

# Case Study: Seizures and Hypoglycemia

Michael R. Brennan, DO, and Fred W. Whitehouse, MD

## PRESENTATION

A.S. is a 64-year-old man admitted to the nephrology service for dizziness and hypotension after dialysis. During his hospital stay, he experienced labile blood glucose levels and had a suspected hypoglycemic seizure. The endocrine service was consulted to assist with these findings.

The patient has a history of previous stroke, remote alcohol abuse, and end-stage renal disease requiring hemodialysis 3 days/week and is awaiting a kidney transplant. He has had type 2 diabetes for 25 years and has been treated with insulin for 10 years.

During the past year and a half, he reports having had two seizures. His family witnessed the first seizure and reports that he was hyperglycemic at that time. Additionally, the patient reports an event during which he suddenly “passed out” and was “out of it” for the rest of the day. At home, he takes 6 units of aspart insulin with meals and 12 units of glargine insulin in the morning. He weighs 84 kg, and his last A1C result was 6.7%.

During the hospitalization, he was placed on his home insulin regimen plus a hospital preprandial correction dose of insulin. The correction dose was 2 units of aspart for blood glucose readings that were 151–200 mg/dl, increasing by 2 units of aspart for every 50 mg/dl increase in blood glucose. While in the hospital, he felt nauseated and did not eat. That afternoon, he had a witnessed

seizure. He was stabilized, and routine laboratory testing was performed. His blood glucose measured 42 mg/dl during the seizure.

## QUESTIONS

1. Does hypoglycemia induce seizure?
2. What is the frequency of unconscious events in patients with diabetes?
3. Do patients with diabetes experience seizures for reasons other than hypoglycemia?
4. What variables determine when a seizure may occur in patients with diabetes?

## COMMENTARY

Health care providers and patients became aware of the relationship between insulin, seizures, and coma almost with the advent of this miracle drug. In the findings of Frederick Banting’s seminal paper on insulin,<sup>1</sup> he noted that rabbits given the pancreatic extract (insulin) became hyper-excitable and had clonic convulsive seizures lasting for several minutes. Banting concluded that, “subcutaneous injections of dextrose solutions antidote the convulsions and other symptoms, so that the animal (rabbit) in a few minutes becomes restored to a tolerably normal condition.”

In the late 1920s and early 1930s, Manfred Sakel and others used insulin in an innovative manner to treat patients with morphine withdrawal and other neuropsychiatric illness by inducing seizure and coma.

From 1930 to 1960, insulin coma therapy was performed on schizophrenic patients. Seizures occurred during these therapies ranging from total convulsions to only jerks and twitches.<sup>2,3</sup> By the end of this experience with therapy, the doctrine that insulin therapy could induce seizure was well established.

Hypoglycemia should be in the differential diagnosis of any individual with seizures. Because diabetes is a condition that typically uses hypoglycemia-causing agents (insulin and oral hypoglycemic agents in the sulfonylurea and meglitinide drug classes), it is important to be aware that seizures in this population could be iatrogenic.

The Diabetes Control and Complications Trial (DCCT)<sup>4</sup> reported the frequency of hypoglycemic “loss of consciousness” events in patients with type 1 diabetes. In the study’s intensive therapy group, loss of consciousness events occurred at a rate of 16.3 episodes per 100 patient-years, which falls within the range of other reports.<sup>4</sup>

Although there have been some reports of the frequency of insulin-induced unconsciousness events, validating the formal relationship in a clinical setting may be difficult for several reasons. First, seizures are not always witnessed and are often reported after the fact. In children, 75% of hypoglycemic seizures are reported as occurring at night.<sup>5</sup> Second, recording of blood

glucose levels before, during, or after seizures rarely occurs. Without this information, it is difficult to determine whether a low blood glucose level was the cause of the seizure. Third, a long duration of diabetes is often accompanied by comorbid conditions associated with microvascular and macrovascular injuries. These injuries could be detrimental to nerve conduction and further confound the relationship between hypoglycemia, diabetes, and seizure. Finally, because of compensatory mechanisms in the body, particularly in type 2 diabetes, euglycemia or even hyperglycemia may occur during and after a seizure. These compensatory mechanisms make correlating the inciting hypoglycemic event difficult, even in a hospital setting.

Although hypoglycemia can induce seizures, other etiologies of seizures should not be overlooked in the diabetic population. A large Australian regional diabetes center found that the prevalence of epilepsy in children with type 1 diabetes was similar to that in the general population and noted that health care providers should not assume that a seizure in a type 1 diabetic patient is the result of hypoglycemia.<sup>6</sup>

Recently, continuous glucose monitoring (CGM) technology has allowed researchers to capture data furthering the understanding of hypoglycemia-induced seizures. Nighttime is the most vulnerable period for hypoglycemia because sleep blunts the counterregulatory responses to hypoglycemia, even in nondiabetic people.<sup>7</sup> Patients with diabetes who have had seizures while wearing a CGM device in some cases display a CGM reading of < 60 mg/dl for more than 2 hours before the seizure occurred.<sup>5</sup> The capturing of these seizure events on CGM suggests that several factors, including nocturnal timing, sleep status, and

preceding duration of hypoglycemia, may be necessary to create the clinical event of a hypoglycemic seizure.

Type 1 diabetes accounts for a small proportion of total diabetes prevalence worldwide. Patients with type 2 diabetes also may have seizures from hypoglycemia, but medical literature on the subject is scant. This further implies that, although seizures and comas can be induced with excess insulin, the frequency with which these events occur in the general diabetic population appears to be low.

After his seizure, A.S. was transferred to the hospital's intensive care unit. While there, he had an electroencephalogram that showed some abnormal conduction pathways. He was euglycemic for the remainder of his hospitalization, his nausea resolved, and his hydration and volume status normalized; he was discharged to home in his usual state of health.

Neither the neurology nor the endocrinology service unequivocally stated that hypoglycemia caused his seizure because of his confounding past alcohol abuse, metabolic derangements with end-stage renal disease, and previous stroke with residual tissue injury noted on magnetic resonance imaging. He will be evaluated as an outpatient for a newly identified seizure disorder.

#### CLINICAL PEARLS

- Insulin coma therapy performed in the past for schizophrenic patients clearly demonstrates that excessive exogenous insulin causes a decrease in blood glucose that induces seizures.
- In seizing patients, particularly those taking insulin, sulfonylureas, or meglitinides, hypoglycemia-induced seizure should be considered. If clinically appropriate, a seizing patient should be

administered glucose as a possible remedy.

- Studies suggest that epilepsy occurs with the same frequency in people with diabetes as in the general population. It should not be assumed that a seizure in a patient with diabetes is caused by hypoglycemia; other neurological and metabolic causes should be considered.
- It is difficult to establish a clear cause-and-effect relationship between hypoglycemia and seizures in the diabetic population. In the future, CGM technology may aid in the diagnosis.
- Observations using CGM devices have demonstrated that hypoglycemic seizures may occur nocturnally, during sleep, and be precipitated by a prolonged duration of hypoglycemia.

#### REFERENCES

- <sup>1</sup>Banting FG, Best CH, Macleod JJR, Noble EC: The effect of pancreatic extract (insulin) on normal rabbits. *Am J Physiol* 62:162–176, 1922
- <sup>2</sup>Doroshov D: Performing a cure for schizophrenia: insulin coma therapy on the ward. *J Hist Med Allied Sci* 62:212–243, 2007
- <sup>3</sup>Jones K: Insulin coma therapy in schizophrenia. *J R Soc Med* 93:147–149, 2000
- <sup>4</sup>DCCT Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
- <sup>5</sup>Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F: Duration of nocturnal hypoglycemia before seizures. *Diabetes Care* 31:2110–2112, 2008
- <sup>6</sup>O'Connell MA, Harvey AS, Mackay MT, Cameron FJ: Does epilepsy occur more frequently in children with type 1 diabetes? *J Paediatr Child Health* 44:586–589, 2008
- <sup>7</sup>Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, Byrne G, Stick S, Tamborlane WV: Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 338:1657–1662, 1998

*Michael R. Brennan, DO, is an endocrine fellow and Fred W. Whitehouse, MD, is division head emeritus of Endocrinology, Diabetes, Bone and Mineral Disorders at Henry Ford Hospital in Detroit, Mich.*