Diabetic Striatal Disease: Clinical Presentation, Neuroimaging, and Pathology

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Abstract

Background  Unilateral movement disorders and contralateral neuroimaging abnormalities of the striatum have been sporadically reported as a rare syndrome associated with diabetes mellitus. Despite characteristic imaging findings and clinical manifestations, the mechanism underlying this syndrome is still unclear.

Methods  Six patients with this syndrome were studied clinically and subjected to MRI neuroimaging; one underwent biopsy of the striatum, and another underwent additional MR spectroscopy at 3.0T and FDG-PET.

Results  Neuroimaging findings were characterized by a T1-hyperintense unilateral lesion restricted to the striatum, contralateral to the symptomatic limbs. The biopsied striatum contained patchy necrotic tissue, severe thickening of all layers of arterioles, and marked narrowing of vessel lumens. Hyaline degeneration of the arteriolar walls, extravasation of erythrocytes, and prominent capillary proliferation were also notable, together with lymphocytic infiltration and macrophage invasion. In one patient, PET examination revealed decreased accumulation of FDG in the lesion. The MR spectrum for the diseased striatum revealed a decrease in the NAA/Cr ratio (1.35), normal Cho/Cr ratio (1.22), and a peak for myoinositol, while the spectrum on the contralateral site revealed a decrease in the NAA/Cr ratio (1.48), increase in Cho/Cr (1.32), but no peak for myoinositol.

Conclusion  The constellation of signs and symptoms and neuroimaging characteristics in previous reports and the six additional cases described here with neuropathological data and findings of MR spectroscopy appears unique enough to be termed “diabetic striatopathy.” This syndrome appears in poorly controlled diabetics due to obliterative vasculopathy with prominent vascular proliferation, vulnerability to which is restricted to the striatum.

Key words: diabetes mellitus, MR spectroscopy, neuropathology, PET, chorea

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Introduction

A variety of neurological abnormalities are associated with non-ketotic hyperglycemia in diabetic patients, including impaired mental function, partial and generalized seizures, focal neurological deficits, and stroke-like syndromes (1). In rare cases, movement disorders occur in non-ketotic hyperglycemia, with chorea noted in association with neuroimaging abnormalities of the basal ganglia (2-10). Although striatal hyperintensity on T1-weighted magnetic resonance images (MRI) is universally recognized in patients affected by this condition, the mechanism responsible for it remains unknown. Moreover, some diabetic patients exhibit abnormal striatal neuroimaging findings without chorea (11-13).

Low signal intensity on gradient-echo T2*-weighted sequences in the basal ganglia suggests evolution of petechial hemorrhage with hemosiderin deposition (8, 14, 15). On the other hand, gradient echo images have also been reported to
Figure 1.  T1-weighted MRI of cases 1-5. (A) Case 1: A small region of hyperintensity was observed in the right caudate nucleus. (B) Case 2: T1-weighted image revealed hyperintensity in the left putamen and globus pallidus, although the caudate nucleus was unremarkable. (C) Case 3: T1-weighted image demonstrated increased signal in the head of the right caudate. (D) Case 4: T1-weighted image revealed a hyperintense lesion including the entire right striatum (putamen, globus pallidus, and head of the caudate). The lateral segment of the contralateral globus pallidus was also slightly hyperintense. (E) Case 5: T1-weighted image revealed a hyperintense, swollen, mottled lesion occupying the entire right striatum.

be normal in hemichorea-hemiballismus with hyperglycemia (16). Proton MR spectroscopy (MRS) at 1.5T revealed a decreased N-acetylaspartate (NAA)/creatine (Cr) ratio and increased choline (Cho)/Cr ratio in the diseased basal ganglia (17, 18). The low NAA/Cr ratio suggests neuronal loss or damage, while the high Cho/Cr ratio indicates gliosis. A lactate peak was noted for eight of nine patients, suggesting mild ischemia (18). The only PET study performed on this syndrome revealed a markedly reduced rate of cerebral glucose metabolism in the corresponding lesions on T1-weighted MRI (13), providing direct evidence of regional metabolic failure.

Only a few patients with this syndrome have undergone postmortem pathological studies (19) or biopsies (17, 20), the common findings of which have been selective neuronal loss, gliosis, and reactive astrogliosis of the basal ganglia, though hemorrhage has also been reported.

We examined six patients with this syndrome, all of whom underwent MRI studies. They included one who underwent biopsy of the striatum and another who underwent PET and MRS studies at 3.0T, which have not been well described in previous reports. The present findings indicate that this syndrome is not due simply to cerebral infarction or petechial hemorrhage, but rather involves a vasculopathy uniquely restricted to the striatum in diabetic patients.

Methods

Six patients with diabetes mellitus (DM) who met the following criteria for the syndrome described: T1-high abnormalities in the MRI restricted to the unilateral striatum with contralateral signs and symptoms which were identified between 1990 and 2006 in our institutions.

Patients and Results

Case 1. A 72-year-old woman with a 5-year history of type 2 DM developed left hemichorea. With the exception of this movement disorder, neurological examination was unremarkable, and no diabetic retinopathy was noted. The following laboratory findings were notable: fasting blood glucose 130 mg/dL, calculated serum osmolarity 305 mOsm/L, and HbA1c 6.2%. Urinalysis was negative for glucose, ketones, and protein. T1-weighted images (Fig. 1A) demonstrated a region of increased signal in the head of the right caudate, which was, however, isointense on T2-weighted images. Findings of CT of the brain were normal. The hemichorea was easily controlled with small oral doses of haloperidol (1.5 mg/d).

Case 2. A 73-year-old man with DM, hypertension, chronic obstructive pulmonary disease, and asthma devel-
oped numbness in the right upper and lower limbs. Oral hypoglycemic agents were begun, since HbA1c was quite high, at 18.9%. Two weeks later, he was hospitalized due to worsening of the numbness. On admission, fasting blood glucose was 151 mg/dL, calculated serum osmolality was 300 mOsm/L, and HbA1c 17.2%. No diabetic retinopathy was noted. Hypodermal insulin was started, but 2 weeks later he suddenly developed right hemichorea. Except for the abnormal movements, neurological examination was normal. Although CT of the brain was unremarkable when the chorea was detected, four weeks later, on MRI examination, T1-weighted (Fig. 1B) and diffusion-weighted images (DWI) demonstrated a region of increased signal restricted to the left putamen and globus pallidus, which was isointense on T2-images. The hemichorea was controlled with oral haloperidol (2.25 mg/d).

**Case 3.** A 68-year-old woman without a history of DM suddenly developed left upper and lower limb weakness. On admission, blood pressure was 206/96 mmHg with a regular pulse of 80/min. Neurological examination was normal except for left hemiparesis and hyperreflexia. Fasting blood glucose was 118 mg/dL, HbA1c 6.5%, and calculated serum osmolality was 294 mOsm/L. Results of brain CT and MRI examinations were normal. Dietary restriction was initiated to treat the diabetes. Two days later, left hemichorea appeared. Repeated MRI disclosed a region of slightly high T1 signal intensity in the right caudate nucleus (Fig. 1C), which was isointense on T2-weighted MRI. The hemichorea was controlled with oral haloperidol (0.75 mg/d).

**Case 4.** A 16-year-old boy with type 1 DM developed numbness in the left upper and lower limbs. Since CT of the brain revealed high density in the right striatum, cerebral hemorrhage was tentatively diagnosed. Fasting blood glucose was 312 mg/dL, HbA1c 17.9%. The following day, the symptoms disappeared, but twelve days later he was again aware of weakness in his left upper and lower limbs, and MRI of the brain demonstrated a T1-hyper (Fig. 1D), T2-isointense lesion localized to the right striatum. Three weeks later, he developed a florid left hemichorea, which was controlled with oral haloperidol (1.5 mg/d).

**Case 5.** A 56-year-old man without history of DM was hospitalized with transient left-sided weakness. Oral hypoglycemic therapy was begun two weeks later, though MRI of the brain performed at that time demonstrated a DWI-hyper-, T1-hyper- (Fig. 1E), and T2-hyperintense and a more swollen mass-like lesion occupying the entire striatum. Results of cerebral angiography were unremarkable. A needle biopsy of the striatum was performed given the possibility of brain tumor, and CT examination of the brain prior to the biopsy revealed a patchy, central region of high density surrounded by low-density zones. The biopsied specimen was formalin-fixed, paraffin-embedded, stained with H&E and Elastica-Masson, and immunostained using specific antibodies to glial fibrillary acidic protein, S100, leukocyte common antigen, lysozyme, Factor VIII, p53, and MIB-1. Brain tumor was excluded, since the specimen was devoid of neoplastic cells and had a rather low count of MIB-1-positive cells. The specimen instead contained patchy necrotic tissue, arterioles with extremely thickened intima, media, and adventitia, and marked narrowing of the arterioles (Fig. 2A, B, C). Macrophage invasion was also conspicuous with modest infiltration of lymphocytes, as identified by immunohistochemical markers (Fig. 2D, E). Hyaline changes of the arteriolar walls, extravasation of erythrocytes, and proliferation of capillaries were also prominent features, as confirmed by factor VIII immunostaining of vascular endothelium (Fig. 2F).

**Case 6.** An 84-year-old woman with a 7-year history of DM, hypertension, and rectal cancer developed transient weakness of the right hand. She had taken a hypoglycemic agent for 7 years until discontinuing it 6 months prior to the present illness. Five weeks before the event, the oral hypoglycemic was re instituted, since HbA1c was 12.3%. Ten days later, she developed right hemiballism. No family members had similar movement disorders. Blood pressure was 130/74 mmHg and the pulse was 77/min and regular. She was alert, but distressed, with violent, involuntary movements involving all portions of both of her right limbs. There was no cranial nerve involvement, and ophthalmoscopy revealed no diabetic retinopathy. Deep tendon reflexes were normal. The movements disappeared during sleep and increased with emotional tension. The following laboratory findings were notable: fasting blood glucose 107 mg/dL, a calculated serum osmolality of 297 mOsm/L, and HbA1c 7.4%. Urinalysis was positive for glucose but negative for ketones and protein. Although CT examination of the brain was unremarkable, MRI (Signa 1.5T SYS# GEMSOWO) on the day of admission revealed that the left putamen and caudate nucleus were hyperintense on T1-weighted images, with sparing of the anterior limb of the internal capsule. Blood pressure was 130/74 mmHg and the pulse was 77/min and regular.
GEMS (GEMS) were positioned bilaterally in the basal ganglia of the patient two weeks after onset. MRS of the left striatum revealed a NAA/Cr ratio of 1.35 (1.74±0.16), Cho/Cr ratio of 1.22 (1.19±0.07), and a myoinositol peak, while that of the right striatum revealed a NAA/Cr ratio of 1.48, Cho/Cr ratio of 1.32, and no myoinositol peak (Fig. 3E).

**Discussion**

The neuroimaging abnormalities of the striatum associated with contralateral focal sensory-motor signs and symptoms in the six diabetic patients presented here comprise a unique syndrome that can be termed “diabetic striatopathy,” which is characterized by the presence of a high signal on T1-weighted MRI confined to the striatum with contralateral hyperkinetic movement disorders or fleeting sensory-motor manifestations.

Chorea and striatal hyperintensity on T1-weighted MRI have been observed in patients with type 2 DM (5, 7-22), although patients with type 1 DM are not exceptional (4), as seen in the present case 4. Although the syndrome occurs mostly in non-ketotic hyperglycemia (2-20), some patients
Figure 3. Neuroimaging findings for case 6. (A) At 10 days after onset, a T1-weighted image showed a circumscribed region of hyperintensity in the left putamen and caudate nucleus, with sparing of the internal capsule. (B) At 10 days after onset, on a T1 fat-suppression image, the extent of striatal hyperintensity was less than that on T1 images. (C) At 10 days after onset, a gradient-echo T2*-weighted sequence revealed a linear region of low signal intensity in the lateral part of the putamen (arrow). (D) At 3 weeks after onset, PET revealed decreased accumulation of FDG in the left striatum. (E) Location of voxels and bilateral abnormality on MRS. At 2 weeks after onset, the spectrum revealed 1) a H2O peak, 2) a myoinositol peak, 3) a Cho peak, 4) a Cr peak, and 5) a NAA peak. The spectrum for the voxel in the left striatum revealed a low NAA/Cr ratio (1.35), normal Cho/Cr ratio (1.22), and a myoinositol peak (arrow), while the spectrum for the voxel in the right striatum revealed a low NAA/Cr ratio (1.48), and a relatively high Cho/Cr ratio (1.32), but no myoinositol peak.

Also have episodes of ketotic hyperglycemia (21, 22).

Five of the present six patients exhibited hemichorea. Notably, numbness (cases 2 and 4) and weakness (cases 3 and 6) appeared prior to the development of chorea, suggesting that chorea is sometimes a delayed clinical manifestation of the contralateral striatal lesion.

Only a few patients with this syndrome have undergone postmortem pathological studies (19) or biopsies (17, 20). Ohara et al described an autopsy in which the principal findings were multiple infarcts (19). These lesions were associated with reactive astrocytosis and interneuronal response, but not with petechial hemorrhage. Shan et al hypothesized that the cause of the MR imaging abnormalities in this syndrome might be mild ischemia with gemistocytic accumulation, based on findings of brain biopsy (17).

However, the striatal pathology in our biopsied patient differed from those noted above in several respects. Although reactive astrocytosis was evident in our patient, the major features were patchy ischemic necrosis with edema, foamy macrophage invasion into the parenchyma, red cell extravasation, and vascular proliferation, together with prominent arteriolar changes in which all three layers of the wall were strikingly thickened. Some hyaline change of the vascular intima was noted in association with narrowing of the lumen and obliteration. The perivascular lymphocytic infiltration, although not prominent, suggests the presence of inflammation. These changes seem analogous to those of proliferative retinopathy, which is characterized by neovascularization of retinal capillaries with hemorrhagic and ischemic changes. Among the complications of diabetes
mellitus, retinopathy has been well-examined with regard to its evolution and sequelae (23-27). The earliest finding noted in the development of this type of retinopathy is increased capillary permeability. Capillary closure, dilatation, microaneurysms, hemorrhage, and soft and hard exudates representing microinfarction subsequently develop, with leaking of protein and lipids.

The present biopsy findings may explain the MRI abnormalities in case 6, in the following fashion: the high signal on T1-weighted MRI is likely due to extensive lipid-laden macrophage infiltration, since on T1 fat-suppression MRI the extent of striatal hyperintensity was less than that on T1 images (28). An experimental study also revealed the accumulation of microglia resembling lipid-laden phagocytes in the striatal region, suggesting that the hyperintensity on T1-weighted images following transient ischemia and reperfusion indicates accumulation and phagocytic activation of microglia (29). The linear low signal intensity on T2 sequences in the lateral part of the putamen suggests evolution of petechial hemorrhage with hemosiderin deposition (8, 14, 15). Decreased isotope accumulation in the striatum on FDG PET is suggestive of regional metabolic failure (13).

The syndrome described appears to occur when diabetic control is less than adequate. However, this appears not always to be the case, since patients with only mild diabetes may develop this syndrome. The finding that striatal symptoms can occur more than several days prior to neuroimaging changes may be explained by biochemical or functional impairment prior to structural changes in this particular syndrome. In fact, the “diabetic striatopathy” discussed here is reminiscent of diabetic retinopathy, in view of its development in association with poor control and its paradoxical worsening following intensive control of blood glucose (30-33). In three of the present six patients, HbA1c improved within a month, from 12.3% to 7.4%, 18.9% to 11.6%, and 17.9% to 11.6%, suggesting that lowering of blood glucose may have a deleterious effect on this striatal disease, as in the retina, in which the cascade of events associated with retinopathy may be triggered by erratic management of blood glucose. The corpus striatum is known to be a selective target of diverse neurological disorders, e.g., Huntington’s disease, Hallervorden-Spatz disease, 3-nitropropionic acid intoxication, cirrhosis, and many others. The present biopsy case exhibited occlusive vasculopathy of the arterioles together with patchy necrosis and prominent neovascularization. However, this is not a simple condition involving multiple lacunae or incomplete striatal infarction secondary to ischemic stroke. The lesion is confined to the neostriatum (putamen and caudate), or sometimes to the entire striatum including the globus pallidus (the paleostriatum), and inflammatory cell infiltration, neovascular formation, and macrophage infiltration are prominent. We therefore speculate that an excitotoxic process occurs within the striatum, a region of the brain known to be vulnerable to this type of process. This process may be initiated in the setting of occlusive microvasculopathy of the basal ganglionic arteries. Striatal hyperintensity on T1-weighted MRI is a distinctive feature of this syndrome, and is confined to the anatomical and functional structures of the corpus striatum, although this anatomical distribution cannot be explained based solely on vascular territories.

On 3.0T MRS, the diseased striatum exhibited a low NAA/Cr ratio (1.35), normal Cho/Cr ratio (1.22), and an increase in myoinositol, whereas the contralateral striatum exhibited a low NAA/Cr ratio (1.48), relatively high Cho/Cr ratio (1.32), but no myoinositol peak. Previous studies have not reported a myoinositol peak in association with this syndrome (15, 17, 18). Similar to previous studies (15, 17, 18), the low NAA/Cr ratio in the diseased striatum suggests neuronal loss or damage. The low NAA/Cr ratio and relatively high Cho/Cr ratio in the contralateral striatum suggest that it is functionally impaired, although normal by neuroimaging criteria. Moreover, the presence of myoinositol suggests the possibility of functional impairment of the sorbitol pathway in the striatum (34, 35), and thus also suggests the existence of a pathogenetic mechanism common to diabetic neuropathy and striatopathy. As is the case with diabetic neuropathy and retinopathy, the striatopathy described here does not necessarily occur in individuals with poorly controlled diabetes, although the determinants of its vulnerability remain elusive.

Therefore, we propose here that the combination of striatal hyperintensity on T1-weighted MRI and contralateral sensory-motor signs and symptoms or movement disorders in diabetic patients be termed “diabetic striatopathy,” a microangiopathic CNS lesion confined to the corpus striatum.

References


