

Zachary Leavitt (MS2), Jay Babu (MS2), Sannah Vasaya, DO, Robert Balsiger, DO, Aroucha Vickers, DO

Purpose

- This case report highlights the detrimental effects of recurrent and prolonged hypoglycemia
- The most severe effect is neuronal death visible on neuroimaging which can be mistaken for acute or chronic hypoxic injury
 - High signal intensity on MRI is commonly seen in encephalitis, and epileptic seizure, can also be seen in metabolic disturbances
 - It can be seen in 8.6% of hypoglycemic patients ³
 - With correction of the hypoglycemia, the high signal intensity also subsequently resolves
- It is important that patients presenting with signs and imaging for ischemic injury also be assessed for recurrent signs and symptoms of recurrent hypoglycemia including:
 - Shaking, sweating, anxiety, and/or dizziness
- Severe hypoglycemia and neurological damage has extensive research in neonates,
 - But limited research exists for adults and diabetics, those commonly affected with recurrent hypoglycemic episodes

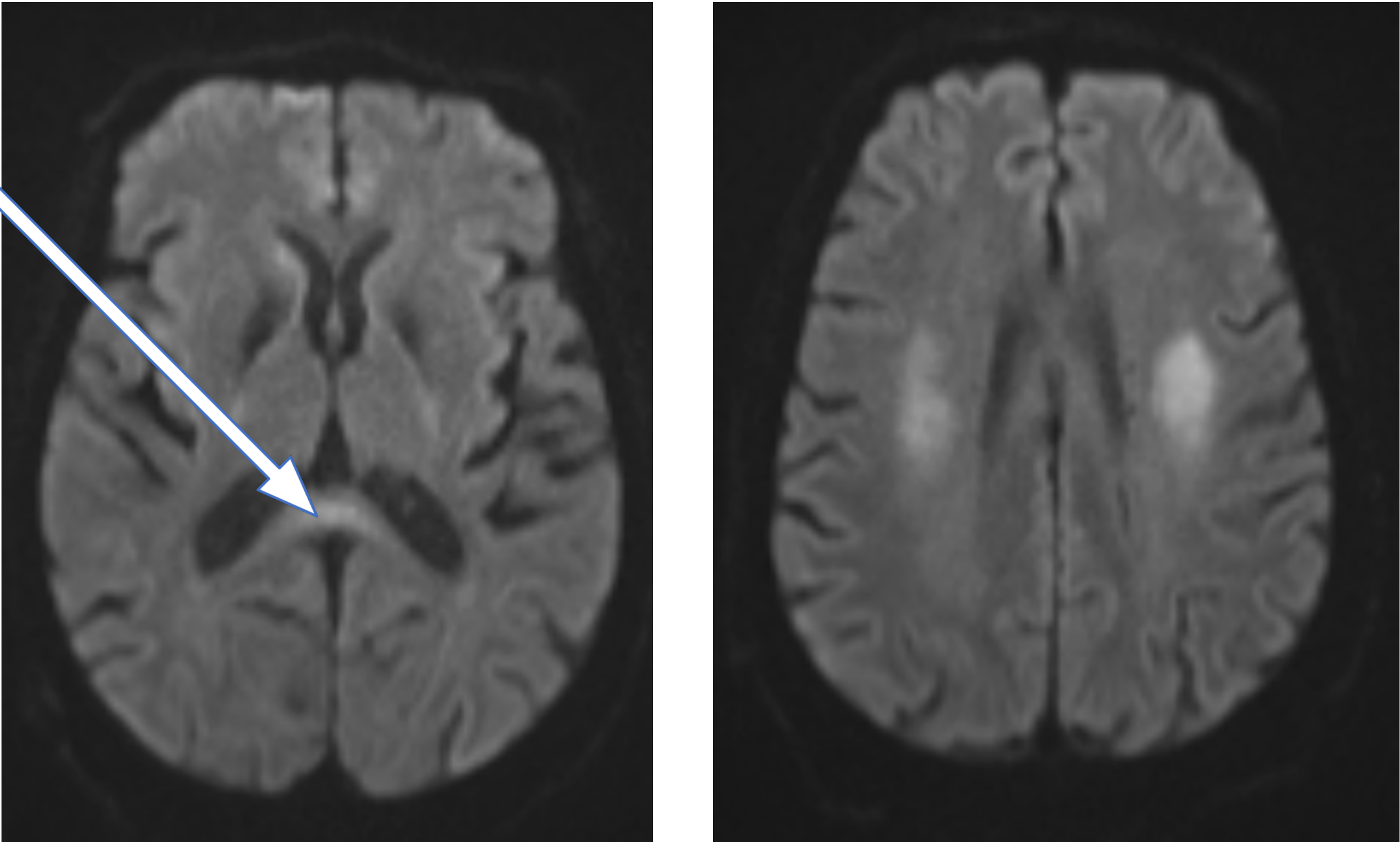
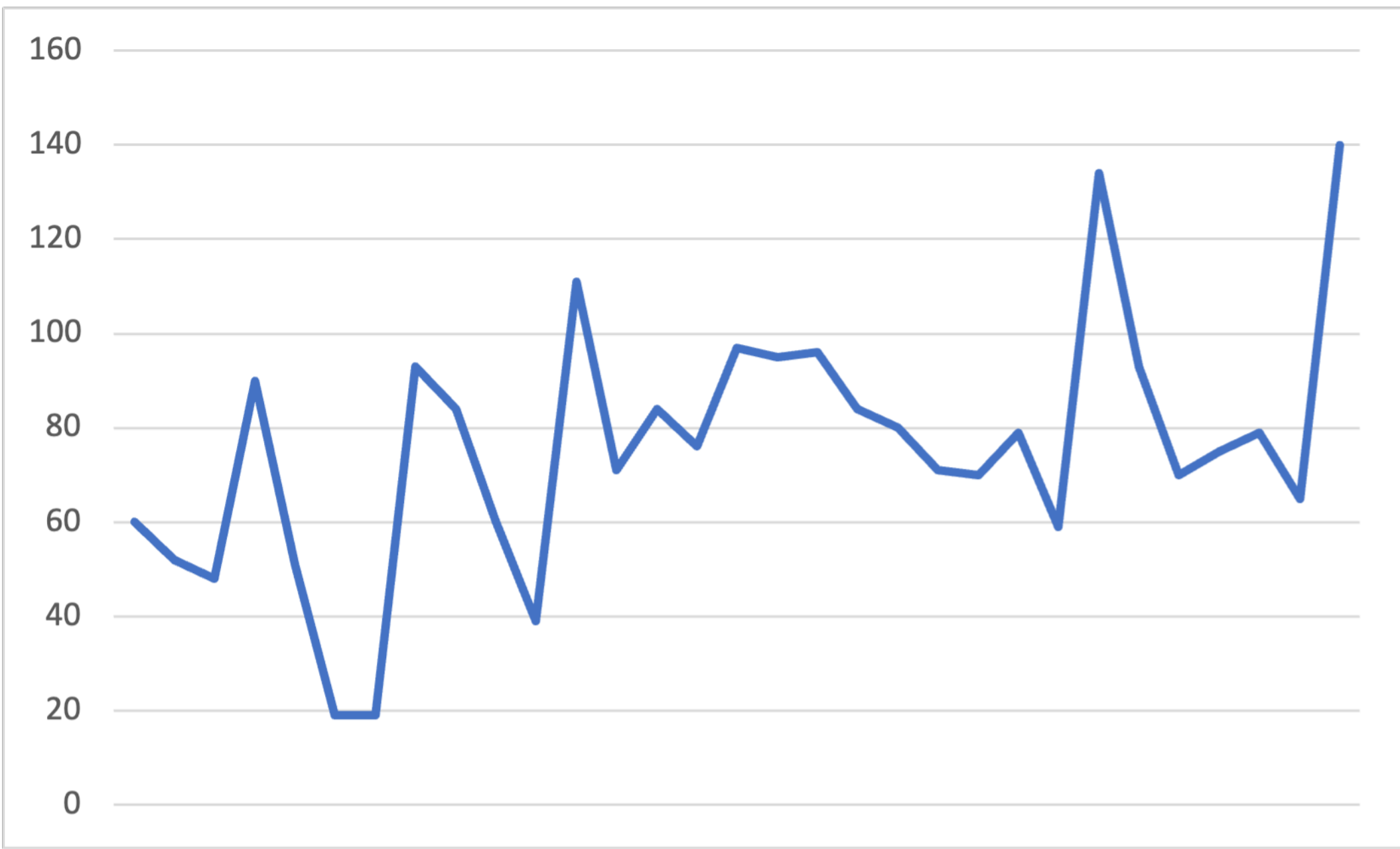


Figure 1 & 2. DWI sequence from non contrast MRI showing restricted diffusion of splenium and corona radiata

Clinical Course and Treatment

- She became progressively obtunded with respiratory decline eventually requiring intubation
- Metabolic derangements were corrected:
 - Patient showed no improvement on neurological exam and family opted for hospice care
- Considerations for the etiology of her spontaneously-resolved hypoglycemia include:
 - Critical illness, malnourishment, and unknown intake of exogenous insulin
 - Potentially lethal causes including cortisol insufficiency and endogenous hyperinsulinism were ruled out

Table 1. Blood Glucose Level Over the Course of the Patients Stay



History of the Present Illness

- 55-year-old female with hypertension, end-stage renal disease noncompliant with hemodialysis, and polysubstance abuse arrives to the ED with altered mentation
- Initially nonverbal and only able to follow simple commands
- Progressed to unresponsiveness with extremity withdrawal to noxious stimuli and intact brainstem reflexes
- She is a nondiabetic with a HgbA1c of 4.8 and not on any insulin regimen

Discussion

- Hypoglycemia commonly presents with coma and seizure and presents late in the course of severe hypoglycemia
 - This happens in part due to depletion of energy-supplying substrates, but also cerebral edema ¹
 - Steroids have had some effectiveness in treating encephalopathy related to hypoglycemia through a proposed mechanism of limiting cerebral edema ⁶
- Studies have shown that Pyruvate can potentially alleviate the grave consequences caused by severe and recurrent hypoglycemia ⁵
 - Increasing Pyruvate levels to 5 mM, about 100-fold higher than normal levels demonstrated a decreased neuronal death after both ischemia and hypoglycemia
 - A proposed mechanism is by bypassing a sustained impairment in glycolysis induced by PARP-1 activation
- Studies have shown that a large amount of the damage from hypoglycemia results from a mechanism similar to reperfusion injury with formation of reactive oxygen species ⁴
 - N-acetyl-cysteine is commonly used to treat acetaminophen toxicity through a replenishing of glutathione, but its ability to cross the blood brain barrier is unclear
 - Can significantly reduce zinc accumulation in postsynaptic neurons and increase the glutathione levels in hippocampal neurons, which decreased hippocampal neuronal death after hypoglycemia

Conclusion

- Physicians treating comatose patients should recognize similarities in presentation in both imaging and history that can be confused with acute or chronic ischemic injury ³
- Studies have shown an increased risk for dementia among patients with diabetes who have presented with multiple episodes of severe hypoglycemia ⁷
- With persistent hypoglycemia, exhaustion of essential nutrients glucose, lactate, and glutamate results in hypoglycemic encephalopathy or coma ²
- Recurrent hypoglycemic states can deplete glutathione stores resulting in oxidative damage and neuronal death ³
- This case demonstrates hypoglycemia's potential for significant and insidious consequences
- There is need for further research into mechanisms of hypoglycemia-induced neuronal death, as well as possible alleviating therapies
- Although reports of experimental treatments including N-acetyl-L-cysteine, pyruvate, and steroids have been published, these are sparse, and additional research would be of benefit ^{4,5,6}
- A majority of the studies performed involve primarily neonatal hypoglycemia, additional research regarding severe hypoglycemia and possibly ischemic damage regarding adults would be of great interest

References

1. Arief AI, Doerner T, Zelig H, Massry SG. Mechanisms of seizures and coma in hypoglycemia: evidence for a direct effect of insulin on electrolyte transport in brain. *Journal of Clinical Investigation*. 1974;54(3):654-663. doi:10.1172/jci107803

2. Languren G, Montiel T, Ramirez-Lugo L, et al. Recurrent moderate hypoglycemia exacerbates oxidative damage and neuronal death leading to cognitive dysfunction after the hypoglycemic coma. *Journal of Cerebral Blood Flow & Metabolism*. 2017;39(5):808-821. doi:10.1177/0271678x17733640

3. Katoh M, Yoshino M, Aoki T, Abumiya T, Imamura H, Aida T. Localized reversible high signal intensities on diffusion-weighted MRI in hypoglycemia: A study of 70 cases. *Asian J Neurosurg*. 2016 Oct-Dec;11(4):412-415. doi: 10.4103/1793-5482.144196. PMID: 27695547; PMCID: PMC4974968

4. Kho AR, Choi BY, Kim JH, Lee SH, Hong DK, Lee SH, Jeong JH, Sohn M, Suh SW. Prevention of hypoglycemia-induced hippocampal neuronal death by N-acetyl-L-cysteine (NAC). *Amino Acids*. 2017 Feb;49(2):367-378. doi: 10.1007/s00726-016-2370-5. Epub 2016 Dec 19. PMID: 27990559

5. Choi BY, Kim JH, Kim HJ, Yoo JH, Song HK, Sohn M, Won SJ, Suh SW. Pyruvate administration reduces recurrent/moderate hypoglycemia-induced cortical neuron death in diabetic rats. *PLoS One*. 2013 Nov 22;8(11):e81523. doi: 10.1371/journal.pone.0081523. PMID: 24278448; PMCID: PMC3838412

6. Mathur JL, Rajabi F, Schroeder A, Becker TK. Case of steroid-responsive encephalopathy from hypoglycaemia. *BMJ Case Rep*. 2017 Aug 24;2017:bcr2017221262. doi: 10.1136/bcr-2017-221262. PMID: 28838925; PMCID: PMC5623988

7. Meneilly GS, Tessier DM. Diabetes, dementia and hypoglycemia. *Canadian Journal of Diabetes*. 2016;40(1):73-76. doi:10.1016/j.cjcd.2015.09.006