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REVIEW ARTICLE

Diabetes-Epilepsy Symbiosis

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ABSTRACT:
Epilepsy is one of the neurological disorder characterised by a period of epileptic seizures. The findings reveal that type 1 diabetes may increase epilepsy risk three fold. About 25% to 45% of epilepsy cases can be due to structural modifications, metabolic disorders, and genetic characters but early research has also claimed that diabetes might explain some idiopathic seizures, Dr Chou and their colleagues wrote. Those people with type 1 diabetes but without hypoglycaemia found to have a 2.67 fold increased risk of developing epilepsy during medication vs. the other group, whereas those with both type 1 diabetes and hypoglycaemia might have about 16.5 fold increased risk of developing epilepsy.

KEYWORDS: Epilepsy, Seizure, Diabetes

INTRODUCTION:
Epilepsy is a group of neurological diseases characterised by epileptic seizures. [1,2] Epileptic seizures are episodes that can vary from brief and nearly unnotable to long periods of vigorous shaking. [3] These episodes commonly result in physical injuries including broken bones in rare cases. [3] In epilepsy, seizures tend to recur more rapidly and there is no immediate underlying cause. [1] Isolated seizures that are provoked by a specific cause such as poisoning are not seemed to represent epilepsy. [4]

People with epilepsy in some parts of the world experience stigma due to their epileptic condition. [3] The causes of most cases of epilepsy is unknown, although it is believed that some people develop epilepsy as the result of brain injury, stroke, brain tumours, infections of the brain and birth defects. [3] Known genetic mutations are directly linked to a small proportion of cases. [5, 6]

TYPES OF EPILEPSY:
Epilepsy is commonly and most widely known for causing convulsions- sudden uncontrolled movements. [7] But seizures can trigger a wide range of other symptoms, from starting to fall to fumbling with clothes. Doctors divide seizures into different types depending on how it affects the brain. Each has their own set of symptoms and the underlying cause is unknown.

- Generalised tonic-clonic seizures
- Tonic-clonic
- Tonic
- Clonic
- Myoclonic
- Absence and
- Atonic seizures.

It results in loss of consciousness and typically happen without warning. [8]

- Partial seizures
- Absence seizures

They are non convulsive and presents a decreased level of consciousness and usually it is seemed to lasts about 10 seconds [9, 10]

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Type1 diabetes mellitus is one of the most common autoimmune disorder in children, with a 3% annual increase in the global increase rate since 1980s.

HYPERGLYCAEMIA IS SEEMED TO LOWER SEIZURE THRESHOLD:

Abnormal glucose levels, whether it is too high or too low, can result in seizures. This problem is especially pertinent to individuals with diabetes, whose blood glucose levels can fluctuate many times a day, may be due to intercurrent illness, variations in insulin levels, or other metabolic factors. Clinical studies proved that adults with hyperglycemia have an increased predisposition to experiencing seizures and epilepsy. Experimental studies done both in vivo and in vitro, suggest that a threshold glucose concentration is obligatory to support synaptic transmission. Conversely, it is seen that elevated extracellular glucose is related with neuronal hyperexcitability, indicating that glucose balance is necessary for normal neurotransmission. The key importance of glucose balance has been found in studies demonstrating that hyperglycaemia exacerbates ischemia-induced brain damage, whereas fasting-induced hypoglycaemia protects against this neurotoxicity. The present study, by Schechter and co-workers, hypothesizes that the reduction of extracellular glucose could ameliorate seizure activity by decreasing neuronal excitability.

First, Schwechter et al. Examined that the relation between extracellular glucose levels and seizure susceptibility in adult rats in vivo. They tested the hypothesis that increased glucose concentration is proactive in the flurothyl model of one type of generalized seizures (flurothyl is a potent gaseous convulsant which is capable of inducing seizures by inhalation). Hyperglycemia was found to be induced in two ways: (a) streptozotocin (STZ) administration, which reliably results in hyperglycemia and results in diabetes; and (b) short-term intraperitoneal injection of 20% glucose to make up a condition of nonketotic hyperglycemia which is independent of diabetes. A wide range of well-chosen controls were used to compare their outcomes. The three groups comprising of “nondiabetic controls” included rats that are injected with the STZ vehicle, STZ-injected rats that did not develop diabetes and are resistant to it, and rats that received no injection but otherwise were handled similarly to the other animals. A final comparison group consisted of rats that underwent a 24-hour fast and thus were hypoglycemic.

Testing with flurothyl indicated a negative correlation between blood glucose level and clonic seizure threshold—with STZ-induced diabetic rats having significantly marked lower seizure thresholds than did nondiabetic controls. Fasted, hypoglycemic rats had the highest thresholds, the result shows. To control the other metabolic or hormonal effects resulting from STZ injection, an additional group of rats was injected with 20% glucose, 30 minutes before flurothyl testing, and then the results were compared with saline-injected controls. Again, the hyperglycemic rats had significantly lower thresholds for clonic flurothyl seizures, claiming that hyperglycemia itself is found to be proconvulsant, in both diabetic and normal rats. Furthermore, no damage is seen to hippocampal neurons in any of the experimental conditions, as assessed by Fluoro-Jade and silver stain techniques, suggesting that neither STZ or elevated glucose leads to structural neuronal injury.

Next, Schwechter and their colleagues evaluated the effects of elevated extracellular glucose on epileptiform activity in vitro. Slices of entorhinal cortex–hippocampus were exposed to a Mg^{2+}-free extracellular medium, causing epileptiform bursts for which amplitude and frequency can be measured and compared under different experimental conditions. In Mg^{2+}-free medium with 10 m*M* extracellular glucose (i.e., the usual glucose concentration used in slice experiments), typical epileptiform discharges occurred. When the glucose was increased to 20 m*M*, epileptiform burst frequency did not change; however, the burst amplitudes increased significantly, showing enhanced neuronal firing. The effect was reversed when the glucose was again switched back to 10 m*M*. In addition, no epileptiform discharges were seen in normal cerebrospinal fluid (CSF), that is 2 m*M* Mg^{2+}, plus a 20 m*M* glucose solution. As a result—consider the fact that nearly all brain-slice electrophysiology experiments have used a CSF-glucose concentration of 10 m*M*, rather than the physiologic concentration, which is closer to 5 m*M*. The traditionally accepted practice of using the higher-glucose-level solutions is based on empiric experience, showing that the synaptic viability of slices is optimized with the higher concentration. [11]

This well-designed study confirms previous work with several animal models of diabetes, which show a reduction in seizure threshold. The important new finding from Schwechter and colleagues is that hyperglycemia, itself, is proconvulsant. How can elevated glucose enhance seizure susceptibility? The answer to this crucial question regarding the mechanism of action awaits further research, as the mechanism per se is not addressed in this report. However, one clue to the answer might be gleaned from the author's observation that hypoglycemia was associated with a higher seizure threshold. Other studies have indicated that restricting calories, thus inducing hypoglycemia, in the epilepsy-prone EL mouse also reduces seizure susceptibility. [12] With any model that induces hypoglycemia, the role of ketosis must be excluded, as ketones themselves can affect seizure threshold. [13]

Moreover, multiple other mechanisms could explain hypoglycemia- and hyperglycemia-induced alterations of neuronal excitability. Furthermore, the effects of age on glucose balance and neuronal excitability must be delineated, as children with diabetes tend to develop seizures with hypoglycemia rather than with hyperglycemia. In addition to clarifying further the relation between hyperglycemia and seizures, Schwechter et al. highlight the link between metabolism and neuronal excitability and emphasize the need for further research on the long-term effects of hyperglycemia on various aspects of brain function. [14]

EPILEPSY OR DIABETES- A CONFUSION OR COMMON CURE?

Though it is surprising to hear, but according to recent research it is confirmed that epilepsy and diabetes are more in common than we thought. The key feature is fluctuating blood sugar. People with hyperglycemia are more prone to have focal or local seizures. And those people who are hypoglycemic, tend to have tonic-clonic seizures. [15]

Although some patients and even some doctors disagree with this study, there's really not much difference between a seizure due to diabetic and other different forms of seizures, such as those caused by epilepsy. While the symptoms doesn't differ- there seem to be one important significant difference – the blood sugar irregularities which can cause a diabetic seizures can also cause the diabetic patient to lapse into a coma sometimes found to be fatal. [16, 17]

One dilemma facing is that both epilepsy has their common source. If the seizures are caused by blood sugar fluctuations, treatment with anti-seizures drugs which cause electrical impulses in the brain are addressing the wrong problems.Yet we all know that diet plays an important key role in controlling epilepsy.Interestingly the study reveals, initial testing shows that a diabetes drug widely used to treat diabetics manages their condition could also become recognised as an effective and easy way for treating epilepsy. According to reports, Metformin (brand name Glucophage) could be particularly very useful in treating epilepsy patients who are drug resistant.Glucophage a popular and effective oral drug for type 2 diabetes, helps lower blood sugar levels by improving the way the body interacts with insulin. Much like the ketogenic diet which treats epilepsy by minimising the levels of dietary starch and sugar.

A team headed up by Dr. Avtar Roopra reported that glucophage was able to turn on a molecule that regulates energy, and then found that they could suppress the extremely active nerve cells by inhibiting the transfer of sugar into excess energy. The key goal is to reduce the rate of epilepsy but not enough to affect the brain's ability to learn and remember. [18, 19, 20]

WHETHER IT IS EPILEPTIC SEIZURE OR DIABETES RELATED HYPOGLYCEAMIA?

Observation of the pattern, duration and characteristics of the seizures, an electroencephalogram, and CT scans, helps doctors in diagnosis. Nocturnal epilepsy increases the difficulty of diagnosis of epilepsy because of the fact that seizures that usually occur at night are not witnessed in the day time mostly.Some case studies referred in the literature show patients who presented with a tonic-clonic seizure associated with hypoglycaemia were mistakenly diagnosed with epilepsy. If you are in a treatment and taking medication that causes the pancreas to release more insulin (like Glucotrol, Amaryl, Prandin, Glipizide, etc) or if you are taking insulin injections it is imperative to discern whether you are having low glucose levels during the night while sleeping as this could be the cause of your seizures. A continuous glucose monitoring system which is used to diagnose diabetes, a pager-sized device typically worn for 2-3 days that continually measures glucose, can determine if you are going too low and guide you.

TYPE 1 DIABETES TO INCREASE EPILEPSY RISK THREEFOLD:

Children and adolescents with type 1 diabetes are nearly 3fold times higher in risk to develop epilepsy than other people without type 1 diabetes, according to a large insurance claims study from Taiwan.The study findings are similar with other, only limited research is carried and that suggests a link between type 1 diabetes and epilepsy, but more research is to be performed in the future to determine how this occurs, according to I-Ching Chou, MD, from China Medical University Children's Hospital, in Taichung, Taiwan, and colleagues. The researchers reported their results in an article published online March 31, 2016 in Diabetologia.
The pathogenic mechanisms of neurological diseases (such as epilepsy) remain unknown but may be associated with significant long term neurological sequelae, they stress. Thus the causative agent between type 1 diabetes and the increased risk of epilepsy require further investigation and keen study, they conclude. [18]

"Teasing out the causes of seizures is tedious to do retrospectively in an administrative database," Kenneth Mandl, MD, MPH, from Harvard Medical School and Boston Children's Hospital, Massachusetts, told Medscape Medical News. However as previously reported his team performed a similar analysis of US insurance claims data and they conclude that patients who had any of 12 autoimmune diseases had an increased risk of epilepsy and those with type 1 diabetes

had a 5.2 fold increased risk of epilepsy.Dr Mandl agrees that the link between diabetes and epilepsy risk "should certainly be studied further", ideally in "populations where coding can be confirmed with clinical review and characterisation of the seizures." [18]

TREATMENT FOR EPILEPSY:

The physician determines the type of seizure and look forward in a preventative manner, and anti-seizure medication is prescribed accordingly. This is a origin of frustration for many people who ask, "Why do i need to take this medication if i am not having seizures?" Antiseizure medication should be taken regularly for the control of seizure as we take high blood pressure or diabetes medication even when the numbers are in the ideal range- to keep the medical condition under control! Plus, there is a higher risk for a second seizure within 3 years after experiencing the first seizure is about 30% and the lifetime risk of recurrence is 14-50%. Other factors are important in the treatment of seizures removing tumors(if that is the cause) and correcting metabolic disturbances.For people with type 1 diabetes, controlling glucose levels to minimise their effect which diabetes has on the nervous system. Also the effect of sleep quality on seizure frequency is well known from the literature. A careful scrutiny of potential sleep disturbing factors such as primary sleep disorders is of utmost importance to the successful management of seizures.Whenever faced with a chronic health condition, like diabetes or epilepsy, it always helps to speak with the experts and those who experience it firsthand as they can share clearly. [20]

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