

MELAS Syndrome (A Case Report)

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= Abstract = MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode) is a rare and currently incompletely defined mitochondrial disease involving mainly muscle and brain. We have recently seen a 17-year-old male patient who, we believe, is the first Korean case. The patient showed the classical picture of MELAS: short stature, generalized limb weakness, lactic acidemia, basal ganglia calcification, migraine-like headache and recurrent strokes with subsequent hemiparesis, hemianopia, and seizures. Electronmicroscopic examination confirmed the diagnosis by demonstrating numerous abnormal muscle mitochondria which contained paracrystalline inclusion bodies. A brief discussion of current status, inherent problems, and possible pathogenic mechanisms of this syndrome will conclude our report.

Key words: *MELAS syndrome, Korean case*

INTRODUCTION

Pavlakakis *et al.* (1984) have recently described the syndrome of MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. In addition, retarded growth, episodic vomiting, seizures, and migraine-like headaches characterize this syndrome. Our review of the literature reveals slightly more than 20 case reports which satisfy all components of this syndrome.

The following 17-year-old male patient, who we believe is the first Korean case, demonstrates the classical picture of MELAS syndrome. A brief discussion of current status, inherent problems, and possible pathogenic mechanisms of this syndrome will conclude this report.

CASE REPORT

A 17-year-old right handed Korean male presented to Seoul National University Hospital because of recurrent strokes and symptoms of epilepsy partialis continua. His family history was unremarkable. His prenatal, perinatal birth

history and early development were normal. However, at age 7, the patient appeared noticeably thin and listless; his exercise tolerance seemed low. Despite continued academic success, the patient was abnormally short and underweight at age 13.

At age 16, the patient began experiencing the following symptoms; on one occasion, after physical exertion, he felt a dull headache over the left parieto-occipital area. This was associated with flashing lights passing through his right visual field. Subsequently, he developed right homonymous hemianopia which resolved in approximately one month. Three months later, after mountain climbing, the patient developed nausea, vomiting, and a pounding headache over the same parieto-occipital area.

Initial evaluation at another hospital revealed right homonymous hemianopia, anomic aphasia and alexia without agraphia. Focal paresis was not present. CT scan demonstrated radiolucencies in the left parietooccipital area and additional bilateral extensive basal ganglia calcification. Following a two-week hospital course, the patient's aphasia resolved; his visual field deficit remained.

One month later, the patient experienced a

sudden bout of right sided weakness with involuntary clonic jerks in his right arm. This abnormal movement persisted for one day and subsided spontaneously. He was then referred to Seoul National University Hospital.

On admission, the patient was short (150 cm), thin (34 kg), and asthenic. Otherwise, physical examination was unremarkable. Neurologically, the patient was alert and oriented. He demonstrated a good fund of knowledge. He did not have aphasia, alexia, or agraphia. Visual testing showed 20/40 acuity bilaterally, normal fundi, but a right homonymous field deficit. Examination of other cranial nerves was normal. Motor testing showed right hemiparesis. Sensory testing was within normal limits. Reflexes were generally decreased. While not frankly ataxic, the gait appeared slightly uncoordinated, likely secondary to general weakness and right sided paresis.

Normal laboratory tests included: CBC, sedimentation rate, urinalysis, serum protein, electrolytes, cholesterol, triglyceride, creatine kinase, lactic dehydrogenase, calcium, phosphorous, parathyroid hormone, BUN, glucose, serum lipoprotein electrophoresis, VDRL, LFT's and TFT's.

EKG and echocardiogram were within normal limits. CSF was under normal pressure, without cells, and with 41 mg of protein per deciliter. Of significant note was an abnormal lactate level of 56.5 mg/dl (normal 5-12 mg/dl), derived from at rest, non-tourniqueted venous sampling.

Electrodiagnostic testing showed normal nerve conduction velocities in all extremities. EMG of the proximal muscles (deltoid, biceps, vastus lateralis) showed positive sharp waves and fibrillation potentials and easily recruitable short duration and small amplitude motor unit potentials.

EEG showed epileptiform discharges localized over the left posterior head region. CT findings were similar to the previous one: a nonenhancing hypodense lesion involving both white and grey matter in the left parieto-occipital area. In addition, bilateral calcification of the caudate, putamen, and globus pallidus was demonstrated (Fig. 1).

Light microscopic examination of the left deltoid muscle showed scattered small, round or angulated degenerating muscle fibers, some of which appeared fractured and contained many red granules—most likely enlarged mitochondria

(Fig. 2). On modified Gomori trichrome staining, many ragged red fibers were seen. Electron microscopy revealed closely aggregated mitochondria in the subsarcolemmal and intermyofibrillar space. These mitochondria were of various sizes and shapes. Many of these abnormal organelles contained paracrystalline inclusions of rectangular shape with occasional globular electron-dense inclusions noted (Fig. 3,4). Some of the mitochondria contained abnormally arranged cristae (Fig. 5).

DISCUSSION

Since Luft *et al.* (1962) described a 35-year-old, euthyroid woman with hypermetabolism and postulated mitochondrial error as its cause, a number of mitochondrial myopathies with multiorgan involvement have surfaced. Terms such as mitochondrial cytopathy (Egger *et al.* 1981) or mitochondrial encephalomyopathy (Shapira *et al.* 1979) have been used to encompass a spectrum of diseases such as trichopoliodystrophy, Leigh's disease, Alpers disease, Kearns-Sayre syndrome, Canavan disease, and cerebrohepato-renal syndrome of Zellweger.

In addition, out of a confusing literature, two novel syndromes have recently emerged: MERRF and MELAS (Dimauro *et al.* 1985). The MERRF (myoclonic epilepsy and ragged red fiber) syndrome, which clinically mimicks Ramsay-Hunt syndrome (Fukuhara *et al.* 1980; Fitzsimons *et al.* 1981), is characterized by, among other signs, cerebellar ataxia and myoclonus. It was first described by Tsairis *et al.* (1973), and named so by Fukuhara *et al.* (1980). The acronym MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode) was first proposed by Pavlakis *et al.* (1984). It characteristically has stroke-like events, but lacks ataxia and myoclonus.

However, clear differentiation of these entities remains difficult in many occasions. For instance, some patients with otherwise typical MELAS syndrome have been reported to show ataxia (McLeod *et al.* 1975; Askanas *et al.* 1978; Kuriyama *et al.* 1984): a symptom usually associated with MERRF. On the other hand, some patients with MERRF syndrome lack the distinguishing feature of ataxia (Fukuhara 1983). Finally, continuous myoclonus, as opposed to epileptic myoclonus, has been thought to be a disting-

uishing feature of MERRF (Pavlakakis *et al.* 1984). However, the differentiation between these two types of myoclonus has often not been made clear in the literature.

Moreover, there are also cases that seem to satisfy only a partial list of the full syndrome. For example, a group of cases have emerged that resemble MELAS but lack an identifiable history of strokes (D'Agostino *et al.* 1968; Hackett *et al.* 1973; McLeod *et al.* 1975; Markesbery 1979; Morgan-Hughes *et al.* 1982; Holliday *et al.* 1983; Kuriyama *et al.* 1984; Servidei *et al.* 1987). However, since the postmortem study of Kuriyama *et al.* (1984) revealed widespread cortical infarcts despite the absence of clinical strokes, these incomplete syndromes might also have had infarction had it been looked for at postmortem. The presence or absence of clinical strokes, therefore, may not be a fundamental distinguishing point.

Conveniently, our patient conforms well to the classical MELAS syndrome. He showed short stature, lactic acidosis, mitochondrial myopathy, seizures and strokes; a constellation of symptoms typical of MELAS. In addition, he complained of migraine-like headache, which, though not hitherto emphasized, has been occasionally described in the literature (Hart *et al.* 1977; Askanas *et al.* 1978; Shapira *et al.* 1979; Skoglund 1979; Kobayashi *et al.* 1982; Morgan-Hughes *et al.* 1982; Holliday *et al.* 1983; Pavlakakis *et al.* 1984; Dvorkin *et al.* 1987; Montagna *et al.* 1988).

The pathogenesis of the stroke in this syndrome remains unknown. Bogousslavski *et al.* (1982) thought that coexisting cardiopathy resulted in cerebral ischemia or embolism in his case. However, thromboembolism is an unlikely explanation for most of the reported strokes in this syndrome for following reasons. First, our patient as well as most of the reported cases failed to show abnormal cerebral vessels or likely sources of embolism (Shapira *et al.* 1979; Kobayashi *et al.* 1982; Pavlakakis *et al.* 1984; Yamamoto *et al.* 1984). Second, the involved infarcted area has frequently been the territory of the posterior cerebral artery (Hart *et al.* 1977; Shapira *et al.* 1979; Skoglund 1979; Pavlakakis *et al.* 1984; Driscoll *et al.* 1987; Dvorkin *et al.* 1987; Montagna *et al.* 1988), an unlikely location for embolic attack. Finally, the multiple infarcts

seen in the autopsy study of Kuriyama *et al.* (1984) did not agree with specific vascular territory. Of note is that our patient's strokes were associated with migraine-like symptoms: headache, vomiting, teichopsia, and hemianopia. Of interest also is the fact that when stroke is associated with migraine, the posterior cerebral artery is preferably involved (Broderick and Swanson 1987): a similar finding seen in MELAS. The pathogenesis of migraine, especially complicated migraine, may therefore overlap with that of MELAS.

The extensive basal ganglia calcification seen in our case is also occasionally observed in MELAS and related syndromes (Hart *et al.* 1977; Askanas *et al.* 1978; Markesbery 1979; Shapira *et al.* 1979; Skoglund 1979; Morgan-Hughes *et al.* 1982; Fukuhara 1983; Kuriyama *et al.* 1984; Driscoll *et al.* 1987; Dvorkin *et al.* 1987). Despite the several postmortem studies revealing iron--mucopolysaccharide-calcium complexes in the capillary bed of the putamen and globus pallidus (Hart *et al.* 1977; Shapira *et al.* 1979; Kuriyama *et al.* 1984), the mechanism of mineralization seems unrelated to aberrant calcium metabolism; our patient as well as reported cases generally have revealed normal calcium-phosphorous metabolism. The only exception was the case described by Hart *et al.* (1977) who did have low serum calcium.

The combination of strokes, seizures, and migraine seems quite unique in this syndrome since association of these three is extremely rare in other neurologic conditions. Basal ganglia calcification, if it exists, further magnifies the uniqueness of the symptomatology of MELAS. The pathogenesis of these CNS manifestations still remains unclear. It seems that some common mechanism may underlie all these manifestations. According to Oldendorf *et al.* (1977), CNS capillaries have more abundant mitochondria compared with those of other organs. It may therefore be assumed that CNS capillaries and consequently, blood-brain barriers might be especially vulnerable to mitochondrial dysfunction. Pavlakakis *et al.* (1984) have already speculated that mitochondrial dysfunction involving the endothelium of brain capillaries may contribute to the development of stroke-like events. Likewise, other CNS manifestations of this syndrome may also be related to dysfunctional CNS

capillaries or an abnormal blood-brain barrier. Morphological clue for this assumption has recently been drawn from studies of Kobayashi *et al.* (1982) and Lach *et al.* (1986), where abnormal muscle and CNS capillaries were described respectively in MELAS patients. With this evidence, MELAS syndrome may be regarded as an inherited vasculopathy (Lach *et al.* 1986). However, the detailed pathogenic mechanism that leads to individual symptoms still awaits further explanation.

Considering its stereotypical clinical features, we believe that MELAS is a distinct disorder. However, as already stated, proper classification of MELAS and related mitochondrial disorders is far from satisfactory at the present time. Moreover, a few recent studies (Morgan-Hughes *et al.* 1982; Pavlakis *et al.* 1984; Goda *et al.* 1987; Montagna *et al.* 1988) have failed to reveal consistent biochemical abnormalities in MELAS patients with apparently homogeneous clinical manifestations. Therefore, accumulation of more cases and further biochemical studies are obviously needed to clarify this disorder. These efforts will also help us answer the question as to how the seemingly unrelated CNS manifestations can coexist in a patient with MELAS.

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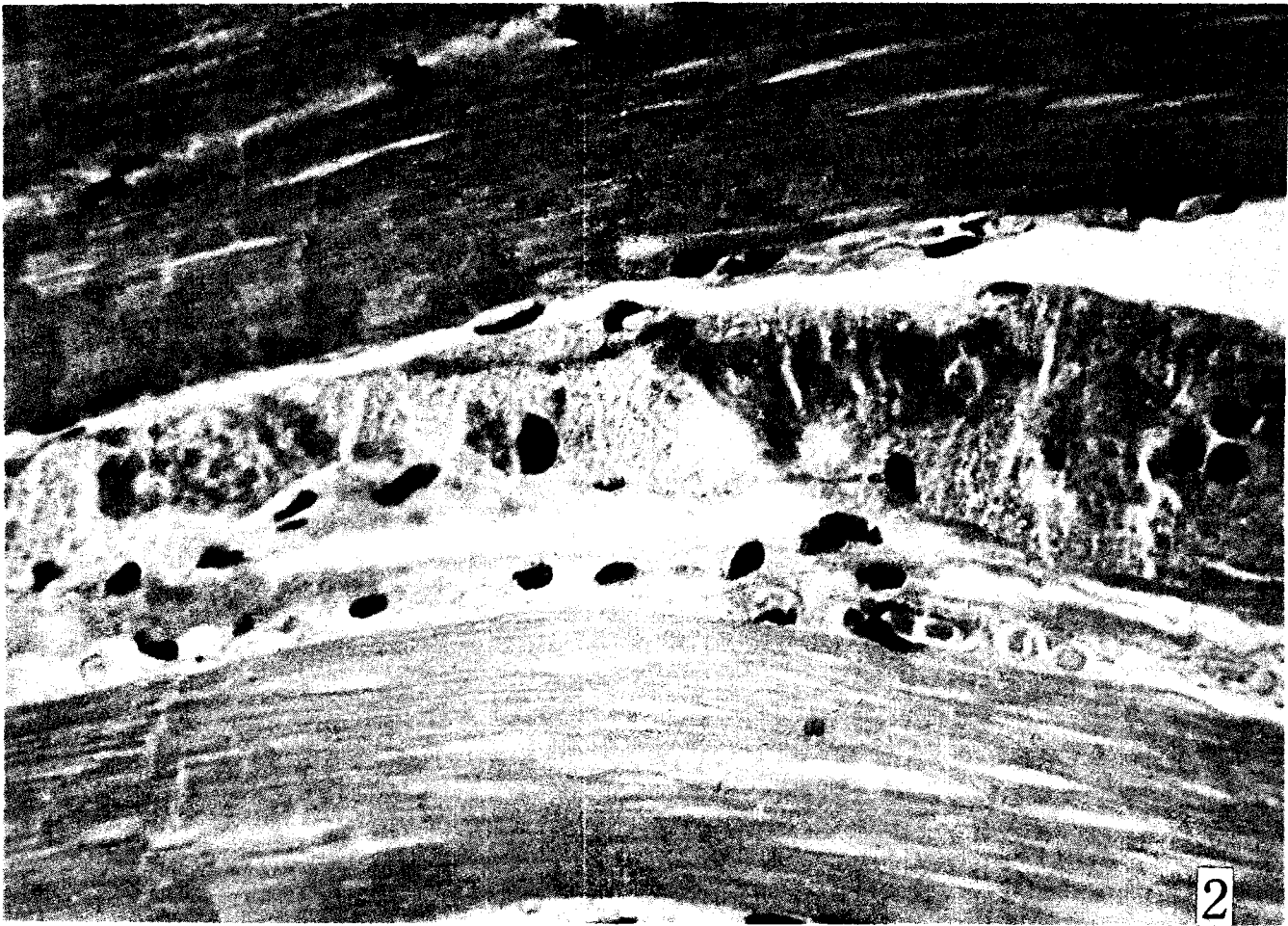
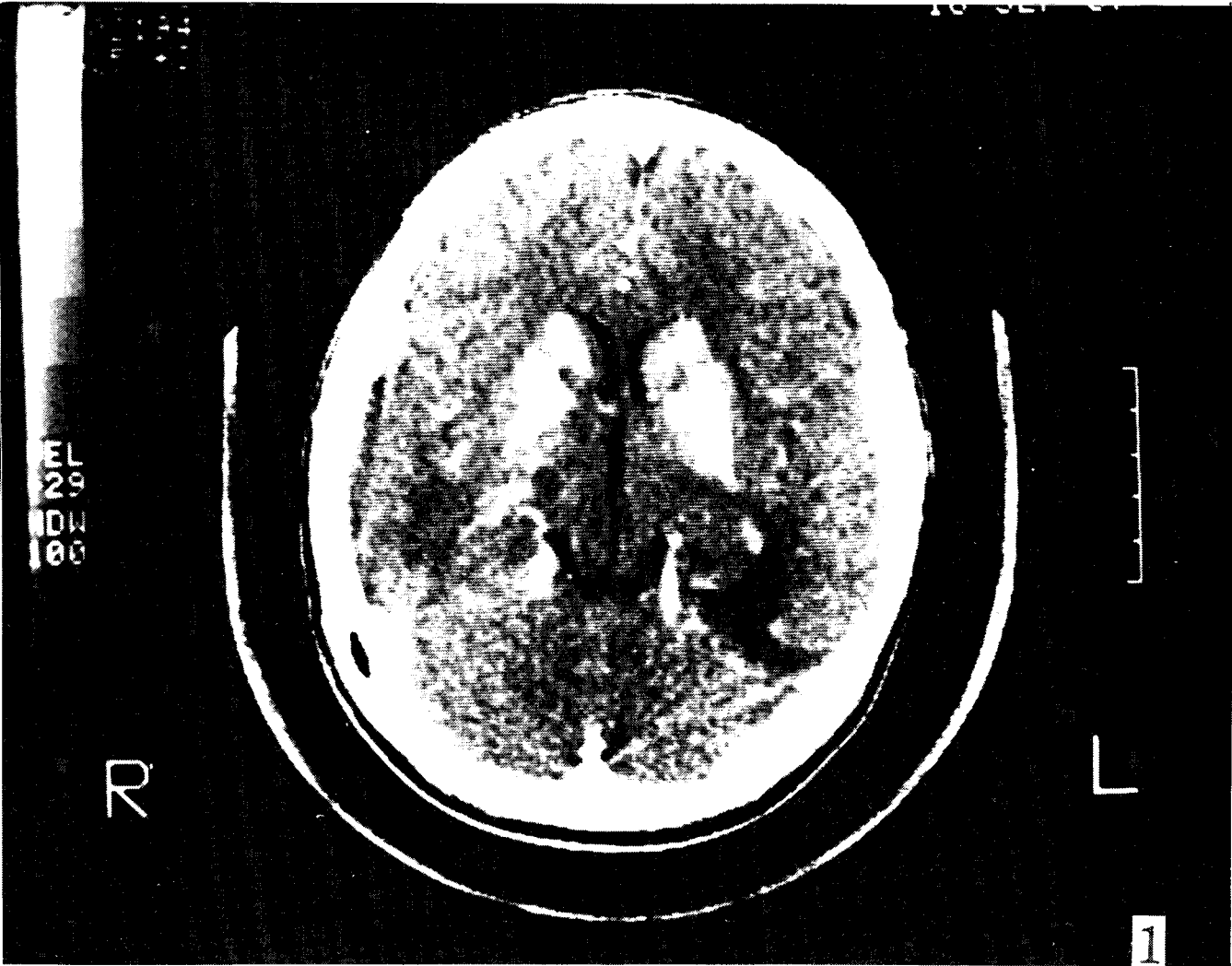
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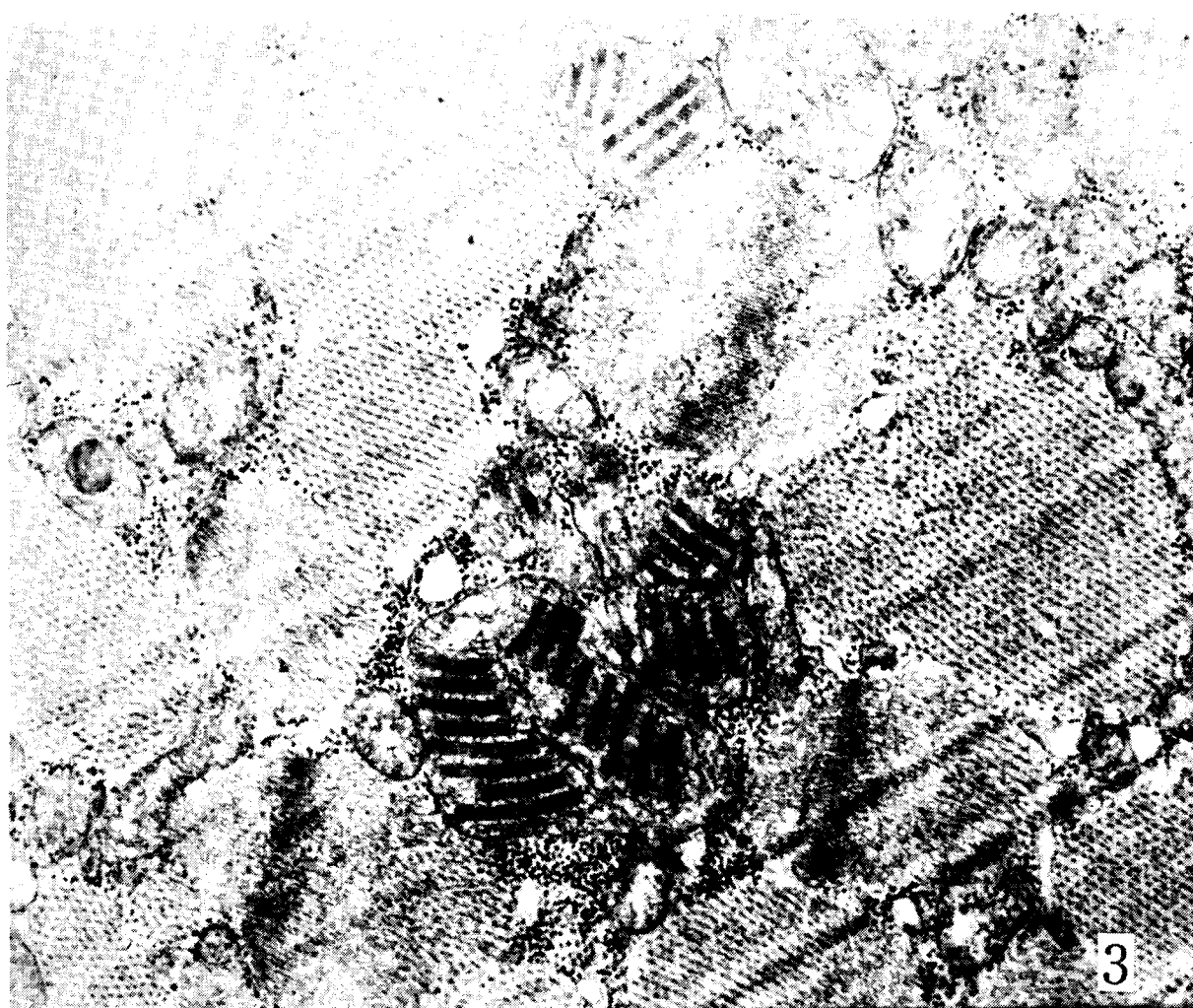
MELAS증후군 (증례보고)

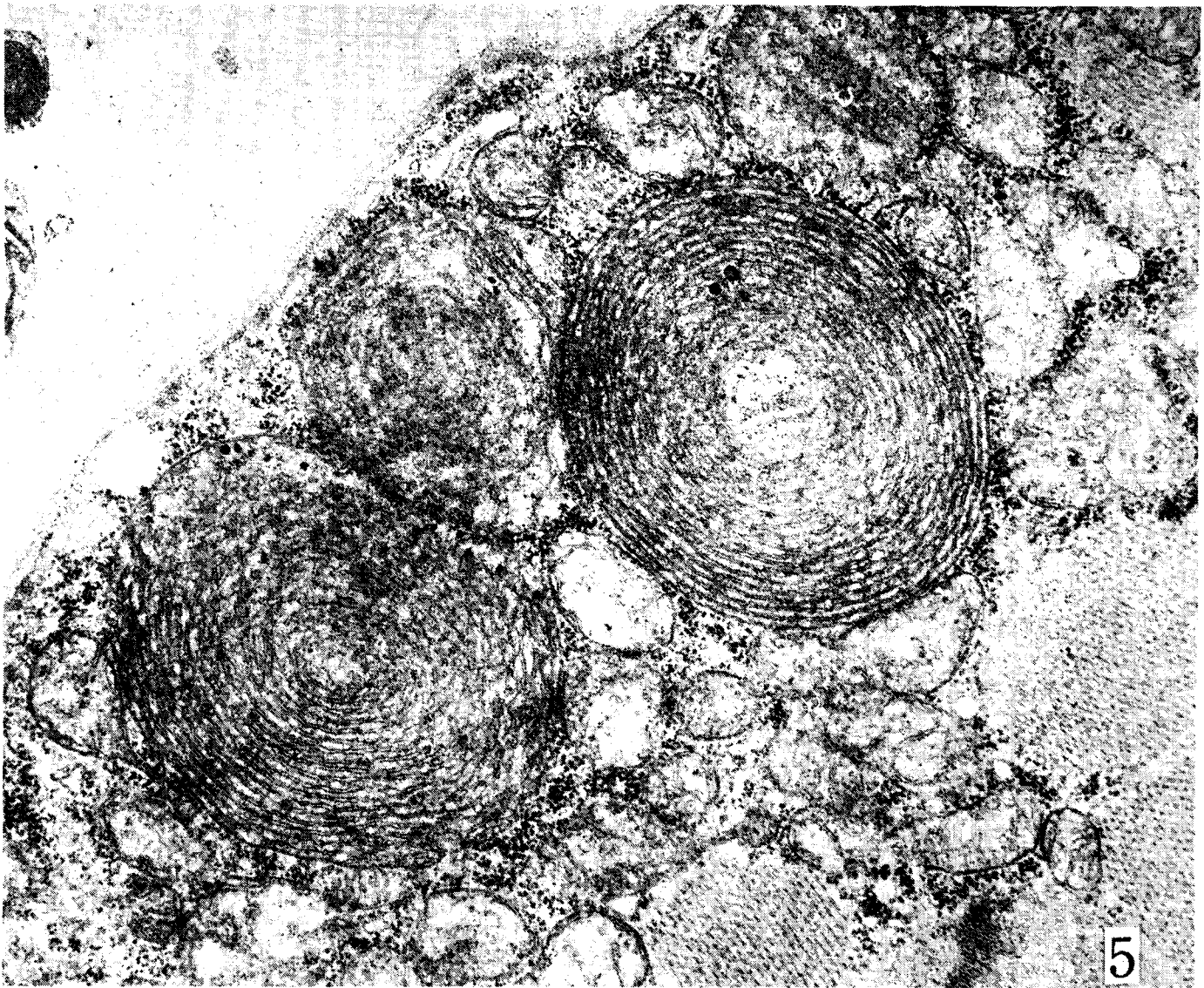
서울대학교 의과대학 신경과학교실 및 병리학교실*

명호진 · 김종성 · 서연림* · 지제근*

MELAS증후군은 최근 기술된 사립체질환의 하나로서 사립체성 근육 및 뇌질환, 유산증, 뇌졸중양 증상 등을 특징으로 한다. 저자들은 최근 우리나라의 첫 증례로 생각되는 환자를 경험하였기에 보고하는 바이다. 환자는 왜소한 체구의 17세 남자로서 근무력, 유산증, 기저핵의 석회화, 편두통양 두통, 수 회의 뇌졸중 및 이에 따른 반신마비, 시야결손, 경련 등의 증상을 나타내었다. 근육생검상 경한 근육질환이 나타났으며, 전자현미경 소견상 봉입체를 갖는 비정상적인 사립체가 관찰되었다.







LEGENDS FOR FIGURES

- Fig. 1. A computed tomogram showing lucent changes in the left parieto-occipital regions and symmetrical bilateral basal ganglia calcification.
- Fig. 2. Degenerating muscle fibers showing clustered red granules which are probably enlarged mitochondria. (H & E. $\times 400$, left deltoid)
- Fig. 3. An intermyofibrillar collection of enlarged mitochondria containing inclusions of rectangular shape. One globular electrondense inclusion is also seen in the left. (E.M. $\times 45,000$, left deltoid)
- Fig. 4. Giant mitochondria containing numerous paracrystalline 'parking-lot' type inclusions. (E.M. $\times 92,000$, left deltoid)
- Fig. 5. Cristae of some enlarged mitochondria are arranged in concentric whorls. (E.M. $\times 55,000$, left deltoid)