Biomarker Research for Moyamoya Disease in Cerebrospinal Fluid Using Surface-enhanced Laser Desorption/Ionization Time-of-flight Mass Spectrometry

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Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by steno-occlusive change in bilateral internal carotid arteries with unknown etiology. To discover biomarker candidates in cerebrospinal fluid from MMD patients, proteome analysis was performed by the surface-enhanced laser desorption/ionization time-of-flight mass spectrometry. Three peptides, 4473Da, 4475Da, and 6253Da, were significantly elevated in MMD group. A positive correlation between 4473Da peptide and postoperative angiogenesis was determined. Twenty MMD patients were enrolled in this pilot study, including 11 pediatric cases less than 18 years of age (mean age, 8.67 years) and 9 adult MMD patients (mean age, 38.1 years). This study also includes 17 control cases with the mean age of 27.9 years old. In conclusion, 4473Da peptide is supposed to be a reliable biomarker of MMD. 4473Da peptide showed higher intensity peaks especially in younger MMD patients, and it was proved to be highly related to postoperative angiogenesis. Further study is needed to show how 4473Da peptide is involved with the etiology and the onset of MMD. **Key Words:** Moyamoya disease (MMD)—surface-enhanced laser desorption/ionization mass spectrometry (SELDI-TOF-MS)—biomarker—cerebrospinal fluid (CSF)—angiogenesis.
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Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by steno-occlusive change in bilateral internal carotid arteries[1] and the appearance of the abnormal vessel network at the base of brain. The abnormal vessel is called "moyamoya" vessel, which is a Japanese term that means "hazy puff of smoke".[2] Revascularization surgery is beneficial for stroke prevention,[3-5] and the definite diagnosis of MMD is determined by the guidelines set by the Research Committee on

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Moyamoya Disease of the Ministry of Health and Welfare of Japan.[6] There are many basic researches related to MMD involving epidemiology,[7,8] genetic,[9-13] pathologic,[14-16] and proteomics studies[17-21]; however, the etiology of MMD is not fully elucidated so far. Because cerebrospinal fluid (CSF) is close to the site of pathology, which reflects biological processes of the disease,[21,22] we focused on small peptides and proteins in CSF by using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS).[23,24] Previously we reported 34 possible biomarker candidates for MMD.[25] As far as we know this report was a first pilot proteomic study in MMD using SELDI-TOF-MS; this time we newly obtained 14 control samples from younger patients with neurologic diseases, and we added 15 newly diagnosed MMD patients.

Materials and Method

Patient Population and CSF Preparation

CSF samples were prospectively collected during operation from 20 MMD patients (8 male and 12 female, ranged 3-46 years; mean age, 21.29 years) at Nagoya University Hospital from April 2009 to July 2012 (Fig 1). The CSF samples from the 17 control patients (13 male and 4 female, ranged 0-58 years; mean age, 27.94 years) were also obtained. The onset of MMD were as follows: 14 cases of TIAs, 4 cases of cerebral infarction, 1 case of loss-of-consciousness attack, and 1 case of asymptomatic (Fig 1). And the control patients were from 9 cases of brain tumor, 3 cases of unruptured aneurysms, 2 cases of hydrocephalus, and 1 case each of arteriovenous malformation, internal carotid occlusion, and facial spasm, respectively (Fig 1). No CSF samples from healthy controls were obtained. After collecting the CSF, the sample was centrifuged, and the supernatants were frozen and stored at −80°C until analysis. All samples were collected after obtaining written informed consent from the patient following approval from the Nagoya University School of Medicine Ethical Review Board.

Sample Preparation and Analysis Procedure

As it was written before in our previous report,[25] in short, all the Q10 ProteinChip (Bio-Rad Laboratories, Hercules, CA) were equilibrated with each binding/washing buffer for activation of the ProteinChip. Then, each CSF was applied and incubated in a humid box. After the procedure, remaining samples were removed and washed with binding/washing buffer. The arrays were desalted with distilled water, and saturated energy absorbing molecule solution (sinapinic acid in 50% acetonitrile and .5% trifluoroacetic acid) was applied to each spot and allowed to analysis by ProteinChip reader. All the protein profiles were analyzed by the detector.

MMD group

	age	sex	Diagnosis	onset	CSF analysis side **suzuki's stage of analyzed side	SPECT	**suzuki'stageR/L	revascularization operation	STA patency	operation side
pediatric MMD	3	F	MMD	TIA	3	preserved	3/2	STAMCA anastomosis+frontal EGS	patent	R→L
	3	F	MMD	TIA	3	preserved	3/2	EDAS and frontal EGS	indirect only	R
	4	M	MMD	TIA	4	none	4/3	EDAS and frontal EGS	indirect only	R→L
	6	F	MMD	LOC	3	none	3/3	STAMCA anastomosis+EMS+frontal EGS	patent	L→R
	7	F	MMD	TIA	3	decreased	3/3	STAMCA anastomosis+EMS+frontal EGS	patent	R→L
	9	F	MMD	CI	4	decreased	4/4	STAMCA anastomosis+EMS+frontal EGS	patent	L→R
	9	F	MMD	TIA	4	decreased	4/3	STAMCA anastomosis+EMS+frontal EGS	patent	R→L
	9	M	unilateral MMD	TIA	2	none	2/0	STAMCA anastomosis+EMS+frontal EGS	patent	R
	11	M	MMD	TIA	3	preserved	3/3	STAMCA anastomosis+EMS	patent	L→R
	16	F	unilateral MMD	TIA	3	none	3/0	STAMCA anastomosis+EMS	patent	R
adult MMD	18	F	MMD	TIA	2	decreased	2/2	STAMCA anastomosis+EMS+frontal EGS	patent	L→R
	28	M	quasi-MMD	CI	4	decreased	4/4	STAMCA anastomosis+EMS+frontal EGS	not patent	L→R
	28	F	MMD	CI	4	none	3/4	STAMCA anastomosis+EMS	patent	L→R
	37	F	quasi-MMD	TIA	3	decreased	2/3	STAMCA anastomosis+EMS	patent	L
	38	M	MMD	CI	4	decreased	4/4	STAMCA anastomosis+EMS	patent	R→L
	40	F	MMD	TIA	3	none	3/3	STAMCA anastomosis+EMS	patent	R→L
	40	F	MMD	TIA	3	none	3/2	STAMCA anastomosis+EMS+frontal EGS	patent	R→L
	42	M	MMD	TIA	3	decreased	3/3	STAMCA anastomosis+EMS+frontal EGS	not patent	L
	44	M	unilateral MMD	TIA	3	decreased	0/3	STAMCA anastomosis+EMS	not patent	L
	46	M	MMD	asymptomatic	3	none	3/3	STAMCA anastomosis+EMS	patent	L →R

control group

	age	sex	Diagnosis
control	0	M	hydrocephalus
	0	M	BT
	1	M	BT
	3	M	BT
	6	M	BT
	15	F	hydrocephalus
	26	F	BT
	27	M	unruptured aneurysm
	33	M	BT
	35	M	AVM
	36	M	BT
	37	M	unruptured aneurysm
	41	M	BT
	47	F	BT
	54	F	facial spasm
	56	M	ICAO
	58	M	unruptured aneurysm

Supplement data

****Suzuki's Six angiographic staging of moyamoya disease**

Stage	angiographic Findings
1	stenosis of suprasellar ICA , usually bilateral
2	development of moyamoya vessels at base of brain
3	increasing ICA stenosis and prominence of moyamoya vessels (most cases diagnosed at his stage)
4	entire circle of Willis and PCAs occluded , extractranial collaterals start to appear , moyamoya vessels begin to diminish
5	further progression of Stage4
6	complete absence of moyamoya vessel and major cerebral arteries

MMD, moyamoya disease; TIA, transient ischemic attack; CI, cerebral infarction; LOC, loss of consciousness; SPECT, Single Photon Emission Computed Tomography; STA MCA, superficial temporal artery middle cerebral artery; EDAS, encephalo-duro-arterio-synangiosis; EGS, encephalo-galeo-synangiosis; EMS, encephalo-myo-synangiosis; R, right; L, left; BT, brain tumor; AVM, arteriovenous malformation; ICAO, internal carotid artery occlusion; ICA, internal carotid artery; PCA, posterior cerebral artery;

Figure 1. *Patient characteristic of moyamoya disease and control group in this study.*

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