

Neuroglycopenia: common etiologies, clinical characteristics, and management

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ABSTRACT

Glucose is primary source of energy substrate for the brain, however, during physiological stresses or other situations with low blood glucose, ketone bodies are another important source of energy for brain. Hypoglycemia has significant impact on the brain and symptomatic hypoglycemia is referred as Neuroglycopenia. Since the brain has minimal endogenous glycogen stores and does not generate glucose intrinsically, it requires a constant supply of glucose from the circulation. Impairment in glucose supply leads to activation of counter regulatory hormone mainly the neuroendocrine response in order to restore the energy requirement. If this response fails to secure the energy demand hypoglycemia can present clinically as headache, stroke, seizure, cognitive impairment or coma. A prompt and accurate diagnosis would allow for more precise treatment and less neuronal damage. This article focuses on common etiology, counter regulatory responses to hypoglycemia, clinical features and management of hypoglycemia.

Keywords: hypoglycemia, neuroglycopenia

INTRODUCTION

Glucose is supposed to be the most important energy substrate for the brain [1]. The brain requires a steady supply of glucose from the blood since it has limited endogenous glycogen stores and does not produce glucose intrinsically [2]. In order to restore the energy need, a decrease in glucose supply causes the activation of counterregulatory hormones, primarily the neuroendocrine response. The biochemical definition of hypoglycemia is variable, but according to American Diabetes association, hypoglycemia is defined as plasma glucose concentrations <70 mg/dl and severe hypoglycemia as <40 mg/dl. The diagnosis of hypoglycemia is not based on an absolute blood glucose level rather it requires fulfillment of Whipple's triad that was given by "Allen Whipple" in 1930 to look for evidence of insulinoma during exploratory pancreatic surgery, whipple's

triad includes: signs and symptoms consistent with hypoglycemia, associated low glucose level and relief of symptoms with supplemental glucose. As per there hypothesis, the amount of glucose in the plasma does not strictly reflect its utilization by the brain. The uptake of glucose by the brain doesn't depend upon the concentration of glucose available in the plasma. To have symptomatic hypoglycemia, rate of change in plasma glucose level is more important than absolute level of glucose in the blood. In situations with low glucose, ketone bodies and lactates may be utilized for energy production. However, present understanding regarding switchover process from glucose to ketone utilization is limited. This switchover may not be seen in insulin induced hypoglycemia, a most common cause of hypoglycemia seen in day-to-day practice, because excess insulin also suppresses ketogenesis or gluconeogenesis.

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ETIOLOGY

Hypoglycemia has profound effects on the brain and symptomatic hypoglycemia is referred as Neuroglycopenia. Symptoms of hypoglycemia can be divided into Autonomic which includes tremors, sweating, palpitation and other being Neuroglycopenic that includes headache, stroke, seizure, cognitive impairment and coma. In 1954, Kauvar and Goldner have discussed on lack of relationship between the blood sugar and neuroglycopenia [3]. This hypothesis holds some relevance as multiple studies in the past have shown neuroglycopenia with cortisol deficiency or hyperglycemia which can be explained due to impaired glucose transport across the membrane or deranged intracellular metabolism [4]. Diabetes mellitus is major cause of hypoglycemia which is more common with type 1 than type 2 diabetes mellitus. Following are the common etiologies for hypoglycemia:

1. Drugs are the most common cause for hypoglycemia which is more common with type 1 Diabetes mellitus than Type 2 Diabetic patients who takes either insulin secretagogues (Glyburide, glipizide, glimepiride, Repaglinide) or insulin. Other drugs leading to hypoglycemia include – Alcohol, Quinolones, quinine, beta blockers, ACE inhibitor and IGF-1
2. Critical illness - Sepsis, Chronic kidney disease, severe liver failure and cardiac failure
3. Hormonal deficiencies - cortisol, glucagon and growth hormone deficiency also leads to hypoglycemia.
4. Non islet cell tumor
5. Endogenous hyperinsulinism – Beta cell disorders, insulinoma, Autoimmune hypoglycemia and others
6. Accidental, surreptitious or malicious hypoglycemia

PATHOPHYSIOLOGY

The physiological response to hypoglycemia is reduction in insulin secretion from beta cells of pancreas followed by increase in glucagon level and activation of counter regulatory neuroendocrine response that includes release of epinephrine, growth hormone and cortisol. The process of utilization of glucose by any tissue including brain depends on a barrier between tissue and its blood supply. This barrier, commonly known as blood-brain barrier (BBB) prevents passive diffusion or movement of glucose and other nutrients into brain. There are two different families of glucose transporters in the brain. First, a sodium-independent glucose transporters (GLUT) and second, a sodium-dependent glucose transporter (SGLT). GLUT family proteins transport glucose based upon concentration gradi-

ent (facilitated transport) and may transport glucose bidirectionally, whereas SGLT family transport glucose based on concentration gradient with co-transport of sodium ions (secondary active transport). Brain has several glucose transporters from these families, out of which, GLUT1 is most abundant followed by GLUT3 [5]. These GLUT transporters, present at the luminal and abluminal membranes of the brain endothelial cells, facilitates the transcellular transport of glucose across the tight junctions between the endothelial cells.

Regulation of glucose transportation in brain

Local need of glucose for a part of brain is probably a deciding factor for local GLUT1 & GLUT3 density, as there is heterogeneous distribution of glucose transporters as well as capillary density in the brain [6]. It's essential to realize that increased local cerebral glucose utilisation is associated with a local elevation of glucose transporters. Also, with persistent hypoglycemia there is moderate induction of GLUT receptors mainly GLUT3, whereas chronic hyperglycemia downregulates GLUT1 in the brain to maintain glucose utilization during adverse situations [7]. Deficiency to these transporters results in relative hypoglycaemia in brain (despite normal serum sugar) and may present as infantile refractory seizures, microcephaly, delayed neurological development and complex motor movement disorders. The brain detects glucose concentration through glucose sensing neurons that are located in the brain and in the periphery [8]. Peripheral glucose sensing neurons are located mainly in the carotid body and hepatic-portal-mesenteric vein, brain glucose sensors are widely dispersed but mostly found in hypothalamus and in the hind brain (Area postrema, dorsal motor nucleus of vagus and Nucleus of solitary tract) [9]. In state of hypoglycemia, there is increase in cerebral blood flow to hypothalamus which plays a vital role in glucose sensing and activation of counter regulatory hormone – epinephrine and glucagon. Once the plasma glucose concentration is maintained their responses are corrected, however prolonged hypoglycemia leads energy failure and brain damage. Previous studies have also reported activation of excitatory amino acid such as aspartate and glutamate which are neurotoxic [9]. During an episode of hypoglycemia, accumulation of oxaloacetate occurs that generates aspartate, which causes preferential neuronal necrosis from cortex, neostriatum and hippocampus [10]. “Hypoglycemia unawareness” or “Happy hypoglycemia” is attenuated sympathoadrenal response to hypoglycemia i.e lack of warning adrenergic and cholinergic features that previously allowed patients to recognise impending hypoglycemia and terminate the event by ingesting carbohydrate. Two

possible mechanisms can explain this phenomenon firstly, release of epinephrine that is associated with increase in lactate concentration which acts as a substrate during energy crisis and secondly, during an episode of hypoglycemia there occurs a upregulation of glucose transport into the brain that may increase availability of glucose [11]. Lactate can cross blood brain barrier and act as energy substrate for the brain. Recently “Dead in bed syndrome” - a term used has been described the sudden unexplained death of young people with type 1 diabetes mellitus which could be related to Hypoglycemia Associated Autonomic Failure (HAAF) rather than autonomic neuropathy [12].

CLINICAL FEATURES

The symptoms of hypoglycemia can be divided into two categories i.e., symptoms of Autonomic dysfunction (Adrenergic and cholinergic) and symptoms of Neuroglycopenia. Norepinephrine, released by sympathetic postganglionic neurons, but also epinephrine, released from the adrenal medulla, mediates adrenal symptoms such as palpitations, tremors and anxiety. Sweating, hunger and paresthesia are all cholinergic symptoms caused by acetylcholine release from sympathetic post ganglionic neurons. Headache, cognitive disturbances, hemiplegia, coma and convulsions are all symptoms of neuroglycopenia. In healthy human individuals undergoing hypoglycemia, Mitrakou et al. investigated the hierarchy of glycemic thresholds for the release of counterregulatory substances, the onset of symptoms, and the development of brain impairment, as illustrated in figure -1 [13]. It is important to note that Few patients may show features of neuroglycopenia without hypoglycemia due to relatively less glucose transport to brain. It may be due to GLUT deficiency or poorly controlled type 1 DM. A Low CSF glucose in presence of normal serum glucose specially in presence of chronic neurological symptoms gives important clinical clue for GLUT1 deficiency disease.

HEADACHE

Fasting and hunger have been associated with precipitating factor for migraine attacks. However, differentiating a hypoglycemia induced headache from migraine is a clinical challenge, especially in a patient with history migraine. Following are the diagnostic criteria for headache attributed to fasting according to ICHD - 3, the diagnostic criteria for headache are

- A. Diffuse headache not fulfilling the criteria for Migraine or any of its types
- B. The patient has fasted for ≥ 8 hours

C. Evidence of causation demonstrated by both of the following:

1. headache has developed during fasting
2. headache has significantly improved after eating

D. Not better accounted for by another ICHD-3 diagnosis.

Cognitive disturbance and dementia

Hypoglycemia can affect cognition and learning abilities. Modalities that can be affected are memory, language, attention, learning, simple motor abilities and visuospatial orientation.

Hypoglycemic hemiplegia

Hypoglycemia masquerading as acute stroke has been frequently encountered, although a rare phenomenon as per recent literature review, 2-4% of hemiparesis is due to hypoglycemia [14]. Hypoglycemia should not be forgotten when treating a patient of acute stroke. Lawrence Tierney stated: ‘A stroke is never a stroke until it has received 50 of D50’. However, in the present time, with sugar monitoring facilities in the emergency, hypoglycemia can be detected immediately.

Hypoglycemic coma

Permanent brain damage is rare, but may be seen with prolonged hypoglycemia. To differentiate hypoglycemic coma from its mimickers, a careful history with brain imaging is necessary. Of note, septic encephalopathy may present with hypoglycemia [15]. Neuron specific enolase (NSE) and S-100, two biochemical indicators for neuronal damage, have been identified as potential predictors of death or poor outcome in individuals with hypoglycemic coma. These markers are not specific for hypoglycemia but can be elevated in any neuronal damage conditions, however previous case reports have shown markedly elevated levels in patients with Hypoglycemic brain injury [16].

Seizures

Acute symptomatic seizures are seizures that occur within a short period of time after an acute brain insult, which can be infectious, inflammatory, metabolic or toxic in nature. During hypoglycemia, excitatory amino acids aspartate and glutamate increase out of proportion to a slight rise in extracellular GABA, which acts as potential epileptic foci [17]. Generalised tonic clonic seizures have been observed with hypoglycemia.

Investigations

The first step in evaluating neuroglycopenic patients is to take a thorough medical history, which

includes the nature and timing of symptoms (especially in connection to meals), the presence of underlying illness, and surgical & medication history. In patients with documented hypoglycemia, based on history, examination and available laboratory data one can often deduce the mechanism of hypoglycemia. Hypoglycemic symptoms with plasma glucose of less than 70 mg/dl establish the diagnosis. Routine investigation including – Complete hemogram, plasma glucose level, Insulin, C-peptide, serum electrolytes, Liver and kidney function test, serum cortisol, thyroid level and growth hormone. Neuron specific enolase and S-100 can be done as a biomarker for neuronal damage. CSF sugar measurement may have diagnostic role in selected patients of younger age presenting with intractable seizure or other movement disorders related neurological deficit.

IMAGING

In acute setting patient invariably undergoes Non contrast CT brain which is often non diagnostic. MRI brain is the imaging modality of choice in cases of neuroglycopenia. Hypoglycemic coma has predilection for posterior and deep regions of the brain. The earliest changes are observed on DWI sequences. However, commonest findings on MRI are symmetric hyperintensities on T2-weighted & FLAIR images and diffusion restrictions in the gyri of parieto-occipital & temporal regions. The regions involved are white matter, mainly the centrum semiovale, internal capsule, corona radiata and splenium of corpus callosum, also involves cortex, neostriatum and hippocampus [18]. The basal ganglia involvement suggests poor outcomes. The extend of these abnormalities depends on duration and severity of hypoglycemia. Changes observed in MRI is usually bilateral though asymmetrical or rarely unilateral can occur. Contrast enhancement is absent but rarely can be seen. These changes are usually reversible once the symptoms have resolved. Thalamus, cerebellum and brainstem are often spared, which are commonly affected in cases of hypoxic brain injury [19].

On the basis of signal abnormalities, three imaging patterns have been described [20] –

1. Predominately gray matter involvement (cortex, neostriatum and hippocampus)
2. Predominantly white matter involvement (internal capsule and splenium of corpus callosum)
3. Mixed pattern involving both white and grey matter.

Figure 2 & 3 shows diffusion restriction with corresponding ADC hypodensity, hyperintensity in T2 weighted image and usually isointense on T1 images

ELECTROENCEPHALOGRAM (EEG)

Hypoglycemia associated EEG changes are observed in patients with normal hypoglycemic awareness. Most common EEG finding in hypoglycemia is diffuse slowing (theta and delta rhythm) with abnormal spike changes [21]. EEG changes are noted in all the cortical regions without any interhemispheric asymmetry but few studies have reported variation in distribution of eeg changes based on glucose levels [22]. Maximum slowing in frontal cortex has been observed in cases of mild hypoglycemia with blood sugar levels between 43-54 mg/dl as anterior cerebral cortex is more sensitive to hypoglycemia, similarly in cases of profound hypoglycemia with blood glucose level between 30-50 mg/dl has posterior predominant EEG changes, mainly in parieto-occipital and temporal regions [23]. EEG changes doesn't correlate with age & duration of Diabetes mellitus, HbA1c levels, initial concentration of glucose and rate of change in glucose levels.

MANAGEMENT

Acute neuroglycopenia is common mimicker of acute stroke or transient ischemic attack. Following are the medical conditions that can be mistaken for hypoglycemia - seizure disorder, sepsis, syncope, drug and alcohol intoxication, psychosis, sympathomimetic drug, Narcolepsy and depression. Acute intervention to minimize neurological damage - if the patient is capable and willing, an oral glucose tablet or glucose-containing fluids, candies, or meals may be administered. If the patient is unable or reluctant to do so due to neuroglycopenia, glucose (25 g) should be given intravenously, followed by a glucose infusion guided by serial plasma glucose measurement. SC or IM glucagon (1mg in adults) can be administered if IV treatment is not available. To prevent Wernicke's encephalopathy in alcoholic patients, IV thiamine at a bolus of 12 mg/kg before starting glucose treatment is recommended. Maintenance therapy to avoid hypoglycemia recurrence - the clinical response to IV glucose in hypoglycemia is quick and dramatic. If the symptoms of neuroglycopenia do not improve within 5-10 minutes, an alternate diagnosis should be considered. Evaluation and treatment of the underlying aetiology - identify hypoglycemic mechanisms, stop offending medicines, cortisol or growth hormone can be replaced if levels are low. If endogenous hyperinsulinemia is found, surgical excision of the insulinoma is recommended, followed by medical treatment with diazoxide or octreotide if surgery is not an option.

CONCLUSION

This is a comprehensive review on neuroglycopenia which explains effect of hypoglycemia in the

brain, counter regulatory neuroendocrine response, evaluation of the patients with their management. Prevention is the key in cases of neuroglycopenia. One of the terrible prognostic factors is profound and sustained hypoglycemia; others include low lac-

tic acid levels, increased body temperature and post-treatment hyperglycemia. Patient education and lifestyle adjustments are part of the nonpharmacological management of recurrent hypoglycemia.

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