Seizures and non-ketotic hyperglycemia

Onset of epileptic seizures in patients aged 50 years or more suggests a lesional origin as an initial hypothesis. Nonetheless, these seizures may be related to a metabolic disorder, such as nonketotic hyperglycemia in diabetes (generally type 2), whether diagnosed or not. The association of nonketotic hyperglycemia and epileptic seizures was first observed in 1965. Since then, several studies and retrospective series have described such a neuroendocrine entity, which must be recognized rapidly to prevent any delay in treatment and to avoid possible serious morbidity or even death. The severity of nonketotic hyperglycemia can vary widely, ranging from asymptomatic (for months, even years) to severely symptomatic (hyperosmolar coma and sometimes even death). Its rapid recognition is vital because treatment with insulin and rehydration can prevent negative outcomes. Diagnosis is also essential for management of the seizures because they are usually refractory to antiepileptic agents, and some treatments (phenytoin) may even aggravate them. These seizures nonetheless stop spontaneously after hyperglycemia is corrected.

Epidemiology

Physicians must be aware that in patients with type 2 diabetes, epilepsy is often associated with nonketotic hyperglycemia. Although rates vary with the studies, we can estimate the frequency of onset of epileptic seizures in patients with nonketotic hyperglycemia at 25%. They occur mostly in patients 50 years or older, although several cases have been described in children. Different studies report that men or women predominate. In more than half the cases, seizures reveal previously undiagnosed diabetes, and they are sometimes preceded by polyuria and polydipsia.

In patients with known diabetes, such seizures demonstrate diabetic decompensation.
Clinical Manifestations

Several types of epileptic seizures have been observed in nonketotic hyperglycemia. They rarely begin as generalized tonic-clonic seizures, but often as partial seizures that generalize secondarily. Indeed, these seizures, especially motor seizures, are most often partial, and they may be followed by a postictal motor deficit. They may be tonic, clonic, tonic-clonic, and affect limbs, the face, or one half of the body. They are sometimes elicited or set off by movement, even passive or active elevation of a limb (arm or leg). The seizures are then followed by a refractory period during which movement will not provoke a seizure. Visual seizures have been described, in the form of colored flashes or, more rarely, elaborate hallucinations, sometimes associated with versive phenomena of the eyes and head. There are also anecdotal reports of aphasics (associated most often with partial motor effects), pilomotor, and gyrotary seizures. Epileptic seizures associated with nonketotic hyperglycemia are often recurrent, and states of “petit mal” are seen in the form of epilepsia partialis continua (EPC). In these cases, the seizures tend to occur at an early stage of hyperglycemia, while osmolarity is still normal or only slightly elevated. They stop when hyperosmolar coma starts, and the prognosis is then unfavorable.

Seizures usually stop once hyperglycemia is under control. The time elapsed between control and seizure cessation ranges from 24 hours to several days; it averaged 4 days in the studies by Lammouchi et al. Neurological examination of these patients is usually normal, although some have peripheral neuropathies, probably related to the length of time they have had diabetes. In some cases, reversible motor deficits of varying magnitude can occur. Some authors interpret this as a secondary deficit in the wake of a seizure (Todd paralysis) and others as possible transient cerebral ischemia.

Work-up

Mean blood glucose readings around 30 mmol/L with values ranging from 15 to more than 50 mmol/L were, in the latter case, sometimes associated with severe disturbances of consciousness or even coma. Plasma osmolarity was normal or slightly elevated, and a substantial rise signals deterioration leading toward hyperosmolar coma. Serum sodium is normal or only slightly elevated, but hyponatremia has been observed, especially in EPC. The duration of EPC in these patients is prolonged, and hyponatremia is probably an aggravating factor in such cases. EEG during seizure confirms the diagnosis. The absence of periodic lateralized epileptiform discharges, reported in various studies in the literature, tends to speak against an acute ischemic origin for these seizures. EEG between seizures is usually normal, but may show localized anomalies, especially in the rare cases where there is an underlying focal cortical lesion. Cerebral imaging is usually normal. A focal morphologic abnormality suggests a preexisting underlying lesion or recent vascular accident related to hyperglycemia. Partial epilepsy may continue in such settings, driven by the hyperglycemia. Anomalies visible only on MRI diffusion, or FLAIR, may also result from the partial epilepsy, thereby complicating image interpretation.

Pathophysiology

The pathophysiology of epileptic seizure onset during nonketotic hyperglycemia remains unclear. It is probably multifactorial and hyperglycemia is undoubtedly one of the factors likely to promote the onset of seizures. Experimental data from rats show that elevated glucose concentrations are associated with a proconvulsive effect. Hyperglycemia may thus create a hyperosmolar gradient between the intra- and extracellular neuronal environments, thereby inducing intracellular dehydration, which induces seizures. Moreover, hyperglycemia increases GABA metabolism and thereby diminishes the seizure threshold. Some authors hypothesize that hyperglycemia may cause transient focal ischemia and may thus explain the postictal deficit observed, and even reveal or provoke the epileptogenicity of a pre-existing cerebral lesion. The latter hypothesis does not appear very convincing, in view of the rarity of associated vascular injuries.

Hyponatremia is sometimes encountered and seems to be an aggravating factor for epileptic seizures secondary to nonketotic hyperglycemia. In the series by Singh and Strobas, patients with both EPC and hyponatremia had prolonged seizures. The role of hyperosmolarity is less clear. Experimentally, in animals, it can induce seizures in the presence of focal cortical injuries. Nonetheless, imagery is usually normal and osmolarity is not always elevated. These various metabolic disorders do not by themselves explain the onset of seizures. That is, the absence of ketosis is apparently also important: seizures in patients with ketoacidosis are very rare. Acidosis increases the bioavailability of GABA by increasing the activity of the enzyme that synthesizes it and by decreasing its transamination. In the absence of acidosis, GABA bioavailability is reduced and the seizure threshold is lowered. This
“protective” role of acidosis is useful in the treatment of some childhood partial seizures: these patients are prescribed ketogenic diets\textsuperscript{19}.

**Treatment**

Treatment involves correction of hyperglycemia and metabolic disorders such as hyperosmolarity or electrolyte disorders. Swift initiation of insulin therapy and rehydration are necessary. Antiepileptic treatment is generally not justified, usually ineffective and, in some cases, likely to aggravate seizures\textsuperscript{8,9}. Phenytoin, in particular, is harmful because it inhibits insulin secretion\textsuperscript{8}. Moreover, cases of EPC are generally relatively resistant to antiepileptic treatments while, in cases of nonketotic hyperglycemia, correction of hyperglycemia stops seizures very effectively\textsuperscript{7}. Antiepileptic treatment must be used in some cases, especially in generalized grand mal seizures, which may be life-threatening. When antiepileptic treatment is necessary, initially it is best to administer a benzodiazepine\textsuperscript{4}. Antiepileptic treatment should neither be initiated nor continued once the acute phase is under control. ■

**References**