

Melas Syndrome

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Abstract. An 11 year old male presented with headache, vomiting and weakness of right side of body. One day after admission he developed right focal seizures. He had 5 previous episodes of stroke, the first at 11 months age. His milestones were normal upto the first episode but subsequent milestones were delayed. His serum and CSF lactic acids were raised. Muscle biopsy showed ragged red fibres on modified Gomori-trichrome staining. His EEG, CT scan and MRI were normal this time. The child improved spontaneously after 7 days. His recovery time progressively became shorter with each episode of stroke. Maximum time for recovery was noted during first episode and least in current episode. This is the first report of Melas syndrome in Indian literature. (Indian J Pediatr 1999; 66 : 621-625)

Key words : *Melas syndrome; Mitochondrial myopathy; Lactic acidosis.*

The syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (Acronym as MELAS) is characterized by short stature, hemiparesis, hemianopsia, cortical blindness, lactic acidemia and ragged red fibres in skeletal muscle¹. Other frequently encountered features of MELAS are sensorineural hearing loss, headache, nausea, vomiting and basal ganglia calcification². Development through infancy is usually normal in MELAS¹. Clinical features usually appear between 5 to 15 years of age and manifestations below the age of one year are rare³. Infants present with symptoms of failure to thrive, vomiting, lactic acidosis, cognitive regression before developing stroke like episodes^{4,5,6}. No case of MELAS has been reported in Indian literature so far.

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CASE REPORT

An 11 year old male was admitted with a 2 days history of hemiparesis of the right side. He had headache on the day before the onset of weakness. Previously, he had 4 episodes of transient hemiparesis, the first at the age of 11 months and subsequently at the age of 2 years, 4 years, and 9 years. Recovery from the 1st episode took 8 months. Recovery from subsequent episodes took 2 months, 6 weeks, and 11 days respectively. After the 1st episode CSF analysis and EEG were normal. The CT scan showed right hemispheric edema and midline shift to the left with right lateral ventricle compression (Fig 1). CT scan was repeated after the 2nd episode and showed a similar picture. Magnetic resonance imaging done a month later was normal. His developmental milestones were apparently normal upto the first episode at 11 months of age. However, an IQ at the age of 4½

es have been recorded¹. A typical EEG pattern consisting of increase in slow activity and a decrease in alpha frequency and epileptiform discharge has been reported¹². PET studies in patients with MELAS have demonstrated a marked decrease in cerebral metabolic ratio of oxygen (CMRO₂) with relatively preserved cerebral blood flow and cerebral metabolic ratio of glucose supporting a disturbance of mitochondrial oxidative metabolism in the brain¹³. Xenon¹³ planar regional cerebral blood flow has shown diffuse hyperperfusion of all cerebral regions. This hyperperfusion persisted even one month later. Cerebral hyperperfusion is thought to represent a sort of adaptation to the altered mitochondrial function leading to impaired intracellular utilization and metabolism¹⁴. In our patient CT scan initially showed right hemispheric edema but basal ganglia calcification was not noted. EEG and MRI were normal. PET study was not done.

Histopathology of brain under light microscopy may show a diffuse fibrillary gliosis with abundant reactive gemistocytes, focal evidence of ischemic neuronal injury and edema¹⁵. Muscle biopsy under light microscopy usually shows ragged red fibres and increase in fat droplets. Electron microscopy shows increase mitochondria and atypical mitochondria in the subsarcolemal region, some with inclusion bodies¹⁰. This syndrome was found to be associated with respiratory chain disorder, particularly complex I (NAD, CoQ reductase)^{1,16}. Multiple defects of respiratory chain enzymes including complex I+III, II+III and complex IV were described in many cases of MELAS syndrome¹⁶. It is conceivable that single defect in any one of the several enzymes of the respiratory chain could produce the same resultant

syndrome². Valproate therapy may precipitate an acute episode by further suppressing complex IV activity which occurs in 50% of MELAS patients¹⁰.

Electron microscopy of blood vessels often shows increased numbers of abnormal mitochondria within vascular smooth muscle and in endothelial cells. It is hypothesised that the stroke like episodes in MELAS may be due to impaired autoregulation secondary to the impaired metabolic activity of mitochondria in the endothelial and smooth muscle cells of blood vessels¹³. MRI changes cannot be explained on the basis of vascular territory and involvement of small arterioles and capillaries may be considered as one of the explanations⁴. Pancreatic dysfunction in form of acute and chronic pancreatitis, peripheral neuropathy and kidney damages is reported in MELAS syndrome^{3,11,17}.

MELAS appears to be transmitted genetically and in most cases it is related to mitochondrial inheritance from mother to child². More than 80% cases show presence of A to G point mutation at nucleotide pair 3243 in the mitochondrial DNA (mtDNA) tRNA^{leu (uur)} and rarely at 3271^{3,17,18}. The proportion of mt-DNA needed to cause disease in muscle is usually between 50-96% in MELAS cases⁴. The percentage of mutant mitochondrial genomes in muscle is higher in patients as compared to relatives and it is higher in symptomatic relatives as compared to asymptomatic ones²⁰. Pathogenesis of MELAS syndrome is not known. It is postulated that secondary somatic mt-DNA mutations can be initiated by 3243 A-G mutation and accumulation of somatic mutations in individuals with deleterious mitochondrial genotype can contribute to progressive mitochondrial dysfunction in MELAS²¹. The course of MELAS is varia-

ble. In certain series cases were asymptomatic in between strokes. As more patients with MELAS are studied for a longer period of time, stepwise course, as opposed to a gradual or progressive course, may become more apparent^{1,2}. Our patient had five discrete episodes of hemiparesis but the time taken for recovery progressively got lesser with each episode.

Various treatments including high carbohydrate diet, carnitine, high dose of thiamine, Vit C, steroids and Vit K have been tried with little or no success. Creatinine was tried in one child, with beneficial effect. This effect seems to be due to both a higher initial creatinine phosphate availability and an increased rate of resynthesis during recovery period¹⁶. COQ and idebenone has lead to improvement in MELAS cases^{13,22}. Nicotinamide treatment lead to decrease in lactate and pyruvate concentration, hence decrease in lesion volume in MRI within first month²³.

Children with recurrent stroke who have delayed milestones but normal early development must be investigated for MELAS. Clinical features, lactic acidemia and presence of ragged red fibres in muscle confirm diagnosis. CT scan, MRI findings may help in diagnosis.

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