Acta neurol. belg., 2002, **102**, 82-86

Leber's hereditary optic neuropathy with intracranial arteriovenous malformation : a case report

Junko FUJITAKE[1], Haruo MIZUTA[1], Hayato FUJII[1], Yasuhiro ISHIKAWA[1], Kenji SASAMOTO[2], Yu-ichi GOTO[3], Ikuya NONAKA[4] and Yoshihisa TATSUOKA[1]

[1]Departments of Neurology and [2]Ophthalmology, Kyoto City Hospital, Kyoto, Japan ; [3]Departments of Mental Retardation and Birth Defect Research and [4]Ultrastructural Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

Abstract

We reported a patient with Leber's hereditary optic neuropathy (LHON) with an intracranial arteriovenous malformation (AVM). Genetic analysis of this patient revealed a point mutation in mitochondrial DNA (mtDNA) at nucleotide position 11778 in the ND4 subunit of complex I. Although the relationship between intracranial AVM and mtDNA mutations remains uncertain, some patients with intracranial AVM may be associated with mitochondrial abnormality. Further study is necessary to confirm whether the above conditions are coincidental or closely interrelated.

Key words : Leber's hereditary optic neuropathy (LHON) ; arteriovenous malformation (AVM) ; mitochondrial DNA.

Introduction

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disorder characterized clinically by an acute or subacute onset of central visual loss prevalently in young males. Several point mutations in mitochondrial DNA (mtDNA) have been identified in patients with LHON and the most frequent mutation is a substitution at nucleotide position (np) 11778 (11778 mutation) in the ND4 subunit of complex I (Wallace *et al*., 1988 ; Newman, 1993).

Intracranial arteriovenous, malformation (AVM) has been considered to originate from intrauterine maldevelopment of cerebral vessels. Familial cases have been rarely reported (Laing *et al*., 1974 ; Snead OC III *et al*., 1979 ; Aberfeld *et al*., 1981 ; Boyd *et al*., 1985 ; Yokoyama *et al*., 1991 ; Amin-Hanjani *et al*., 1998), though a genetic defect has not yet been established.

We report here, a patient with LHON associated with intracranial AVM. Genetic analysis of this patient revealed the 11778 mutation in mtDNA common to LHON. Although we could not ascertain how the mtDNA mutation is related to AVM, this disease combination was of interest to explain vascular abnormalities in both diseases.

Case report

A previously healthy 9-year-old Japanese boy suddenly developed severe headache and vomiting, and was admitted to our hospital. His parents were healthy with no consanguinity. The patient had one brother and one sister who were healthy with no visual disturbance. On admission, he was lethargic and showed inward deviation of both eyes, left hemiparesis and hemiataxia. Brain computed tomography revealed right thalamic and intraventricular hemorrhage. Angiography revealed AVM located from the right posterior thalamus to the midbrain with feeders from the posterior thalamoperforate artery (Fig. 1). Ventricular drainage was performed and all symptoms were improved except for upward gaze palsy of both eyes. Since a conventional direct operation was difficult in this area, he underwent gamma radiation in the U.S.A. Six months after this therapy, the AVM disappeared on angiography, though he developed left hemiparesis, and postural and intention tremor of the left upper limb, which were thought to have been induced by radiation injury. He underwent a right thalamotomy (nucleus ventralis intermedius) 8 years after the radiation, then the tremor disappeared.

At the age of 18 years, he first noticed a visual disturbance on the left, and the right 8 months after the onset. He visited the ophthalmologic clinic in our hospital and was referred to the neurology section for further evaluations.

He was 163 cm in height and 62 kg in weight. His mental status was normal with normal speech. He had mild left hemiparesis and hemiataxia, but no tremor. Deep tendon reflex was mildly hyperactive on the left side, but no pathologic reflexes were seen. He showed mild hypesthesia in the left upper limb.

On ophthalmological examination, his visual acuity was 0.03 OD and 30 cm/nd OS. He had bilateral central scotoma, which was more severe in the left than the right eye. Optic disc examination showed mild optic atrophy in the temporal side of

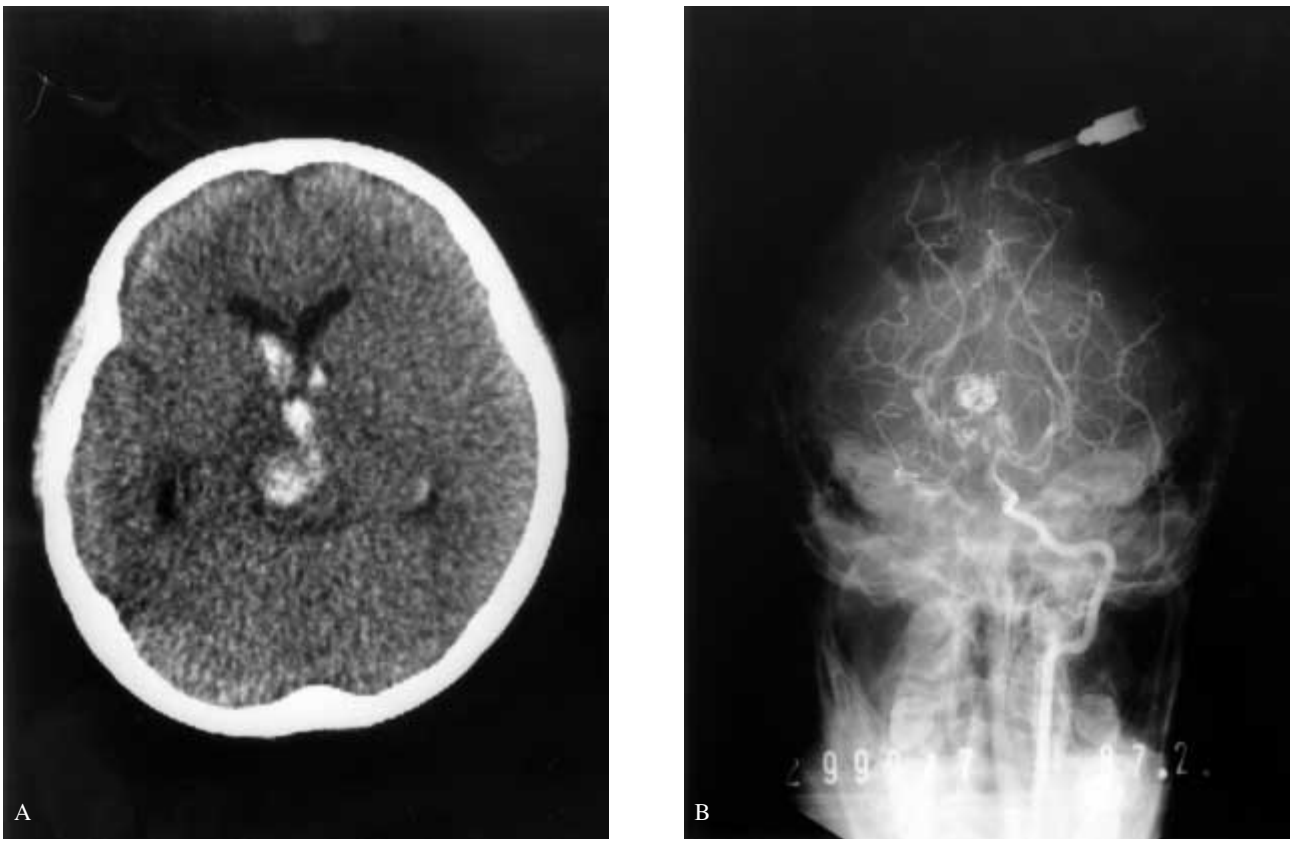

FIG. 1. — (A) Computed tomography of the brain shows a right thalamic hemorrhage and intraventricular rupture.
(B) Left vertebral angiography reveals arteriovenous malformation (AVM) at the right posterior thalamus to the midbrain with feeders from the posterior thalamoperforate artery.

the left eye, but normal in the right. Retinal microangiopathy was not recognizable during the course. Critical fusion frequency (CFF) was 25 cycles/sec OD and 13 cycles/sec OS. Fluorescein fundus angiography showed neither dye leakage nor dilated capillaries. Pattern-reversal visual evoked potentials failed to exhibit P-100 waves in both eyes.

His routine blood analysis (complete blood count, liver enzyme activities, electrolytes, glucose, urea nitrogen, etc) yielded normal results. Lactate and pyruvate levels in the blood were 8.4 mg/dl (normal 3.7-16.3) and 0.86 mg/dl (0.1-0.9), respectively. The cerebrospinal fluid was normal including a cell count of 2/mm^3, protein level of 24 mg/dl, lactate of 15.1 mg/dl (11.1-16.6), and pyruvate of 1.10 mg/dl (0.75-1.29). Electrocardiography was normal. Electroencephalography showed a slow background of 7-8 Az and θ waves.

A small area in the right thalamus and midbrain had a low signal on the T1-weighted image and a high signal on the T2-weighted image of magnetic resonance imaging (MRI), thought to be caused by the ruptured AVM and gamma radiation.

He was placed on corticosteroid pulse therapy (methylprednisolone 1000 mg div/day for 3 days per week, three times) with the tentative diagnosis of optic neuritis. After LHON was diagnosed, coenzyme Q_{10} supplement therapy was started. About two weeks after the steroid pulse therapy, his visual acuity improved to 0.08 OD and 0.04 OS. His visual acuity became 0.04 OD and 0.01 OS some months later, but it further improved to 0.20 OD and 0.03 OS after the next 2 years.

MtDNA analysis

To detect the LHON mutation, DNA was extracted from peripheral lymphocytes. Two large mtDNA fragments were amplified using long PCR by a method described previously that avoid the amplification of nuclear mtDNA-like sequences (Akanuma *et al*., 2000). The PCR products were directly purified using Microspin S-400 HR columns (Amersham Pharmacia Biotech). With 96 primer sets designed for sequencing, fragments were subject to the BigDye Terminator Cycle Sequencing reaction (PE Applied Biosystems) and sequence determination on an ABI 3700 automated sequencer according to the manifacturer's protocol. We identified the 11778 G → A mutation but did not find any other LHON mutation or new polymorphism (Table 1). To determine whether the mutation was homoplasmic or heteroplasmic, we applied PCR-RFLP method using SfaNl restriction enzyme. The all PCR products were not cut by the enzyme indicative homoplasmy.

TABLE 1

Sequence analysis of whole mtDNA

region	mutation	amino acid replacement	frequency in normal controls
D-loop	a73g		98%
	c150t		14%
	t199c		10%
	a263g		83%
	ins-303c		44%
	ins-311c		85%
	t489c		62%
12SRMA	a750g		99%
	a1438g		92%
16SRMA	a2706g		99%
	ins-3168c		0%
ND1	g4048a.	D → N	3%
	c4071t	syn	5%
	a4164g	syn	4%
ND2	a4769g	syn	99%
	a5351g	syn	4%
	g5460a	A → T	5%
CO I	c6455t	syn	13%
	t6680c	syn	4%
	c7028t	syn	99%
CO II	t7684c	syn	3%
	g7853a	V → A	4%
ATP 6	a8701g	T → A	45%
	a8860g	T → A	100%
CO III	t9540c	syn	52%
	t9824c	syn	14%
ND3	t10345c	I → T	4%
	a10398g	T → A	70%
	c10400t	syn	63%
ND4	t10873c.	syn	63%
	g11719a	syn	100%
	g11778a	R→ H	0%
ND5	c12405t	syn	4%
	c12705t	syn	73%
	t12811c	Y → H	4%
cyt b	c14766t	I → T	100%
	t14783c	syn	65%
	g15043a	syn	63%
	g15301a	syn	49%
	a15326g	T → A	99%
D-loop	g16129a		21%
	c16223t		75%
	t16297c		4%
	t16298c		10%

syn : synonymous.

Discussion

Our patient presented the typical symptoms of LHON, including subacute onset of bilateral visual loss at the age of 18 years. He had no family history, however, and mtDNA analysis disclosed the 11778 mutation. The most interesting feature of this patient was an association with intracranial AVM.

It is well known that some pedigrees with LHON have exhibited some additional neurological findings and have been called Leber's 'plus'. The symptoms include dystonia, tremor, parkinsonism, spasticity and polyneuropathy (Meire *et al*., 1995 ; Nikoskelainen *et al*., 1995 ; Schoffner *et al*., 1995). Multiple sclerosis-like symptoms and MR findings have also been reported (Harding *et al*., 1992). However, AVM has not been complicated with LHON, with myoclonus epilepsy associated with ragged-red fibers (MERRF) nor mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Although it is difficult to conclude whether the combination with AVM and LHON was coincidental or interrelated, further cumulative study of the combination may resolve this issue. It would be interesting to screen the many reported families with LHON for the occurrence of intracranial AVM by CT or MRI study.

Our patient's visual acuity improved from 0.03 OD and 30 cm/nd OS to 0.20 OD and 0.03 OS

after about 2 years suggesting a beneficial effect of coenzyme Q_{10} therapy. The treatment of LHON is not yet established. Newman (1993) described in the review of LHON that attempts to treat or prevent the acute phase of visual loss with systemic steroids, hydroxycobalamin, or cyanide antagonists have, in general, proved not efficacious. He also stated that use of coenzyme Q and succinate in patients with LHON and visual loss had been limited, but his preliminary results were not particularly encouraging. Nakamura *et al*. (1994) reported a patient with LHON with a mtDNA mutation at np 3460, whose visual acuity improved after coenzyme Q_{10} supplemention, steroid pulse therapy and hydroxycobalamine injection. Mashima *et al*. (1992) reported a patient who had a remission of LHON with idebenone, which is a quinor that stimulates net ATP formation in cerebral metabolism and inhibits lipid peroxidation in the mitochondrial membrane. Nishikawa *et al*. (1989) reported a case of mitochondrial encephalomyopathy with cytochrome c oxidation deficiency, treated with high doses of coenzyme Q_{10}. Abnormal elevation of serum lactate over pyruvate ratio and the increased concentration of serum lactate plus pyruvate induced by exercise decreased with coenzyme Q_{10} treatment. They suggested that coenzyme Q_{10} had clinical value in the long-term management of patients with mitochondrial encephalomyopathies, even though there were clinical limitations to the effects of this therapy.

Familial occurrence of AVM is rarely reported. Yokoyama *et al*. (1991) reported 3 families in which a father and his son, cousin, and a mother and her son were respectively affected. Amin-Hanjani *et al*. (1998) reviewed familial AVM patients reported in the literature, consisting of parent-child combinations from 7 families (41%), including 2 mother-daughter, one mother-son, 4 father-son, as well as sibling combinations in 7 families (41%), and cousin combinations in 3 families (18%). Analysis of familial patients has revealed that some appear to have autosomal dominant inheritance and others mtDNA (maternal) inheritance or autosomal recessive inheritance.

Genetic mechanisms that contribute to pathogenesis and phenotype of intracranial AVM are still unknown. A lot of research is currently going on exploring the molecular aspects of vascular proliferation/malformation. Recently, a gene and mutations causing cerebral cavernous malformations (CCM) in a subset of families with the disease were identified. CCMl mapping to 7q encodes KRIT1, Krev-1/rap1a binding protein (Laberge-le Couteulx *et al*., 1999 ; Sahoo *et al*., 1999). Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by cutaneous vascular dysplasia and a high propensity to develop systemic and intracranial vascular lesions or AVMs. Endoglin, a transforming growth factor beta binding protein of endothelial cells, has been proved to be the gene for HHT type 1 mapping to 9q3 (McAllister *et al*., 1994).

Blood vessel involvement has been observed in some mitochondrial diseases, especially MELAS in which abnormal mitochondria are accumulated in the small arteries showing "strongly succinate dehydrogenase-reactive blood vessels" (SSV) (Hasegawa *et al*., 1991 ; Goto *et al*., 1992). Sakuta *et al*. (1989) examined biopsy specimens of muscles from patients with mitochondrial myopathy and revealed that some pericytes around a few arterial capillaries contained aggregates of slightly enlarged mitochondria. Kishi *et al*. (1988) reported an autopsy case of MELAS, describing that the cerebral cortex was in spongy state and capillary proliferation and fibrillary gliosis were noted. Bertrand *et al*. (1996) also reported a case of mitochondrial encephalomyopathy of mixed MELAS type, showing numerous focal and so called pseudolaminar cortical necrosis in the brain with characteristic proliferation of capillary vessels in a microscopic study. Microangiopathy is the first abnormal finding in the optic disc in LHON. In conjunction with these findings, some patients with intracranial AVM may have an associated mitochondrial abnormality. A link could be found between molecular mechanisms of AVM and the mitochondrial defect. Further genetic research is necessary to understand the relationship between AVM and LHON.

Acknowledgements

We gratefully thank Dr. Tetsuaki Teraura for his help in providing clinical information.

REFERENCES

1. Aberfeld D. C., Rao K. R. Familial arteriovenous malformation of the brain. *Neurology*, 1981, **31** : 184-186.
2. Akanuma J., Muraki K., Komaki H., Nonaka I., Goto Y. Two pathogenic point mutations exist in the authentic mitochondrial genome, not in the nuclear pseudogene. *J. Hum. Genet*., 2000, **45** : 337-341.
3. Amin-Hanjani S., Robertson R., Arginteanu M. S., Scott R. M. Familial intracranial arteriovenous malformations. Case report and rewiew of the literature. *Pediatr. Neurosurg*., 1998, **29** : 208-213.
4. Bertrand E., Fidzianska A., Schmidt-Sidor B., Mendel T. Mitochondrial encephalomyopathy of mixed MELAS type. *Folia Neuropathol*., 1996, **3**4 : 193-198.
5. Boyd M.C., Steinbok P., PatY D.W. Familial arteriovenous malformations. Report of four cases in one family. *J. Neurosurg*., 1985, **62** : 597-599.
6. Goto Y., Horai S., Matsuoka T., Koga Y., Nihei K. *et al.* Mitochondrial myopathy, encephalopat by, lactic acidosis, and stroke-like episodes (MELAS) : A correlative study of the clinical features and

mitochondrial DNA mutation. *Neurology*, 1992, **42** : 545-550.
7. HARDING A. E., SWEENEY M. G., MILLER D. H., MUMFORD C. J., KELLAR-WOOD H. *et al*. Occurrence of a multiple sclerosis-like illness in women who have a Leber's hereditary optic neuropathy mitochondrial DNA mutation. *Brain*, 1992, **115** : 979-989.
8. HASEGAWA H., MATSUOKA T., GOTO Y., NONAKA I. Strongly succinate dehydrogenase-reactive blood vessels in muscles from patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. *Ann. Neurol*., 1991, **29** : 601-605.
9. KISHI M., YAMAMURA Y., KURIHARA T., FUKUHARA N., TSURUTA K. *et al*. An autopsy case of mitochondrial encephalomyopathy : biochemical and electron microscopic studies of the brain. *J. Neurol. Sci*., 1988, **86** : 31-40.
10. LABERGE-LE COUTEULX S., JUNG H. H., LABAUGE P., HOUTTEVILLE J.-P., LESCOAT C. *et al*. Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous angiomas. *Nat. Genet*., 1999, **23** : 189-193.
11. LAING J. W., SMITH R. R. Intracranial arteriovenous malformations in sisters : a case report. *J. Miss. State Med. Assoc*., 1974, **15** : 203-206.
12. MASHIMA Y., HIIDA Y., OGUCHI Y. Remission of Lever's hereditary optic neuropathy with idebenone. *Lancet*, 1992, **340** : 368-369.
13. MCALLISTER K. A., GROGG K. M., JOHNSON D. W., GALLIONE C. J., BALDWIN M. A. *et al*. Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat. Genet*., 1994, **8** : 345-351.
14. MEIRE F. M., VAN COSTER R., COCHAUX P., OBERMAIER-KUSSER B., CANDAELE C. *et al*. Neurological disorders in members of families with Leber's hereditary optic neuropathy (LHON) caused by different mitochondrial mutations. *Ophtalmic Genetics*, 1995, **16** : 119-126.
15. NAKAMURA M., TANIGAWA M., YAMAMOTO M. A case of Leber's hereditary optic neuropathy with a mitochondrial DNA mutation at nucleotide position 3460. *Jpn. J. Ophtalmol*., 1994, **38** : 267-271.
16. NEWMAN N. J. Leber's hereditary optic neuropathy. New genetic considerations. *Arch. Neurol*., 1993, **50** : 540-548.
17. NIKOSKELAINEN E. K., MARTTILA R. J., HUOPONEN K., JUVONEN V., LAMMINEN T. *et al*. Leber's "plus" : neurological abnormalities in patients with Leber's hereditary optic neuropathy. *J. Neurol. Neurosurg. Psychiatry*, 1995, **59** : 160-164.
18. NISHIKAWA Y., TAKAHASHI M., YORIFUJI S., NAKAMURA Y., UENO S. *et al*. Long-term coenzyme Q_{10} therapy for a mitochondrial encephalomyopathy with cytochrome c oxidase deficiency : a ^{31}P NMR study. *Neurology*, 1989, **39** : 399-403.
19. SAHOO T., JOHNSON E. W., THOMAS J. W., KUEHL P. M., JONES T. L. *et al*. Mutations in the gene encoding KRIT1, a Krev-1/rap1a binding protein, cause cerebral cavernous malformations (CCM1). *Hum. Mol. Genet*., 1999, **8** : 2325-2333.
20. SAKUTA R., NONAKA I. Vascular involvement in mitochondrial myopathy. *Ann. Neurol*., 1989, **25** : 594-601.
21. SCHOFFNER J. M., BROWN M. D., STUGARD C., JUN A. S., POLLOCK S. *et al*. Leber's hereditary optic neuropathy plus dystonia is caused by a mitochondrial DNA point mutation. *Ann. Neurol*., 1995, **38** : 163-169.
22. SNEAD O. C. III, ACKER J. D., MORAWETZ R. Familial arteriovenous malformation. *Ann. Neurol*., 1979, **5** : 585- 587.
23. YOKOYAMA K., ASANO Y., MURAKAWA T., TAKADA M., ANDO T. *et al*. Familial occurrence of arteriovenous malformation of the brain. *J. Neurosurg*., 1991, **74** : 585-589.
24. WALLACE D. C., SINGH G., LOTT M. T., HODGE J. A., SCHURR T. G. *et al*. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science*, 1988, **242** : 1427-1430.

J. FUJITAKE, M.D.,
Department of Neurology,
Kyoto City Hospital,
1-2 Higashitakada-cho,
Mibu, Nakagyo-ku,
Kyoto 604-8845, Japan.