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A Comparative Study of Blood Flow in the Cerebellum and Brainstem between Machado-Joseph Disease and Olivopontocerebellar Atrophy

Nobuyoshi FUKUMITSU[1], Masahiko SUZUKI[2], Yasuhiko ITO[2], Yasuyuki IGUCHI[2], and Yutaka MORI[1]

[1]*Department of Radiology, The Jikei University School of Medicine*
[2]*Division of Neurology, Department of Internal Medicine, The Jikei University School of Medicine*

ABSTRACT

In recent years, the neurogenic and pathological differences between Machado-Joseph disease (MJD) and sporadic olivopontocerebellar atrophy (OPCA) have been clarified. We performed N-isopropyl-p-[I-123] iodoamphetamine (IMP) SPECT on 9 patients with MJD and 12 patients with OPCA. The blood flow of the cerebellum in the MJD group was significantly decreased than that of the control group ($p<0.0001$). That of OPCA group was significantly decreased than those of the control and MJD groups ($p<0.0001$, respectively). The blood flow of the brainstem in the MJD group was significantly decreased than that of the control group ($p<0.001$). That of OPCA group was significantly decreased than those of the control and MJD groups ($p<0.0001$, respectively). The blood flow of cerebellum and brainstem in the OPCA group were much decreased than those of MJD group. IMP distribution pattern in MJD patients obviously differed from that of OPCA patients. (Jikeikai Med J 2002 ; 49 : 157-62)

Key words : Machado-Joseph disease, Olivopontocerebellar atrophy, ^{123}I-IMP SPECT, cerebellum, brainstem

INTRODUCTION

In 1972, Nakano et al. reported the hereditary spinocerebellar degeneration in Portuguese or descendants of Portuguese from the Portuguese Azores Islands as Machado disease[1]. Rosenberg et al. also reported the hereditary spinocerebellar degeneration in emigrants from the Azores Islands as Joseph disease[2]. The above mentioned diseases were considered to be the same disease and have been called Machado-Joseph disease (MJD)[3]. There have been many reports of this disease, MJD, since 1980's[3-6]. MJD is an autosomal dominant disorder in which the symptoms that occur range from gait disturbance, opthalmoplegia, bulging eyes, faciolingual fasciculation and myokimia.

When Dejerine and Thomas described two patients with ataxia during life and atrophy of the olives, pons, and cerebellum at autopsy, they commented that their new disease was "neither hereditary, nor familial, nor congenital, it comes on at an advantaced age. Its etiology is obscure"[7,8]. One of their patients had an immobile face, decreased arm movement, and late incontinence. Although many families with dominantly inherited atrophy of olives, pons, and cerebellum were later described, there have also been a large number of patients with no family history (often interpreted as evidence for recessive

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福光　延吉，鈴木　正彦，伊藤　保彦，井口　保之，森　　豊
Mailing address : Nobuyoshi FUKUMITSU, Department of Radiology, The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo, 105-8461, Japan.
E-mail address : GZL13162@nifty.ne.jp

inheritance), usually with some combination of levodopa-unresponsive parkinsonism and autonomic failure as well as ataxia, lumped under the rubric "olivopontocerebellar atrophy" (OPCA)[8,9].

In recent years, gene analysis has progressed at a surprising rapid pace. Molecular genetics studies became active in 1990's, and the gene locus for MJD was reported to be located in chromosome 14q in 1993[10]. CAG repeat in 14q32.1 was reported, in 1994, to expand 2-3 times normality[11].

Both MJD and OPCA have neurodegeneration in cerebellum and brainstem, and they are reported to have decreased blood flow in cerebellum and brainstem[12-14]. However, the reports before gene analysis was progressed had several questions in patients selection. In our previous study, the blood flow of cerebellum and brainstem were reported to be decreased in MJD patients who were diagnosed by gene analysis[15]. There were no comparative studies of cerebral blood flow of MJD and OPCA patients who were diagnosed by gene analysis. In this study, we investigated the distribution pattern of cerebral blood flow of MJD and OPCA patients, using N-isopropyl-p-[^{123}I] iodoamphetamine (IMP) SPECT.

Materials and Method

Materials

Nine patients with MJD and 12 patients with OPCA were studied and compared to 7 normal controls. Table 1 shows the patients of MJD and OPCA in detail.

The subjects with MJD were those who were diagnosed through family history and gene analysis. The MJD group was as follows: age range 28-60 years; mean age, 47.3±10.5 years, 4 male patients and 5 female patients. As far as gait disturbance is concerned, 4 ambulatory patients and 5 non-ambulatory patients. The morbid term of the MJD group was 8.1±2.7 years. Patients who could walk with or without help were classified as ambulatory patients, and those who could not walk even with help were classified as non-ambulatory patients. MJD patients showed CAG expansion of the repeat-number (from 66-80).

We based the diagnosis of OPCA on a history of

Table 1. The patients of MJD and OPCA.

Case	Age	Sex	Diagnosis	Duration	Gait disturbance	CAG repeat
1	60	F	MJD	4	Ambulatory	66
2	46	F	MJD	7	Ambulatory	74
3	46	F	MJD	10	Ambulatory	71
4	28	F	MJD	7	Ambulatory	80
5	57	M	MJD	6	Non-ambulatory	72
6	56	M	MJD	12	Non-ambulatory	74
7	36	M	MJD	7	Non-ambulatory	78
8	44	F	MJD	8	Non-ambulatory	75
9	53	M	MJD	12	Non-ambulatory	72
10	58	F	OPCA	6	Ambulatory	−
11	52	F	OPCA	6	Ambulatory	−
12	57	M	OPCA	3	Ambulatory	−
13	66	F	OPCA	4	Ambulatory	−
14	63	M	OPCA	1	Ambulatory	−
15	52	M	OPCA	3	Ambulatory	−
16	54	F	OPCA	1	Ambulatory	−
17	64	F	OPCA	unknown	Non-ambulatory	−
18	53	F	OPCA	5	Non-ambulatory	−
19	49	F	OPCA	7	Non-ambulatory	−
20	64	M	OPCA	6	Non-ambulatory	−
21	69	F	OPCA	13	Non-ambulatory	−

sporadically occurring progressive deterioration of cerebellar function manifested by at least two of the following features: limb ataxia, gait ataxia, ocular dysmetria, and ataxic dysarthria. The diagnosis required the exclusion of ataxia, medications, toxins, cerebellar degeneration, multiple sclerosis, or other diseases that can cause progressive cerebellar ataxia. We took a detailed family history to ensure that the disorder was sporadic. The diagnosis was assisted by finding cerebellar and brainstem atrophy in MRIs. Those OPCA subjects who were suspected of having spinocerebellar degeneration due to neurological findings by a neurologist were excluded from having existing hereditary spinocerebellar degeneration through gene analysis. The OPCA group was as follows: age range 49–69 years; mean age, 58.4±6.6 years, 4 male patients, 8 female patients. As far as gait disturbance is concerned, 7 ambulatory patients, 5 non-ambulatory patients. The morbid term of the OPCA group was 5.0±3.3 years.

Normal controls had no neurologic finding and normal MRIs. All patients were performed after obtaining the patients' consensus. The normal control group was as follows: age range 39–71 years; mean age, 56.0±14.1 years, 4 male patients, 3 female patients.

Methods

Intravenous infusion of 222 MBq IMP for 1 minute was done. SPECT scan was performed, with mid-scan time set up to 40 minutes after infusion of IMP.

The SPECT scanner used was a RC-2600I (HITACHI Corp., Tokyo, Japan), equipped with a two-head rotating gamma camera. A low-energy, high-resolutign collimator was used which provided a measured system spatial resolution of 7.8 mm FWHM.

Data was obtained from 64 projections (60 sec/projection in a 64×64 matrix). Images were collected using a 20% energy window, centered on 159 keV photopeak of ^{123}I. Prefiltered raw data (Butterworth filter) was used to construct transaxial sections using a filtered back-projection algorithm (Ramp filter). Attenuation correction was performed using Chang's method ($\mu = 0.067\ cm^{-1}$), scatter correction was performed using an elliptical approximation method.

Image slices were set up parallel to the orbitomeatal (OM) line and obtained at approximately 4-mm intervals through the whole brain. Regions of interest (ROIs) were established in the brainstem, bilateral cerebellar and occipital cortices. The ROIs of bilateral cerebellar cortices were established on the selected slice cut surfaces, 3–4 slices above the OM line, in which the mid-level of the cerebellum and pons were passed through. The ROIs established in the cerebellar cortices were the ones which accumulation was highest in the cerebellar cortices. The ROI that was established in the brainstem was the one matched for pons. When the ROI of pons was established, the same slice cut surface which cerebellar cortices were established was selected, and the most appropriate slice cut surface was decided from three consecutive slices, which were the slice cut surface first selected and ones 1 slice above and below. The size of ROIs was 2 pixel×2 pixel (Fig. 1). The blood flow of the cerebellum and occipital lobes were defined as the mean of bilateral blood flow. The blood flow of the cerebellum divided by the blood flow of the occipital

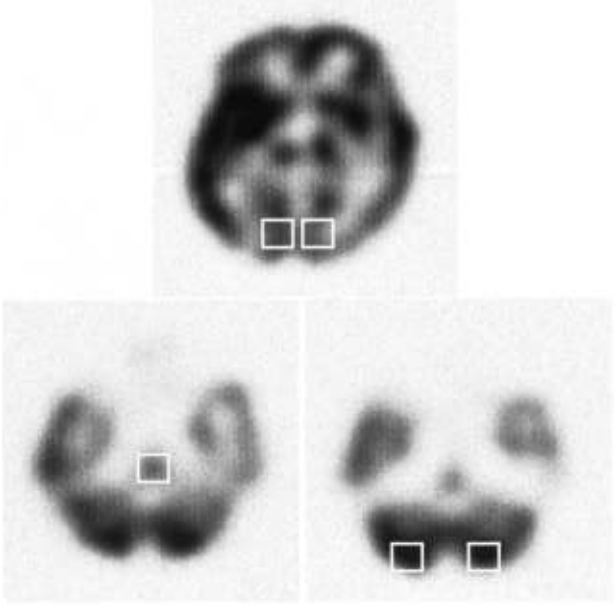

Fig. 1. ROIs of cerebellar hemispheres, brainstem and occipital lobe.

lobes shows as C/O ratio. The blood flow of the brainstem divided by the blood flow of the occipital lobes shows as B/O ratio.

Data analysis

All results were expressed as mean ± standard deviation (SD). The C/O and B/O ratios were compared in the control, MJD, and OPCA groups. The significant difference was calculated using Bonferroni/Dunn (Dunn's Procedure As A Multiple Comparison Procedure), with a p value of less than 0.0167 being considered significant.

Results

The blood flow of cerebellum

The C/O ratio was 0.82±0.13 in MJD, 0.54±0.10 in OPCA, and 1.070±0.03 in control group. The C/O ratio of the MJD group was significantly decreased than that of the control group ($p<0.0001$). The C/O ratio of the OPCA group was significantly decreased than those of the MJD and control groups ($p<0.0001$, respectively) (Fig. 2).

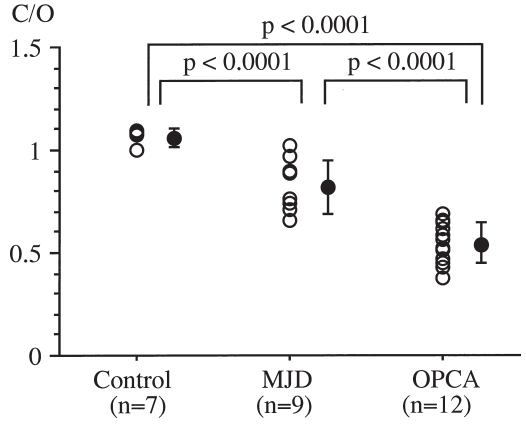

Fig. 2. The C/O ratio of MJD, OPCA.
(C : blood flow of cerebellum, O : blood flow of occipital lobes)
The C/O ratio of the MJD group is significantly decreased compared with that of control group. The C/O ratio of the OPCA group is significantly decreased compared with those of MJD and control groups.

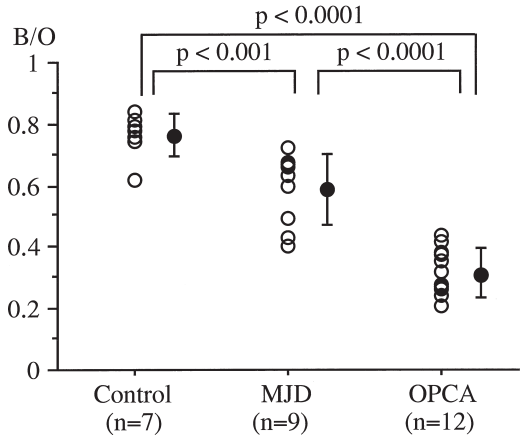

Fig. 3. The B/O ratio of MJD, OPCA.
(B : blood flow of brainstem, O : blood flow of occipital lobes)
The B/O ratio of the MJD group is significantly decreased compared with that of control group. The B/O ratio of the OPCA group is significantly decreased compared with those of MJD and control groups.

The blood flow of brainstem

The B/O ratio was 0.59±0.12 in MJD, 0.31±0.08 in OPCA, and 0.76±0.07 in control group. The B/O ratio of the MJD group was significantiy decreased than that of the control group ($p<0.001$). The B/O ratio of the OPCA group was significantly decreased than those of the MJD and control groups ($p<0.0001$, respectively) (Fig. 3).

Case Presentation

Case number 4, MJD, ambulatory patient.

28-year-old female.

She had felt dizzy when walking from about 21 years old, gait disturbance has been progressing, and ocular motor apraxia and faciolingual fasciculation has occurred. IMP SPECT at 28 years old showed that the C/O ratio was 0.89, the B/O ratio was 0.63 (Fig. 4).

Case number 11, OPCA, ambulatory patient.

52-year-old female.

She had been inarticulate with palsy from about 46 years old and dysarthria and gait disturbance occurred and had been progressing. IMP SPECT at

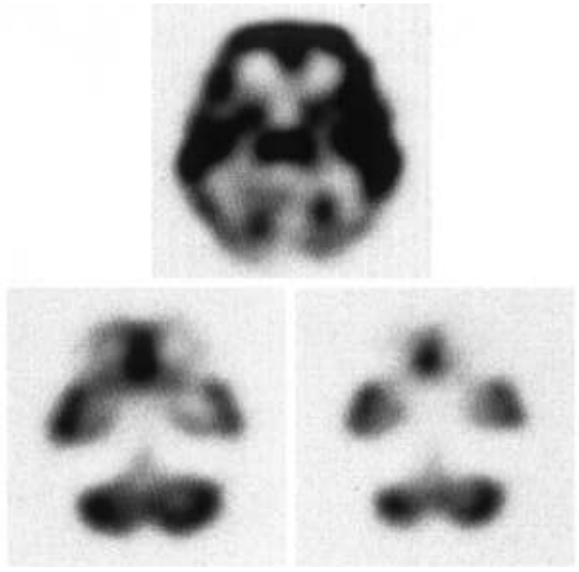

Fig. 4. 28-year-old female with MJD.
IMP SPECT shows marked decreased accumulation in the brainstem. The C/O ratio was 0.89, the B/O ratio was 0.63.
(C : blood flow of cerebellum, B : blood flow of brainstem, O : blood flow of occipital lobes)

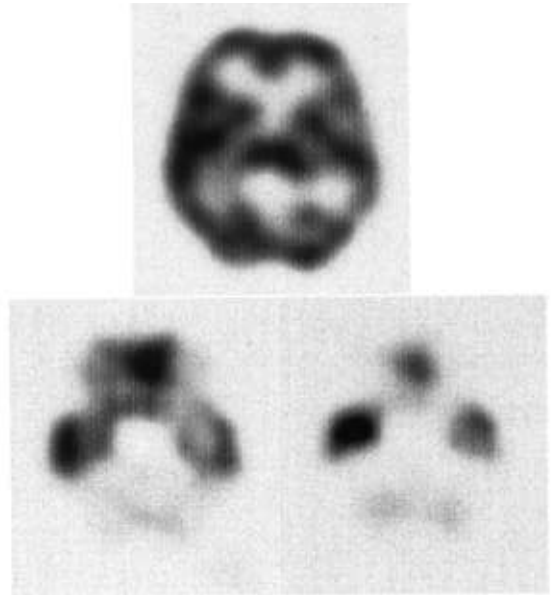

Fig. 5. 58-year-old female with OPCA.
IMP SPECT shows severe decreased accumulation in the cerebellum and brainstem. The C/O ratio was 0.43, the B/O ratio was 0.25.
(C : blood flow of cerebellum, B : blood flow of brainstem, O : blood flow of occipital lobes)

52 years old showed that the C/O ratio was 0.43, the B/O ratio was 0.25 (Fig. 5).

Discussion

There have been some reports of cerebral blood flow in MJD or OPCA patients indicating decreased blood flow in cerebellum and/or brainstem[12–14]. There were no comparative studies of cerebral blood flow of MJD and OPCA patients who were diagnosed by gene analysis.

As shown in the results, both MJD and OPCA groups had decreased blood flow of the cerebellum and brainstem compared with control group. However, blood flow pattern of MJD group was obviously different from that of OPCA group. The blood flow of cerebellum and brainstem was demonstratively decreased in OPCA group compared with those of MJD group. We believe that the blood flow of the cerebellum and brainstem was lower in the OPCA group than in the MJD group because of differences between these patients in the area or severity or both of lesions.

The main pathological lesion of MJD is reported the degeneration of the spinocerebellar tracts, dentate nuclei, pontine and vestibular nuclei, extrapyramidal structures (substantia nigra, locus coeruleus, and the pallidoluysian complex), and neuronal loss in motor cranial nerves, anterior horn cells, and the posterior root ganglion. The cerebral and cerebellar cortices and inferior olives are spared and Purkinje's cells and granulosa are normal[4,5,16–20]. On the other hand, the main pathological lesion of OPCA is reported the degeneration of intermediolateral nucleus of the spinal cord, pontine nuclei, cerebellar cortex, inferior olivaris nucleus, and putamen[21–24]. Additionally, a glassy structure that showed intense argyrophilia is recognized in oligodendroglial cells[25]. Lesions in the cerebellum and brainstem in OPCA patients are wider than in MJD patients.

It is well known that IMP is a radioligand which binds to non-specific amine-receptors and IMP distribution reflects the blood flow in brain[26–28]. We believe that the area or severity or both lesions in cerebellum and brainstem cause different IMP distribution between OPCA and MJD patients. We conclude that our results may be well reflected with pathological differences between MJD and OPCA.

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