg/dL, there may be a mixture of theta and delta frequencies with intermixed rhythmic delta activity [9,10]. Others have found that mental status is more closely related to the rate of blood glucose decline than absolute level [11]. In a study of 5 nondiabetic subjects monitored with quantitative EEG, EEG power and blood glucose was tracked before and after acute administration of insulin to induce hypoglycemia [12]. Twenty to 35 minutes after insulin infusion, EEG power increased in beta, theta and delta frequencies, which was associated with declining blood glucose levels and nadir. Triphasic waves were present on EEG during this time interval. Between 45 and 50 minutes, total EEG power fell below baseline at all frequencies, reaching its nadir, and was associated with rising glucose levels. Nonetheless, as demonstrated by the current

case, in certain individuals, hypoglycemia-associated Triphasic wave resolution may be demonstrated in the immediate setting with acute correction of blood glucose. This significantly affects the management of a patient presenting with altered mental status and TWs on EEG. Of note, however, the return of mentation to baseline may be delayed in comparison to EEG resolution of TWs, underscoring the fact that chronic effects from the inciting metabolic disturbance remain, and that EEG may lack the sensitivity and specificity to directly assess this.

## CONCLUSIONS

Quasiperiodic Triphasic wave activity due to hypoglycemia may be distinguished from electrographic seizures after acute correction of blood glucose, with corresponding transient resolution of Triphasic Waves. However, clinical response to correction of metabolic dysfunction may be delayed for up to 72 hours.

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