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Case Reports

MELAS SYNDROME IN TWO IRANIAN CHILDREN

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ABSTRACT

MELAS syndrome is a mitochondrial disorder with progressive nature, because adequate treatment is not available. Diagnosis of this mitochondrial disorder depends initially on clinical suspicion, which is strengthened by additional metabolic evidence of impaired oxidative metabolism such as high serum or C.S.F. lactate levels and confirmed by demonstration of mitochondrial abnormalities in muscle biopsy. Here we present the clinical course and management of two children with MELAS syndrome who exhibited progressive neurologic deterioration.

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INTRODUCTION

The MELAS syndrome (*mitochondrial abnormality, encephalopathy, lactic acidosis and stroke-like episodes*) is a progressive neurodegenerative disease which can be inherited maternally or occur sporadically.[1,3] The molecular pathology which underlies this syndrome is a point mutation on the mitochondrial genome leading to deficiency in one or more respiratory chain enzymes, most commonly complex I (*NADH Co-enzyme Q reductase*).[2] Affected children are normal at birth and may develop normally until late childhood. The cardinal neurologic features are reccurent attacks of prolonged migraine headaches, vomiting, encephalopathy, and seizures with sudden onset of focal neurologic deficits. Neurological abnormalities are initially intermittent but later become constant, leading to coma and death.[1,3]

Here we present two cases of MELAS syndrome which are probably the first being reported in Iran, in order to draw the attention of our collegues to a syndrome of mitochondrial disorder, the proper diagnosis of which currently depends on clinical suspicion based on recognizing one or more components of it's clinical features.

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Case 1

M.H. was a 4 years and 10 months old boy when admitted in the Child Neurology Ward at Mofid Children's Hospital in Tehran for drowsiness, seizures and right-sided weakness. His parents complained of episodic attacks of abdominal pain, vomiting and loss of consciousness in their child since 2 years ago, which repeated every 1 to 4 weeks, each episode lasting 24 to 48 hours. Parents also reported complex partial seizures on several occasions. After the last episode which was 20 days before admission, the patient became speechless and unambulatory. He had been treated for abdominal migraine and cyclic vomiting without any benefit during the past two years.

The patient was from a nonconsanguinous marriage and his birth history was uneventful. He also had normal psychomotor development until his recent attack. His growth milestones were also appropriate for his age. Neurological examination revealed the patient to be confused, speechless and unambulatory because of weakness in both sides

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with left sided predominance.

Laboratory evaluation exhibited an elevated lactate level of 2.5 mmol/L (*normal range: 0.5-2 mmol/L*) and increased liver enzymes [SGPT 119 IU/L (*normal range: 5-40 IU/L*) and SGOT 180 IU/L (*normal range: 5-40 IU/L*].

Blood gases, glucose level, lipid profile, serum ammonia, muscle enzymes, blood coagulation factors, and cardiovascular evaluation were all within normal limits.

A brain MRI showed at least two areas of infarct in the temporal and temporoparietal regions with concomitant brain edema.

Electromicroscopic muscle biopsy revealed abnormal mitochondrial proliferation and structure, suggestive of a mitochondrial myopathy. DNA analysis for mitochondral DNA defect and biochemical study of oxidative phosphorylation complex enzymes were not available.

Considering the above clinical features and lab findings, our diagnosis was MELAS syndrome for this patient.

We initiated treatment with steroids (*dexamethasone*). an anticonvulsant (*phenytoin in the acute phase and then switching to carbamazepine when liver function tests decreased to normal limits*), carnitine, vit. B (*B_1, biotin, B complex*), vit. C and vit. K according to suggested doses mentioned in the *Discussion.*

The patient became more alert and communicative after the first week of treatment. During the next six months he got better functionally on this treatment, concomitant with occupational therapy, until the 3rd episode of stroke occurred and made the patient completely bedridden.

Case 2

H.R. was a 10 year old boy with too much interest in soccer. He was doing well until age six, when parents noticed decreased vision and gradually progressive tremor in the hands. Subsequently, two episodes of stroke occurred at age 8 and 9 years leading to right-sided weakness in the child. At age 10, he was admitted to Mofid Children's Hospital for the 3rd episode of stroke, myoclonic seizures, slurred speech and progressive functional disability.

None of his family members had neurological problems and there was no consanguinity between the parents.

Neurological examination revealed the patient ataxic and unable to walk unassisted. He had scanning speech and intentional tremor in both hands. Myoclonus was evident in his neck and shoulder, and mild scoliosis was also present. His height was 131 cm and he weighed 28 kg which both corresponded to the 25th percentile on the growth chart.

The fasting serum lactate level was elevated; 2.7 mmol/L (*normal range: 0.5-2mmol/L*).

Blood gases showed compensated metabolic acidosis. CBC, ESR, coagulation factors, ANA, LE cell, muscle enzymes, serum ammonia and aminoacids, and cardiovascular evaluation were all normal. Visual evoked potentials demonstrated prolonged latency and raised threshold of P100-waves in both eyes. Nerve conduction studies of lower limbs were in the normal range.

Brain MRI showed two areas of ischemic infarcts in left temporal and right temporo-parietal regions, hypointense in T1 and hyperintense in T2-weighted studies.

MR angiography didn't show any vascular abnormality.

Electromicroscopic muscle biopsy revealed abnormal fibers with subsacrolemmal deposits and pleomorphic mitochondria, suggestive of mitochondrial myopathy.

We couldn't perform biochemical assays of oxidative phosphorylation enzymes and DNA analysis to evaluate mitochondrial mutations due to lack of facilities.

With a diagnosis of MELAS syndrome, we initiated treament with carnitine, vitamin B (B_1, B complex, biotin), vitamin C, vitamin K, short term prednisolone and different anticonvulsant drugs with best response to Mogadon.

With this treatment, the patient showed improvement in locomotion, cognition and seizure control during the first 6 months. However, gradually myoclonic jerks became refractory by the time of this writing.

18 months having elapsed on this treatment, the patient is still ambulatory but suffers from spasticity, difficulty in locomotion and intractable myoclonic jerks.

DISCUSSION

Pavlakis and his collegues were first to describe two cases of MELAS syndrome and reviewed 9 other reported cases classically in 1984.[6]

As mentioned, the molecular pathology concerning this syndrome is a point mutation on the mitochondrial genome, most commonly at nucleotide number 3243 encoding the tRNA for leucine.[2-4]

In about less than 10 percent of cases the mutation is at postions 3271 to 3302; however, the affected gene product with each of these mutations is the tRNA for leucine.

In about 90 percent of pedigrees, family history is compatible with maternal transmission but in 10 percent of cases no familial transmission is found, as in our cases.[2]

Patients are usually asymptomatic in infancy and have normal early development for the first several years. However, some may display muscle weakness, fatiguability and myalgia before presentation of MELAS.[3,5]

Neurological symptoms begin between infancy and late childhood. These children develop short stature and recurrent epileptic seizures which may be focal, generalized or myoclonic. They also suffer prolonged migraine-like attacks of headaches with vomiting, which are prominent in some patients. In the wake of seizures or headaches, the patient abruptly develops stroke-like episodes.

Hemiparesis can alternate from side to side. Repeated infarctions lead to gradual decline of motor, sensory and cognitive functions. There is usually a history of dementia, dysarthria and progressive auditory and visual impairment.

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Most patients eventually become deaf, blind and bedridden secondary to multiple strokes. A progressive myoclonic seizure can appear late in the course of the illness.

Systemic symptoms may result from cardiac, renal or endocrine involvement.[3] The prognosis for patients with the full syndrome is dismal and death usually occurs a few years from onset.

Laboratory findings of MELAS syndrome are variable. Most patients present with elevation of lactate and pyruvate in the blood and CSF. Lactic acidosis is an inconsistant feature that may become symptomatic intermittently. CSF proteins may be elevated. Neuroimaging may show hypodensity and swelling of the cortex in multiple areas with a predilection for parieto-occipital regions, as we observed in our 2 reported cases.

Calcium deposits may also be found in the basal ganglia, particularly in the globus pallidus.[3]

Hypoperfusion in the areas of infarct can be detected by SPECT when MRI or CT findings are normal. Brain MRI reveals the lesions more precisely than CT scan and may show cerebellar lesions which could not be detected on CT scan.

The mechanism of the stroke-like episodes is still unknown, and neuropathological studies show necrotic foci in the cortex.

The point mutation can be demonstrated in blood or muscle in mildly symptomatic or asymptomatic relatives. Blood DNA can be used to diagnose the mitochondrial deletion. This technique is especially useful in children in whom mutant mitochondrial levels in the blood are higher in relation to those in muscle.

Many cases of MELAS syndrome have an isolated complex I (NADH Q reductase) deficiency in biochemical studies of muscle mitochondria. However, multiple defects of the respiratory chain affecting complex I, III and especially IV have been documented.[3,4]

Enlargement and proliferation of mitochondria as a result of impaired respiration usually but not always show ragged red fibers in electromicroscopic study of the muscle biopsy.

Unfortunately, treatment for mitochondrial disorders remains very limited. Many agents have been given to affected individuals as therapeutic trials but their beneficial effects are not long lasting. Potential strategies include[4] correction of the metabolic milieu and avoiding exacerbating situations that lead to further compromise of mitochondrial function. This can be achieved by rapid treatment of infection, fever and avoidance of fasting and strenuous exercise.

1. Frequent or high caloric intake may be necessary to avoid the catabolic state.
2. Drugs to avoid are those that inhibit mitochondrial protein synthesis (*e.g., tetracyclines, chloramphenicol*), sequester carnitine (*valproic acid*) and inhibit the respiratory chain (*barbiturates, phenytoin*).
3. Removal of reactive oxygen with antioxidants (*e.g., vit. C, vit. E, lipoic acid*).
4. Replacement of products missing because of enzyme deficiency (complex I): sodium succinate 2g/daily and cofactor precursors such as thiamine (*vit.* B_1) 250 mg/daily, riboflavin (B_2) 100 mg/daily, biotin 5 mg bid and coenzyme Q10, 120 mg/daily, that function as part of the respiratory chain complex.
5. Low-dose synthetic steroids (*prednisolone or methyl-prednisolone*) have been found beneficial in improvement of systemic and encephalopathic symptoms of patients, including better seizure control, strengthening muscle force and lowering lactate and pyruvate levels.

Sodium dichloro-acetate 50 mg/kg/d orally every 12 hours has also been suggested to activate residual mitochondrial oxidative enzyme activity and decreasing serum lactate levels, especially in patients with severe lactic acidosis.[7] Using this agent (*DCA*) in the second case, our patient complained of loss of energy and feeling bad. Carnitine 50-100 mg/kg/d is another product that is recommended to be administered to patients with respiratory chain enzyme deficiency who develop secondary carnitine deficiency.

CONCLUSION

The knowledge of mitochondrial disease is still very new, and the recent growth of information suggests that the relevance may be much greater than current clinical diagnostic tools permit us to recognize.

The majority of palliative therapies should be viewed as temporary rather than permanent solutions. Our understanding of treatment options are woefully inadequate. For example, we don't know how to get rid of damaged mitochondria or how to restore their function. Efforts to develop gene therapy through substitution of a functional gene for a deficient one is the most important and promising area of continuing investigations.[4]

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