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Diabetic Central Neuropathy: CNS Damage Related to Hyperglycemia

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Diabetes is a syndrome defined by higher than normal blood glucose levels. Those higher blood glucose levels are associated with the development of physical abnormalities termed complications. Those abnormalities are found in small blood vessels and cause pathology termed retinopathy and nephropathy. Small-vessel abnormalities are part of cardiovascular and peripheral nerve pathology as well. Larger–blood vessel abnormalities are manifest as atherosclerotic plaques that stiffen and reduce blood flow while causing embolic occlusions. This results in ischemic hearts, lungs, and brains, causing life-devastating and -ending events. High glucose levels have been associated with nonvascular damage to the lens of the eye, peripheral nerve, myelin sheath, and nonmyelinated autonomic nerves. These abnormalities cause cataracts, loss of sensation, and proprioception, as well as dysregulation of autonomic function. Autonomic dysfunction compromises normal blood flow, gastric motility, temperature regulation, and sexual function. Preventing these issues has made lowering blood glucose a major goal in the management of diabetes.

There has been little concern about the influence of hyperglycemia on the structure or function of the central nervous system (CNS). The major CNS concern related to diabetes is the opposite issue, hypoglycemia. The symptoms of hypoglycemia are very dramatic, involving intoxicated behavior and mentation, seizures, and loss of consciousness. On occasion, hypoglycemia-induced hemiparesis will result in an extensive medical evaluation and rehabilitation. Generally, these abnormalities are transient and result in no enduring problem for the patient. Moreover, the brain is protected from high glucose exposure in the peripheral blood by the blood-brain barrier, which reduces the brain exposure to two-thirds of the peripheral blood level. A clinical impression for subjects with diabetes is that it is better to have high rather than normal blood glucose because of the greater risk of brain and physical injury associated with severe hypoglycemia. Evidence is now beginning to show that axiom is not correct.

Meta-analytic reviews have documented subtle neurocognitive deficits in pediatric (1) and adult (2) populations with type 1 diabetes. Basic intelligence, psychomotor processing speed, mental flexibility, and attention are specific skills noted to be permanently reduced (3). Neurophysiologic studies (electroencephalogram, evoked potential studies, and response latencies) provide further evidence of CNS changes in association with type 1 diabetes (4). We have known for a long time that children with diabetes onset before 5 years of age have permanent neurocognitive impairment more commonly than age-matched peers and siblings (5). One study showed that children with diabetes onset before 7 years of age have reduced intellectual performance and mild central brain atrophy when compared with similarly aged adults with the same duration of diabetes but later age of onset (6). A structural neuroimaging study has demonstrated that patients with diabetes have changes in metabolites in both brain gray and white matters when compared with similar control subjects without diabetes (7). These changes seem to be related to higher HbA_{1c} levels, suggesting that high glucose levels may contribute to these pathologic abnormalities. A recent clinical report states that high blood glucose levels (HbA_{1c}) were associated with poorer cognitive function after 12 years of follow-up evaluation (8).

When considering the mechanisms for tissue damage in diabetes (Fig. 1), abnormal glucose levels are considered the primary agent; associated abnormal insulin levels are commonly overlooked. In the brain, insulin regulates multiple cellular processes. Insulin stimulates neuronal growth, differentiation, synaptic plasticity, cellular proliferation, and neurotransmission (9). In type 1 diabetes, insulin levels are maintained exogenously at arbitrary, variable levels without any relationship to physiologic need. Insulin levels do respond

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See accompanying article, p. 476.

COMMENTARY

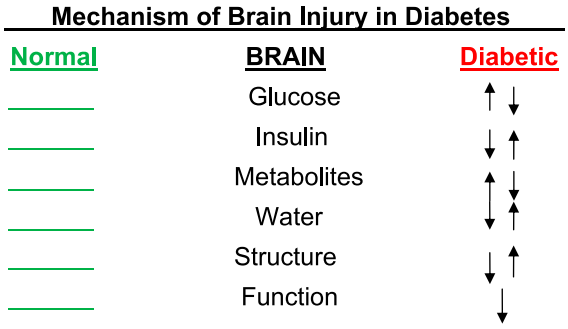

Figure 1—Diabetes causes chaos in the brain, which compromises function.

to physiologic signals in type 2 diabetes but apparently inappropriately as judged by abnormal coincident blood glucose response.

In this issue of *Diabetes*, the article by Mazaika et al. (10) (one in a series [11–13]) shows structural cortical brain changes occurring in children 4–8 years of age who have diabetes. The current report indicates cortical surface smoothing rather than wrinkling, suggesting a delay in cortical structural maturation and possible delayed functional maturation. The authors mention in the RESEARCH DESIGN AND METHODS section that they tested cortical function, but no results are provided. We must assume that the previous article (13) that stated no cognitive or executive function changes applies to the individuals in this report as well. The conclusion of the previous article was that children with diabetes have slower growth of gray and white matter during the period of rapid brain maturation. Mazaika et al. (10) add a new brain measurement of cortical surface, which shows that the brains of children with diabetes have slower growth rates of cortical volume and total surface area. These observations emphasize that the brain changes physically in response to hyperglycemia. It is noted that within-subject differences in blood glucose levels cause responsive changes in gray and white matter volume. It is also noted that the brain measures were all negatively correlated with the blood glucose level except for the ventricular volume, which naturally increases when the surrounding mass is shrinking. We are told that these measures indicate brain growth and maturation are impaired by diabetes. That may be a fact, but these observations could simply be a transient artifact of comparing brain structures in children with wide-ranging blood glucose levels to age-matched children who have relatively stable glucose levels. It seems clear that peripheral blood glucose levels have a significant effect on the structure of the developing brain. Whether this represents permanent structural damage and functional impairment or transient changes in gray and white matter volume in response to the variable glucose levels characteristic of type 1 diabetes remains unclear.

These imaging observations (6,7,10–14) bring attention to the fact that hyperglycemia is affecting structural changes in the developing brains of children and even in the more mature brains of adults. The abundance of glucose in the brain is also changing the metabolites in that tissue (7). It has been noted in laboratory animals and humans that hyperglycemia in the brain reduces brain taurine (15) and increases brain inositol (7). Taurine and insulin stimulate neuronal growth and development. Elevated inositol reflects gliosis, an indicator of brain injury. By reflecting abnormal insulin levels and reducing intracellular taurine, hyperglycemia may impair neuron growth and maturation. The increase in inositol may reflect gliosis (16) and increased amylin production, which may be a mechanism for Alzheimer disease. This suggests that hyperglycemia, a biomarker for insulinopenia, is toxic for the brain at any stage of life rather than an effective brain prophylaxis for symptomatic hypoglycemia.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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