RESEARCH ARTICLE

Diabetic Central Neuropathy: A Cause of Central Sleep Apnea

Author

John Malone

Email: j.boyne@mumc.nl

Abstract

Diabetes Mellitus, prolonged hyperglycemia, causes peripheral and central nervous system dysfunction. Chronic hyperglycemia causes changes in the sorbitol, inositol and taurine content of peripheral and central nervous system tissue. The proteins in these tissues are also altered by glycosylation end products. The changes in metabolites impair growth and development of nerves and the increased glycosylation end products make the proteins stiff, sticky and prone to physical injury. This activity stimulated by hyperglycemia impairs the normal function of the peripheral and central nervous system. Manifestations of this tissue injury have been loss of sensation and increased pain in the extremities, loss of proprioception when standing, dysregulation of gastrointestinal motility, and heart rate. Also noted in children are delayed maturation of cognitive function during childhood and more rapid decline of cognitive function with increasing age and increasing HbA1c.

Sleep apnea has become an important cause of heart failure and death commonly linked to type 2 diabetes and obesity. Continuous pressure airway pressure (CPAP) does overcome the periods of obstruction and prevents the morbidity associated with obstructive sleep apnea (OSA). Forty-Six percent of type 1 diabetic patients have absence of effort sleep apnea which means it is a central lack of drive to breath. There is evidence of change of structure in the medulla of subjects with type 1 diabetes as well as evidence of injuries in the medulla that cause cessation of breathing. These observations indicate that central neuropathy caused by hyperglycemia does cause central sleep apnea and possibly death.

Introduction

Central nervous system dysfunction (Central Neuropathy) is caused directly by hyperglycemia (diabetes mellitus) and reduced vascular flow caused by atherosclerosis which is promoted by diabetes mellitus [1,2,3]. Clinical diabetes mellitus is associated with structural and functional damage to the central nervous system [4]. Essential intelligence, psychomotor processing speed, mental flexibility, and attention to detail are specific skills that are reduced [5]. Memory and learning skills in children with early-onset diabetes are variably impaired [6], particularly in those with a history of recurrent hypoglycemia [7]. Neurophysiologic studies provide further evidence of central nervous system (CNS) changes in type 1 diabetes that are associated with hyperglycemia. Cerebral hypoperfusion has been documented in adolescents [8] and young to middle-aged adults [9], with no clinical evidence of cerebrovascular degeneration that is commonly observed in elderly patients with type 1 diabetes. Electroencephalogram (EEG) studies have shown increased delta and theta slow-wave and decreased alpha peak frequencies in both adults [10] and children [11] with diabetes. Increased response latencies, suggestive of slow mental processing, have also been found in evoked potential studies [11]. These observations are particularly evident in individuals with early-onset diabetes and a history of severe hypoglycemia [11]. A small number of structural neuroimaging studies have demonstrated that patients with type 1 diabetes have reductions in brain grey matter, microstructural damage to brain white matter, and alterations in levels of brain neuro-metabolites (particularly glutamate). These changes appear to be related to elevated HbA1c levels. A recent clinical report suggests that high levels of glucose (HbA1c) are associated with more significant microvascular disease, as demonstrated during a 12-year evaluation [12]. Individuals participating in the DCCT/EDIC when they entered their late 50s or early 60s show a significant cognitive decline, particularly in those with higher HbA1c levels, elevated systolic blood pressure, and microvascular complications [13]. Long-standing, high average blood glucose levels (high HbA1c) are associated with declining cognitive function.

Brain dysfunction is also associated with coincident low blood glucose levels. There are clinically evident modest reductions in cognitive efficiency and evidence of central brain wave slowing measured using electroencephalography. Reduced evoked potential studies have been attributed to changes in cerebral blood flow associated with low blood glucose levels [10]. These abnormalities are transient and completely resolve with the return of normal blood glucose levels. As with structural CNS damage, there is little agreement on which biomedical factors increase the risk of functional changes. Although a growing body of literature indicates that patients with higher HbA1c levels are more likely to manifest permanent neurocognitive dysfunction, one cannot yet rule out the possible contributory role of recurrent, moderately severe (subclinical) hypoglycemia.

Structure and Cognition

Magnetic resonance imaging (MRI) observations (6,7,10–14) bring attention to the fact that hyperglycemia is associated with structural changes in the developing brains of children [15] and even in the more mature brains of adults [16]. The abundance of glucose in the brain is also changing the metabolites in that tissue (7). In laboratory animals and humans, it has been noted that hyperglycemia in the brain is associated with reduced brain taurine (17) and increased brain inositol (18). Reduced or absent insulin is the cause of type 1 diabetes which results in hyperglycemia. Insulin and taurine are neurotrophic agents required for neuronal growth and development. Reduced levels of insulin and taurine may be the cause of decreasing brain growth and development in children with diabetes. Elevated inositol is a metabolic indicator of brain gliosis [19], a marker of brain injury. The increased inositol in the brain may reflect gliosis (16) and increased amylin production, a mechanism for Alzheimer's disease. These observations suggest that hyperglycemia, a biomarker for diabetes, is toxic for the brain at any stage of life rather than a helpful brain protection from symptomatic hypoglycemia. Participants in the DCCT/EDIC study were followed with completed cognitive assessments at entry into the study, 2, 5, 18, and 32 years. The cognitive function of 1051 T1D subjects in this study declined in psychomotor and mental efficiency five times more from 18 to 32 years than from baseline to 18 years. Higher levels of HbA1c and elevated systolic blood pressure were associated with more significant declines in psychomotor and mental efficiency [17]. Hearing impairment is also known to contribute to cognitive decline with increasing age [19]. Hyperglycemia, elevated HbA1c, is also a significant predictor of hearing impairment in type 1 diabetes [20]. Hearing impairment is now shown to have an indirect central effect on cognitive function in subjects who have diabetes.

Changes in brain structure occur in the brains of subjects who have diabetes mellitus indicating that hyperglycemia can change the anatomy of the CNS. Another study shows measurable changes in brain structure occur in non-diabetic adults 30 minutes after the oral consumption of 53.7 grams of glucose [21]. The structural change associated with higher glucose is loss of substance and an increase of ventricular volume. This apparent loss of brain structure suggests brain atrophy. Still, it could also reflect a change of brain hydration as indicated by the acute changes in brain ventricle size occurring in non-diabetic individuals in response to a quick rise and fall of glucose levels [21].

Parkinson's Disease

A new report now provides evidence that diabetes mellitus is a determinant increasing the onset and progression of the movement disorder Parkinson's disease (PD), and the cognitive decline associated with PD [22]. Parkinson's disease represents another CNS defect caused by hyperglycemia. There is evidence for shared biology between type 2 diabetes (T2DM) and Parkinson's disease [23]. In T2DM, islet amyloid polypeptide (IAPP) or amylin aggregates to form amyloid plaques in the pancreatic islet cells [24]. Similarly, PD is pathologically defined by the

accumulation of alpha-synuclein intraneuronally. Some evidence suggests that alpha-synuclein aggregation in PD occurs faster in the presence of IAPP [25]. Using meta-analyses, the researchers at the Preventive Neurology Unit in Quebec concluded that T2DM is associated with an increased risk for PD and may contribute to the faster decline of motor and cognitive skills [22].

Abnormal Gait and Falls

Older patients with diabetes are known to have gait instability and falls [26]. The presence and severity of diabetic peripheral neuropathy (DPN) have been shown to increase postural instability [27, 28]. It has been reported that morphologic and structural changes are also occurring in the peripheral vestibular system of animals with experimentally induced diabetes [29]. These animals had an overproduction of extracellular matrix and a higher level of lysosomes and lipid droplets in the connective tissue of the utricle and the saccule [29]. The accumulation of extracellular matrix reduces diffusion of oxygen, nutrients, and waste products. The reduced oxygen and nutrients causes' hair cell degeneration. Hair cell degeneration, plus thinning of the myelin sheath and smaller axon fiber diameter, is evidence of neuronal physical damage that is associated with hyperglycemia [29]. There is clinical evidence of vestibular dysfunction in subjects 6 to 28 years of age who have type 1 diabetes mellitus [30]. These individuals have impaired optokinetic responses and eye-tracking and reduced responses to caloric stimulation and positional nystagmus. The frequency of these abnormal responses in young people was directly related to the longer duration of diabetes and severity of retinopathy and neuropathy [31], suggesting that glucose is the toxin. Proprioception is the subconscious sensation of body and limb position and movement obtained from non-visual sensory input from muscle spindles and joint capsules. The cerebellum seems to be the site of proprioception based on lesion-symptom mapping [32]. Ataxia of stance and gait is correlated with atrophy of the medial/intermediate cerebellum and ocular disorders within the medial cerebellum [33]. Defects in this area of the brain may contribute to the poor balance and falls for which people with diabetes are at significant risk [34].

Sleep Apnea

Obstructive sleep apnea (OSA) is a chronic sleep disorder frequently found in subjects with type 2 diabetes mellitus (T2DM) [35]. Features of OSA include intermittent hypoxemia and sleep fragmentation [35]. The mechanism of OSA is obstruction of the upper airway frequently caused by exogenous obesity that physically blocks the upper airway. The relationship between OSA and T2DM has been related to the link between T2DM and obesity and its potential for physical airway obstruction. However, the prevalence of sleep apnea in subjects with type 1 diabetes is significantly higher than in the general population [36]. Sleep apnea was found in 46 % of type 1 diabetic subjects with a mean BMI (24.4-26.4 kg/m2), suggesting that obesity is an unlikely cause of airway obstruction [36]. Central sleep apneas (CSAs) occur when there is a transient

reduction by the pontomedullary respiratory rhythm generator.

In contrast, obstructive sleep apnea (OSA) involves continuous respiratory efforts made against a closed airway [37]. In most forms, CSA is manifest by phases of hyperventilation alternating with lack of effort apnea [38]. This abnormal type of breathing is seen in preterm infants [39], adults sojourning to high altitudes [40], and one-third of adults in heart failure [41]. This type of breathing is of concern when it causes arterial oxygen desaturation, hypercapnia, post-apnea arousals from sleep, and swings in arterial blood pressure [42]. These events can also cause cardiac arrhythmias and are strongly associated with mortality [42, 43].

Breathing is a complex process that originates in the medulla [44]. Breathing is an automatic and rhythmic act produced by networks of neurons in the pons and medulla. The neural networks direct muscles that form the walls of the thorax and abdomen and create pressure gradients that move air into and out of the lungs. Respiratory neurons (neurons phasically firing in synchrony with the respiratory cycle are located in three main brainstem areas: 1) The dorsal respiratory group, 2) The ventrolateral medulla from the level of the spinal-medullary junction through the level of the facial nucleus, 3) in the pontine respiratory group within the dorsolateral pons. This aggregate of brainstem respiratory neurons are interconnected and, together with respiratory-related sensory afferents, are collectively responsible for automatic control of breathing and adaptive changes in breathing to address homeostatic and environmental challenges [44]. In addition, electrical stimulation of the amygdala, hippocampus, anterior-parahippocampal, and anteromedial fusiform gyri in both hemispheres independently stops central breathing [45]. This effect of electrical stimulation suggests that physical or chemical disruption of these structural areas of the brain could cause breathing to stop, or apnea.

Since CSA is associated with injury and biochemical alterations to neurons in the CNS, it is reasonable to believe that hyperglycemia (diabetes mellitus) may cause appropriate changes in the CNS structure and biochemical milieu to cause CSA. CSA appears to be an acquired dysfunction of breathing caused by CNS injury which could be hyperglycemia in subjects who have diabetes mellitus. CSA does worsen renal and cardiac function independent of diabetes. As a complication of diabetes, it may magnify pathology in patients who have diabetes mellitus. CSA has also been shown to cause sudden nocturnal death during sleep in the general population. Nocturnal sleep death is a problem commonly attributed to hypoglycemia in people who have insulin-requiring diabetes. CSA is a clinical problem that should be screened for in all subjects with Type 1 diabetes more than ten years, especially those over 50 years of age, because it is an acquired breathing defect [44] that will make other hyperglycemic complications worse. It is also important to remember that these at-risk subjects are more likely to have CSA than OSA because the effective treatment of sleep apnea requires understanding the mechanism of dysfunctional breathing to select the most appropriate treatment equipment [44]. Each

patient should have a sleep study performed to define the type of sleep apnea and determine whether CPAP or BIPAP should be used to manage the problem [46].

In conclusion

Individuals who have had diabetes mellitus for ten or more years [47] are at risk for manifesting signs/symptoms of central neuropathy. The clinical signs and symptoms include cognitive decline, hearing loss, movement disorders (Parkinson's disease), loss of balance, and central sleep apnea. Central sleep apnea will worsen the cardiac, renal, and cognitive decline already associated with diabetes. Sleep apnea is an accepted cause of sudden nocturnal death in the general population. Still, it is frequently overlooked in subjects with insulin-requiring diabetes who many believe have sudden nocturnal death as the result of severe hypoglycemia. Finding unexpected central sleep apnea as a manifestation of Diabetic Central neuropathy should lead to sleep management that prevents sudden nocturnal death caused by diabetes-induced central sleep apnea.

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