## CASE REPORT

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# MELAS with prominent white matter gliosis and atrophy of the cerebellar granular layer: a clinical, genetic, and pathological study

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Abstract This report concerns an autopsy case of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) with unusual neuropathological findings. The patient was a Japanese woman who was 21 years old at the time of death. Her mother is a patient with genetically confirmed MELAS. Her clinical manifestations included convulsions and lactic acidosis in the latter half of the first decade of life, followed by deafness, dementia, muscle weakness in the lower extremities, slight ataxia in the upper and lower extremities, and diabetes mellitus. Muscle biopsy revealed ragged-red fibers, and genetic study showed a point mutation at nucleotide pair 3243 in mitochondrial DNA. She died of lactic acidosis. In the clinical course, she did not develop strokelike episodes. The neuropathological examination revealed not only minute to small necrotic foci in the cerebral cortex, amygdala, hippocampus, and cerebellum, but also prominent white matter gliosis in the central nervous system and cerebellar cortical degeneration of granular cell type. Our neuropathological findings, including prominent white matter gliosis of the central nervous system and cerebellar cortical degeneration of granular cell type,

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**Key words** Atrophy of cerebellar granular layer · MELAS · Neuropathology · White matter gliosis

## Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) was first proposed by Pavlakis et al. [22]. They believed that MELAS represented a distinctive clinical syndrome and that it could be differentiated from two other clinical disorders that were also associated with mitochondrial myopathy and cerebral disease: Kearns-Sayre syndrome and myoclonus epilepsy with ragged-red fiber syndrome (MERRF) [4]. Recently, analysis of mitochondrial DNA (mtDNA) has proven that the point mutation at nucleotide pair 3243 is responsible for about 80% of MELAS cases [6, 7]. Neuropathological findings reported in patients with MELAS generally include necrotic lesions in the cerebral cortex without correlation to vascular supply, calcification in the basal ganglia, and peculiar vascular changes called "mitochondrial angiopathy". Prominent white matter gliosis in the central nervous system and cerebellar cortical degeneration of granular cell type have not been previously noted in the neuropathology of MELAS.

We report here unusual neuropathological findings in a patient with MELAS who did not develop stroke-like episodes in the total clinical course.

#### Case report

The patient was a Japanese woman who was 21 years old at the time of death. Her mother is a patient with genetically confirmed MELAS. Her mother developed deafness at age 26, followed by convulsion at age 55. Genetic analysis of her mother revealed a point mutation at nucleotide pair 3243 in mtDNA. Her mother is

now alive at the age of 56. The patient presented with convulsions and lactic acidosis in the latter half of the first decade of life. She also developed deafness and dementia in the first half of the second decade of life. At age 19, she began to exhibit dysphagia and had difficulty with pronunciation. A neurological examination at the age of 20 showed severe dementia, deafness, muscle weakness and hyperreflexia in the lower extremities, and slight ataxia of the upper and lower extremities. The electroencephalogram revealed spikes and slow waves. Computerized tomography (CT) of the brain showed brain atrophy and calcification of the bilateral basal ganglia. Muscle biopsy revealed ragged-red fibers. We also detected a mtDNA point mutation at nucleotide pair 3243 causing an A to G transition, which is a common mutation in MELAS in various tissues including the muscles and white blood cells. This mutation was heteroplasmic in all examined tissues. At age 21, she fell into diabetic coma. Her diabetes mellitus was controlled by insulin therapy. At this time, her height was 137 cm, with a body weight of 30 kg. She died of lactic acidosis at the age of 21. In the total clinical course she did not develop stroke-like episodes. The total duration of her disease was 13 years. The main pathological findings outside the central nervous system were degeneration with fibrosis of the skeletal muscles and a decreased number of the islets of Langerhans with fibriosis in the pancreas.

#### **Neuropathological findings**

The weight of the brain before fixation was 830 g. Only the right side of the brain was available for neuropathological examination. A macroscopic examination revealed not only atrophy of the frontal and temporal lobes, but also scattered small necrotic foci in the cerebral cortex (Fig. 1A, B). The cerebellum showed slight atrophy, prominently in the dorsal part of the vermis. A histological examination revealed minute to small, recent and old, necrotic foci with relative preservation of the neurons and proliferation of the capillaries in the cerebral cortex, amygdala, hippocampus, and cerebellar cortex. Necrotic foci of the cerebral cortex were more pronounced in the posterior portion of the cerebral cortex were not corre-

lated to the vascular supply of the cerebrum. In the cerebral white matter, fibrillary gliosis was evident in spite of the absence of myelin loss (prominent white matter gliosis) (Fig. 1). Immunocytochemistry using antibodies against glial fibrillary acid protein (GFAP) also showed prominent gliosis, prominently in the cerebral white matter (Fig. 1). Slight astrocytosis without neuronal loss was evident in the caudate nucleus, putamen, pallidum, thalamus, subthalamic nucleus, red nucleus, substantia nigra, locus coruleus, oculomotor nuclei, trochlear nuclei and hypoglossal nuclei. There was pseudocalcification and a minute infarct in the globus pallidus. There was cerebellar cortical degeneration of granular cell type in the cerebellar cortex, which was more apparent in the vermis than in the hemisphere. Cerebellar cortical degeneration of granular cell type with prominent cactus-like expansions and stellate bodies in the dendrites of Purkinje cells was more pronounced in the crest than in the depth of the cerebellar folia (Fig. 2). The dentate nucleus showed slight neuronal loss, proliferation of the glia, and pseudocalcification. There was degeneration of the pyramidal tracts, which was more obvious in the medulla oblongata than in the midbrain.

## Discussion

We think that our case belongs to the category of MELAS because the case showed not only the typical clinical manifestations of MELAS, except the absence of stroke-like episodes, but also genetical evidence compatible with MELAS.

The outstanding clinical feature of our patient was the absence of stroke-like episodes. Pavlakis et al. [22], who proposed MELAS as a distinctive clinical syndrome, reported that stroke-like episodes, including cortical blindness, hemiparesis, and hemianopsia, were evident in 10 of 11 patients. Goto et al. [7], who studied 40 MELAS patients to characterize the clinical features, as well as the

Fig.1A–D Prominent white matter gliosis. A, B Right cerebrum through the anterior part of the striatum showing relative preservation of the myelin. with the exception of a necrotic focus (arrow), and prominent fibrillary gliosis. **C–H** Right cingulate gyrus through the anterior part of the striatum. C Relative preservation of the myelin. D, E Prominent gliosis in the cingulate gyrus (D), particularly in the white matter (E). F-H Immunocytochemistry using antibodies against GFAP. Positive immunoreactivity for GFAP in the cingulate gyrus (F), particularly in the white matter (G, **H**) (GFAP glial fibrillary acidic protein) A, C Klüver-Barrerra stain; B, D, E Holzer stain. A,  $\mathbf{B} \times 1.1, \mathbf{C}, \mathbf{D}, \mathbf{F} \times 7.8,$ **E**, **H**  $\times$  360, **G**  $\times$  48





biochemical and muscle biopsy findings relating to the mtDNA mutation at nucleotide pair 3243, reported that stroke-like episodes including episodic headaches with vomiting, unconsciousness and convulsions were present in more than 80% of MELAS cases, regardless of the presence or absence of the point mutation at nucleotide pair 3243. Hirano and Pavlakis [10], who reviewed 110 patients with MELAS to define the clinical spectrum of this disease, reported that stroke-like episodes were evident in 99% of the patients. Recently, Kaido et al. [12] reported an unusual autopsy case of MELAS with a point mutation at nucleotide pair 3243 in mtDNA, with no clin-

ical evidence of stroke-like episodes during the last 10 years of the patient's life.

From the literature concerning the clinical features of MELAS, it is apparent that absence of stroke-like episodes in MELAS is very rare. In this regard, our case is noteworthy.

The pronounced neuropathological features of our patient were prominent white matter gliosis in the central nervous system and cerebellar cortical degeneration of granular cell type. Neuropathological findings which have been reported so far in patients with MELAS are multiple infarct-like lesions without correlation to vascular supply,

**Fig.2A–C** Cerebellar cortical degeneration of showing prominent rarefaction of granule cells in

moderately fibrillary gliosis in the cerebral and cerebellar white matter. They speculated that widespread gliosis might be due to metabolic disturbance including lactic acidosis. The pathogenesis of prominent white matter gliosis is not apparent, but the prominent white matter gliosis observed in our case suggests an abnormality of the glia in the brain pathology of MELAS.

Cerebellar cortical degeneration of granular cell type has been observed in a variety of neurological disorders including familial cerebellar degeneration [20], a sporadic case of cerebellar hypoplasia [23], cerebral lipidosis [3], organic mercury poisoning [11, 24], an ataxic form of Creutzfeldt-Jakob disease [2, 25], and Menkes' kinky hair disease [15].

From the literature on the neuropathology of MELAS, it is apparent that there have been no descriptions of cerebellar cortical degeneration of granular cell type as seen in our case. In this regard, the autopsy case described by Hart et al. [9] is of interest, as their study revealed that profound neuronal alterations were present in the granular layer of the cerebellum. They did not, however, notice



predominantly in the posterior cerebral cortex, calcifica-

tion in the basal ganglia, and peculiar vascular changes

called "mitochondrial angiopathy" [1, 9, 18, 21]. Accord-

ing to Pavlakis et al. [22], who reviewed three previously

reported autopsy cases of MELAS, the fundamental neu-

ropathological findings of MELAS were microcystic liq-

uefaction or focal softening of the cerebral cortex and cal-

cification in the basal ganglia. Neuropathological findings

in our case, which showed necrotic foci in the cerebral

cortex and pseudocalcification in the pallidum, fundamen-

dissociation glio-myelinique, is a neuropathological en-

tity: hyperactivity of the glia and/or degree of fibrillary

gliosis is more prominent than the degree of myelin loss.

Prominent white matter gliosis has been observed in vari-

ous neurological diseases including subacute sclerosing

panencephalitis [26], Nasu-Hakola's disease [14], a spe-

cial form of senile dementia of Alzheimer's type [17], and

progressive subcortical gliosis [19]. Mizukami et al. [16],

who described an autopsy case of MELAS, noted diffuse

Prominent white matter gliosis, which is also termed

tally agree with the findings of Pavlakis et al. [22].

Β



cactus-like expansions in the dendrites of Purkinje cells. Kishi et al. [13] reported a Japanese autopsy case of MELAS, in which neuropathological findings revealed severe loss of granule cells in almost all areas of the cerebellar cortex. However, they did not describe whether cactus-like expansions in the dendrites of Purkinje cells were present.

Various theories exist regarding the etiology of strokelike episodes in MELAS. One of the two most common theories is that the cells become metabolically unstable and cease to function normally, with subsequent failure of energy production. This theory has been supported by cerebral blood flow studies [8]. The other theory is that blood vessels are involved, with resultant malfunction and downstream ischemia. Evidence for this includes reported abnormalities of cerebral pial arterioles and small arteries [21]. Recently, Gilchrist et al. [5] reported a brain biopsy done in a case of genetically confirmed MELAS, which showed that 82% of the brain mitochondria carried the disease mutation. They concluded that MELAS represents widespread cellular dysfunction, not restricted to either neuronal or vascular derangement. Our pathological findings, including prominent white matter gliosis of the central nervous system and cerebellar cortical degeneration of granular cell type, provide morphological support for the conclusions of Gilchrist et al. [5].

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