Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS) in a Two-Year-Old Filipino Child

Mary Ann R. Abacan[1, 2] and Mary Anne D. Chiong[1,2]

[1] *Department of Pediatrics, College of Medicine and Philippine General Hospital, University of the Philippines Manila*
[2] *Institute of Human Genetics, National Institutes of Health, University of the Philippines Manila*

ABSTRACT

MELAS is a mitochondrial respiratory chain disorder characterized by progressive neurodegeneration associated with stroke-like episodes, increased plasma lactate levels and distinctive findings on neuroimaging studies. Here we describe a 2-year-old female who presented with sudden onset of right-sided hemiplegia accompanied by lactic acidosis and CT Scan findings of diffuse hypodensity of the cerebral white matter at the time of the stroke-like episode. The diagnosis was confirmed by mutation analysis on blood and hair which showed the typical mtDNA A3243G mutation. This is the first local report of a confirmed case of MELAS.

Key Words: MELAS, mitochondrial respiratory chain disorder, childhood stroke

Introduction

MELAS or Mitochondrial myopathy, Encephalopathy, Lactic acidosis and Stroke-like episodes is a multisystem progressive disorder caused by mitochondrial dysfunction. The major function of mitochondria is to generate energy for cellular processes in the form of ATP. This is facilitated by oxidative phosphorylation which is the final metabolic pathway in oxidative metabolism. This process is achieved by the five multi-subunit protein complexes of the mitochondrial respiratory chain.[1] Complex I (Nicotinamide Adenine Dinucleotide Hydrogenase or NADH Co-enzyme Q reductase) carries reducing equivalents from NADH to coenzyme Q (CoQ, ubiquinone) and consists of more than 40 different polypeptides, seven of which are encoded by mitochondrial DNA. Complex II (succinate CoQ reductase), the only complex that does not contain any mtDNA coded proteins, carries reducing equivalents from $FADH_2$ or flavin adenine dinucleotide hydrogenase to CoQ and contains four polypeptides, including flavin adenine dinucleotide-dependent succinate dehydrogenase and three iron-sulfur centers. Complex III (reduced CoQ-cytochrome c reductase) carries electrons from CoQ to cytrochrome c. Complex IV (cytochrome oxidase, COX), the terminal oxidase of the respiratory chain, catalyzes the transfer of reducing equivalents from cytochrome c to molecular oxygen.[2] The end product of this reaction results in the formation of adenosine triphosphate that provides energy for the cell (Figure 1).

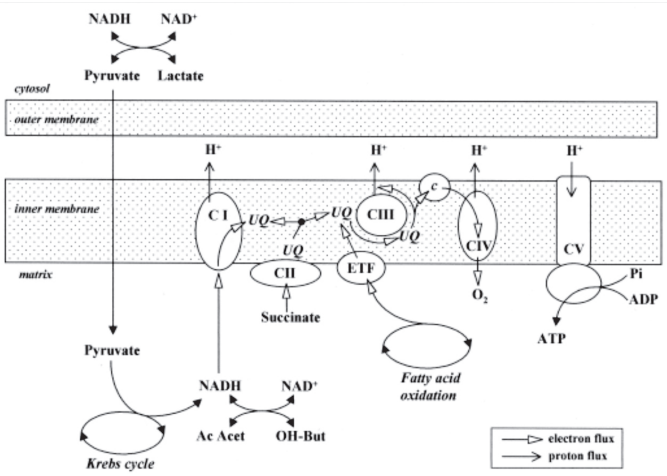

Figure 1. The mitochondrial respiratory chain.[2]

The mitochondrial genome has a mutation rate 10-fold greater than that of nuclear DNA and with no protective histone proteins or effective DNA repair mechanism, it is highly vulnerable to nucleolytic attack by free radicals generated by oxidative phosphorylation.[1] Because oxidative phosphorylation is a fundamental pathway of cellular metabolism, any organ can be involved in patients with mitochondrial disorders[3] which is why mitochondrial DNA defects can present with clinical heterogeneity.[4]

The acronymic designation of "MELAS" was first introduced by Pavlakis and colleagues to describe two children and nine other similar cases from literature as a distinctive syndrome.[5] It is characterized by normal early development followed by stroke-like episodes (typically

Corresponding author: Mary Anne D. Chiong, MD
Institute of Human Genetics
National Institutes of Health
University of the Philippines Manila
625 Pedro Gil Street, Ermita, Manila 1000 Philippines
Telephone: +632 5261725
Email: maryannechiong@gmail.com

before the age of 40 years old), mitochondrial encephalopathy and lactic acidosis.[6] Other signs and symptoms include recurrent vomiting, migraines, seizures, hemianopsia, limb weakness, psychomotor retardation, dementia and ataxia.

To date, there are at least 24 pathogenic mutations in mtDNA that have been reported in association with the MELAS phenotype.[5] There are currently 23 missense point mutations and one 4 base pair deletion spanning different mitochondrial genes.[7] Approximately 80% of cases have a mitochondrial DNA A to G transition at nucleotide 3243 of transfer RNA leucine gene.[8]

The prevalence of the most common MELAS mutation is estimated to be 7.59 per 100,000 persons in Northeast England, 16.3 per 100,000 in Northern Finland and 236 per 100,000 in Australia.[5] We present the first reported case of MELAS in a Filipino child with the mtDNA A3243G mutation.

Clinical Report

The patient is a 2-year-old female who presented with sudden onset of right-sided hemiplegia. She was born at term to a 19-year-old primigravid, small for gestational age with a birth weight of 1600 grams. At birth, she was noted to have good cry and activity. She is the only child of a non-consanguineous couple of Filipino descent with a family history of hypertension in her maternal grandfather and cerebral palsy in a maternal uncle. There was no other family history of significance. She was noted to have developmental delay with no expressive speech and delayed gross motor skills. She is unable to walk alone at two years of age.

At the time of examination, two days after the episode of acute hemiplegia, the patient had right-sided facial weakness, inability to move the right upper and lower extremities and hyporeflexia. Cranial CT Scan showed diffuse hypodensity of the cerebral white matter. A blood gas showed metabolic acidosis with high anion gap, 21.7. The plasma lactate was 1.9mmol/L (NV 2.0mmol/L) and urine organic screen showed a moderate lactic acidosis and severe ketosis. Based on the clinical and laboratory features, a possible mitochondrial respiratory chain disorder, in particular MELAS, was suspected. A brain MRI scan performed two months after the initial stroke-like episode showed hyper-intensities in both fronto-temporo-parietal white matter and deep periventricular white matter with portions of the anterior-inferior frontal and posterior temporal subcortices also involved. Magnetic Resonance Spectroscopy (MRS) showed some areas with decreased N-acetyl-aspartate (NAA) levels but no lactate or lipid elevations. Mutation analysis for the common, mA3243G mutation for MELAS both in hair and peripheral blood leukocytes showed the A3243G mutation of mtDNA (Figure 2). Other investigations, which included an electrocardiogram, echocardiography and ultrasound of the kidneys and urinary bladder, were all normal.

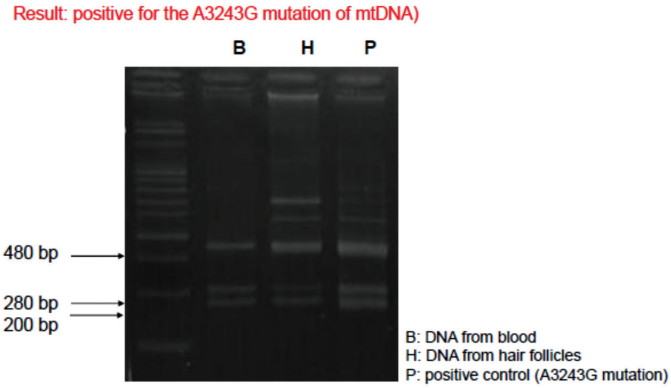

Figure 2. Molecular Diagnosis for the A3243G mutation of mtDNA

The patient was started on co-enzyme Q (5mg/kg/day), thiamine (15mg/kg/day), carnitine (50mg/kg/day), Vitamin C (25mg/kg/day), Vitamin E (15mg/kg/day) and arginine (100mg/kg/day). At the time of this report, the patient's neurologic status was back to baseline. She has no neurologic deficits, had regained motor function of her right upper and lower extremities but had expressive speech delay. She is currently undergoing rehabilitation.

Discussion

MELAS was originally described as a distinct clinical syndrome of mitochondrial encephalomyopathy characterized by episodic vomiting, seizure, encephalopathy, migraine headache and recurrent stroke-like episodes causing hemiparesis, hemianopsia or cortical blindness.[5] In a study by Debray et al[3], they found that among 73 diagnosed cases in their institution, 90% of patients with MELAS presented with neurologic symptoms such as seizures, ataxia, extrapyramidal signs, muscle weakness or pain, and headaches. Hemiparesis is reported in 22-83% of patients in a large series.[9] These findings are consistent with our patient who presented with sudden onset of right- sided hemiplegia.

The age of onset of MELAS is reported to occur variably between the age of 2 and 40 years old.[10] The average age of onset is 5.2 years; the average age of the first "stroke" is 14.7 years (range of 7 to 33 years old).[11] However, DiMauro and Hirano[12] report that among 87 patients diagnosed with MELAS, the majority present between the ages, 6-10 years (27 individuals or 31%) followed by 21-40 years old (20 individuals or 23%) and the 2-5 years old age group (17 individuals or 20%). Our patient falls into the last category.

The pathogenesis and etiology of stroke-like episodes in MELAS is still being studied. Iizuka and Sakai[5] have described four cardinal features of stroke-like episodes including neuronal hyper-excitability, neuronal

vulnerability, increased capillary permeability and hyperaemia of the vessels presumably associated with increase in lactate production due to increased anaerobic mechanism. One proposed theory to explain these findings is mitochondrial angiopathy. Lesions are ischemic in nature and are caused by cerebral small-vessel mitochondrial and vascular dysfunction.[6] Another hypothesis is generalized cytopathy caused by oxidative phosphorylation defect in neurons or glia cells or both.[5,6] A final theory combines both neuronal and vascular mechanisms. It surmises that stroke-like episodes are more likely non-ischemic neurovascular events initiated by neuronal hyper-excitability which leads to increased energy demand, leading to a mismatch between demand and availability of ATP due to the underlying oxidative phosphorylation defect and lastly to a vasogenic edema and cortical necrosis.[5,13]

The diagnosis of MELAS may be challenging because the clinical presentation varies among members of the same family. A high index of suspicion is a key factor in the diagnosis of MELAS.[6] Supporting laboratory examinations include increased lactate and pyruvate levels in serum and cerebrospinal fluid. In our patient, plasma lactate was within normal range. Debray[3], found that although 72% of 73 patients with MELAS had chronic lactic acidemia, 61% had plasma lactate concentration within the reference range showing high variability of this biochemical parameter. This led to their conclusion that lactic acidosis is useful but not specific.

Neuro-imaging studies are also useful in the diagnosis. CT Scan may show calcification of the basal ganglia or bilateral hypodensities and atrophy, which are valuable diagnostic indicators of mitochondrial disease.[2] However, in a review of cases by Debray[3], it was found that although the most common findings were present in most cases of MELAS, some neuro-radiological features less specific to a mitochondrial disorder were also commonly observed. These included white matter abnormality (21 out of 59), corpus callosum hyper-intensities (5 out of 59) and cerebellar atrophy (9 out of 59). In our patient, the findings on CT Scan were diffuse hypodensity of cerebral white matter which is a non-specific finding.

On MRI, the stroke-like lesions are often transient and lesions predominantly affect gray matter and are not confined to vascular territories, which is an important feature. Diffuse white matter lesions have occasionally been observed in MELAS usually involving the periventricular white matter.[14] The brain MRI scan of our patient was performed eight weeks after the acute episode. It showed hyperintesities in both fronto-temporo-parietal white matter segments, deep periventricular white matter segments and portions of the anterior-inferior frontal and posterior temporal subcortices were similarly involved. In our patient, the MRI did not show the classical findings, probably because it was not performed during the acute stroke-like event. However, it did show involvement of the white matter. It must be noted that many mitochondrial diseases have no MRI abnormalities or only show non-specific changes.[15]

Magnetic Resonance Spectroscopy (MRS) in MELAS present with lactate peaks. In our patient, the MRS showed some areas with decreased NAA levels and no evident lactate or lipid elevation. However, just as serum lactate is only a moderately sensitive marker, brain lactate peaks are also not 100% sensitive.[15] In a study by Lin,[16] only 8 out of 29 patients were found to have lactate peaks on MRS. Further, some studies suggest that in MELAS, decreased NAA which is a sign of neuronal rarefaction or dysfunction in the brain may be more highly correlated to lesions visible in MRI.[14] These findings may be consistent with what was seen in our patient.

The diagnosis of MELAS can be confirmed by skeletal muscle biopsy and genetic studies. The histologic landmark of mitochondrial myopathy are the ragged red fibers demonstrated with the modified Gomori trichome stain, but these are not usually present in young children.[17] Approximately 80% of patients harbour an A3243G mutation making it useful for the diagnosis of MELAS. Although the mutation was initially identified in DNA isolated from muscle, it is usually present in all tissues from patients and, in lower abundance, in tissues from oligosymptomatic or asymptomatic maternal relatives. Therefore, it became common practice to look for the mutation in blood, although it was noted that mutant loads were consistently lower in blood than in muscle.[18] It is also possible to detect mutations in urinary epithelial cells, and this is now the preferred sample.[19] The mutation analysis done on blood and hair sample of our patient showed A3243G mtDNA mutation confirming the diagnosis.

A variety of pharmacological agents have been used in the treatment of patients with mitochondrial disease by intervening at each level of the pathological cascade thought to be responsible for cellular dysfunction and death.[1] Mode of action of the medications may include removing noxious metabolites, supplementing artificial electron acceptors, supplementing vitamins or cofactors, and scavenging reactive oxygen species.[5]

Coenzyme Q10 has antioxidant properties and has been used to improve transfer of electrons in the mitochondrial respiratory chain in patients with mitochondrial disease.[6] In theory, artificial electron acceptors could lead to symptomatic improvement in patients with respiratory chain disease.[1] Among those given are: ascorbic acid and menadione which may accept electrons from reduced coenzyme Q10 and deliver them to cytochrome c, effectively by-passing complex III of the mitochondrial electron transport chain; riboflavin indirectly acts as a cofactor for respiratory chain complexes I and II; thiamine is a cofactor for pyruvate dehydrogenase and may stimulate respiratory

chain through the production of NADH[1,6] and L-carnitine which may enhance fatty acid transport into the mitochondrion, facilitating the production of an alternative energy source in the form of ketone bodies.

In a study by Koga et al.[20], arginine, the only agent to be studied systematically, was significantly lowered in both acute and interictal phases of MELAS compared to control subjects. Intravenous L-arginine administration has been given to induce vasodilation. Further, arginine is an important precursor of nitric oxide, which may reduce ischemic damage in the acute phase of focal brain ischemia by increasing microcirculation in the cerebral blood flow, inhibiting post-ischemic leukocyte-endothelial adhesion, decreasing quantities of hydroxyl radical and reducing brain damage in early stages of cerebral ischemia. Maintenance with oral supplementation of L-arginine, leads to the decrease in frequency and severity of clinical symptoms after the initial attack of stroke-like episode making it a valuable therapeutic agent.[19,21]

Any mode of inheritance can be observed in mitochondrial diseases: sporadic, autosomal recessive, dominant, X-linked or maternal. Indeed, among the numerous genes encoding the respiratory chain proteins, most are located in the nucleus and undergo classic Mendelian inheritance.[15] In a review by Iizuka and Sakai[5] on mitochondrial genetics, maternal inheritance is a rule of mtDNA-related disorders. Only a mother carrying a mutation in mtDNA can pass it on to all her children and only her daughters can transmit it to their progeny. Mutant mtDNA generally coexists with wild-type mtDNA in a condition called heteroplasmy. There is a threshold or a minimal number of mutated mtDNAs that are required to induce a biochemical defect of respiratory chain or expression of clinical manifestations. Since mtDNA-related disorders are maternally inherited, all offspring of females with the mtDNA mutation are at risk. Thus, in the case of our patient, there is a need to test her mother and other family members. However, the expression of signs and symptoms will be dependent on the mutation load.

The clinical presentation of MELAS may vary, but overall, it has been found that patients tend to have poor outcome.[6] Patients may die during a stroke-like episode. They may have recurrent stroke-like episodes and often develop mental deterioration, loss of vision, hearing impairment, and a severe myopathy.[22] It has also been found that age at which first symptoms appeared is a major independent predictor of mortality, particularly in patients who presented before 6 months of age.[3] Our patient presented with her first stroke-like episode at 2 years, which is below the average age of onset of symptoms. The clinical course can be unpredictable and she will require frequent monitoring and evaluation.

In summary, MELAS is a mitochondrial disorder that may present with acute stroke-like episodes in children. Diagnosis is made by characteristic brain imaging findings, presence of the typical mtDNA mutations and in general, elevated blood and cerebrospinal fluid lactate levels. Further out-patient care include monitoring of neurologic sequelae, neuropsychological evaluation and monitoring for ophthalmologic abnormalities, hearing loss and cardiomyopathy.[11] Genetic counselling is important to inform the family of the recurrence risk, to identify asymptomatic carriers and monitor pre-symptomatic individuals.

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