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WHITE MATTER CHANGES IN PATIENTS WITH DIABETES MELLITUS

Neurology

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ABSTRACT

Diabetes is a metabolic disorder that affects many systems in the body. Nephropathy, retinopathy, peripheral neuropathy, and cardiac disease are major complications in the advanced stage of the disorder. Sub-cortical white matter hyperintensities (WMH), which are seen as multifocal and diffuse areas of hyperintensity on T2-weighted magnetic resonance imaging (MRI), are strongly associated with diabetes and some other conditions. We review the white matter changes and some peculiar neurological manifestations of uncontrolled blood sugar levels.

KEYWORDS

White Matter, Blood Sugar, MRI Brain, Non-ketotic coma

Background:
Diabetes is a metabolic disorder that affects many systems in the body. Nephropathy, retinopathy, peripheral neuropathy, and cardiac disease are major complications in the advanced stage of the disorder [1]. Although it is known that diabetic patients are at increased risk for stroke, little is known about the risk for other brain pathology, such as that associated with neurodegeneration or small vessel disease [2]. Sub-cortical white matter hyperintensities , which are seen as multifocal and diffuse areas of hyperintensity on T2-weighted magnetic resonance imaging (MRI), are strongly associated with diabetes, hypertension, and other cardiovascular risk factors [3-5]. WMHs have been prospectively linked to dementia, functional decline, and silent infarcts therefore, WMHs may be manifestations of clinically significant cerebral microvascular disease [4-6].

Brain changes in diabetes:
Numerous studies have shown an association between type 2 diabetes and mild to moderate cognitive impairment and an increased risk of dementia [7,8]. However, the underlying mechanisms are still unclear. Structural correlates of diabetes-related cognitive impairment can be assessed with brain magnetic resonance imaging (MRI) [9]. The association of type 2 diabetes and white matter hyperintensities (WMH) is less robust, since some studies found an association to more extensive WMH [10], whereas other studies did not [11].

Relatively stable plasma glucose levels are essential for survival and are maintained through a highly complex network of enzymes, hormones, and signaling mechanisms, with insulin playing a dominant role [12]. Enterically absorbed glucose is transported by the portal circulation to the liver, which is the primary organ involved in glucose homeostasis. Here, excess glucose is converted to glycogen and stored for subsequent use. A drop in plasma glucose level triggers a fall in plasma insulin levels, increased glucagon secretion, glycogenolysis, and gluconeogenesis (primarily in the liver) and helps to restore plasma glucose levels whenever needed [12].

Seizures associated with nonketotic hyperglycemia(NKHG):
Epileptic seizures are common in hyperglycemia and are often presenting features, particularly in NKH with blood glucose levels more than 20 mmol/L. [13-15] NKH-related seizures are mostly focal motor, sometimes it can be epileptia partialis continua (EPC). In this patient, hyperglycemia was de novo. In patients presenting with EPC, NKH should be considered and ruled out. Seizures associated with NKH are resistant to antiepileptic drugs and remit with correction of hyperglycemic state [16]. In general, hyperglycemia-induced oxidative injury to the vascular endothelium, either by interruption of focal cerebral blood flow or by focal breach of the blood-brain barrier, induces serious diabetic complications in the brain. High glucose was shown to activate several proteins involved in apoptotic cell death, including anti-apoptotic and pro-apoptotic Bcl-2 family members and caspases [17,18]. Therefore, neuronal protein's activity is one possible cause of neuronal damage induced by severe hyperglycemia, but the molecular mechanisms are unclear. Other studies suggested that insulin deficiency played a compounding role to that of hyperglycemia in neuronal damage underlying primary diabetic encephalopathy [19]. The study of postictal MRI in brain lesions from hyperglycemia confirmed that the subcortical high signal represents a cell edema [20,21], whereas the study of postictal MRI in non NKH seizures confirmed that the cortical high signal is a cell edema compatible with laminar necrosis [22]. It is unclear how hyperglycemia precipitates seizures. Elevated blood glucose levels have a pro-convulsant effect and reduce seizure threshold [23-25]. As pointed out earlier, a hyperglycemic state also induces cellular anaerobic metabolism and depletes GABA, which is an inhibitory neurotransmitter [24]. The presence of con- current ketoacidosis is thought to offer some protection against seizures because ketone bodies can serve as substrate for GABA generation [25].

Chorea, Hyperglycemia, Basal Ganglia Syndrome (C-H-BG) :
HC-HB refers to an involuntary, nonrhythmic, and poorly patterned movement disorder that involves one side of the body [26,27]. It most commonly results from a vascular insult involving the contralateral basal ganglia [26-28]. NKHG is the second most common cause for such presentation [26]. Occasionally, HC-HB may result from neoplastic or infective conditions involving the brain [27, 29]. The pathogenesis of C-H-BG syndrome is not fully understood but several theories have been suggested. Hyperglycemia im¬pairs cerebral autoregulation, causing hypoperfusion and the ac¬tivation of anaerobic metabolism and depletion of gammaami¬nobutyric acid (GABA) in basal ganglia neurons [30,31]. GABA is the main inhibitory neurotransmitter in the basal ganglia. GABA and acetate are depleted rapidly in non-ketotic hyperglyce¬mia, causing a reduction in acetylcholine synthesis [31,32].

The hyperviscosity induced by hyperglycemia causes a disruption of the blood brain barrier and transient ischemia of vulnera¬ble striatal neurons [32]. The synergistic effects of uncontrolled hyperglycemia and vascular insufficiency cause an incomplete transient dysfunction of the striatum, which eventually leads to hemichorea-hemiballism in these patients [33]. Magnetic resonance imagining (MRI) shows T1-weighted hyperintensi¬ties in striatum and globus pallidus, with restricted diffusion on diffusion-weighted imaging [34]. An abnormal signal may extend into the globus pallidus and up to the medial part of the cerebral peduncle in the midbrain along the striatonigral pathway [35]. Magnetic resonance spectroscopy may show low N-acetylaspartate to creatinine ratio and high choline-to-cre¬atinine ratio and associated lactate peak [36]. Positron emis¬sion tomography (PET) has shown decreased glucose metab¬olism in the basal ganglia.

White matter hyperintensities in patients with type 2 diabetes:
White matter hyperintensity (WMH) is a lesion that appears around the cerebral ventricles and/or deep subcortical white matter, showing high intensity in magnetic resonance imaging (MRI) T2-weighted and fluidattenuated inversion recovery (FLAIR) images [37]. WMH can be

distinguished from brain infarction, as the former shows brighter intensity in FLAIR images and darker intensity in T2 images [38]. WMH has been considered to reflect damage to small vessels in periventricular and subcortical areas, and autopsy studies have shown that the pathogenesis of WMH includes myelin pallor, dilatation of perivascular spaces and tissue myelin rarefaction [39,40]. It has been reported that WMH is related to the incidence of stroke, [41] but recent evidence has accumulated to suggest that it also has an influence on cognitive decline [42] or functional disability [43] in the normal elderly population. In contrast, as hypertension is known to be the greatest risk factor for WMH progression, several recent reports have shown a significant relationship between DM and WMH [44-46].

Tamura Y et al, performed a cross-sectional study to investigate the associations of WMH with cognitive function and instrumental ADL (IADL), as well as metabolic and vascular risk factors in a total of 178 elderly patients with diabetes [47]. The study assessed WMH volumes and the functional status of cognition and IADL. In this study, white matter hyperintensity volumes were evaluated using Software for Neuro-Image Processing in Experimental Research (SNIPER), volumes were calculated as the total volume in the cerebrum and were divided in two parts (periventricular hyperintensity [PVH] and deep WHM [DWMH]), which were distinguished using SNIPER. They concluded that, a significant negative association between WMH and cognitive function and between WMH and IADL status in a group of elderly patients with DM. Glucose variability is the most influential factor, and the avoidance of glucose fluctuations may be a key strategy to prevent WMH and the further progression of cognitive impairment and IADL decline in elderly patients with DM [47].

Conclusion:

- Abnormal variations in plasma glucose levels are common observations and can show various imaging findings. Clinical presentation is often nonspecific, and objective findings of HC-HB, memory loss, hemiparesis, and coma often clinically mimic stroke.
- Glucose variability is the most influential factor, and the avoidance of glucose fluctuations may be a key strategy to prevent WMH and the further progression of cognitive impairment and IADL decline in elderly patients with DM
- A vigilant work up and early diagnosis would expedite correct treatment and limit neuronal injury in the early stage, when changes are potentially reversible.

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