Hemichorea-hemiballism Associated with Hyperintense Putamen on T1-weighted MR Images: An Update and a Hypothesis

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Abstract- In 1998 some patients with hyperglycemia-related hemichorea-hemiballism have been reported with a hyperintense putamen on T1-weighted MR images, presumably resulting from petechial hemorrhage. I questioned this explanation from my experience because (1) the areas of hyperintense lesions and their time evolutions did not match with those of the high density lesions on CT, (2) these hyperintense lesions persisted for years, and (3) the hyperintense lesions extended inferiorly to the midbrain. Therefore, a biopsy was performed in one patient and disclosed a fragment of gliotic brain tissue with abundant gemistocytes, which I proposed was sufficient to explain the shortening of T1 relaxation time. In addition, because two of our patients were associated with cortical infarcts and without hyperglycemia, I have suggested that cerebral ischemia might be a more important cause. In 1999 Fujioka et al reproduced the MR finding in animals 7 days after 15-minute occlusion of the middle cerebral artery. Therefore, both studies have suggested that the MRI finding resulted from a progressive pathological reaction in an incomplete infarction. In 2003 Fujioka et al further reported that the hyperintensity on T1-weighted MR images after mild ischemia may involve a paramagnetic effect resulting from tissue manganese accumulation in reactive astrocytes.

Key Words: Astrocyte, Hemiballism, Hyperglycemia, Ischemia, Magnetic resonance imaging, Manganese

Acta Neurol Taiwan 2004;13:170-177

The term of "hemichorea-hemiballism" has been used to describe a clinical spectrum that consists of uncontrollable, random, large or small amplitude jerking, flinging, or kicking motions involving proximal or distal parts of the limbs; furthermore, hemiballism often evolves into hemichorea[1]. The movements are usually continuous, but may be intermittent[2]. It may occur with other types of involuntary movements, such as dystonia, myoclonus, or orofacial dyskinesia[2]. The most common cause of hemiballism is a vascular lesion[1,3,4]. However, hemiballism is frequently associated with hyperglycemia and may be the first clinical manifestation of this disorder[5-14].

The site of lesions commonly responsible for the occurrence of hemiballism is the subthalamus[15,16]. However, in a recent review of 120 patients, lesions of the subthalamus are only a minority (18%) of the cases of hemiballism[17]. Lesion sites other than the subthala-

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Received September 15, 2004. Revised September 20, 2004. Accepted October 15, 2004.
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mus account for 57% of cases. These lesions usually involve the afferent or efferent pathways of the subthalamus, i.e., caudate, putamen or globus pallidus, but may involve thalamus, subcortical white matter, or cerebral cortex[2,5,12,18-34].

Hemiballism associated with hyperglycemia and a hyperintense putamen on T1-weighted magnetic resonance (MR) images was first reported from Japan, followed by Taiwan and the United States[5,10,35-43]. Unlike the hyperintense lesions associated with parenteral nutrition, liver cirrhosis, manganese intoxication, or calcification of basal ganglia, which are more localized in the globus pallidus, the hyperintense lesions associated with hemiballism appear to be more laterally situated[44-47].

Because of the transient presence of high density in the corresponding regions on computed tomography (CT) scans, it is assumed that the hyperintense lesions on T1-weighted MR image are related to petechial hemorrhages[35,42]. On the other hand, because one of the 5 patients with hyperintense lesions on T1-weighted MR images had a normal CT, myelin destruction has also been considered as a possible cause of the signal changes[35].

In our 1998 article reporting the findings of 10 patients I questioned this explanation because in one patient the hyperintense lesions extended caudally along a tract and in another patient the hyperintense lesions persisted for as long as 6 years; both were unlikely to be explained by petechial hemorrhage[48]. Another key finding in my article was that there was a mismatch between the sizes of lesions detected on CT scans and on T1-weighted MR images and also a mismatch between their time evolutions[48]. It appeared that the lesions on CT and on T1-weighted MR images resulted from two different pathophysiologic mechanisms. To determine the pathological process underlying the high signals on T1-weighted MR images, we had performed stereotactic biopsy in one patient.

Hematoxylin and eosin-stained sections of the biopsy specimen of our patient revealed a fragment of gliotic brain tissue with abundant gemistocytes and a fragment of relatively normal brain tissue[48]. There was no apparent hemorrhage or infarction, although occasional hemosiderin-laden macrophages were found scattered in the relatively normal brain tissue. On Luxol fast blue stain or immunohistochemical stain for myelin basic protein, there was no evidence of demyelination. In addition, high resolution 1H NMR spectroscopy demonstrated that lactic acid, acetate, and lipids were markedly increased while N-acetylaspartate and creatine were relatively decreased. According to these findings, I have proposed several hypotheses, most of which turn out to be correct[48].

Hypothesis 1

Calcification is unlikely the cause of high signals on CT scan

A recent report suggested that high signals on T1-weighted images might be resulted from calcification detected on CT scans[49]. However, the reported lesion was confined mainly to the globus pallidus. The first hypothesis that I have proposed appears correct in that calcification was not found on our biopsy specimen and that calcification was not likely to disappear on CT scans, as it was demonstrated in our paper[48].

Hypothesis 2

Petechial hemorrhage may be the cause of high signals on CT scan, but is unlikely the cause of high signals on T1-weighted MR image

This hypothesis is correct based on our biopsy results that no apparent hemorrhage was detected[48]. The presence of occasional hemosiderin-laden macrophages suggested that microbleeds might have occurred before the time of biopsy, but these hemosiderin laden macrophages could not explain the high signals on T1-weighted images. Although the hyperintense lesion on T1-weighted images could result from the presence of extracellular methemoglobin, it is usually found in an subacute stage of parenchymal hematoma and is unlikely persistent[50]. In addition, none of our patients or others showed coexistence of hyperintense change on T2-weighted images presumably resulting from the extracellular methemoglobin. Therefore, petechial hemorrhage is unlikely the cause of high signals on T1-weighted MR images.

Hypothesis 3

A unifying theory of vascular etiology

Based on the following three findings, I have proposed a unifying theory of vascular etiology in 1998[48]. First, since not all of our patients were diabetic, cerebral ischemia alone seemed sufficient to induce the dysfunction. Second, proton MR spectroscopy on the biopsy specimen of our patient showed an increase in lactic acid and a decrease in creatine and N-acetylaspartate, which suggested the presence of anaerobic glycolysis, energy depletion, and neuronal dysfunction. These findings were consistent with the presence of an ischemic injury. Third, even in those patients with hyperglycemia, ischemia might also play a role. This was demonstrated in two of our patients with hyperglycemia. After years of follow-up, their T2-weighted MR images revealed slit-shaped cystic lesions in the lateral part of the putamina, consistent with the presence of watershed infarction.

In 1999 Fujioka et al. reported four cases with cardiac embolism and transient ischemic attacks; serial MRI revealed hyperintensity on T1-weighted images in the caudate/putamen in all patients and in the cerebral cortex in two patients[51]. In the following paper Fujioka et al. reproduced the MRI finding in rats by 15-minute occlusion of middle cerebral artery but not by 60-minute occlusion[52]. The hyperintensity on T1-weighted images appeared seven days after brief ischemia. Histological examination revealed that this specific ischemic change on MRI corresponded to selective neuronal death and gliosis with preservation of the macroscopic structure of the brain.

I mentioned in 2000 that the MRI finding corresponded to an incomplete infarction, which was not only demonstrated by the relative preservation of the macroscopic structure of the brain in both studies but also by the presence of a mixture of relatively normal brain tissue in the biopsy specimen of our patient[53]. Fujioka's study confirmed my hypothesis that the MRI finding was related more to vascular compromise than to petechial hemorrhage or hyperglycemia.

Hypothesis 4

The hyperintensity on T1-weighted MR images is due to the presence of abundant gemistocytes

I have proposed that the hyperintensity on T1-weighted MR images could be due to the presence of abundant gemistocytes because in one of our patients the hyperintense lesion extended to the level of the midbrain, a location presumably remote from the site of vascular compromise or petechial hemorrhage[48]. The MR signal could be due to changes along the striatonigral fibers and gemistocytes is a good candidate because they situate along the axons and may persist for years. Gemistocytes are swollen reactive astrocytes that usually appear during acute injury; after that, their size gradually shrinks. However, gemistocytes are also found in some chronic diseases, suggesting the presence of a long-lasting pathologic reaction. Astrocytosis in the form of large-bodied astrocytes, hypertrophied astrocytes, swollen astrocytes, or gemistocytic astrocytes have been reported in several autopsy cases of ballism[14,33,54]. The first biopsy report from a hyperintense lesion on T1-weighted MR images described the presence of astrocytosis[37]. Following my report in 1998[48], an autopsy study in 2001 disclosed multiple foci of recent infarcts associated with reactive astrocytes in the hyperintense putamen[55]. Another biopsy from a hyperintense lesion of a diabetic patient with uremia also showed plump astrocytosis[56]. It is correct that the hyperintensity on T1-weighted MR images is due to the presence of abundant reactive astrocytes; however, it appears that the hyperintensity is not due to their morphological change as I have originally proposed[48].

It is now clear that the hyperintensity on T1-weighted MR images is related to the manganese accumulation in the reactive astrocytes[57]. In 2003 Fujioka et al. demonstrated a similar time course of the appearance of high signals on T1-weighted MR images and the accumulation of tissue manganese[57]. The manganese accumulation was accompanied by induction of Mn-superoxide dismutase and glutamine synthetase in reactive astrocytes after brief ischemia, reflecting a state of increased oxidative stress[57].

Hypothesis 5

Progressive nature of the lesion

I have proposed that although the ischemic or hyperglycemic insult occurred acutely, the pathological

changes might exist continuously because of the progressive changes on T1-weighted MR images and the persistence of chorea in some patients[48]. As Fujioka et al. demonstrated the delayed appearance of hyperintensity on T1-weighted MR images seven days after ischemic insult[52], the onset of hemichorea-hemiballism in some of our patients was also delayed up to 14 days after transient ischemic attacks[48]. Both findings suggested the existence of a progressive course in an incomplete infarction.

Although hemichorea-hemiballism disappeared in most patients when their hyperglycemia was brought under control, choreiform movements persisted in a few patients even after their hyperglycemia was corrected[48]. Others also reported poor responsiveness to haloperidol or recurrence of hemiballism associated with hyperglycemia[5,6,9,13]. It appeared that some irreversible change might have occurred in these patients, and was very likely due to coexisting cerebral ischemia. Cerebral hypoperfusion may result from an increase in cerebrovascular resistance due to higher brain water content during hyperglycemia or to a loss of flow regulation caused by impaired metabolism[58]. While most patients with hyperglycemia did not have severe cerebral ischemia and improved after their hyperglycemia was corrected, more extensive cerebral ischemia might have occurred in a few patients and resulted in their persistence of symptoms.

Different extent of cerebral ischemia might have occurred in patients with hyperglycemia. It is not clear that how severe was the ischemic injury elicited by each attack of hyperglycemia; however, it is clear that attacks of hyperglycemia must have occurred more frequently than those of cardiac embolism. These repetitive but mild ischemic attacks during hyperglycemia may account for the persistence of chorea or persistence of MR imaging abnormality in some patients.

Hypothesis 6

The coexistence of an activated direct pathway and an incompetent indirect pathway is necessary for generation of ballism

I have proposed patchy involvement of caudate-putamen to be the role rather than the exception for the occurrence of hemichorea-hemiballism[48]. Patchy distribution of relative normal tissue and abnormal tissue was found not only in the biopsy specimen of our patient but also in other's pathological reports[14,28]. In animal experiments, partial but not complete lesions of caudate-putamen result in contralateral choreo-athetoid movements[59,60].

Basal ganglion is an important part in the cerebral cortex - basal ganglion - thalamus - cerebral cortex feedback loop. There exist segregated striatal output pathways, including a direct pathway from the caudate-putamen to the internal segment of globus pallidus (GPi)/pars reticulata of substantia nigra (SNr), and an indirect pathway going through the caudate-putamen, external segment of globus pallidus (GPe), subthalamus, and GPi/SNr[61,62]. Lesions in the subthalamus result in reduced pallidal activities and thalamic disinhibition, producing ballistic movements[63,64]. On the other hand, lesions in the caudate-putamen result in disinhibition of inhibitory GPe activities on the subthalamus, producing similar effects as subthalamic lesions[4,61,62,65]. Therefore, I have proposed that lesions involving the indirect pathway in caudate-putamen are sufficient to produce ballistic movements[48].

In addition, I have proposed that induction of dyskinetic movements depends on the loss of some functional areas in the indirect pathway while preserving some functional areas in the direct pathway[48]. Periodical discharges have been recorded from the caudate-putamen, which, possibly through the direct pathway, inhibit neurons in the SNr and are the primary events for dyskinetic movements in rodents and monkeys[59,60]. Another indirect evidence from in situ hybridization of brain tissues from parkinsonian patients and animals with levodopa-induced dyskinesias demonstrates that it is opioid peptide transmission within the direct pathways that is increased by levodopa[66]. However, there is no direct proof of a relatively intact direct pathway in patients with hyperglycemia-related hemiballism yet.

Hypothesis 7

Neurons in the ventral striatum and the striatonigral pathway may play a critical role in generating ballistic movements

I have proposed that neurons in the ventral striatum might play a critical role in generating ballism[48], because most of the hyperintense lesions in our patients were located in the ventral striatum and in monkeys with kainic acid-induced chorea burst-generating neurons were also located in the rostral ventromedial putamen[60]. Fujioka et al. has proposed that the MRI changes correspond to striatal neurodegeneration with a chronic inflammatory response and signs of oxidative stress[57]. However, it is possible that some neurons might be protected by these reactive astrocytes and survived. These neurons inside the high-signal areas might generate nerve impulses abnormally and induce dyskinetic movements themselves, or they might lose their function, for example, surround inhibition to nearby neurons in the relatively normal tissue so that synchronous bursts appeared. In either case, it is not so common for some neurons having the capacity to generate ballistic movements to be spared in an ischemic insult; this may explain the rarity of ballism with lesions in lentiform nuclei[67]. Nevertheless, the importance of ventral striatum waits to be proved.

Although the hyperintensity on CT scans, hyperintensity on T1-weighted MR images, and hemiballism frequently occurred concurrently, they may reflect three pathophysiologic mechanisms triggered by the same event and running in parallel. They tend to occur together, but not absolutely. I have demonstrated a few patients with hyperintensity on CT scans several days before the occurrence of hemiballism[48]. In Fujioka's four patients and in another two diabetic patients, the hyperintensity on T1-weighted MR images was not associated with any involuntary movements[51,68]. In another report, high density on CT turned into normodensity in 4 months; hyperintensity on T1-weighted MR images was resolved in 18 months; and the hemiballism persisted without the striatal T1-hyperintensity[69].

In 2004 Wintermark et al. reported another case with hyperintensity on CT scans, on T1-weighted MR images and on the exponential diffusion-weighted (DW) images[70]. The restricted diffusion on the DW images provided another evidence that ischemia did occur early in the course[71]. To my best knowledge, manganese deposition in the brain is not associated with hyperintensity on CT scans. While the mechanism responsible for the hyperattenuation on CT scans remains inconclusive, microbleeds or 'reversible calcium deposition or influx' remains a possible explanation.

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