Paraparesis as a Presenting Manifestation of Type 2 Diabetes

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PRESENTATION

A 60-year-old patient with an insignificant medical history came to our outpatient department with complaints of sudden-onset leg weakness, urinary incontinence, and difficulty in speaking for the past 2 days. He reported no history of trauma, loss of consciousness, headache, vomiting, convulsions, or preceding fever.

On examination, he was conscious, with a blood pressure of 170/96 mmHg and a regular pulse of 84 bpm. Spinal palpation revealed no abnormality or tenderness. He had abulia, trans-cortical motor aphasia, and urinary incontinence. Frontal release reflexes—the snout reflex, forced grasping reflex, and glabellar tap—were enhanced. Cranial nerves were normal bilaterally. Sensory loss was present in both lower limbs. Motor examination revealed spastic paraparesis. Bilateral Babinski, Chaddock, and Hoffmann signs were positive.

Routine investigations revealed normal hemogram, liver, and renal function test results. However, his fasting and postprandial plasma glucose values were found to be 246 and 350 mg/dl, respectively. To know whether this hyperglycemia represented previously undiagnosed type 2 diabetes or stress hyperglycemia, we ordered an A1C, with a result of 9.6%. The patient was thus identified as having type 2 diabetes.

Examination of ocular fundi showed bilateral nonproliferative diabetic retinopathy, urine examination documented proteinuria of 1 g/day, and a nerve conductions velocity study revealed bilateral sensory motor neuropathy. His lipid profile revealed triglycerides of 224 mg/dl, total cholesterol of 160 mg/dl, HDL cholesterol of 29 mg/dl, VLDL cholesterol of 32 mg/dl, and LDL cholesterol of 116 mg/dl.

In view of clinical findings suggestive of frontal lobe involvement, we ordered a magnetic resonance imaging (MRI) study of the brain. The MRI showed bilateral, ill-defined, wedge-shaped lesions in the anterior cerebral artery territories that were hyper-intense on T2W imaging (Figure 1). Diffusion-weighted imaging confirmed these lesions to be acute infarcts (Figure 2). Magnetic resonance angiography (MRA) revealed narrowing of the A1 segment of the right anterior cerebral artery (ACA) and occlusion of the A2-A3 junction of the left ACA (Figure 3). Thus, the patient was diagnosed as having a bilateral ACA territory infarction.

Two-dimensional transthoracic echocardiography revealed no

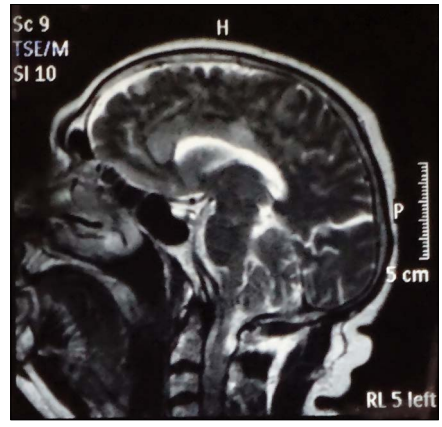

Figure 1. T2W MRI of the brain showing hyper-intense lesions in the rostrum, genu, and trunk of the corpus callosum, cingulate gyri, anterior parts of superior frontal gyri, precuneus, and paracentral lobules.

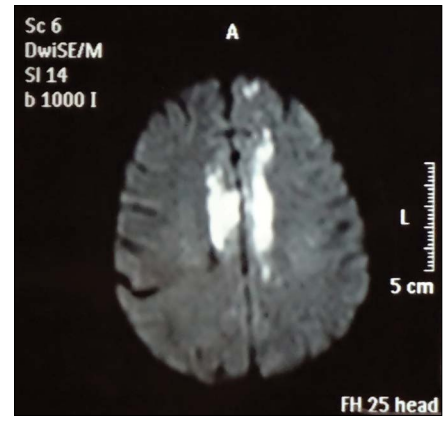

Figure 2. Diffusion-weighted imaging showing the lesions to be acute infarcts.

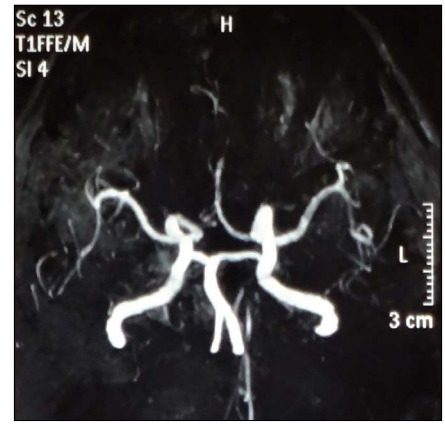

Figure 3. MRA revealing narrowing of the A1 segment of right ACA and occlusion of the A2-A3 junction of the left ACA.

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cardiac source of the embolism. No cardiac rhythm disturbance was apparent on electrocardiogram or Holter monitoring. Color Doppler imaging of carotid arterial systems was remarkable of diffuse increase in carotid intima media thickness, but no focal arterial stenosis or plaque was documented. We thus attributed the ACA occlusion to in situ arterial thrombosis.

Because the patient presented 2 days after the onset of symptoms, thrombolysis was not performed. We prescribed aspirin, 75 mg/day. The patient belonged to the high-risk category for atherosclerosis, as described in the National Cholesterol Education Program Adult Treatment Panel III guidelines.[1] Therefore, we also prescribed atorvastatin, 20 mg/day.

The patient's hyperglycemia was managed through medical nutrition therapy and metformin, 1 g daily at bedtime, and a basal-bolus insulin regimen including insulin glargine, 16 units at bedtime, and insulin lispro, 8 units at each meal. Fasting and postprandial plasma glucose levels were maintained at < 140 and < 180 mg/dl, respectively.

Because the patient had nephropathy and hypertension, we also prescribed olmesartan, 40 mg/day. Active physiotherapy and cognitive rehabilitation therapy was encouraged.

After a week of hospitalization, the patient was discharged on the aforementioned medications. His plasma glucose and blood pressure levels were monitored. Six months after the initial presentation, he has made good recovery. Strength in his lower limbs has improved, and he is no longer incontinent. He is continuing with his rehabilitation program.

QUESTIONS

1. How does diabetes predispose patients to stroke?
2. How common is bilateral ACA infarction, and what are the clinical features and proposed stroke mechanisms?
3. What are the causes and significance of inpatient hyperglycemia?
4. How should hyperglycemia be managed in noncritically ill hospitalized patients?
5. What measures can be taken by primary care physicians for primary prevention of stroke in patients with diabetes?

COMMENTARY

Diabetes is a major risk factor for stroke and is associated with increased stroke mortality. The etiology of stroke in diabetes can be either microvascular disease from fibrinoid necrosis, causing small subcortical infarcts called lacunar stroke, or large-vessel intracranial vascular disease, producing atherosclerotic occlusion and/or thrombosis.[2] In our patient, the latter process was likely to be responsible.

Whereas a direct and continuous relationship exists between hyperglycemia and microvascular complications, hyperglycemia is not as significant a determinant of diabetic macrovascular disease. However, patients with diabetes develop extensive and more rapidly progressive macrovascular disease than those without diabetes. The implicated mechanisms include insulin resistance, which leads to less endothelial nitric oxide (NO) production, and a characteristic lipoprotein profile (high VLDL, low HDL, and small, dense LDL cholesterol). Both of these mechanisms facilitate atherogenesis and hence macrovascular disease.[2]

Four hypotheses have been put forward regarding the pathogenesis of diabetes-induced vascular disease:

- Increased polyol pathway flux. In diabetes, there is increased flux of glucose through the polyol pathway that leads to intracellular sorbitol accumulation. Sorbitol in turn causes cellular damage by a variety of mechanisms.
- Increased advanced glycation end product (AGE) formation. Intracellular hyperglycemia leads to nonenzymatic reactions of glucose with proteins, resulting in AGE formation. These modified intra- and extracellular proteins have altered functions and cause target cell damage.
- Activation of protein kinase C (PKC) isoforms. Hyperglycemia increases intracellular diacylglycerol (DAG) content. Increased DAG de novo synthesis activates PKC, which has deleterious actions such as reduced NO formation, promotion of vascular occlusion, and proinflammatory gene expression.
- Increased hexosamine pathway flux. Hyperglycemia increases glucose flux through the hexosamine pathway, producing fructose-6-phosphate, which is a substrate for O-linked glycosylation. This alters function of many proteins as NO synthase and causes altered gene expression.

It has been emphasized that these different mechanisms actually reflect a single hyperglycemia-induced process: overproduction of superoxide or reactive oxygen species (ROS) by the mitochondrial electron transport chain.[2] ROS may activate all four of the pathways described above.

Cerebral infarction in the territory of ACA is rare and reported to account for 0.6–3% of all ischemic strokes in various studies.[3] Moreover, bilateral ACA territory infarction is very rare and is reported only in isolated case reports.[3–7] Its clinical features include paraparesis, hypobulia or abulia, aphasia (global or transcortical motor), frontal release reflexes,

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urinary incontinence, and sensory deficits in the lower limbs.[8] Our patient had paraparesis, urinary incontinence, abulia, and transcortical motor aphasia.

The proposed mechanisms of bilateral ACA territory infarction include *1*) vasospasm after subarachnoid hemorrhage, *2*) embolism or thrombosis of the A1 segment with contralateral A1 hypoplasia, *3*) atherothrombotic occlusion of both ACAs, and *4*) combined A1 local occlusion with artery-to-artery embolism through the anterior communicating artery to the contralateral ACA.[9] In our patient, there was no source of embolism from the heart or internal carotid arteries. We thus attributed cerebral infarction to local atherothrombotic occlusion of the A1 segment of the left ACA and artery-to-artery embolism through the anterior communicating artery to the right A2-A3 junction.

Inpatient hyperglycemia is defined as any plasma glucose value > 140 mg/dl in a hospitalized patient.[10] Its significance lies in the poor prognosis it portends for both critically ill and noncritically ill patients regardless of their primary disease. Observational studies have documented hyperglycemia in 32–38% of inpatients in community hospitals. Among these, ~ 33% of noncritically ill and 80% of critically ill patients had no history of preexisting diabetes.[10]

Other than preexisting diagnosed or undiagnosed diabetes, hyperglycemia may be caused by stress or changes in diet associated with hospitalization, or it can be iatrogenic, as seen with administration of corticosteroids, octreotide, intravenous fluids containing dextrose, and total parenteral nutrition. Preexisting diabetes can be differentiated from other causes by performing an A1C test.

Because our patient had an elevated A1C as well as bilateral nonproliferative diabetic retinopathy on fundus examination, we diagnosed him as having preexisting diabetes. We also screened him for diabetic nephropathy and neuropathy and identified him as having all three microvascular complications of diabetes.

The presence of these complications in newly diagnosed diabetes has been reported variously to be 5–35% in different populations.[10] Also, the U.K. Prospective Diabetes Study documented microvascular complications in as many as half of its subjects with newly diagnosed diabetes.[12] Hence, the American Diabetes Association (ADA) recommends screening all patients with type 2 diabetes for microvascular complications at the time of diagnosis and periodically thereafter.[13]

The Endocrine Society has issued guidelines for the management of hyperglycemia in hospitalized patients in noncritical-care settings.[11] These guidelines recommend that, independent of a previous diabetes diagnosis, all admitted patients have laboratory blood glucose testing on admission, as well as an A1C test if one has not been performed within the preceding 2–3 months. The glycemia targets for noncritically ill patients include a premeal glucose target of < 140 mg/dl and a random blood glucose target of < 180 mg/dl. These targets are to be achieved by scheduled subcutaneous insulin therapy consisting of basal or intermediate-acting insulin given once or twice daily in combination with rapid- or short-acting insulin administered before meals.

Primary care providers play an important role in detecting and managing diabetes. The ADA has published criteria for screening for type 2 diabetes in asymptomatic individuals.[13] Even in the absence of risk factors for diabetes, all individuals > 45 years of age should be screened.

The patient described in this case study was never screened by the health care providers he had visited previously. Earlier detection and management of diabetes and associated hypertension, dyslipidemia, and albuminuria could have averted his stroke. Moreover, now that he is known to have diabetes, his overweight (BMI ≥ 25 kg/m^2) first-degree relatives should also be screened for diabetes.

Apart from screening, primary care providers can also play an important role in prevention of diabetic complications by frequently and repeatedly advising patients about the vascular complications of the disease and their warning signs, with the aim of encouraging the adoption of primary and secondary preventive measures.

CLINICAL PEARLS

- The etiology of stroke in diabetes can be either microvascular disease from fibrinoid necrosis, causing small subcortical infarcts called lacunar stroke, or large-vessel intracranial vascular disease, producing atherosclerotic occlusion and/or thrombosis.
- Cerebral infarction in the territory of ACA is rare and reported to account for 0.6–3% of all ischemic strokes. The clinical features of bilateral ACA territory infarction that have been described include paraparesis, hypobulia or abulia, global or transcortical motor aphasia, frontal release reflexes, urinary incontinence, and sensory deficits in the lower limbs.
- The proposed mechanisms of bilateral ACA territory infarction include vasospasm after subarachnoid hemorrhage, embolism or thrombosis of the A1 segment with contralateral A1 hypoplasia, atherothrombotic occlusion of

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both ACAs, and combined A1 local occlusion with artery-to-artery embolism through the anterior communicating artery to the contralateral ACA.

- Inpatient hyperglycemia may be the result of undiagnosed diabetes, stress, or changes in diet associated with hospitalization, or it may be iatrogenic. It portends a poor prognosis for both critically ill and noncritically ill patients, regardless of their primary disease.
- Primary care providers can play an important role in the timely diagnosis of diabetes by following ADA screening recommendations and implementing measures to prevent diabetes-related complications in patients identified as having diabetes.

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