Hemichorea-Hemiballism: An Explanation for MR Signal Changes

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PURPOSE: Some cases of hemichorea-hemiballism (HCHB) are associated with a hyperintense putamen on T1-weighted MR images, the cause of which remains unclear. Our purpose was to determine the cause and significance of these MR signal changes.

METHODS: We analyzed the clinical and neuroimaging findings in 10 patients with HCHB, focusing on locations of the hyperintense lesions on T1-weighted images, comparing them with those on CT scans, and evaluating their changes after years of follow-up. A biopsy was performed in one patient.

RESULTS: Seven patients had hyperglycemia and two had cortical infarcts. HCHB recurred in four patients. A hyperintense putamen preceded the occurrence of HCHB in two patients. T1-weighted MR images revealed hyperintense lesions limited to the ventral striatum in six patients. Hyperintense lesions extended to the level of the midbrain in one patient and persisted for as long as 6 years in another patient. T2-weighted MR images revealed slit-shaped cystic lesions in the lateral part of the putamina 2 to 6 years after the onset of symptoms in two patients. A biopsy specimen from the hyperintense putamen in one patient revealed a fragment of gliotic brain tissue with abundant gemistocytes. Proton MR spectroscopy of the specimen showed an increase in lactic acid, acetate, and lipids, and a decrease in N-acetylaspartate and creatine, suggesting the presence of pronounced energy depletion and neuronal dysfunction.

CONCLUSION: Gemistocytes are sufficient to explain the shortening of T1 relaxation time. Our investigation suggests that neurons in the ventral striatum and striatonigral pathway may play a critical role in generating ballism.

The involuntary movements of chorea consist of random and fast jerking motions in distal parts of the limbs, whereas those of ballism consist of larger-amplitude, random, and violent flinging or kicking, mainly in the proximal joints. Since hemiballism often evolves into hemichorea, the term hemichorea-hemiballism (HCHB) has been used to describe this clinical spectrum (1, 2). HCHB is usually continuous, but may be intermittent, and it may occur with other types of involuntary movements, such as dystonia, myoclonus, or orofacial gestures (1). The most common cause of HCHB is a vascular lesion (1, 2); however, it is also associated with hyperglycemia, and may be the first clinical manifestation of this disorder (3–8). HCHB that accompanies hyperglycemia may exhibit a hyperintense putamen on T1-weighted MR images (7–10). Because of the transient presence of high density in the corresponding regions on CT scans, these lesions appear to result from multiple petechial hemorrhages (7, 8); however, we questioned this explanation and therefore analyzed MR images in 10 patients and performed a stereotactic biopsy in one to determine the cause and significance of these MR signal changes.

Methods

We surveyed the clinical and imaging studies in 33 patients with HCHB obtained during a period of 7 years. Standard T1- and T2-weighted spin-echo brain MR images were obtained with a 1.5-T magnet. Images were acquired in the axial plane with a section thickness of 5 mm, a matrix of 256 × 256, and a field of view of 20 cm. Most T1-weighted images were obtained without contrast enhancement. All imaging studies were evaluated first by the senior author for lesion location, attenuation abnormalities on CT scans, and signal changes on MR images, and then reevaluated by an experienced neuroradiologist who
was blinded to the clinical status of the patients. A consensus was reached at the final interpretation.

We excluded 14 patients with lacunar infarcts, one patient with subthalamic hemorrhage, and six patients with no lesions other than small calcifications limited to the internal segment of the globus pallidus. None of these 21 patients had a hyperintense putamen on CT or T1-weighted MR studies. In another two patients, CT scans showed high-density lesions in the caudate putamen similar to those in the patients in the study group; unfortunately, MR examinations were not obtained. Finally, 10 patients had a hyperintense lentiform nucleus on T1-weighted images. They were referred from four neurologists to a specialist in movement disorders. The movements were analyzed according to the joints involved, their lack of rhythmicity, their speed, amplitude, duration of each contraction, unpredictability of subsequent movements, and absence of precipitating factors. Seven of the patients were videotaped and the diagnosis of HCHB was made unanimously. None had a family history suggestive of Huntington disease. The laboratory data did not show any evidence of Wilson disease, systemic lupus erythematosus, hyperthyroidism, or acanthocytosis.

Results

Clinical Features

Table 1 summarizes the clinical characteristics of the 10 patients. Seven patients had hyperglycemia; the other three (cases 1, 2, and 8) did not. While HCHB was brought under control in five patients within 3 weeks after hyperglycemia was corrected, it persisted in two patients (cases 3 and 6). In one patient (case 5) HCHB recurred on the same side, while in three patients (cases 3, 4, and 10) HCHB occurred on the other side with intervals from 10 days to 3 years. Response to haloperidol was poor in four patients (cases 1, 2, 3, and 6), although two improved with the addition of reserpine or clonazepam. Three patients (cases 1, 5, and 9) died after a period ranging from 4 months to 3 years; all had episodes of stroke, and the cause of death was aspiration pneumonia.

CT and MR Features

Table 2 summarizes the neuroimaging characteristics of the 10 patients. In cases 1 and 2, HCHB was associated with concomitant temporoparietal or frontal infarct ipsilateral to the hyperintense putamen. In four patients (cases 2, 6, 7, and 8), hyperintense lesions on T1-weighted images occurred in the ventral part of the putamen contralateral to the side of HCHB, but bilateral in case 10. In case 5, the lesion was more limited to the ventroposterior putamen. More extensive involvement was present in the other four patients.

CT scans in cases 3, 4, 5, and 10 revealed prominent high densities in the caudate putamen. Areas of slightly high density in the contralateral putamen were identified retrospectively on CT scans in cases 8 and 9. Interestingly, in cases 3 and 10, the putaminal high densities appeared 10 to 14 days before the onset of HCHB.

The areas in which the hyperintense lesions were located on T1-weighted MR images did not match the areas of high density on CT scans. In case 3, the area of the hyperintense lesion on the T1-weighted image (Fig 1) appeared larger than that on the corresponding CT scan. On the other hand, in cases 5 and 10, the areas of the hyperintense lesions on T1-weighted images appeared smaller than those on CT scans.

In case 4, hemiballism recurred at intervals of 3
years, when CT scans showed high densities predominantly in the contralateral lentiform nuclei (Fig 2A and B). T1-weighted MR images obtained 6 years later still showed the hyperintensities bilaterally (Fig 2C). Follow-up T2-weighted MR images in cases 3 and 4 showed cystic lesions in the lateral part of the putamina bilaterally (Fig 2D).

Pathologic Findings

In case 1, a stereotactic biopsy was performed under MR guidance in the anterior part of the right putamen 3 months after the onset of hemiballism because of a mismatch in the high-signal lesions on the CT and T1-weighted MR studies (Fig 3A). Follow-up T2-weighted MR images in cases 3 and 4 showed cystic lesions in the lateral part of the putamina bilaterally (Fig 2D).

Proton MR Spectroscopic Findings

High-resolution proton MR spectroscopy was performed on perchloric acid brain tissue extracts, as previously described, to investigate the metabolic profile of the biopsy specimen (11). Since this MR analysis was performed at pH 1.5 and the chemical shifts of brain metabolites were sensitive to pH variations, peak assignments were accomplished by comparing them with the chemical shifts of individual model compounds, as previously described (12). In particular, the acetate peak shifted from the right of N-acetylaspartate (NAA) at a neutral pH, overlapped with NAA at pH 4.7, and shifted to the left of NAA at a more acidic pH (13). The MR spectra showed marked increases in lactic acid, acetate, and lipids, while NAA and creatine peak intensities were relatively decreased as compared with rough estimates of spectra from human control samples obtained from another laboratory (14) (Fig 3F).

Discussion

Cause of Hyperintense Putamen on T1-Weighted Images

Although the hyperintense lesions on T1-weighted images could result from the presence of extracellular methemoglobin, none of our patients had the hyperintense changes on T2-weighted MR images usually found in the subacute stage of parenchymal hematoma (15). Although petechial hemorrhage could explain the high densities on CT scans and partly explain the hyperintense lesions on T1-weighted MR images, we considered an alternative explanation...
based on the following reasons: first, in case 3, the hyperintense lesions extended inferiorly along a tract (Figs 1B and C), which was unlikely to occur in petechial hemorrhage; second, the hyperintense lesions persisted for years (Fig 2C); and, third, the areas in which hyperintense lesions were seen on MR images did not match with the areas of petechial hemorrhage on CT scans. Demyelination may be another explanation for the hyperintensity, as occurs in some cases of extrapontine myelinolysis (16); however, we did not find any evidence of demyelination in our biopsy sample. We found only one biopsy report of such a lesion (9), and that described the presence of astrocytosis without mentioning the types of astrocytes, the presence of patchy lesions, or the presence of hemosiderin-laden macrophages. Therefore, we propose that the hyperintensity on T1-weighted MR images is due to the presence of abundant gemistocytes (Fig 3B and D), which are located along the axons and persist for years. Shortening of T1 relaxation time can result from the protein hydration layer inside the cytoplasm of swollen gemistocytes, as in a reported case of gemistocytic astrocytoma (17). T1 relaxation time depends on the movement of molecules, and the rich protein content makes electrostatic forces that restrict motion of water molecules. In addition, astrocytosis in the form of large-bodied astrocytes, hypertrophied astrocytes, swollen astrocytes, or gemistocytic astrocytes has been described in the few autopsy reports on patients with ballism (3, 4, 18). In our MR spectra (Fig 3F), the increase in acetate, which is a possible marker for glial metabolism (19), also indicates an active role of gemistocytes in ballism.

Gemistocytes are swollen reactive astrocytes that usually appear during acute injury; after that, their size gradually shrinks. Gemistocytes are also found in some chronic diseases, such as subacute sclerosing panencephalitis or epilepsy, suggesting the presence of a long-lasting pathologic reaction. In certain situations, astrocytic hypertrophy may occur out of proportion to the degree of neuronal loss or myelin loss. Astrocytes play an important role in maintaining an appropriate ionic composition in the extracellular fluid; an increase in extracellular potassium concentration can lead to epileptiform discharge. To keep extracellular potassium low, reactive astrocytes have a very high intracellular potassium concentration (20). When the astrocytes fail, excessive neuronal discharges become inevitable.

The Implication of Patchy Lesions

In humans, there are segregated striatal output pathways, including a direct pathway and an indirect pathway (21) (Fig 4). The site of lesions commonly responsible for HCHB is the subthalamus (22); however, sites other than the subthalamus have been identified (1, 3, 4, 7, 18, 23–29). Lesions in the subthalamus and caudate putamen (indirect pathway) can result in reduced pallidal activity and thalamic disinhibition, producing ballistic movements (29, 30).

For the occurrence of HCHB, patchy involvement of the caudate putamen appears to be the rule rather than the exception. Patchy distribution of relatively normal and abnormal tissue was reported in autopsies of patients with HCHB (3, 26). In animals, partial but not complete lesions of the caudate putamen result in contralateral choreoathetoid movements (31, 32). The onset of dyskinetic movements appears to depend on the loss of some functional areas but the preservation of others. Indeed, periodic discharges have been recorded from the caudate putamen in rodents and monkeys, which, possibly through a direct pathway, inhibit neurons in the substantia nigra pars reticulata and activate neurons in the thalamus and cerebral cortex (31, 32) (Fig 4). If the indirect pathway was responsible for suppressing unwanted movements, and if the patchy lesions involved mainly the indirect pathway, activation of the direct pathway...
should occur along with insufficient suppression of unwanted movements and result in ballism. Therefore, we assumed that the coexistence of an activated direct pathway and an incompetent indirect pathway was necessary for the generation of ballism.

Evidence of an incompetent indirect pathway came from our two longest-term follow-up patients with cystic lesions in the lateral part of the putamina (Fig 2C and D), where neuronal loss should have occurred. Although our biopsy specimen did not clearly show neuronal loss, a decreased NAA level in the MR spectra (Fig 3F) suggested that neuronal dysfunction might have occurred early. Some neurons with decreased NAA might recover, but some continue to die.

An activated direct pathway was suggested by the presence of a hyperintense tract to the midbrain (Fig 1B and C), which appeared to be the striatonigral fibers. While it is the frontopontine tract that occupies the medial part of the cerebral peduncle (33), the striatonigral fibers also pass obliquely through the peduncle, ramify in the substantia nigra pars reticulata, and run in the anteromedial to posterolateral direction (34, 35). Interestingly, in monkeys with kainic acid–induced chorea, burst-generating neurons are located in the rostral ventromedial putamen (32), and six of our patients had hyperintense lesions limited to the ventral striatum. Therefore, neurons in the ventral striatum and the striatonigral pathway may play a critical role in generating ballistic movements.

**The Implication of Proton MR Spectroscopic Findings**

The marked elevation of lactic acid and the decrease of creatine (Fig 3F), which reflects a pronounced depletion of energy, suggested that most neurons in the caudate putamen were functionally incompetent. The presence of abundant glucose in ischemic brain tissues can lead to severe lactic acidosis through anaerobic glycolysis and augment ischemic injuries (36, 37). Some neurons in the caudate putamen must have escaped from injury and become the origins of periodic discharges, generating ballistic movements. Indirect evidence suggesting the existence of an active focus includes the ability to activate epileptogenic foci in the cerebral cortex by inducing hyperosmolality (38); a similar activating process might occur in the caudate putamen. In addition, an increase in lipids, as seen in our MR spectra (Fig 3F), has also been reported in patients with seizures (39). These lipids may result from an excessive breakdown of phosphatidylinositol during repetitive neuronal...
FIG 3. Case 1.

A, Axial T1-weighted (550/10/1) MR image at the level of the basal ganglia shows hyperintensities in the right putamen and the external segment of the globus pallidus (arrow), along with an infarct in the right temporoparietal cortex.

B, Section of stereotactic biopsy from the right putamen reveals abundant enlarged reactive astrocytes with a homogeneous, eosinophilic cytoplasm and an eccentrically located nucleus. (arrows) (hematoxylin-eosin, original magnification ×330).

C, Essentially unremarkable brain tissue with occasional hemosiderin-laden macrophages (arrow) (hematoxylin-eosin, original magnification ×400).

D, Bodian stain, a stain for axons, of the gliotic brain tissue reveals well-preserved axons (black lines) distorted by gemistocytic astrocytes (arrows) (original magnification ×330).

E, Bodian stain of the relatively normal area reveals normal appearance of axons (black lines) (original magnification ×250).

F, High-resolution proton NMR spectra of brain biopsy tissue extracts. The peaks are assigned as follows: 1, CH3 of creatine; 2, CH2 of succinate; 3, γ-CH2 of glutamate; 4, γ-CH2 + α-CH2 of glutamine + GABA; 5, β-CH2 of glutamate + glutamine; 6, CH3 of acetate; 7, CH2 of NAA; 8, β-CH2 of GABA; 9, CH3 of alanine; 10, CH2 of lactate; 11, lipids. Chemical shifts were referenced to an external standard, 3-(trimethylsilyl)-2,2,3,3-tetradeteropropionic acid, at 0 ppm.
discharges, with a resulting increase in arachidonic acid and other free fatty acids.

A Unifying Theory

On the basis of our clinical, neuroimaging, pathologic, and proton MR spectroscopic findings, we propose that the primary event is either hyperglycemia or cerebral ischemia in the caudate putamen, leading to dysfunction of the GABAergic projection neurons. Since not all patients were diabetic, cerebral ischemia alone seems sufficient to induce the dysfunction. In contrast, for those patients with hyperglycemia, ischemia may also play a role, because hyperglycemia can cause a decrease in regional cerebral blood flow and augment infarct size (36) and because these patients eventually incur lacunar infarcts. Cerebral hypoperfusion may result from an increase in cerebrovascular resistance due to the higher brain water content during hyperglycemia or to a loss of flow regulation caused by impaired metabolism (36). During ischemia, neurons in the indirect pathway become functionally incompetent, whereas neurons in the direct pathway are spared and become burst-generating, in a way similar to a lowered seizure threshold by hyperosmolarity. The overactivity in the direct pathway with the resulting metabolic derangement stimulates the reaction of astrocytes, which become gemistocytes and result in the shortening of T1 relaxation time along the tract. In contrast, petechial hemorrhage occurs in areas that suffer from the more severe ischemic damage, most likely the areas of indirect pathway, which explains the mismatch of the hyper-intense areas on CT and MR studies. Although the ischemic or hyperglycemic insult occurs acutely, the pathologic changes may occur constantly, as evidenced by the progressive changes seen on MR images and the persistence of chorea seen in some patients.

The Clinical Implications

Two patients with large cortical infarcts also had hyperintense putamina, which are more likely responsible for HCHB than are the cortical lesions. This finding suggests that patients with lesions in the cerebral cortex (1) or subcortical white matter (25, 27) may have a hyperintense putamen. The CT findings in most patients with HCHB and ipsilateral or contralateral striatal hemorrhage (7, 23, 24, 28) or calcification (5, 40) are similar to those in our patients. An MR examination may be obtained to disclose a hyperintense putamen, particularly in those cases in which there is slightly high density, sparing of the internal capsule, lack of mass effect, or hyperglycemia. HCHB with a hyperintense putamen does not always have a benign course. HCHB persists in some patients after hyperglycemia is corrected, and it tends to recur (4–7). The presence of a hyperintense putamen may precede the occurrence of HCHB. Mortality appears more related to the progression of underlying disease.

The stereotactic biopsy done in one of our patients is an experimental procedure; we do not recommend similar invasive investigation in such patients because of the high risk of hemorrhagic transformation (7, 37).

Conclusion

A hyperintense putamen may result from the presence of abundant gemistocytes. These signal changes may spread along the striatonigral pathway and persist for years, suggesting that neuronal activity in the pathway is responsible for generating HCHB. Confirmation of this theory awaits further autopsy data and experimental confirmation.

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References
