

Epileptogenicity of diabetes and antiepileptogenicity of ketogenic states: Clarity or confusion?

Sanjay Kalra, A. G. Unnikrishnan¹, Yashdeep Gupta²

Department of Endocrinology, Bharti Hospital, Karnal, Haryana, ¹CEO, Chellaram Diabetes Institute, Pune, Maharashtra, ²Department of Endocrinology, AIIMS, New Delhi, India

“Those who worship ignorance, Enter blind darkness

Those who delight in knowledge, Enter darkness, as it were, yet deeper.”

The Upanishads: Ishavasya: 9

EPILEPTOGENICITY OF DIABETES

Diabetes and seizures have a multifaceted relationship. An association of diabetes and epilepsy was first described a century ago by Labbe,^[1] who suggested acidosis and “degeneracy” as the etiology of seizures. Epilepsia tarda (or onset of seizures after age 40) was noted in insulin-treated persons as well.^[2] Diabetes may be associated with hypomagnesemia, hypocalcemia, and nonketotic hyperglycemia: All these can cause seizures.^[3] Diabetes therapy can be proepileptogenic, too, as some glucose-lowering drugs may cause hypoglycemia. Multiple other hypotheses have been proposed to explain the increased occurrence of seizures in diabetes.^[4] These include microvascular damage, local brain damage, immune abnormalities, metabolic factors, and gene mutation.

More recently, McCorry *et al.* compared the population prevalence of Type 1 diabetes, in a cohort aged 15–30 years old, to a cohort of 518 persons of similar age, with idiopathic generalized epilepsy (IGE).^[5] They found an odds ratio of 4.4 (95% confidence interval [CI]: 2.1–9.2) of Type 1 diabetes occurring in persons with IGE. Another population-based cohort study, using claims data from the Taiwan National Health Insurance Research Database, reported a hazard ratio of 2.84 for epilepsy in Type 1 diabetes patients (95% CI: 2.11–3.83).^[6] Chou *et al.*

interpreted this risk as being due to long-term sequelae of both hyperglycemia and hypoglycemia. A population-based cohort study, conducted using the Dutch PHARMO database (1998–2010), evaluated 915 patients with Type 1 diabetes aged <19 years. When compared with an age- and gender-matched cohort, the hazard risk of epilepsy was 2.0 (95% CI: 1.1, 3.7).^[7]

Focusing on 2016 persons with pharmaco-resistant epilepsy, admitted to a tertiary medical center, Keezer *et al.* found a 9.9/1000 prevalence of Type 1 diabetes mellitus, which was more than twice the overall prevalence of Type 1 diabetes. In 80%, onset of diabetes predated that of epilepsy by 1.5 years.^[8] Persons with Type 1 diabetes had focal epilepsy, usually of temporal lobe origin (similar to those without Type 1 diabetes), and no etiology could be determined in 85% patients (as compared to 35% in those with Type 2 diabetes and 49% in euglycemic persons, $P = 0.045$). A Brazilian cross-sectional study collected data on 375 Type 1 diabetes patients ages 11–66 years and recorded a confirmed diagnosis of epilepsy in 17 persons (4.5%). This was 4.5–9 times than that noted in the general population (0.5–1.0%).^[9] An observational cohort study based on the Diabetes Patienten Verlaufsdokumentation database including data from 45 851 patients with Type 1 diabetes mellitus, identified 705 patients with epilepsy were identified, giving a prevalence of 15.5 of 1000. Patients with epilepsy were younger at the onset of diabetes mellitus and shorter than patients without epilepsy but had similar metabolic control, treatment, dose, and prevalence of B-cell specific autoantibodies. The frequency of severe hypoglycemia was lower in patients treated with antiepileptic medication. The risk for diabetic ketoacidosis was almost double in patients with epilepsy compared with patients with Type 1 diabetes mellitus alone ($P < 0.01$).^[10]

Case reports suggest that specific autoimmune factors, e.g., high GAD65 antibody expression, and stiff-person syndrome may have a role to play in the pathogenesis of epilepsy.^[11]

Corresponding Author: Dr. Sanjay Kalra,
Department of Endocrinology, Bharti Hospital,
Karnal, Haryana, India.
E-mail: brideknl@gmail.com

In summary, a review of published evidence, both population-based and hospital- or clinic-based, reveals strong epileptogenic mechanisms at play in Type 1 diabetes.

NEUROPROTECTIVE EFFECT OF KETOGENIC DIET

In stark contrast, extensive preclinical and clinical research documents the neuroprotective effect of ketosis, created by adhering to a ketogenic diet.^[12] The ketosis achieved with a high-fat, high-protein, and low-carbohydrate (ketogenic) diet is of a much lower degree than that experienced by persons in diabetic ketoacidosis. The low levels of ketonemia act as a metabolic adaptive mechanism, encouraging various tissues of the body to utilize ketones, in the face of carbohydrate restriction, as a metabolic fuel. Such a shift improves the efficiency of mitochondrial energetics and protects tissue from starvation. In the setting of diabetes, a ketone-based fuel economy reduces the load on the compromised glucose pathways shifting the burden of creating energy to lipid metabolism.^[13]

A century ago, the ketogenic diet was used as the treatment of choice for seizures. With the development of anticonvulsant drugs, however, it went out of vogue. In recent years, there has been renewed interest in the exaptation of this treatment modality for epilepsy management as well as other neurologic disorders.^[14,15]

These include epilepsy syndromes such as intractable epilepsy, glucose transporter 1 mutations, pyruvate dehydrogenase deficiency, infantile spasms, Dravet syndrome, and Doose syndrome (myoclonic-astatic epilepsy). The ketogenic diet may also be of benefit in neurodegenerative disorders such as Parkinson's disease, Alzheimer disease, and amyotrophic lateral sclerosis.^[14,15] In fact, the ketogenic diet has also been used safely in intractable epilepsy in pediatric Type 1 diabetes.^[16] Mechanisms proposed to explain the antiseizure benefits of ketogenesis include increased resilience of neurons, inhibition of transporter on channels by ketone bodies and/or fatty acids, and increased synthesis of the inhibitory neurotransmitter gamma-amino butyric acid. At the same time, we wish to caution readers that uncontrolled ketosis may increase the risk of complications in Type 1 diabetes.^[17]

THE INDIAN EXPERIENCE

If Type 1 diabetes is a ketosis-prone or proketogenic state, it stands to reason that diabetes should protect against epilepsy.

Unpublished data, from our centers in Karnal (Haryana) and Pune (Maharashtra), reveal a zero prevalence of seizures in children and adolescents with Type 1 diabetes. Upon detailed questioning, we were able to identify three children (out of 480) at Karnal, who had experienced febrile seizures before onset of diabetes. This implies a 0.602% prevalence of febrile seizures. Similar dissociation between Type 1 diabetes and epilepsy is reported by pediatric centers from Karnal (Rajat Mimani, personal communication), which care for a large number of children with diabetes. We also note that, as of date, there is no publication highlighting a causal or associative relationship between Type 1 diabetes and epilepsy from South Asia.

SUGGESTED HYPOTHESES

Many plausible hypotheses can be put forward to explain this. It is possible that lesser emphasis on tight control in children prevents hypoglycemia, and thus avoids hypoglycemic insult or injury to the brain. Suboptimal control, with lower than optimal levels of insulin replacement, may permit minimal ketogenesis which while not severe enough to cause ketoacidosis, does help achieve neuroprotection.

Another possible explanation for the diabeto-epileptic dissociation noted in North and West India may be the diet. While the Indian plate is carbohydrate rich, a higher fat and/or protein content (relative to those of other children) may explain the lower risk of epilepsy. Genetic causes may invoke to rationalize our findings as well.

A simpler explanation, however, may be related to the health care-seeking behavior of children with comorbid Type 1 diabetes and epilepsy. Recall bias may lead to incomplete reporting of history of seizures, but it is unlikely that such a bias will extend to current medical symptoms. Patients with "dual disease" may seek treatment from tertiary care centers or may succumb to the combined insults of uncontrolled seizures and uncontrolled glycemia before reaching an endocrine or neurological care facility.

Whatever the cause, this association deserves detailed study and analysis in India, and beyond.

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