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*Review Article*

# Nonketotic Hyperglycaemia Induced Seizure: A Review

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Nonketotic hyperglycaemia-induced seizures (NKH) are rare but serious neurological complications of uncontrolled type 2 diabetes mellitus, often associated with poor glycaemic management. These seizures are unresponsive to traditional antiepileptic therapy but show significant improvement with metabolic correction using insulin and fluids. Nonketotic hyperglycaemia-induced seizures are rare but serious neurological complications of uncontrolled type 2 diabetes mellitus, often associated with poor glycaemic management. These seizures are unresponsive to traditional antiepileptic therapy but show significant improvement with metabolic correction using insulin and fluids. These seizures typically present as focal motor seizures that can progress to secondary generalized seizures with structural changes noted on MRI. Pathophysiological mechanisms include disruption of the GABA system, hyperosmolarity, and transient ischemia. NKH is characterized by severe hyperglycaemia (>200 mg/dL), dehydration, increased serum osmolarity, negative urinary ketones, and metabolic acidosis. Early detection and intervention are essential, as the condition carries a mortality rate exceeding 50%. Treatment involves glycaemic control through insulin therapy, rehydration with fluids, and correction of metabolic derangements. Nonketotic hyperglycaemia-induced seizures require prompt recognition and management to improve outcomes. Understanding the mechanisms and clinical features is critical for effective diagnosis and timely intervention, ultimately reducing the associated high mortality risk.

**Keywords**: Nonketotic hyperglycaemia, Hyperglycaemic seizure, Diabetes Mellitus, GABA system, Metabolic correction.

## INTRODUCTION

Non-ketotic hyperglycemia (NKH), frequently overlapping with the hyperosmolar hyperglycemic state (HHS), represents a severe and potentially life-threatening acute metabolic complication of diabetes mellitus characterized by profound hyperglycemia, marked plasma hyperosmolality, and little to no ketone production. Unlike diabetic ketoacidosis (DKA), the relative absence of significant ketosis in NKH can delay clinical recognition, thereby increasing the risk of underdiagnosed or misdiagnosed neurological complications. Among these, seizures are an important but often under-recognized manifestation and may be the initial presenting symptom in some patients with otherwise undetected or poorly controlled diabetes [1,2]. Seizures associated with NKH are typically focal in nature, commonly presenting as focal motor seizures or, less frequently, Epilepsia partialis continua, and may secondarily generalize into tonic–clonic activity in a subset of cases [1,3,9]. These seizures often show relative resistance to conventional antiepileptic drugs (AEDs) while the metabolic derangement persists, yet tend to resolve rapidly and completely following correction of hyperglycaemia, plasma osmolality, and electrolyte balance, underscoring their predominantly metabolic

rather than structural etiology [11]. In clinical practice, this syndrome may closely mimic acute stroke or de novo primary epilepsy, raising the risk of misdiagnosis and unnecessary long-term AED therapy if the underlying hyperglycemic crisis is not promptly identified [3,4,5]. The exact mechanisms underlying NKH-induced seizures are not fully elucidated but are believed to involve multiple interrelated factors, including intracellular dehydration and altered neuronal membrane potentials due to hyperosmolarity, impaired inhibitory neurotransmission (particularly depletion or dysfunction of GABAergic pathways), and cerebral ischemia secondary to hyper viscosity and reduced regional perfusion [8]. These disturbances converge to lower the seizure threshold and promote focal cortical hyperexcitability, especially in posterior cortical regions such as the occipital and parietal lobes, where imaging abnormalities are frequently observed. Diagnosis therefore requires a high index of clinical suspicion in adults with diabetes who present with new-onset focal or continuous focal motor seizures, markedly elevated blood glucose levels, minimal or absent ketosis, and absence of clear structural brain lesions on initial imaging [6,7,9]. Neuroimaging often reveals transient cortical or subcortical hyperintensities, particularly in the occipital and parietal territories, while electroencephalography (EEG) typically shows focal or generalized slowing, focal epileptiform discharges, or non-specific changes that tend to improve after metabolic correction, reinforcing the reversible nature of the syndrome. Management centers on prompt and controlled correction of the underlying hyperglycemic crisis using intravenous fluid resuscitation, low-dose intravenous insulin, and careful electrolyte replacement, with the understanding that seizures usually subside once metabolic homeostasis is restored [10]. Long-term antiepileptic therapy is generally not required unless there is independent evidence of a structural or primary epileptic disorder, and early recognition and intervention are therefore essential to prevent complications such as prolonged status epilepticus, cerebral edema, thromboembolic events, and death. This review aims to provide a comprehensive, evidence-based synthesis of NKH-associated seizures emphasizing their clinical presentation, pathophysiological underpinnings, diagnostic challenges, and therapeutic strategies to improve awareness among clinicians and reduce the risk of misdiagnosis and inappropriate long-term treatment [1,2,8].

## Epidemiology and Clinical Burden

### Prevalence and setting

NKH itself occurs in roughly 10-25% of hyperglycemic emergencies, predominantly in patients with type 2 diabetes, and carries a mortality rate of about 10-20% in modern series. Among patients with NKH, acute seizures are reported in approximately 10-25%, usually as focal motor or epilepsia partialis continua-like events rather than generalized tonic-clonic seizures [1,2,3,4].

### Age, sex, and comorbidities

Focal NKH-induced seizures are most frequently described in middle-aged to elderly adults (often >50-60 years), reflecting the demographic with long-standing, poorly controlled type 2 diabetes. Several case series report a mean age around 60-65 years, with no consistent strong sex bias, although some cohorts show a slight male predominance. Common comorbidities include hypertension, coronary artery disease, and chronic kidney disease, which may both predispose to and complicate NKH [1,2,4].

### Geographical and health-system patterns

NKH and NKHIS are reported worldwide but appear more commonly in regions with high prevalence of late-diagnosed or poorly managed type 2 diabetes, including South Asia, sub-Saharan Africa, and some Middle Eastern countries. In resource-limited settings, delayed presentation, limited access to glucose monitoring, and variable insulin availability contribute to higher rates of NKH and its neurological complications [1,2,4].

## Pathophysiology and Mechanisms Of Seizures

Seizures in non-ketotic hyperglycemia (NKH) are now widely regarded as a multifactorial acute symptomatic phenomenon, resulting from the interplay of hyperglycemia, hyperosmolarity, electrolyte shifts, and secondary cerebral ischemia,

rather than from a single isolated mechanism. Neuroimaging and clinical series increasingly support the concept that these metabolic stressors transiently alter cortical excitability and neuronal-network synchrony, particularly in posterior cortical regions, leading to focal hyperexcitability and reversible seizures once the hyperglycemic crisis is corrected [12,13].

- **Hyperosmolarity and neuronal dehydration**

Extremely high plasma glucose (>600 mg/dL) markedly elevates serum osmolality, creating a strong osmotic gradient that draws water out of neurons and into the extracellular space, thereby causing cellular dehydration and shrinkage. This osmotic stress disturbs ion-pump function and transmembrane ion gradients, which in turn destabilizes neuronal membrane potential and lowers the seizure threshold, particularly in structurally metabolically active cortical areas such as the occipital and parietal lobes. Transient neuronal hyperexcitability provoked by such hyperosmolar dehydration is thought to underlie the focal, often hemispheric-onset, seizure patterns observed in NKH [14].

- **Glucose driven energy and inhibition imbalance**

Hyperglycemia-induced downregulation of oxidative metabolism can impair Krebs-cycle activity and reduce ATP-dependent neuronal processes, creating a state of relative energy stress in the brain despite abundant glucose. In NKH, this energetic imbalance may favor catabolism of γ-aminobutyric acid (GABA), deplete inhibitory neurotransmitter pools and shift the local cortical milieu toward net excitation. Reduced GABAergic tone removes an important inhibitory brake on cortical networks, thereby lowering the seizure threshold and promoting focal or generalized epileptiform activity [12].

- **Absence of ketosis and loss of neuroprotection**

In contrast to diabetic ketoacidosis, NKH is defined by severe hyperglycemia without significant ketosis, depriving the brain of ketone-derived metabolic substrates and regulatory effects. Experimental and clinical observations suggest that ketone bodies such as β-hydroxybutyrate exert mild neuroprotective and anti-excitatory actions by modulating synaptic activity and chromatin-associated pathways; their absence in NKH may therefore unmask or exacerbate hyperglycemia-induced cortical hyperexcitability. This lack of endogenous ketone-mediated modulation may contribute to the selective vulnerability of certain cortical regions to seizures during prolonged non-ketotic hyperglycemia [12].

- **Electrolyte disturbances**

Chronic hyperglycemia and osmotic diuresis commonly lead to hyponatremia or pseudohyponatremia, hypokalemia, and hypomagnesemia, which directly alter neuronal membrane potential and impulse propagation. In a broader review of acute symptomatic seizures, electrolyte disturbances particularly severe hyponatremia and hypomagnesemia are strongly associated with lowered seizure thresholds and transient cortical hyperexcitability. In the setting of NKH, these electrolyte perturbations likely amplify the intrinsic hyperexcitability generated by hyperosmolarity and metabolic stress, contributing to the onset and persistence of focal seizures [15].

- **Cerebral ischemia and microvascular injury**

Hyperglycemia-associated hyper viscosity, endothelial dysfunction, and microangiopathy may impair regional cerebral perfusion, especially in watershed and posterior cortical territories, leading to transient ischemic-type stress and reversible cytotoxic edema. A systematic review of stroke-like deficits in NKH-hyperosmolar states attributes many acute neurological signs to metabolic neuronal dysfunction rather than structural infarction, with hyperglycemia itself inducing hypoperfusion-like changes and cortical vulnerability. These ischemia-like microvascular insults may create transient epileptogenic foci, explaining the frequent occipital-lobe-predominant electroclinical seizure patterns seen in NKH-related seizures [16].

- **Insulin-deficient brain metabolism**

Dysfunction in insulin signalling due to hypoinsulinemia, insulin resistance, or chronic hyperglycemia can impair glucose uptake and utilization in certain insulin-sensitive neuronal

populations, generating a state of functional "cerebral energetic stress" despite systemic hyperglycemia. This metabolic mismatch promotes oxidative stress, mitochondrial dysfunction, and alterations in ion-channel behaviour, all of which enhance neuronal hyperexcitability and seizure susceptibility. Emerging evidence linking insulin-pathway dysregulation with epilepsy-like hyperexcitability provides a mechanistic basis for the metabolic origin of seizures in NKH [17].

- **Blood-brain barrier and ionic shift**

Hyperosmolarity and sustained hyperglycemia have been shown to transiently disrupt the blood-brain barrier, increasing capillary permeability and permitting leakage of water and ions into the brain parenchyma. In patients with NKH-related seizures, delayed gadolinium enhancement on MRI has been observed in affected cortical regions, suggesting blood-brain barrier breakdown coincides with focal hyperintensity and neurological symptoms. Disruption of the barrier is known to promote seizures in its own right, as it allows abnormal shifts in extracellular calcium, potassium, and pH, which can depolarize neuronal membranes and synchronize large cortical ensembles, precipitating focal seizures [18,19].

## CLINICAL FEATURES AND PHENOTYPES

- **Systemic features of NKH**

Extreme hyperglycemia is a hallmark of non-ketotic hyperglycemia (NKH), with blood glucose levels typically exceeding 600 mg/dL (33 mmol/L) and often reaching 800–1000 mg/dL in severe episodes. Plasma osmolality is usually elevated above 320 mOsm/kg, frequently ranging between 330 and 350 mOsm/kg, reflecting the profound hyperosmolar state. Unlike diabetic ketoacidosis, NKH shows absent or minimal ketosis and no significant metabolic acidosis; arterial pH is often normal or mildly alkalotic, emphasizing the relative lack of ketone-driven acid–base disturbance [2,13,14]. Dehydration is a consistent systemic feature, manifesting clinically as dry mucous membranes, hypotension, tachycardia, poor skin turgor, and elevated blood urea nitrogen (BUN) and creatinine due to prerenal azotemia. Mental status changes commonly precede or accompany seizures, including drowsiness, confusion, or obtundation, which may fluctuate but generally improve as glucose and osmolality normalize [2].

- **Seizure semiology**

- **Focal motor seizures**: The most frequent seizure pattern in NKH-induced seizures is focal motor activity, characterized by unilateral or focal clonic or rhythmic jerking of one limb, the face, or one hemi body, often persisting for minutes to hours. Case series focusing on NKH-related epilepsy report that approximately 75–85% of seizures in this context are focal motor in nature, underscoring their central role in the clinical phenotype [4].

- **Occipital-lobe-type seizures**: Occipital-lobe-origin seizures may present with visual hallucinations (such as flashes, shapes, or colours), other elementary visual phenomena, or transient homonymous hemianopia, often heralding an occipital-onset seizure. These visual auras can occur before or alongside focal motor seizures and are liable to be mistakenly interpreted as a posterior circulation stroke or migraine aura in the absence of metabolic clues [4].

- **Epilepsia partialis continua (EPC) and focal status epilepticus**: Epilepsia partialis continua—continuous or near-continuous focal motor activity (e.g., repetitive twitching of a hand or face)—represents a relatively rare but pathognomonic presentation of NKH-related seizures. NKH-associated EPC or focal status epilepticus typically lasts hours to days and usually resolves within 24–72 hours after correction of hyperglycemia and plasma osmolality, reinforcing its metabolic basis [20].

- **Generalized seizures**: Generalized tonic–clonic seizures are reported in NKH but are far less common than focal events; they may represent secondary generalization of an already established focal onset or arise from more diffuse metabolic encephalopathy. When generalized seizures occur in the setting of NKH, they often coexist with other systemic features of hyperglycemic crisis and may be less responsive

to antiepileptic drugs until glucose levels are controlled [13,21].

- **Postictal features**: Postictal confusion, transient focal deficits resembling Todd's paresis, or transient cortical blindness can accompany NKH-related seizures but are usually short-lived and resolve as blood glucose and osmolality return to normal ranges. The reversibility of these postictal phenomena, together with normalization of imaging and EEG findings, supports the concept of transient, metabolic-induced cortical dysfunction rather than permanent structural injury in most patients [22].

## Diagnosis

The diagnostic process hinges on maintaining a high index of clinical suspicion, particularly in adults with known or newly recognized diabetes who present with new-onset focal seizures, altered mental status, recurrent focal motor activity, or continuous focal twitching, all in the setting of markedly elevated blood glucose but without significant ketosis. Prompt recognition is essential, as delayed diagnosis may lead clinicians toward inappropriate long-term antiepileptic therapy instead of targeted correction of the underlying hyperglycemic crisis [23, 24,25]. Laboratory evaluation typically reveals blood glucose levels exceeding 600 mg/dL, reflecting severe hyperglycemia, although some case series describe patients with "moderate hyperglycemia" that still falls clearly within the NKH spectrum. Serum osmolality is usually elevated above 320 mOsm/kg, often ranging between 330 and 350 mOsm/kg, consistent with the hyperosmolar nature of the syndrome. Serum and urinary ketones are absent or minimal, and arterial blood gas analysis commonly shows normal or mildly alkalotic pH without major anion-gap metabolic acidosis, which helps distinguish NKH from diabetic ketoacidosis. Dehydration-related abnormalities such as elevated blood urea nitrogen (BUN) and creatinine, along with variable hyponatremia or pseudohyponatremia, frequently accompany the hyperglycemic state and provide further support for a metabolic emergency rather than an isolated epileptic disorder [23,25]. Neuroimaging findings are not uniform but add critical context once the metabolic picture is established. MRI often reveals transient cortical or subcortical hyperintensities on T2/FLAIR sequences, most commonly in the occipital and parietal regions, with restricted diffusion on diffusion-weighted imaging in some cases, reflecting reversible cytotoxic or hypoperfusion-like changes. These abnormalities frequently resolve or markedly improve after correction of glucose and osmolality, reinforcing the notion that they represent a metabolic, rather than structural, lesion. By contrast, non-contrast CT of the head is frequently normal or only mildly abnormal, which underscores the importance of not relying on CT alone to exclude NKH-related seizures and highlights the need for MRI when the clinical and metabolic picture suggests a reversible metabolic encephalopathy [25,26]. Electroencephalography plays a complementary role but does not provide a pathognomonic pattern. Routine EEG in patients with NKH-related seizures may show focal or generalized slowing, focal epileptiform discharges over posterior or lateral cortical regions, or non-specific triphasic-like waves, without characteristic features that are unique to NKH alone. The EEG background and focal abnormalities often improve or normalize after normalization of blood glucose and plasma osmolality, further supporting the idea that the seizures are acute symptomatic phenomena rather than evidence of an underlying primary epileptic focus. In selected cases, repeat EEG after metabolic correction or video-EEG monitoring can help distinguish residual epileptic activity from transient metabolic encephalopathy, guiding decisions about whether short-term antiepileptic therapy is warranted [24,25].

## Treatment

The management of NKH induced seizures is primarily directed toward rapid but controlled correction of the underlying hyperglycaemic and hyperosmolar state. Unlike primary epilepsy, the seizures associated with NKH are often acute symptomatic events and may respond poorly to conventional antiseizure medications when the metabolic abnormality remains uncorrected. Therefore, restoration of metabolic homeostasis with fluid therapy, insulin and appropriate electrolyte replacement constitutes the cornerstone of treatment. Published clinical series have demonstrated that

seizures frequently resolve following correction of hyperglycaemia and dehydration. [26,27]

**1. Initial stabilization**

Patients presenting with seizures and suspected NKH should initially undergo standard emergency assessment, including evaluation of airway, breathing and circulation. Blood glucose should be measured immediately, followed by assessment of vital signs, neurological status, capillary blood glucose, serum electrolytes, renal function, serum osmolality, venous or arterial blood gas and ketone levels. [27,28,29] Continuous cardiac monitoring is advisable in patients with significant electrolyte abnormalities or severe hyperosmolarity. The precipitating cause of the hyperglycaemic crisis should also be identified. Common triggers include infection, inadequate diabetes treatment, newly diagnosed diabetes, acute illness, corticosteroid therapy and other physiological stresses. Treatment of the precipitating condition is an important component of recovery. If a seizure is prolonged or meets criteria for status epilepticus, emergency seizure management should be initiated according to standard status epilepticus protocols. [27,28]

**2. Fluid replacement**

Fluid replacement is the initial component of therapy because patients with severe hyperglycaemia commonly have substantial water and electrolyte deficits resulting from osmotic diuresis, which should be corrected with intravenous isotonic fluids. Fluid therapy restores intravascular volume, improves tissue perfusion and contributes to a gradual reduction in serum glucose and osmolality. Intravenous 0.9% sodium chloride or an appropriate isotonic crystalloid may be initiated, with the rate individualized according to age, haemodynamic status, cardiac function and renal function. In patients without significant cardiac or renal compromise, an initial rate of approximately 500–1000 mL/hour during the first 2–4 hours may be considered, followed by adjustment according to clinical response and corrected sodium/osmolality. Fluid administration should be controlled carefully in older adults and in patients with heart failure or kidney disease because excessive rapid volume administration can result in pulmonary oedema and other complications. The objective is not merely normalization of blood glucose but gradual restoration of circulating volume and reduction of serum osmolality. Excessively rapid correction of hyperosmolarity should be avoided because it may increase the risk of neurological complications. [30,31]

**3. Intravenous insulin therapy**

Insulin is essential for correcting the underlying hyperglycaemic state by reducing the elevated blood glucose levels. In Hyperosmolar Hyperglycaemic State (HHS) without significant ketonaemia or acidosis, a fixed-rate intravenous short-acting insulin infusion at approximately 0.05 units/kg/hour is recommended. If significant ketonaemia or metabolic acidosis is present, suggesting a mixed DKA/HHS presentation, an insulin infusion of 0.1 units/kg/hour is generally recommended. [29,30] Insulin should be administered with close monitoring of blood glucose and serum electrolytes. In patients with profound dehydration, initial fluid replacement is particularly important because insulin administration before adequate volume restoration may produce an excessive fall in plasma osmolality and may worsen circulatory instability. Once plasma glucose falls substantially, dextrose-containing fluids may be introduced to prevent hypoglycaemia while insulin is continued until the hyperosmolar metabolic disturbance has adequately resolved. The reduction in blood glucose should be controlled rather than excessively rapid because an abrupt fall in serum osmolality may increase the risk of neurological complications. Therefore frequent glucose measurements are necessary during intravenous insulin therapy. Once the acute metabolic crisis has resolved, insulin therapy can be transitioned to an appropriate subcutaneous regimen based on the patient's diabetes status and long-term glycaemic requirements. [31,32,35]

**4. Potassium and electrolyte replacement**

Electrolyte disturbances should be identified and corrected during treatment. Total body potassium is usually depleted in severe hyperglycaemic states because of osmotic diuresis, even when the initial serum potassium concentration is normal or elevated. Potassium requires particular attention because insulin administration promotes intracellular movement of potassium and can precipitate or worsen

hypokalaemia. Serum potassium should therefore be assessed before and repeatedly during insulin treatment. If significant hypokalaemia is present, potassium replacement and appropriate adjustment or temporary delay of insulin therapy may be necessary according to the patient's biochemical status and established hyperglycaemic-crisis protocols.

- Potassium <3.5 mmol/L: potassium replacement should be initiated and insulin therapy delayed until the potassium concentration is safely corrected.
- Potassium 3.5–5.0 mmol/L: potassium can generally be added to intravenous fluids to maintain serum potassium within approximately 4–5 mmol/L.
- Potassium >5.0 mmol/L: potassium replacement is usually withheld initially, with frequent reassessment.

Sodium and other clinically significant electrolyte abnormalities should also be monitored and corrected appropriately. The precise replacement regimen should be individualized according to renal function, urine output, ECG findings and local institutional protocols. The 2024 consensus report recommends frequent potassium monitoring during treatment because potassium levels can fall considerably following insulin administration. Other electrolyte abnormalities should also be corrected when clinically significant. Routine phosphate replacement is not generally required unless severe hypophosphataemia is associated with clinical complications. [28,31,32]

**5. Management of seizures**

Correction of hyperglycaemia and dehydration is the most important intervention for NKH-associated seizures. Evidence from case series indicates that these seizures may be resistant to conventional antiseizure treatment but frequently improve after insulin therapy and rehydration. For an actively ongoing convulsive seizure or status epilepticus, standard emergency seizure management should not be delayed. A benzodiazepine may be administered as first-line therapy according to institutional status epilepticus protocols. Persistent seizures may require a second-line antiseizure medication such as levetiracetam, fosphenytoin/phenytoin or sodium valproate should be selected according to the patient's clinical condition, organ function, drug interactions and contraindications. [35,36] In NKH, antiseizure medication should therefore be considered an adjunct when seizures are prolonged, recurrent or refractory rather than a substitute for correction of the metabolic abnormality. Routine prolonged antiseizure therapy is generally unnecessary once the metabolic abnormality has been corrected and the patient has returned to the neurological baseline. Continued therapy may be considered when seizures persist despite metabolic correction, neuroimaging demonstrates an underlying structural lesion, EEG suggests an independent epileptic disorder, or another persistent risk factor for recurrent seizures is identified. [37,38].

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