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Adult-onset diabetes mellitus and its neurological perspective

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Abstract

Type 2 Diabetes Mellitus is one of the most common chronic diseases across the world, and number of diabetic patients is on the rise. Diabetes Mellitus has been established as one of the leading causes of morbidity and mortality throughout the world. Most of these ill-effects on health can be attributed to the long term microvascular and macrovascular complications of diabetes mellitus.

Neuropathy is the most common and troublesome complication which very often remains silent and unnoticed by the patient until they develop a diabetic foot. Screening and early identification of neuropathy offers a crucial opportunity for the patients with diabetes to actively modulate the course of suboptimal glycemic control to currently recommended targets and to implement improved foot care before the onset of significant morbidity.

Keywords: NIDDM, CAD, CVA.

Introduction

Diabetes mellitus is a complex and heterogenous disorder of human beings known since ancient origin and marked with persistent high blood sugar in blood stream well beyond the defined normal range.

There are two main types of diabetes Type I and Type II:

Type I (insulin dependent diabetes mellitus - IDDM) is a chronic illness which occurs due to T-cell-mediated autoimmune destruction of the insulin producing beta cells of the pancreas. This can occur at any age but the peak is around puberty, usually requiring insulin lifelong and more threatened complication of both disease entity and the long-term use of insulin.

Type II (non-insulin dependent diabetes mellitus - NIDDM) occurs because of relative insulin deficiency, which may be due to defective insulin secretion, reduced insulin-secretion or impaired insulin sensitivity in peripheral metabolic organs, mostly in liver and also in muscles as a result of insulin resistance. Hyperglycemia is the final result of insufficient insulin action on the target substrate. A severe deficiency of insulin produces ketosis and alterations of fatty acids, lipids, and protein turnover as well.

Complications of diabetes may be either microvascular including nephropathy, neuropathy, and retinopathy (the three well known Pathy) or macrovascular such as peripheral arterial disease, CVA and coronary artery disease (CAD).

It is well known that acute or chronic hyperglycemia/ hypoglycemia can affect mainly the brain but also the other part of neuraxis. Conversely, the brain also has a role in maintenance of glucose in body (homeostasis). Hormones such as insulin and other like leptin act in the hypothalamus to regulate energy balance and glucose metabolism.

Cerebrovascular disease

There is an increased incidence of stroke due to increased risk of atheroma in large, medium, and small vessels, as well as microangiopathy — arterial and venous (arterial more than venous).

Various studies proved that patients with uncontrolled hyperglycemia have a two-fold more chances of acute ischemic cerebrovascular event than those with euglycemia and it was established that seen that stroke occurred at a reasonably constant rate of a 5 year or longer follow-up.

The stroke registry system suggest that the commonest type of ischemic strokes was small artery disease (lacunar), followed by large artery disease (mostly MCA), and embolism from the heart (embolic).

Hyperglycemia is common during the acute period of stroke and can occur in patients either with/without diabetes.

It should be noted that high levels of glucose on admission do not distinguish between stress hyperglycemia and diabetes, however raised amounts of HbA (6.5%) could help to identify people with previously undiagnosed diabetes. A persisting hyper glycemia after ischemic stroke is an independent determinant of infarct expansion and is consequently associated with worse clinical outcome. Possible mechanisms accounting for this effect include promotion of disruption of the blood-brain barrier, and accumulation of lactate and acidosis in the penumbra tissue facilitating its conversion to infarction, enhancement of brain edema formation and possibly through aggravation of ischemic damage by disturbing recanalization and increasing reperfusion injury.

Furthermore, a novel finding is that the serial profile of glycemic status is more robust indicator of infarct evolution and clinical outcome than the isolated measure of glucose upon hospital admission. Hyperglycemia may influence neuronal damage through marked tissue acidosis and lactate generation but the exact mechanism involved in infarct evolution is still poorly understood. Many studies have shown a benefit from lowering hyperglycemia with intravenous insulin in terms of reduction and mortality and morbidity in diabetic patient with acute stroke. Thus presence of hyperglycemia itself is a risk factor for poor outcome in patients with ischemic stroke.

Conversely, acute stroke itself can give rise to abnormalities in glucose Meta bolism, which in turn could affect outcome of the stroke.

The effect of hyperglycemia may also be dependent on the type of stroke. The association between hyper glycemia and poor outcome after stroke is mainly relevant to patients with large vessel infarction.

Even after thrombolysis, patients with high admission glucose levels and history of diabetes mellitus are associated with poor clinical outcome, well evident in large cohort-based experience.

However, though it should be logical that the treatment of hyperglycemia would be helpful, this has not been demonstrated clearly and in fact danger of worsening due to hypoglycemia remains a risk of treatment.

Therefore, the goal of therapy should be to normalize glucose levels not only during the management of acute stroke duration but also later in rehabilitation phase for an overall better outcome and a close watch should be

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instituted to avoid hypoglycemia with its consequent secondary deterioration in overall clinical recovery.

Cognitive impairment and hyper glycemia

A persistent high blood sugar level is associated with high incidence of cognitive impairment and subsequent dementia specially in those patients who have uncontrolled type 2 diabetes mellitus. The mood changes and poor memory function, possibly by causing alterations in cerebral blood flow or osmotic changes in neurones and correction of acute hyper glycemia are rewarding beyond doubts. Chronic hyper glycemia may cause structural changes in the brain, such as cerebral micro vascular disease, and there are strong associations between the presence of retinal micro vascular abnormalities and cognitive function. Patients treated with insulin generally shows mood changes and especially behavioral changes in form of irritability, anger, restlessness along with poor ability to concentrate and at times difficulty in performing the activity of daily life may be because of persistent hyper glycemia. In a few targeted studies over both the types of diabetic patients with uncontrolled hyper glycemia, the cognitive functional scale was lower as compared to matched cohort. None of the employed anti diabetic agent is shown to improve the cognition in these patients but short-term improvements in glycemic control may be cognitively beneficial presumably by factors such as changes in regional cerebral blood flow or osmotic shifts across neuronal membranes.

The higher incidence of Alzheimer's dementia in type 2 diabetes is associated with factors like hyperglycemia, hyper insulinemia and insulin resistance, and other factors such as hyper cholesterolemia, hypertension, and obesity (a previous syndromic mani festation as – syndrome X).

Diabetic encephalopathy

Oxidative stress and inflammation are being thought of as important in causation of diabetic encephalopathy. It establishes a strong link between uncontrolled long duration glycemic status and the future development of AD. It is characterized by structural and electro physiological CNS changes.

Diabetic encephalopathy along with chronic hyper glycemia and dyslipidemia. The exact pathophysiology and mechanism of generation of this complex entity is not well understood till date but the cause-and-effect relationship is beyond doubt.

The signalling mechanisms by insulin and insulin-like growth factor type I and II (IGF-I and IGF-II) is the most acceptable mechanism for development of AD in these patients.

Alzheimer's disease is fundamentally a metabolic disease with substantial and progressive derangements in brain glucose utilization and responsiveness to insulin and IGF stimulation. The significance of these results is that therapeutic strategies designed to treat diabetes mellitus, obesity, and systemic insulin resistance could help slower the progress or reduce the severity of AD.

Insulin deficiency through multiple mechanisms is thought to result in defects in neuronal integrity, connectivity, and neuronal loss of the developing brain especially in type 1 diabetic patients.

Hypoglycemia

Often a result of OHA, excess of insulin in combination with poor dietary intake manifesting as tachycardia, loss of consciousness, hunger, increased perspiration, tremors as a combined result of neuroglycopenia and adrenergic outburst. In the presence of beta blockers or diabetic autonomic neuropathy, these initial warning signals of hypoglycemia may be masked. This may result in a delayed diagnosis of hypoglycemia.

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The symptoms of decreased glucose in the CNS are headache, malaise, progressive mental confusion, and gradually worsening level of consciousness. Seizures and myoclonic jerks may also occur. At a level of about 10 mg /dl blood glucose the medullary phase of hypo glycemia occurs. This manifests as bradycardia, shallow breathing, dilatation of pupils, and decreased tone and deep coma.

Reversal of adrenergic symptoms is rapid, but reversal of neuro glycogenic symptoms may be slower and prolonged hypoglycemia may result in persistent deficits.

In hypo glycemic encephalopathy brain-imaging abnormalities involving the basal ganglia, hippo campus and cortical area predominantly in the occipital lobes with extensive, bilateral signal changes on MR sequences depending upon the severity and duration of hypo glycemia.

Cortical laminar necrosis seen as high signals along the cerebral cortex on diffusion-weighted magnetic resonance imaging (MRI), during the subacute phase of hypo glycemic encephalopathy has been reported. The electro encephalogram (EEG) demonstrates slower background which correlates with the confessional state.

Extrapyramidal Involvement

In rare cases hemi ballism-hemichorea is caused by nonketotic hyperglycemia. The occurrence of Epilepsia partialist continua (EPC) is a more common entity than hemi ballism-hemichorea, which gets controlled only with correction of hyperglycemia and in majority of cases the effect of AED commences only with hyper glycemic control.

A correction of associated electrolyte imbalance is also mandatory to prevent the recurrence of this difficult to treat symptomatic epilepsy condition. The high incidence of EPS is noted in patients with advancing age.

Conclusion

A good and prompt glycemic control is the corner stone of management of patient with diabetic mellitus to avoid all the minor and major complications of CNS and to prevent high morbidity and mortality associated with hyperglycemia despite the poorly understood exact pathophysiological changes in the neuraxis.

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