Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Change in striatal metabolism in diabetic haemichorea-haemiballism

Takao Hashimoto,¹ Kazuhiro Oguchi,² Ryo Takeuchi²

¹Center for Neurological Diseases, Aizawa Hospital, Matsumoto, Japan

²Department of Radiology, Aizawa Hospital, Matsumoto, Japan

Correspondence to Dr Takao Hashimoto, sinke-dr@ai-hosp.or.jp

Summary

We studied metabolic changes in relation to chorea in two patients with diabetic haemichorea-haemiballism using positron emission tomography with ¹⁸F-fluorodeoxyglucose. Metabolism of the striatum and globus pallidus did not change in the acute choreic stage, but it decreased in the later stage after the amelioration of chorea. Striatal and pallidal hypometabolism in the late stage in diabetic haemichorea-haemiballism may reflect tissue ischaemia with gliosis. Previous studies have demonstrated striatal hypometabolism in neurodegenerative choreic disorders and striatal hypermetabolism in acute inflammatory choreic disorders. Previous findings as well as our results suggest that striatal and pallidal metabolic changes may be correlated with histological changes more than with functional changes relevant to chorea.

BACKGROUND

Pathogenic relations of metabolic changes in the basal ganglia to chorea or ballism are still controversial: hypometabolism has been observed in the striatum in Huntington's disease¹ and in McLeod neuroacanthocytosis syndrome,² whereas hypermetabolism has been reported in some inflammatory and drug-induced diseases.^{3–5} Diabetic haemichorea-haemiballism (DHH) is a unique syndrome characterised by non-ketotic hyperglycaemia at onset, chorea-ballism and T1-MRI hyperintensity in the contralateral striatum.^{6–7} The pathohistology of the striatal lesions remains unclarified, but autopsy revealed the striatal lesions consisting of multiple foci of infarcts associated with reactive astrocytosis without haemorrhage.⁸ The pathophysiology underlying chorea-ballism in relation to striatal lesions and hyperglycaemia remains obscure.^{7–9} We investigated the metabolic changes in the basal ganglia in DHH by positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (FDG) and we clarified their pathogenic relations to chorea-ballism.

CASE PRESENTATION

Case 1

A 77-year-old woman was admitted to our hospital because of acute-onset haemichorea on the left side. She had suffered from diabetes mellitus and was treated with insulin injection, but had discontinued the medication on her own. She had no history of neuroleptic exposure or rheumatic fever and no family history of chorea. Her blood glucose was 632 mg/dl and glycosylated haemoglobin A1c was 19% (normal range 4.3–6.1%), but she was non-ketotic on admission. CT showed slightly high density, and MRI showed high intensity on T1-weighted image and low intensity on T2-weighted image in the right striatum (figure 1A). She was treated with

intravenous administration of insulin and oral administration of haloperidol. Blood glucose level was gradually controlled, and haemichorea gradually subsided and disappeared 9 days after onset; then haloperidol was discontinued. Follow-up MRI taken 19 days after onset revealed that the T2-hypointensity in the right striatum changed into a slight hyperintensity and T1-hyperintensity became more remarkable (figure 1B).

Case 2

A 78-year-old woman with a history of cerebral infarction, hypertension, hyperlipidaemia and poorly controlled diabetes mellitus acutely developed gait disturbance and involuntary movements of the left upper and lower limbs. She had no neuroleptic exposure, rheumatic fever or family history of chorea. She was non-ketotic. Examination revealed severe choreic and ballistic movements in the left upper and lower limbs without paresis. She was not demented. Laboratory tests revealed that her blood sugar was 455 mg/dl and glycosylated haemoglobin A1c was 14.4%. She was non-ketotic. MRI taken on admission demonstrated a markedly high-intensity signal on T1-weighted images and a slightly low-intensity signal on T2-weighted images in the bilateral striatum and globus pallidus (figure 1C). Some old multiple lacunar infarctions were also recognised. Her blood sugar was controlled using insulin after admission, and her choreic movements were treated with oral administration of haloperidol. Her involuntary movements gradually ameliorated, but moderate choreic movements persisted in the left leg for longer than 3 months after onset. Haloperidol was discontinued 23 days after onset because of the induction of somnolence. The striatal T1-hyperintensity persisted, but the T2-hypointensity changed into a slight hyperintensity 35 days after onset (figure 1D). A right pallidotomy was

Figure 1 (A) T2-weighted axial MRI, T1-weighted axial MRI obtained 4 days after onset in Case 1. T2-weighted MRI showed decreased signal intensity, and T1-weighted MRI showed increased signal intensity in the right striatum. ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) studied 5 days after onset revealed a high uptake in the right putamen compared with the left putamen in the early choreic stage (arrow), though it was within 2SD from the mean normal value. (B) Follow-up MRI taken 19 days after onset revealed that the T2-hypointensity in the right striatum changed into a slight hyperintensity and T1-hyperintensity became more remarkable. FDG-PET studied 19 days after onset showed a low uptake in the right putamen and globus pallidus. (C) T2-weighted axial MRI, T1-weighted axial MRI obtained 3 days after onset in Case 2. T2-weighted MRI showed decreased signal intensity, and T1-weighted MRI showed markedly increased signal intensity in the bilateral striatum and globus pallidus. FDG-PET studied 8 days after onset revealed a normal uptake in the bilateral striatum (arrow heads). (D) Follow-up MRI taken 35 days after onset revealed that the T2-hypointensity changed into hyperintensity, and T1-hyperintensity became more remarkable in the bilateral striatum. FDG-PET studied 31 days after onset showed a low uptake in the bilateral putamen and the right caudate and globus pallidus.

performed 3 months after onset and successfully abolished the persistent chorea in the left leg. Intraoperative microrecording during chorea revealed that the neuronal firings were significantly slower and irregular compared to those in off-state Parkinson's disease. The physiological results have been reported elsewhere.¹⁰

INVESTIGATIONS

The patients fasted at least 4 h prior to each PET study. They received an intravenous injection of 5 MB/kg FDG 60 min before the PET scan. Brain FDG-PET was done in a dimly lit quiet room with a GE Advance NXi PET system (General Electric Medical Systems, Milwaukee, Wisconsin, USA) using three-dimensional acquisition mode. Image acquisition protocol was started with emission scans (2–10 min) followed by postinjection transmission scans (3–5 min). Attenuation-corrected image data were reconstructed with Fourier Rebinning and Ordered Subsets–Expectation Maximization (FORE+OSEM) algorithm with reconstruction parameters of five iterations with 40 subsets. Resulting transaxial images were displayed on 128×128×35 matrices with a size of 2×2×4.25 mm. Putamen, caudate head, globus pallidus, precentral and postcentral frontal regions of interest were defined following the three-dimensional stereotaxic region of interest template. The internal segment and external segments of the globus pallidus (GPi and GPe) could not be evaluated separately due to the resolution level. Regional glucose metabolism was expressed as regional metabolic rates (RMRs) which were regional values normalised by cerebellum metabolism. RMRs were compared with control values calculated in eight normal subjects (mean age, 77.5 ±2.7 years), and the values in the acute stage with severe chorea and in the late stage after improvement of chorea were also compared (5 and 19 days after onset in Case 1 and 3 days and 1 month after onset in Case 2). Each patient gave informed consent.

OUTCOME AND FOLLOW-UP

Normalised metabolic rates for each PET study and the normal control group are given in the table 1.

Case 1

The RMR of the right putamen measured 5 days after onset, during the period with chorea, was increased compared with that of the left putamen, but not increased compared with those of normal subjects (figure 1A). The RMRs of the right putamen and globus pallidus were decreased by 14.9% and 6.2%, respectively, 19 days after onset (figure 1B). Haloperidol was initiated after the first PET study and discontinued 10 days prior to the second study. The chorea disappeared 10 days prior to the second PET study.

Case 2

FDG-PET performed 3 days after onset, during the period with severe chorea, revealed no change in the RMRs of the bilateral striatum compared with those of normal subjects (figure 1C). Metabolic rates of bilateral putamen and the right caudate and globus pallidus were decreased by ≥15% a month after onset (figure 1D). The moderate chorea in the left leg persisted beyond the time of the follow-up PET. Haloperidol was initiated after the first

Table 1 Regional glucose metabolism in two cases who showed left haemichorea, expressed as regional metabolic rates normalised by cerebellum metabolism

Region	Case 1-first	Case 1-second (% change)	Case 2-first	Case 2-second (% change)	Normal mean (SD)
Putamen					
L	1.006	1.088 (+8.1)	1.118	0.934* (–16.4)	1.14 (0.09)
R	1.064	0.905* (–14.9)	1.179	0.909* (–22.9)	1.14 (0.09)
Caudate head					
L	0.720	0.725 (+0.6)	0.718	0.698 (–2.8)	0.87 (0.15)
R	0.775	0.836 (+7.9)	0.704	0.597* (–15.2)	0.91 (0.13)
Globus pallidus					
L	0.907	0.906 (–0.1)	0.954	0.889 (–6.8)	0.1 (0.05)
R	0.907	0.850* (–6.2)	0.967	0.810* (–16.3)	0.97 (0.05)
Precentral					
L	0.874*	0.969 (+11.8)	0.764*	0.750* (–1.9)	1.02 (0.06)
R	0.880*	0.949 (+7.8)	0.767*	0.794* (+3.5)	1.04 (0.05)
Postcentral					
L	0.839*	0.910* (+8.5)	0.774*	0.775* (+0.1)	1 (0.06)
R	0.856*	0.898* (+4.8)	0.732*	0.783* (+7.0)	1.02 (0.05)

*≤ 2 SD as compared with normal controls.

Changes by ≥10% are indicated by italic figures.

PET study and discontinued 8 days prior to the second PET study.

DISCUSSION

Clinical findings of our patients, that is, acute onset of chorea-ballism, non-ketotic hyperglycaemia at onset, and marked hyperintensity in the striatum on T-weighted MRI fulfil characteristic features of DHH.^{6–7} Usually, the MRI lesions and involuntary movements appear unilaterally in this disorder, but bilateral lesions can develop simultaneously⁷ as they did in Case 2. The pathohistology of the lesions has been investigated based on histological findings. There are two reports on striatal tissue biopsy and three autopsy studies in this disorder, and common findings are multiple infarcts with proliferation of gemistocytic astrocytes in the striatum contralateral to chorea-ballism.^{8–11} Fujioka *et al* found that transient internal carotid artery-middle cerebral artery occlusion can lead to basal ganglionic and cortical lesions showing T1-MRI hyperintensity in four patients.¹² They demonstrated that the striatal lesions after transient ischaemia involve tissue manganese (Mn) accumulation and degeneration with chronic inflammatory response and signs of oxidative stress, and they suggested increases in the concentrations of Mn and Mn-binding enzymes are causative for T1-MRI hyperintensity.¹³

The present metabolic study demonstrates that metabolism of the striatum and globus pallidus contralateral to chorea did not change in the acute stage with severe chorea and changed into hypometabolism in the late stage in both cases. Hsu *et al*⁹ reported hypometabolism in all three patients with DHH, but they examined FDG-PET in the late period, 20 days, 40 days and 1 month after onset, respectively. Striatal hypermetabolism was observed in correspondence with acute development of chorea in autoimmune, inflammatory and drug-induced disorders,^{3–5} and pathogenetic correlation between the striatal hypermetabolism and chorea was speculated. On

the contrary, Furie *et al* observed striatal hypermetabolism during the choreic period and also during the non-choreic period in primary antiphospholipid syndrome.⁴ In contrast, striatal hypometabolism has been observed associated with neurodegenerative choreic disorders, for example, Huntington's disease¹ and McLeod neuroacanthocytosis syndrome.² In Case 2, chorea persisted during the period of striatal hypometabolism. Thus, metabolic changes of the striatum, either hyper in inflammatory diseases or hypo in neurodegenerative diseases, may not have a pathogenetic relevance to chorea but may result from histological changes. Striatal and pallidal hypometabolism in the late stage may reflect tissue ischaemia with gliosis in DHH.

With regard to neuronal activity underlying chorea and ballism, decreased firing rate in the GPi has been commonly observed in chorea and ballism caused by striatal or subthalamic lesions in humans.¹⁴ In the motor circuit, the GPi projection to the thalamus is inhibitory to the thalamocortical excitatory projection. Decrease in the firing rates in the GPi in chorea and ballism leads to disinhibition of the thalamocortical projection and to excessive increase in excitability of the frontal motor areas. Irregular firing pattern with pauses in the GPi is another firing property underlying chorea or ballism.¹⁴ In Huntington's disease, a selective loss of the striatal inhibitory neurones containing both γ -aminobutylic acid and enkephalin, which originate in the indirect pathway, is assumed to cause disinhibition of the GPe, which results in decreased activity of the subthalamic nucleus and GPi.¹⁵ Slow and irregular firing in the GPi was also observed in Case 2 in the stage of striatal hypometabolism.¹⁰ Functional imbalance between the direct and indirect pathways of the basal ganglia, leading to decreased and irregular GPi activity, is probably pathogenic for chorea and ballism.^{14 15}

In conclusion, striatal and pallidal metabolic changes presented by FDG-PET may be correlated with histological changes more than with functional changes relevant to chorea and ballism.

Learning points

- ▶ Diabetic haemichorea-haemiballism is a unique syndrome characterised by non-ketotic hyperglycaemia at onset, chorea-ballism and T1-MRI hyperintensity in the contralateral striatum.
- ▶ Metabolism of the striatum and globus pallidus did not change in the acute choreic stage, but it decreased in the later stage after the amelioration of chorea in diabetic haemichorea-haemiballism.

- ▶ Striatal hypometabolism in the late stage in diabetic haemichorea-haemiballism may reflect tissue ischaemia with gliosis.
- ▶ Metabolic changes of the striatum associated with choreic disorders, either hyper in inflammatory diseases or hypo in neurodegenerative diseases, may not have a pathogenetic relevance to chorea but may result from histological changes.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Young AB, Penney JB, Starosa-Rubinstein S, *et al*. PET scan investigations of Huntington's disease: cerebral metabolic correlates of neurological features and functional decline. *Ann Neurol* 1986;**20**:296–303.
2. Oechsner M, Buchert R, Beyer W, *et al*. Reduction of striatal glucose metabolism in McLeod choreoacanthocytosis. *J Neurol Neurosurg Psychiatry* 2001;**70**:517–20.
3. Goldman S, Amrom D, Sziwowski HB, *et al*. Reversible striatal hypermetabolism in a case of Sydenham's chorea. *Mov Disord* 1993;**8**:355–8.
4. Furie R, Ishikawa T, Dhawan V, *et al*. Alternating hemichorea in primary antiphospholipid syndrome: evidence for contralateral striatal hypermetabolism. *Neurology* 1994;**44**:2197–9.
5. Vela L, Sfakianakis GN, Heros D, *et al*. Chorea and contraceptives: case report with PET study and review of the literature. *Mov Disord* 2004;**19**:349–52.
6. Yahikozawa H, Hanyu N, Yamamoto K, *et al*. Hemiballism with striatal hyperintensity on T1-weighted MRI in diabetic patients: a unique syndrome. *J Neurol Sci* 1994;**124**:208–14.
7. Oh SH, Lee KY, Im JH, *et al*. Chorea associated with non-ketotic hyperglycemia and hyperintensity basal ganglia lesion on T1-weighted brain MRI study: a meta-analysis of 53 cases including four present cases. *J Neurol Sci* 2002;**200**:57–62.
8. Ohara S, Nakagawa S, Tabata K, *et al*. Hemiballism with hyperglycemia and striatal T1-MRI hyperintensity: an autopsy report. *Mov Disord* 2001;**16**:521–5.
9. Hsu JL, Wang HC, Hsu WC. Hyperglycemia-induced unilateral basal ganglia lesions with and without hemichorea. A PET study. *J Neurol* 2004;**251**:1486–90.
10. Goto T, Hashimoto T, Hirayama S, *et al*. Pallidal neuronal activity in diabetic hemichorea-hemiballism. *Mov Disord* 2010;**25**:1295–7.
11. Mestre T, Ferreira JJ, Pimental J. Putaminal petechial haemorrhages as the cause of non-ketotic hyperglycaemic chorea: a neuropathological case correlated with MRI findings. *J Neurol Neurosurg Psychiatr* 2007;**78**:549–50.
12. Fujioka M, Taoka T, Hiramatsu KI, *et al*. Delayed ischemic hyperintensity on T1-weighted MRI in the caudoputamen and cerebral cortex of human after spectacular shrinking deficit. *Stroke* 1999;**30**:1038–42.
13. Fujioka M, Taoka T, Matsuo Y, *et al*. Magnetic resonance imaging shows delayed ischemic striatal neurodegeneration. *Ann Neurol* 2003;**54**:732–47.
14. Vitek JL, Chockkan V, Zhang JY, *et al*. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann Neurol* 1999;**46**:22–35.
15. Starr PA, Kang GA, Heath S, *et al*. Pallidal neuronal discharge in Huntington's disease: support for selective loss of striatal cells originating the indirect pathway. *Exp Neurol* 2008;**211**:227–33.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Hashimoto T, Oguchi K, Takeuchi R. Change in striatal metabolism in diabetic haemichorea-haemiballism. *BMJ Case Reports* 2012;10.1136/bcr-2012-006405, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow