

CPEO and carnitine deficiency overlapping in MELAS syndrome

Hsu C-C, Chuang Y-H, Tsai J-L, Jong H-J, Shen Y-Y, Huang H-L, Chen H-L, Lee H-C, Pang C-Y, Wei Y-H, Chen S-S. Overlapping Syndrome of CPEO and Carnitine Deficiency in MELAS Syndrome
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Mitochondrial myopathy, encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome is one of the mitochondrial encephalomyopathies that has distinct clinical features including stroke-like episodes with migraine-like headache, nausea, vomiting, encephalopathy and lactic acidosis. We report a 27-year-old woman who presented with partial seizure, stroke-like episodes including hemiparesis, hemianopia and hemihypesthesia, sensorineural hearing loss, migraine-like headache, and lactic acidosis. Brain computed tomographic scan showed encephalomalacia in the right parieto-occipital area and recent hypodensity in the left temporoparieto-occipital area with cortical atrophy. Muscle biopsy revealed ragged-red fibers and paracrystalline inclusions in the mitochondria. Genetic study revealed an A to G point mutation at nucleotide position (np) 3243 of mitochondrial DNA. External ophthalmoplegia and ptosis were also found during two exaggerated episodes in this patient. Therefore, the overlapping syndrome of chronic progressive external ophthalmoplegia in the MELAS syndrome is considered in this case. Furthermore, we also found carnitine deficiency in this patient and she was responsive well to steroid therapy. Muscle biopsy also revealed excessive lipid droplets deposits. Therefore, the carnitine deficiency may occur in MELAS syndrome with the A to G point mutation at np 3243. We recommend the steroid or carnitine supplement therapy be applied to the MELAS syndrome with carnitine deficiency.

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Mitochondrial encephalomyopathy was first introduced in 1975 by Shapira et al., to describe mitochondrial diseases in which both muscle and the central nervous system (CNS) are involved (21). But these disorders are obviously multisystemic and affect a combination of the CNS, peripheral nerve, skeletal muscle, heart, retina, liver, kidney, intestine, endocrine gland and other organs (1, 2). The syndrome of mitochondrial myopathy, encephalopathy with lactic acidosis and stroke-like episodes (MELAS), which was first introduced by Pavlakis et al. in 1984, is now recognized as one of the several major distinct syndromes of mitochondrial encephalomyopathy (6). Others include the Kearns-Sayre syndrome (KSS) (3, 4), myoclonic epilepsy with ragged-red fibers disease (MERRF) (5) and chronic progressive external ophthalmoplegia (CPEO). A few overlapping syndromes of KSS with MELAS, KSS with MERRF, MELAS with MERRF and MELAS with CPEO have been described and reported over the past few years (7–11,

15). We report here a case whose clinical manifestations and genetic defect were comparable with overlapping syndrome of MELAS and CPEO (9, 11, 14). Furthermore, we found a low carnitine level in this patient. The relationship of mitochondrial encephalomyopathy and carnitine deficiency is discussed.

Case report

A 27-year-old woman had a normal birth history, perinatal development and normal motor milestone. She was rather healthy and had a nursing occupation. Unfortunately, at the age of 25 years, several episodes of focal motor seizure occurred over the left side of face marching to the left hand with an aura of numbness followed by weakness in the left arm. Besides she had a body weight loss of 9 kg/half month. As a result, she was admitted to Changhua Christian Hospital for medical treatment. After surveying for stroke and epilepsy, mitochondrial myo-

pathy was highly suspected. Then she was transferred to our ward for muscle biopsy and further management. During admission, episodic migraine-like headache, focal motor seizure, and vertigo with transient blindness were noticed. Physical examination revealed short stature with a body length of 149 cm and a body weight of 29 kg. External ophthalmoplegia with episodic diplopia appeared (Fig. 1) but there was no retinitis pigmentosa on fundoscopic examination. On neurologic status, stroke-like episode with decreased muscle power and sensation in the left side, dysarthria, bilateral sensorineuronal hearing loss and ataxia were manifested. After clinical examination, she received a short course of steroid therapy and anticonvulsant medication until 6 months ago. After skip medication for half a year, the symptoms recurred unfortunately. Acute episodic onset of numbness of face and hand in the right side followed slurred speech were found since Sep. 23, 1994. Dysarthria, dysphagia, loss of sensation in the right side, and exacerbated hearing loss were complained. Right hemianopia occurred after migraine-like headache. Mild mental insufficiency and childhood-behavior were also found. As a result, steroid therapy and anticonvulsant medication were re-prescribed.

Clinical biochemistry laboratory investigations revealed high serum lactate concentration (4.2 mmol/L, normal 0.8–2.2 mmol/L) and high serum lactate dehydrogenase (556 IU/L, normal 90–200 IU/L). Normal hemogram and creatine phosphokinase were

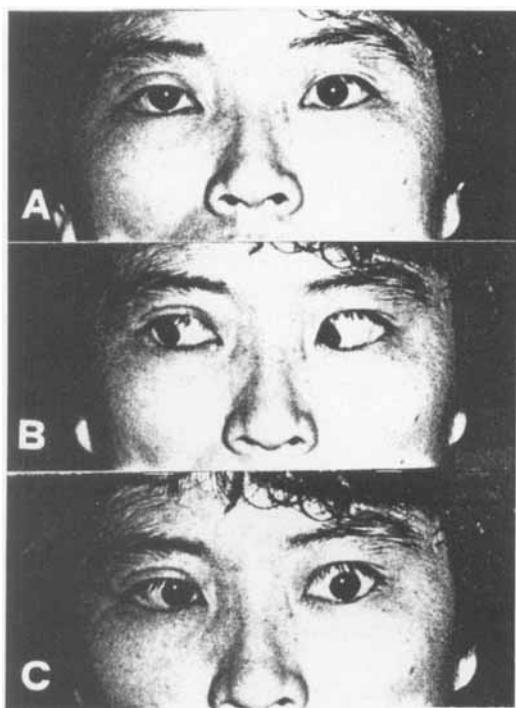


Fig. 1. Eyelid ptosis and restriction of movements on both eyes when gazing, A: natural position, B: right gazing, C: left gazing.

noted. Besides, serum cortisol, prolactin, and thyroid function were normal. An electrocardiogram showed sinus tachycardia but no conduction dysfunction. Chest radiogram was normal. Electroencephalography showed intermittent epileptiform discharges over the left temporo-parietal area with a background of slow activities. Brainstem auditory evoked potential (BAEP) revealed bilateral cochlear dysfunction, but somatosensory evoked potential (SSEP) was normal. Forearm ischemia test and glucose challenge tolerance test revealed persistent high lactate level (0', 7.7; 1', 7.6; 2', 6.9; 4', 6.1; 5', 5.8; 10', 5.4 mmol/L and 0', 4.62; 30', 4.14; 60', 5.05; 120', 5.22; 180', 5.46 mmol/L). No specific findings were found on cerebral angiogram. Repetitive stimulation test showed no decrement of amplitude. Nerve conduction velocity (NCV) was normal. Results of electromyogram were consistent with myopathy. Brain computed tomographic scan showed encephalomalacia in the right parieto-occipital area

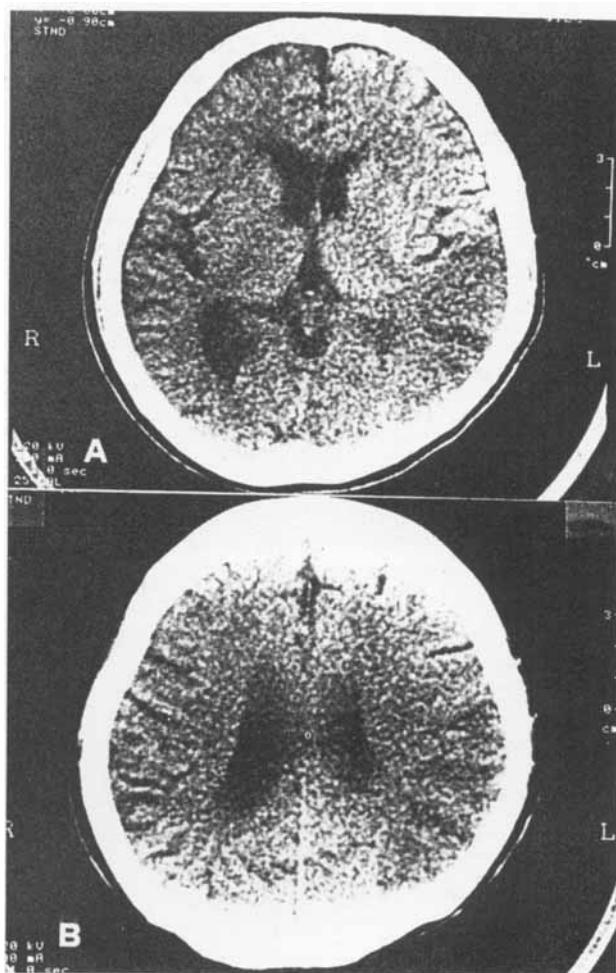


Fig. 2. Brain computed tomographic scans (A and B) showed encephalomalacia in the right parieto-occipital area and recent hypodensity in the left temporo-parieto-occipital area with cortical atrophy.

and recent hypodensity in the left temporoparieto-occipital area with cortical atrophy (Fig. 2). Muscle biopsy specimens were obtained from the left vastus lateralis muscle and revealed myopathic changes with ragged-red fibers, partial cytochrome c oxidase deficiency, excessive deposits of fat droplets in some fibers, and strongly succinate dehydrogenase-reactive vessels (Fig. 3). Under the electron microscope, paracrystalline inclusions with electron dense particles increased numbers of mitochondria and lipid droplets were found. By use of Apa I digestion of the PCR-amplified DNA of fragment encompassing the putative MELAS mutation, we found an A to G point mutation at nucleotide position 3243 in the

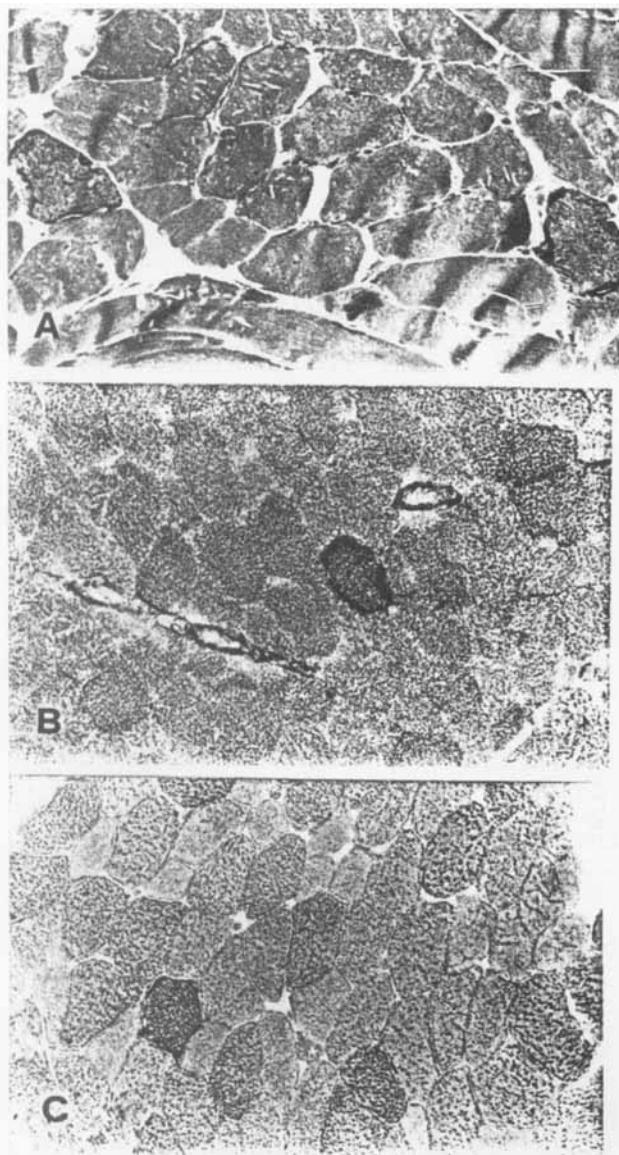


Fig. 3. Histochemical stains of the muscle biopsy specimens showed ragged-red fibers (A, modified Gomori trichrome stain), increased SDH activity in the vessels (B, succinate dehydrogenase stain), and increased fat droplets in some muscle fibers (C, Sudan black stain). Magnification 100 \times .

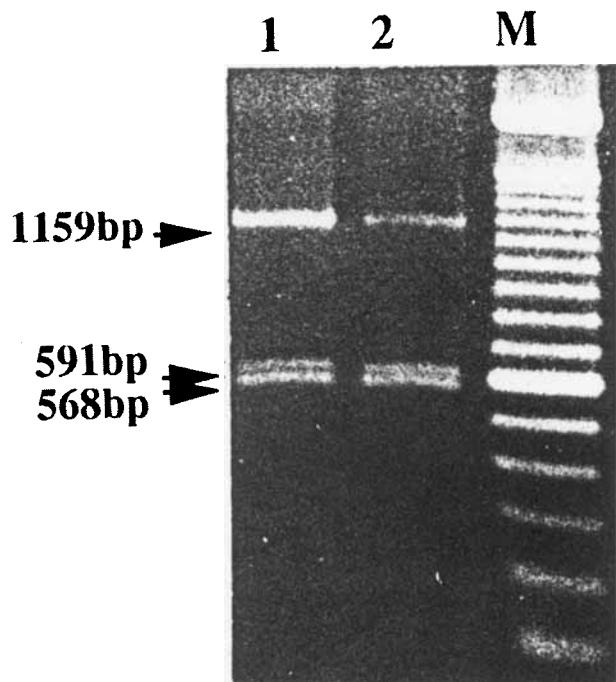


Fig. 4. Molecular analysis of the polymerase chain reaction (PCR) amplified DNA fragment encompassing the 3243 point mutation in the mtDNA of this MELAS patient. Lanes 1 and 2 are the Apa I-digested PCR products amplified from the blood cell mtDNAs of this MELAS patient and another previously-reported MELAS case (14). Lane M represents the BRL 100bp ladder DNA size marker. PCR and agarose gel electrophoresis were performed essentially according to the protocol described by Chen et al. (15), and the amplified PCR products were digested with 10 units of Apa I under the conditions recommended by the manufacturer.

mtDNA of the patient (Fig. 4). Most importantly, by use of a Boehringer Mannheim kit (22), we found that serum carnitine concentration was rather low (2.5 mg/l, normal 5–7 mg/l) in this MELAS patient.

After steroid therapy with 30mg prednisolone medication daily for one month, her condition got remarkable improvement. Two months later, she had neither seizure nor focal sign. Her external ophthalmoplegia improved moderately and the persistent low serum carnitine level during acute stage returned to normal level (9.0 mg/l).

Discussion

The MELAS syndrome has distinct clinical features including stroke-like episodes with migraine-like headache, nausea and vomiting, encephalomyopathy and lactic acidosis. Molecular analysis of mtDNA has been well-developed for the diagnosis of mitochondrial encephalomyopathy in the past few years. Point mutation at nucleotide position 3243 (A \rightarrow G) (80%) and 3271 (T \rightarrow C) (10%) have been identified to be associated with the MELAS syndrome (12, 13, 23). Recently, more and more overlapping syn-

dromes have been found in mitochondrial encephalomyopathies, notably MELAS with KSS, MERRF with KSS, MELAS with MERRF, and MELAS with CPEO (7-11, 14-15). The patient reported here has been clearly diagnosed to be a MELAS case both clinically and genetically. External ophthalmoplegia was also noted in this patient while retina pigmentosa and optic atrophy were not found. Therefore, overlapping syndrome is considered in this patient and the genetic analysis revealed an A→G point mutation at nucleotide position 3243 of mt DNA.

Peripheral neuropathy was not found in this patient and repetitive stimulative test shows no decrement of amplitude. Therefore, no neuromuscular junction problems are manifested in mitochondrial encephalomyopathy of the MELAS syndrome.

Carnitine is required for the transport of long chain fatty acids into mitochondria where beta-oxidation occurs (17). Two types of human carnitine deficiency were first described in 1972. Primary (systemic and myopathic) carnitine deficiency is manifested with skeletal myopathy, cardiomegaly, with episodic vomiting, encephalopathy, hepatomegaly and Reye's-like syndrome (16, 18). Secondary carnitine deficiency syndromes are now well recognized in some metabolic disorders, inadequate intake, and excessive loss of carnitine (16). In carnitine therapy, it may have the effects that were reported in the administration of carnitine and corticosteroids (17). In our patient, muscle biopsy revealed deposits of lipid droplets and response to steroid therapy. Laboratory investigations show low serum carnitine concentration. It may be the form of secondary carnitine deficiency caused by defects of the mitochondrial electron transport chain (19, 20). Therefore, further study is warranted to establish the relationship of mitochondrial encephalopathy and carnitine deficiency as well as the possibility to apply steroid or carnitine supplement therapy to the patient with mitochondrial encephalomyopathy such as the MELAS syndrome.

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