Noninsulin-Dependent Diabetes Mellitus-Related Encephalopathy Presenting with Amnesia, Personality Change, and Autonomic Seizure

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We describe a patient with noninsulin-dependent diabetes mellitus presenting with an amnestic disorder, personality change, and autonomic seizure. Magnetic resonance images of the brain showed T2-high signal lesion in the hippocampi bilaterally and nonspecific white matter disease, while single photon emission computed tomography revealed a diffuse reduction of cerebral blood flow. Sensory and auditory evoked potentials revealed delayed impulse conduction velocities in the central nervous system. Degenerative changes caused by a microvascular angiopathy related to noninsulin-dependent diabetes mellitus may underlie the central nervous system manifestations in our patient.

Key words: type 2 diabetes mellitus, central nervous system, angiopathy, memory

Introduction

Peripheral neuropathy is a common complication of diabetes mellitus. Central nervous system complications of diabetes mellitus, in contrast, are less frequent. The most common reported cerebral complications of diabetes mellitus include cerebrovascular accident (1–3), hypoglycemia (1, 4), and diabetic coma. Recently, electrophysiologic studies including sensory evoked potentials and auditory evoked brainstem responses have demonstrated impaired impulse conduction velocities in the central nervous system of diabetic patients without neurological symptoms (5–8). Several neuropsychologic studies have reported an impairment of memory and/or increased irritability in patients with diabetes mellitus (7, 9, 10). However, many of these selected patients have insulin-dependent (Type I) diabetes mellitus. In this report, we present a patient with noninsulin-dependent diabetes mellitus (NIDDM) who presented with amnesia, personality change, and autonomic seizure, without evidence of focal cerebral ischemia on magnetic resonance imaging (MRI).

Case Report

A retired, right-handed postman was diagnosed with diabetes mellitus at the age of 44 years. He had a family history of diabetes in both his father and paternal grandfather. The patient was on no regular medication for diabetes mellitus, and he was otherwise in good health. He neither drank alcohol nor smoked tobacco.

Seven months prior to admission, when the patient was 58 years of age, his wife began to notice his memory problems and personality change. For example, at noon he was unable to remember what he had eaten in the morning. In addition, he became increasingly irritable and unusually aggressive and argumentative. On October 25, 1991, 3 months prior to admission, the patient complained of the sudden onset of chest discomfort and was admitted to a hospital. Although the electrocardiogram was normal, the patient was admitted for increased blood sugar levels, and oral medication with glibenclamide (5 mg/day) was started. The patient was subsequently admitted to two other hospitals with recurrent complaints of chest discomfort and hyperglycemia. However, repeated explosive outbursts of rage prompted premature discharge from each of the three hospitalizations. During the third hospitalization, in December 1991, he experienced his first generalized tonic-clonic convulsion. The blood sugar level detected soon after the seizure was 335 mg/dl. The patient was subsequently admitted to our hospital on January 18, 1992. There was no known prior episode of hypoglycemia.

On admission, the patient was oriented to person only, not to time or location. His temperature was 36.7°C and blood pressure was 90/62 mmHg. Physical examination of the heart,
lungs, and abdomen was normal. Neurologic examination revealed reduced deep tendon reflexes in the upper and lower limbs. Motor testing revealed normal bulk, tone, and strength. Light touch, pain, and vibration sensation were mildly impaired in the hands and feet. Ophthalmologic examination revealed simple diabetic retinopathy with small retinal hemorrhages.

Routine laboratory testing revealed a fasting blood glucose level of 263 mg/dl and an elevated percentage of glycosylated hemoglobin (12.8). Other hematologic and serologic tests including the complete blood count, electrolytes, liver and renal function were normal. Analysis of the cerebrospinal fluid revealed increased protein (59 mg/dl) and glucose (193 mg/dl) levels with a normal cell count. The increased protein level has been described in diabetic patients and is thought to be related to radiculopathy (1). The serum level of immunoreactive insulin was normal (11.3 μg/ml) and flucloxacillin was increased to 450 μM (normal; 205 to 285). Urinary excretion of glucose (129 g/day) and microalbumin (42.5 mg/day) were also increased.

MRI of the brain showed several small regions of increased signal intensity in the white matter on T2-weighted images, suggesting the presence of microvascular disease or enlarged Virchow-Robin spaces (Fig. 1). T2- and proton density-weighted images also showed focal lesions of increased signal intensity in the hippocampi bilaterally (Fig. 2). However, there was no evidence of gross infarction. An electroencephalogram revealed background activity of 8 to 9 Hz α frequencies with an excessive admixture of 5 to 6 Hz θ activity. Subsequent electroencephalograms disclosed the emergence of spike wave activity in the left frontoparietal leads. Single photon emission computed tomography using N-isopropyl [123I]-P-iodoamphetamine showed a diffuse decrease in cerebral blood flow. Motor nerve conduction velocities were normal for the right median nerve and delayed (37.7 m/s) for the right tibial nerve. Sensory nerve conduction velocity was also delayed (39.4 m/s) for the right sural nerve. The cerebral sensory evoked potential from the median nerve at the wrist was delayed with a P1 latency of 16.8 ms (normal 13.8±0.9); N1, 22.4 (18.1±1.0); P2, 28.0 (23.0±1.8); N2, 34.4 (30.9±2.5); and P3, 56.0 (42.4±3.1). Auditory evoked brainstem responses stimulated from the right ear at 80 dB showed a marked delay of latencies for wave III (4.04 ms, normal; 3.76±0.16) and wave V (6.20 ms; 5.68±0.17), but not for wave I (1.58 ms; 1.49±0.11).

Neuropsychologic testing of the patient showed normal intellectual functioning, but with a significant memory impairment. Wechsler Adult Intelligence Scale test (11) revealed a full scale intelligence quotient of 95 with verbal intelligence quotient of 96 and performance intelligence quotient of 94. Results of Bender Gestalt test was normal at 66. Memory testing showed marked impairment. On a modified Wechsler Memory Scale, the patient scored an intelligence quotient of 77, with particular difficulties in immediate recall (1 for maximum score of 24) and associative learning (easy association; 4.5 for maximum score of 7, hard association; 0 for maximum score of 6). Among memory tests, immediate memory, visual reproduction evaluated by Benton Visual Retention Test, and remote memory were relatively preserved. Confabulation was not noted.

Insulin therapy was initiated for more aggressive glycemic control. The patient continued to have intermittent episodes of
agitation requiring increased sedatives. In addition, he had episodes of chest discomfort, headache, and sometimes abdominal pains lasting for several seconds to hours, and occurring once or twice a week. Serial measurements of blood glucose levels during these attacks were high, while the electrocardiogram remained normal. An interictal electroencephalogram revealed paroxysmal spike wave discharges in the left frontoparietal leads, and injection of benzodiazepines stopped the episodes. Therefore, it was thought that the episodes might represent autonomic seizures; oral medication with phenytoin alleviated the attacks.

By the end of April 1992, the daily excretion of urine glucose became less than 10 g/day and the fasting blood glucose level became less than 200 mg/dl. In addition, the patient was less irritable. The patient was discharged on May 25, 1992. Since then, both his glycemic control and mental status have remained stable for 5 years; however, his memory remains impaired.

**Discussion**

The present patient manifested symptoms of short-term memory loss, personality change with marked disinhibition and aggression, and the subsequent development of epilepsy in the setting of NIDDM. What is unique to our patient is that he presented these central nervous system symptoms as most prominent complication of NIDDM, having only a mild degree of retinopathy, peripheral neuropathy, and renal failure, the more common complications of diabetes mellitus. The short-term memory impairment was the most persistent symptom in this patient. Several brain structures including the hippocampus, temporal neocortex, and thalamus have been associated with amnesia (12). Brain MRI of the patient revealed high signal intensity within the hippocampus on T2- and proton density weighted images. Because there was no history of hypoglycemia or gross cerebrovascular accident, these changes were most likely related to the microvascular angiopathy which is inevitable in diabetes (1).

Although it is likely that both the personality change and the seizure disorder were related to a small vessel angiopathy, there appeared to be a clear relationship between blood sugar elevation and a worsening of the agitation and behavior changes. While Surridge et al (9) denied a relationship between blood glucose levels and irritability, the frequency and severity of our patient’s aggression became markedly reduced after achieving better glycemic control.

Cognitive impairment and encephalopathy have previously been reported in patients with insulin-dependent diabetes mellitus. Bale (13) found a higher incidence of learning deficits in patients with insulin-dependent diabetes mellitus. Similarly, Surridge et al (9) reported a higher incidence of irritability and cognitive deficits in insulin-dependent diabetes mellitus patients. In contrasts, Lawson et al (7) and Dejgaard et al (14) found no evidence of impaired intellectual function in insulin-dependent diabetes mellitus, although the latter group demonstrated asymptomatic evidence of central nervous system disease by means of brainstem auditory evoked responses and magnetic resonance imaging in patients with long-duration insulin-dependent diabetes mellitus. Likewise, there have been several reports of abnormalities in both sensory and brainstem auditory evoked potentials in asymptomatic patients with insulin-dependent diabetes mellitus (5–8, 15). In patients with NIDDM, Partanen et al (16) demonstrated a high incidence of polyneuropathy in patients with poorer glycemic control and lower serum insulin concentrations. The present patient initially presented with poor glycemic control and a normal serum insulin level, but had similar central nervous system signs reported in insulin-dependent diabetes mellitus with pronounced amnesia as a cardinal symptom.

It is unclear what pathology related to NIDDM produced such symptoms in the present case. Metabolic disturbances and vascular disease are probable factors in the pathogenesis of the central nervous system involvement (17). Results of autopsy studies have demonstrated an increased frequency and severity of cerebrovascular disease and arteriosclerosis in the central nervous system of diabetic patients (1, 2, 18). Although some reports have focused on the importance of hypoglycemia as a causative factor of brain damage in diabetes mellitus (4, 19), the present patient had no documented episodes of hypoglycemia. Reviewing pathologic studies, DeJong (20) described degeneration of the ganglion cells and nerve fibers in the cerebrum. He proposed that cell loss, demyelination, and gliosis, and infarction secondary to severe angiopathy was the basis for diabetic encephalopathy; he emphasized the importance of angiopathy as their cause. Because the results of single photon emission computed tomography and evoked potentials suggest diffuse hypofunction of the brain, such diffuse angiopathologic changes appear to underlie the central nervous system manifestations of our patient. MRI showing hippocampal lesions and electroenencephalogram with focal paroxysmal spike discharges appear compatible with such pathology of the central nervous system. Thus it appears that diabetes mellitus, even NIDDM may produce encephalopathy whose main symptoms are amnesia without a history of gross infarction or hypoglycemia.

**References**

KASHIHARA et al


