SPECT Findings in Mitochondrial Encephalomyopathy

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We investigated the alterations in regional cerebral blood flow (rCBF) in mitochondrial encephalomyopathy (MEM), using [^{123}I]N-isopropyl-p-iodoamphetamine (IMP) or ^{99m}Tc-hexamethyl propyleneamine oxime SPECT in 10 MEM patients. **Methods:** Four of the patients had MEM with lactic acidosis and strokelike episodes (MELAS), 2 had Kearns-Sayre syndrome (KSS), 1 had myoclonic epilepsy with ragged red fibers (MERRF) and 3 had cytochrome C oxidase deficiency (CCOD). Cerebral perfusion reserve was obtained from 6 patients (3 MELAS, 1 MERRF, 1 KSS, 1 CCOD) for a comparative analysis using the split-dose ^{123}I-IMP SPECT method before and after the injection of acetazolamide. **Results:** All patients with MELAS showed focal hypoperfusion in the parietal and/or occipital lobes. Follow-up studies (3 MELAS patients) revealed extension or improvement in the abnormal perfusion. The hypoperfused lesions were correlated with abnormal CT/MRI findings. Perfusion was normal in 1 MERRF, 2 KSS and 3 CCOD patients, whereas CT/MRI findings in 1 MERRF, 1 KSS and 1 CCOD patient were abnormal. The cerebral perfusion reserve in 3 MELAS patients was decreased significantly compared with that in patients with other types of MEM (MELAS 7.4%, other MEM 33.8%; $p < 0.05$). **Conclusion:** The rCBF was altered specifically in patients with MELAS, suggesting that brain perfusion SPECT will be useful in diagnosing and assessing such patients. The decreased cerebral perfusion reserve in patients with MELAS may represent an important feature of the pathogenesis of the strokelike episodes. The SPECT findings of patients with other types of MEM (MERRF, KSS and CCOD) were normal.

Key Words: mitochondrial encephalomyopathy; lactic acidosis; SPECT; cerebral perfusion reserve

J Nucl Med 1998; 39:961–964

Mitochondrial encephalomyopathies (MEM) are neuromuscular disorders characterized by encephalopathy and myopathy and by the presence in the brain and muscle of structurally or functionally abnormal mitochondria (*1*). MEM have been divided into somewhat ill-defined categories on the basis of their phenotypic, biochemical and genetic manifestations (*2–4*). Three syndromes have been defined based on clinical features. These are MEM with lactic acidosis and strokelike episodes (MELAS) (*5*), Kearns-Sayre syndrome (KSS) (*6,7*) and myoclonic epilepsy with ragged red fibers (MERRF) (*8*). Another definition has been based on biochemical anomalies of mitochondrial metabolism, including cytochrome C oxidase deficiency (CCOD; Complex IV) and nicotinamide adenine dinucleotide-coenzyme Q reductase deficiency (Complex I) (*2*).

The aim of this study was to determine if brain perfusion and perfusion reserve are impaired in patients with MEM and to compare the SPECT findings with those from CT or MRI.

Received Apr. 14, 1997; accepted Aug. 14, 1997.

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MATERIALS AND METHODS

Patients

We studied 10 patients with MEM (age range 4–24 yr; mean age 14.9 yr) (Table 1). Four patients were diagnosed with MELAS, 2 with KSS, 1 with MERRF and 3 with CCOD. Six patients participated in a [^{123}I]N-isopropyl-p-iodoamphetamine (IMP) study and 8 patients underwent an investigation using ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO). Two patients with MELAS, 1 with KSS and 1 with CCOD were studied with both ^{123}I-IMP and ^{99m}Tc-HMPAO. Sequential studies were performed on 3 patients with MELAS and 1 with KSS and CCOD. All patients underwent brain CT or MRI as part of their evaluation. The study protocol was in accordance with the standard ethical guidelines of Osaka University Medical School and informed consent was obtained from all patients or their guardians.

Imaging Procedures

SPECT images (both ^{123}I-IMP and ^{99m}Tc-HMPAO) were acquired using a high-performance, four-head rotating gamma camera (Gamma View SPECT 2000H, Hitachi Medical Co., Tokyo, Japan) (*9*). On 6 MEM patients (3 MELAS, 1 MERRF, 1 KSS, 1 CCOD), ^{123}I-IMP SPECT was performed using the split-dose ^{123}I-IMP SPECT method before and after the injection of acetazolamide (*10*) without arterial sampling. Data were acquired in a continuous rotating mode in reciprocal directions at 20 sec/revolution for 58 min, 14 frames with 8 revolutions followed by 2 frames with 32 revolutions from 64 directions in a 64 × 64 matrix. The first dose of ^{123}I-IMP (2.75 MBq/kg) was injected intravenously at the beginning of imaging under resting conditions. Acetazolamide (20 mg/kg) was injected intravenously over 1 min, at the start of the fourth frame of acquisition, and the second dose of ^{123}I-IMP (2.75 MBq/kg) was administered at the start of the tenth frame. A second image (vasodilated image) was reconstructed from original data after the second ^{123}I-IMP injection by subtracting the baseline images obtained from the first ^{123}I-IMP injection. Square regions of interest (ROIs) 2 cm × 2 cm were placed on the cerebral and cerebellar cortices and the basal ganglia. The percent change (PC) of regional cerebral blood flow (rCBF) was estimated from the uptake ratio of the vasodilated image: resting image, using the equation generated in our previous studies (*11*).

For ^{99m}Tc-HMPAO, SPECT acquisition was performed 10 min after intravenous administration 18.5 MBq/kg ^{99m}Tc-HMPAO. SPECT acquisition was performed in 64 steps with a rotation 360° and a 64 × 64 matrix. SPECT acquisition datasets of both ^{123}I-IMP and ^{99m}Tc-HMPAO were prefiltered with a Butterworth filter and then reconstructed with a Ramachandran backprojection filter. Chang's postreconstruction attenuation correction was applied with an attenuation coefficient of 0.08 cm^{-1} to the transaxial image data. All SPECT images were interpreted by two nuclear medicine physicians who were blinded to the diagnosis.

MRI was performed using a 1.5 T unit (MagnetomH15, Sie-

TABLE 1
Clinical and Laboratory Features of Patients (n = 10) with Mitochondrial Encephalomyopathy (MEM)

Patient no.	Diagnosis	Age (yr)	Sex	Tracer	No.	CT/MRI	mtDNA	Enzyme
1	MELAS	5	M	HMPAO	2	CT/MRI	pm:3243	ns
2	MELAS	15	F	IMP	1	CT/MRI	nt	nt
3	MELAS	17	M	IMP, HMPAO	4	CT/MRI	pm:3243	NCRD
4	MELAS	21	M	IMP, HMPAO	2	CT	pm:3243	ns
5	MERRF	17	M	IMP	1	CT/MRI	nt	ns
6	KSS	18	F	HMPAO	1	CT	d:5205kb	ns
7	KSS	16	M	IMP, HMPAO	2	CT/MRI	d:8470kb	p-CCOD
8	CCOD	4	F	HMPAO	1	CT/MRI	ns	CCOD
9	CCOD	12	M	HMPAO	1	CT	nt	CCOD
10	CCOD	24	F	IMP, HMPAO	2	CT/MRI	nt	CCOD

No. = number of SPECT studies; mtDNA = mitochondrial DNA; MELAS = MEM with lactic acidosis and strokelike episodes; MERRF = myoclonic epilepsy with ragged red fibers; KSS = Kearns-Sayre syndrome; CCOD = cytochrome C oxidase deficiency; pm = point mutation; d = deletion; ns = nonspecific; nt = not tested; NCRD = nicotinamide adenine dinucleotide-coenzyme Q reductase deficiency; p-CCOD = partial deficiency of cytochrome C oxidase.

mens, Erlangen, Germany or Signa Advantage, GE Medical, Milwaukee, WI). CT images were obtained using a TCT 70A scanner (Toshiba Medical System, Tokyo, Japan). Two radiologists, who were blinded to all clinical information, independently reviewed the CT and MRI.

Statistical Analysis

Data are expressed as mean ± s.e.m. Statistical significance was determined using Student's t-test for unpaired data. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Rest Study

The SPECT, CT and MRI findings are summarized in Table 2. All patients with MELAS showed focal hypoperfusion in the parietal and/or occipital lobes. The hypoperfused areas on SPECT corresponded to lesions of low density on CT or T1,T2 prolonged areas on MRI. Focal hyperemia was evident in the left frontal lobe in two patients. In one patient (Patient 3; Fig. 1C), MRI revealed a T2 prolonged area with swelling, predominantly involving the cortex of the hyperemic frontal lobe, whereas MRI findings were normal in the hyperemic areas in another patient. Follow-up studies of three patients with MELAS revealed extension or improvement in the areas of abnormal perfusion. SPECT revealed normal perfusion in one patient with MERRF (Fig. 2B), however MRI/CT showed generalized atrophy of the cerebellum and calcification of the basal ganglia. Perfusion in two KSS and three CCOD patients was also normal, whereas one KSS and one CCOD patient showed abnormal findings on MRI/CT (Fig. 2A and C).

Acetazolamide Stress Study

There were no serious adverse effects of acetazolamide administration. The PC of rCBF is summarized in Table 3. In three patients with MELAS, PC was decreased in all brain areas and the difference was significant for the frontal lobe and for the average of all ROIs compared with that of other types of MEM. PC was decreased in both the hypoperfused and normal perfusion areas in three patients with MELAS and there were no significant differences between these areas.

DISCUSSION

Mitochondrial Encephalomyopathy with Lactic Acidosis and Strokelike Episodes

MELAS refers to a group of disorders characterized by episodes of nausea, vomiting and strokelike episodes (hemianopsia and hemiparesis) (*5,12*).

This study revealed focal hypoperfusion predominately in the parietooccipital areas in all MELAS patients. These findings are in agreement with previously published case reports (*13–17*). Quantitative rCBF measurement has demonstrated generalized hyperemia at sites of normal perfusion pattern (*16,18,19*). Watabiki et al. (*18*) found that the hyperemia was accompanied

TABLE 2
Summary of SPECT, MRI and CT Findings in Patients (n = 10) with Mitochondrial Encephalomyopathy (MEM)

Patient no.	Diagnosis/ interval	Tracer	SPECT	MRI T2 prolonged area	MRI atrophy	CT LDA	CT calc
1	MELAS	HMPAO	R.Pa-Oc ↓	No data	No data	No data	No data
	1 mo	HMPAO	R.Pa ↓, L.Oc ↓	R.Pa, L.Oc, B.BG	–	R.Pa, L.Oc	–
2	MELAS	IMP	R.Pa-Oc ↓, B.Ce ↓	R.Pa	Ce	R.Pa	+
3	MELAS	HMPAO	R.Oc ↓	R.Oc	–	R.Oc	+
	16 mo	IMP	R.Oc-Te ↓, B.Ce ↓, L.Te ↑	R.Oc	Ce	No data	No data
	5 mo	HMPAO	R.Oc ↓, L.Fr ↑	R.Oc, L.Fr*	–	No data	No data
	3 mo	HMPAO	R.Oc ↓, L.Fr ↓, L.Pa-Oc ↓	R.Oc, L.Fr, L.Pa-Oc	–	No data	No data
4	MELAS	HMPAO	B.Oc-Pa ↓	No data	No data	R.Oc-Pa	+
	3 yr	IMP	B.Oc-Pa ↓, R.Fr ↑	No data	No data	No data	No data
5	MERRF	IMP	np	–	Ce	none	+
6	KSS	HMPAO	np	No data	No data	none	–
7	KSS	HMPAO, IMP	np	B.IC, B.CR, B.MCP	–	B.IC	–
8	CCOD	HMPAO	np	B.CR, B.PU	–	B.CR	–
9	CCOD	HMPAO	np	No data	No data	none	–
10	CCOD	HMPAO, IMP	np	–	–	none	–

*T1,T2 prolonged area with swelling of cortex.

LDA = low density area; calc = calcification at basal ganglia; MELAS = MEM with lactic acidosis and strokelike episodes; MERRF = myoclonic epilepsy with ragged red fibers; KSS = Kearns-Sayre syndrome; CCOD = cytochrome C oxidase deficiency; L = left; R = right; B = bilateral; Fr = frontal lobe; Pa = parietal lobe; Oc = occipital lobe; Te = temporal lobe; Ce = cerebellum; IC = internal capsule; CR = corona radiata; PU = putamen; MCP = middle cerebellar peduncle; ↑ = hyperemia; ↓ = hypoperfusion; np = not particular; – = no abnormal findings.

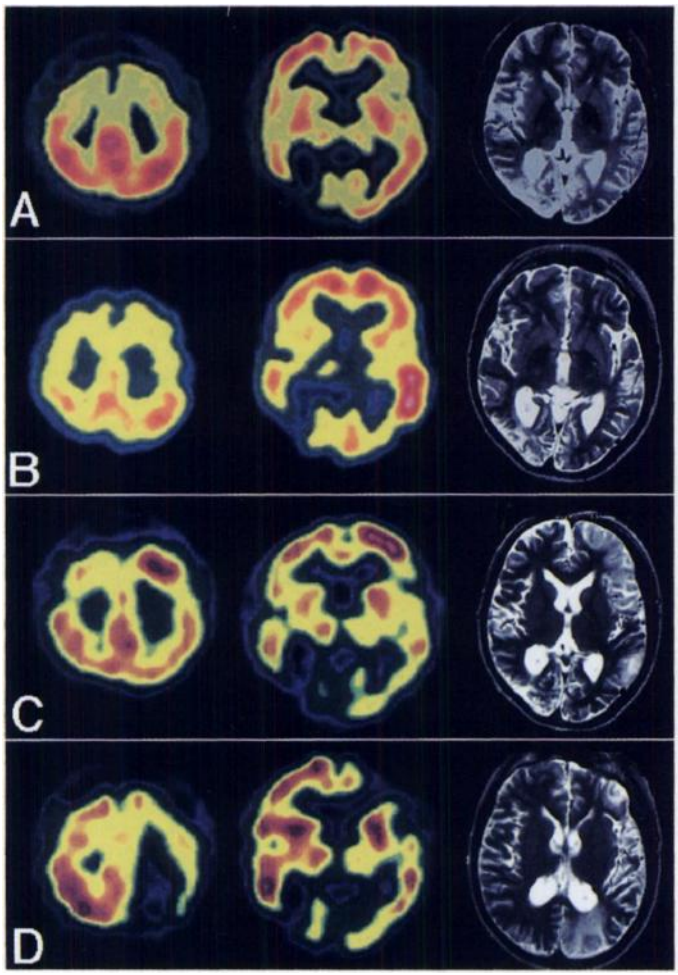

FIGURE 1. Sequential ^{99m}Tc-HMPAO (A, C and D) and ^{123}I-IMP (B) SPECT and T2-weighted MRI in MELAS (Patient 3). (A) SPECT shows hypoperfusion in right occipital lobe. MRI shows a T2 prolonged area at right occipital lobe. These findings are observed in all studies of Patient 3. (B) Sixteen months after A, SPECT shows hyperemia in left parietotemporal region. MRI shows no corresponding areas of signal abnormality. (C) Five months after B, SPECT shows hyperemia in left frontal lobe. MRI shows T2 prolonged area with swelling predominantly involving cortex of left frontal lobe. (D) Three months after C, Some areas of left frontal hyperemia have progressed to infarction and new lesions are observed in left parietooccipital region.

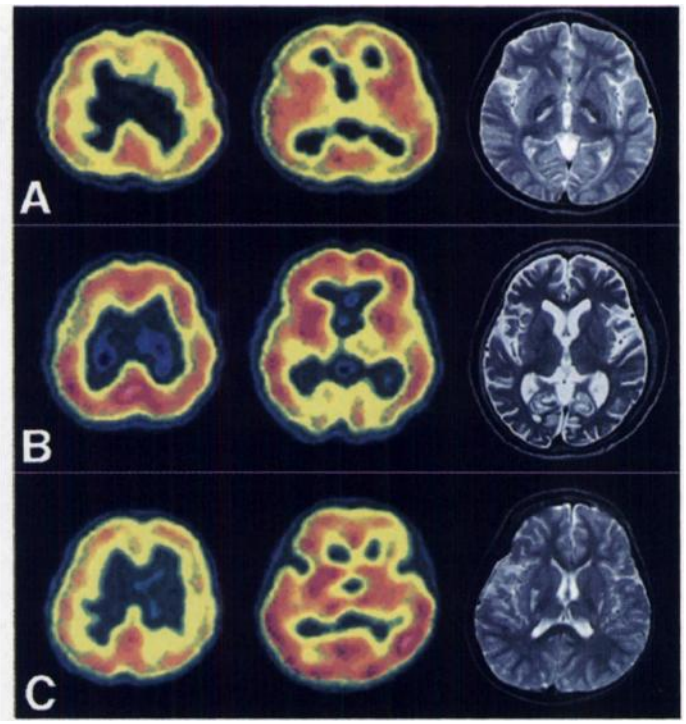

FIGURE 2. (A) SPECT and T2-weighted MRI in KSS (Patient 7), (B) MERRF (Patient 5) and (C) CCOD (Patient 8). (A) SPECT shows normal perfusion. MRI shows a T2 prolonged area at bilateral internal capsule. (B) SPECT and MRI findings reveal no abnormalities. (C) SPECT shows normal perfusion. MRI shows a T2 prolonged area at bilateral putamen.

by a low value of the cerebral metabolic ratio for oxygen and the oxygen extraction fraction, whereas the cerebral metabolic ratio for glucose was preserved. They speculated that the reduced oxygen metabolism is primarily associated with a breakdown of aerobic glycolysis due to mitochondrial dysfunction.

Our study showed that PC in patients with MELAS was significantly decreased compared with PC in patients with other types of MEM. Moreover, PC in patients with MELAS was decreased in both hypoperfused areas and nonhypoperfused areas. Gropen et al. (*19*) have reported that the vascular reserve evaluated with inhalation of 4% CO_2 was decreased both in infarcted and normal regions. The cerebral perfusion reserve was also decreased in abnormal and normal areas using the xenon/CT with an acetazolamide challenge (*20*). These results suggest that the strokelike episodes in MELAS may be due to impaired autoregulation of the cerebral blood vessels. However, autoregulation is impaired in almost all cerebral regions in patients with MELAS and the reason why only some areas become ischemic and infarcted remains unknown.

Sequential studies (three MELAS patients) revealed extension or improvement in the areas of abnormal perfusion suggesting that perfusion changes are reversible in MELAS. In one patient (Patient 3; Fig. 1C), MRI revealed a T2 prolonged area with swelling, predominantly involving the cortex in the hyperemic frontal lobe 5 days after the strokelike episodes. These findings were consistent with those of other investigators who reported that the multifocal, laminar cortical pattern of hyperintensity on MRI appears specific to MELAS (*21*). Some of the hyperemic areas progressed to infarction and some appeared normal in a follow-up MRI study. In Patient 3, the SPECT study using ^{99m}Tc-HMPAO was performed during the subacute phase of infarction. Thus, the possibility remains that the hyperaccumulation observed at the left frontal lobe is due to HMPAO hyperfixation (*22*). These various abnormal findings on MRI and SPECT may be related to temporal changes during the course of the disease. Sequential SPECT studies must be performed to assess MELAS patients.

TABLE 3
Percent Change in Regional Cerebral Blood Flow in Brain Regions (n = 6) with Mitochondrial Encephalomyopathy (MEM)

Region	MELAS	non-MELAS
Cerebellum	9.5 ± 6.4	27.3 ± 10.6
Basal ganglia	24.4 ± 6.1	42.0 ± 6.6
Frontal	7.4 ± 2.5*	33.8 ± 8.0
Temporal	14.4 ± 7.7	37.5 ± 10.1
Parietal	8.0 ± 5.3	32.7 ± 8.7
Occipital	9.6 ± 10.1	36.9 ± 7.1
Total	8.4 ± 3.2*	34.7 ± 8.3
Lesion	10.8 ± 5.4	
Nonlesion	5.6 ± 2.3	34.7 ± 8.3

*$p < 0.05$ vs. non-MELAS patients.
MELAS = MEM with lactic acidosis and strokelike episodes.

Myoclonic Epilepsy with Ragged Red Fibers

MERRF is characterized by myoclonus as well as ataxia, weakness and generalized seizures (*8*). Genetic studies have shown that some MERRF patients have a point mutation of mitochondrial DNA leading to deficiencies of Complex I and IV of the respiratory chain (*23*). SPECT findings in MERRF have never been published. This study revealed normal SPECT findings, whereas MRI showed generalized cerebellar atrophy and CT showed calcification in the basal ganglia. Barkovich et al. (*24*) have reported diffuse cortical and white matter atrophy and T2 prolongation was present in the periventricular white matter.

Kearns-Sayre Syndrome

KSS is characterized by the triad of onset before age 15, progressive external ophthalmoplegia and pigmentary degeneration of the retina plus one of the following: heart block, cerebellar syndrome or high cerebrospinal fluid protein (*7,25*). Patients with chronic progressive external ophthalmoplegia (CPEO) have ophthalmoplegia, ptosis and myopathy with few or no other symptoms. Some investigators have claimed that these two syndromes are different expressions of the same underlying defect (*26*).

SPECT in this study showed normal perfusion in two patients with KSS and MRI/CT showed a focal white matter abnormality in one patient with KSS. SPECT in CPEO has been reported to show hypoperfusion in the basal ganglia and in the occipital lobes (*17*). The discrepancy between the previous findings and our study may be due to differences between KSS and CPEO or to the heterogeneity of these syndromes.

Cytochrome C Oxidase Deficiency

MEM can be divided into three groups according to the portion of mitochondrial metabolism affected. They are substrate utilization, oxidation and phosphorylation and the respiratory chain. CCOD (Complex IV) involved a specific biochemical defect in the respiratory chain (*2*). Perfusion was normal in the three CCOD patients in our series, which agrees with the findings that CBF measured by ^{133}xenon showed no abnormal perfusion (*27*).

CONCLUSION

SPECT images of patients with MELAS showed specific alterations in rCBF, which suggests that brain perfusion SPECT is useful in the diagnosis and assessment of MELAS patients. Decreased cerebral perfusion reserve in patients with MELAS may represent an important feature of the pathogenesis of the strokelike episodes. SPECT revealed no abnormal findings in patients with other types of MEM (MERRF, KSS and CCOD).

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