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Image findings in Mitochondrial encephalomyopathy, Lactic acidosis, and Stroke-like episodes (MELAS) - A rare case report

ARUNPRASAD S

Department of Radio Diagnosis,MADRAS MEDICAL COLLEGE AND GOVERNMENT GENERAL HOSPITAL

Abstract : Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome is a progressive neurodegenerative disorder caused by defects in intracellular energy production that begins in childhood, usually between two and fifteen years of age. Seizures, diabetes mellitus, hearing loss, cardiac disease, short stature, endocrinopathies, exercise intolerance, and neuropsychiatric dysfunction are common features. The most common mtDNA point mutation is an A.G transition at the tRNA Leu (UUR) 3243, causing a defect in the mitochondrial protein synthesis leads to depletion of NAD and NADH.with build up of lactic acid in brain causing neuronal death. We are presenting a rare case of MELAS in an adolescent girl with typical imaging features.
Keyword :mitochondrial disease, lacunar infarcts, encephalomyopathy, microhemorrhages, basal ganglia calcification, lactate peak

Introduction :

MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes) is a rare, multisystem disorder which belongs to a group of mitochondrial metabolic diseases. It is inherited in the maternal line. Early symptoms of the disease are varied and nonspecific, which complicates diagnosis. It is very important to slow down the progression of the disease with the appropriate treatment. tRNA mutations lead to the absence or deficit of subunits of the respiratory chain protein complexes. This results in abnormal intracellular energy production, which in turn leads to impaired function of cells, or even to their death. We would like to describe characteristic radiological features of MELAS syndrome in CT, MRI and MR spectroscopy of the brain and differential diagnosis. With the typical clinical features, the radiologists are able to effectively guide the clinician to a correct diagnosis.

Case report :

A 19 year old girl from Pondicherry with presenting complaints, started from age 12 with left sided upper and lower limb weakness which is progressively increasing. Now had bilateral sensineural deafness. History of recurrent resistant seizures noted. No history of visual disturbances. Her birth history was uneventful. Developmental milestones are normal Family history uneventful. No history of fever , rashes or altered sensorium at onset of illness. She was evaluated in various private institutions but in vain.

INVESTIGATIONS :

• Complete hemogram - normal
• RFT, LFT ,TFT – normal
• Urine for Inborn errors of metabolism – negative
• ECG, ECHO –normal
• 4 vessel Doppler – normal
• Bone marrow examination – normal
• Varicella ,JE,EBV,Herpes Ig M and IgG antibodies - negative
• ANA- negative
• Anti ds DNA - negative
• ANCA - negative
• Anticardiolipin antibody - negative
• Lupus anticoagulant - negative
• Protein C,S - negative
• Vitamin B12 – normal

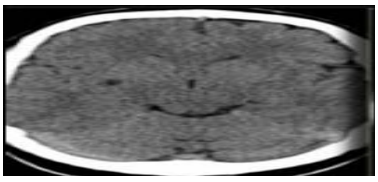
ENT EXAMINATON :

Pure tone audiometry:

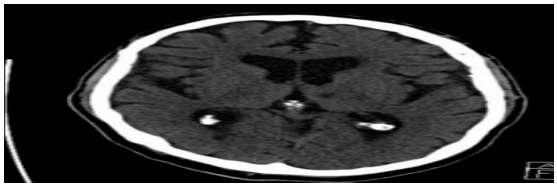
Right Ear - Total sensineural hearing loss Left Ear - Profound sensineural hearing loss Otoacoustic emissions– Absent Brain-stem evoked response audiometry– peak 5 cound not be obtained bilateral severe hearing loss

Images :

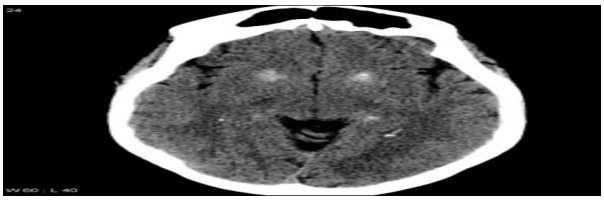
CT images showing evolving infarcts first in right gangliocapsular region , later left thalamus and last image showing bilateral basal ganglia calcification



CT taken in 2010

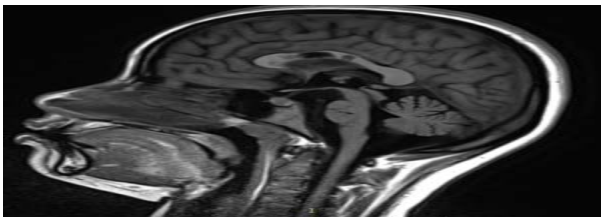


CT taken in 2012

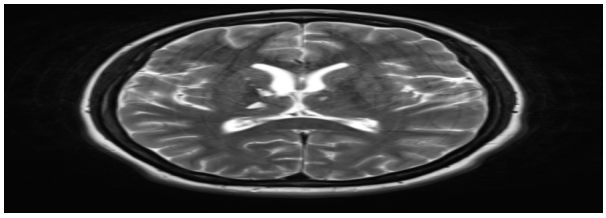


CT taken in 2015

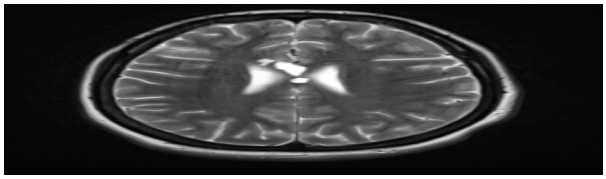
MR images showing multiple chronic infarcts involving bilateral gangliocapsular region , midbrain and corpus callosum suppresed on FLAIR images and acute infarct in right centrum semiovale region. Diffusion weighted images shows hypointense chronic infarcts and hypertense acute infarcts with only slightly low ADC values indicating vasogenic edema.Susceptibility weighted Images showing blooming basal ganglia calcifications, hypointense on PHASE images and few microhemorrhages ,hyperintense on PHASE images. on contrast no significant enhancement in these lesions. spectroscopy revealed lactate peak at 1.3 ppm



T1 sagittal

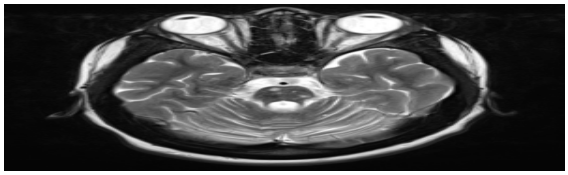


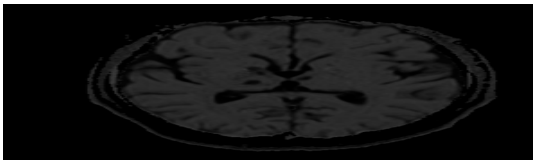
T2 Axial



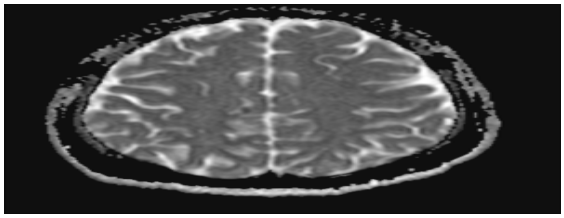
T2 Axial

FLAIR Coronal

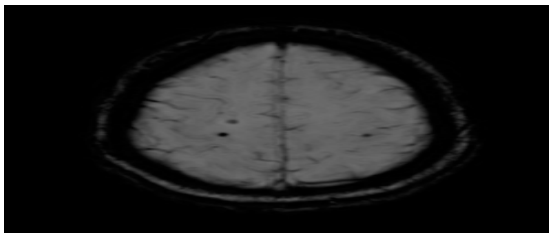




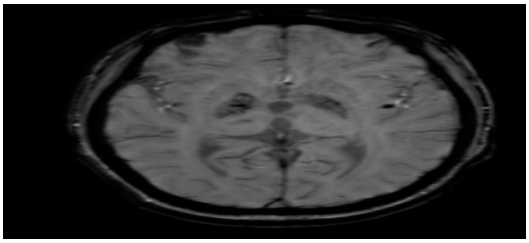
Diffusion weighted images



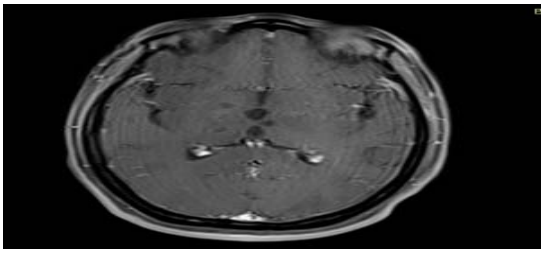
Apparent diffusion coefficient

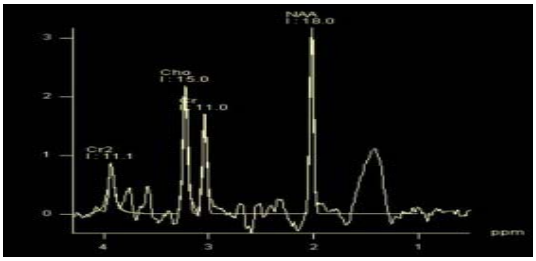


Susceptibility weighted Images



PHASE images





Spectroscopy

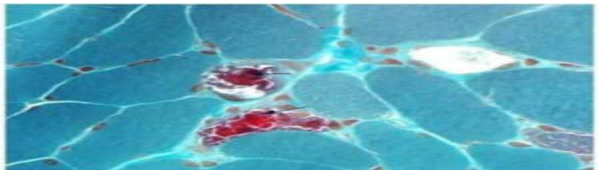
FINDINGS :
• Multiple chronic infarcts involving bilateral gangliocapsular region , midbrain and corpus callosum • Acute infarct involving right centrum semiovale region with slightly high ADC values (1.3x 10-3 mm2/s)
• Basal ganglia calcification
• Few microhemmorhages in the bilateral parietal lobe whitematter
• Spectroscopy- increased lactate levels

Diagnosis :

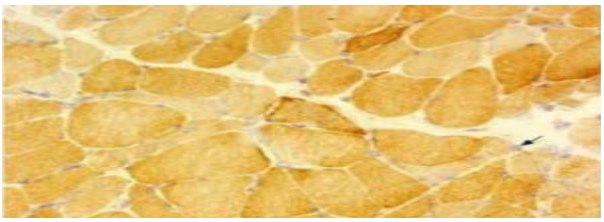
Multiple acute and chronic infarcts with basal ganglia calcification and microhemorrhages with raised lactate levels suggestive of Mitochondrial encephalomyopathy, lactic acidosis,and stroke-like episodes (MELAS)

MUSCLE BIOPSY :

• Muscle biopsy -Ragged red fibers on Modified Gomori trichrome stain
• Negative muscle biopsy findings do not preclude consideration of this syndrome.
• Ragged red fibers, common to MELAS, myoclonic epilepsy with ragged red fibers (ME RRF), Kearns-Sayer, and overlap syndromes, reflect proliferation of abnormal mitochondria under the Sarcolemma



Modified Gomori trichrome stain showing several ragged red fibers



Cytochrome c oxidase stain showing Type-1 lightly stained and Type II fibers, darker fibers, and a few fibers with abnormal collections of mitochondria

Mitochondrial DNA analysis :

Mitochondrial DNA analysis reveals point mutation is at position 3243 of the nucleotide sequence—Confirms the diagnosis

Differential diagnosis :

• Leigh's disease,
• Kearns-Sayre syndrome,
• myoclonic epilepsy with raggedred fibres
• vasculitis (moyamoya disease, Kawasaki disease)
• viral encephalitis
• Infarcts, due to embolism,dissection,CADASIL .

Discussion :

MELAS was first described in 1984 by SG Pavlakis. It is a multisystem disorder with special predilection for the nervous system and muscles.It is a mitochondrial metabolic disease inherited in the maternal line with onset of the disease between 2 and 10 years of age

Criteria :

The clinical diagnosis of MELAS is based on the following features:
1) stroke-like episodes occurring before the age of 40,
2) encephalopathy with seizures and/or dementia,
3) the presence of lactic acidosis, ragged red muscle fibres

Additional criteria :

1)Recurrent headaches
2)Recurrent vomiting

Clinical presentation :

Most common features are
– stroke like episodes
– seizures
– lactic acidosis
• encephalopathy
• dementia
• muscle weakness
• deafness

Less common symptoms include involuntary muscle spasms (myoclonus), impaired muscle coordination (ataxia), cardiomyopathy, diabetes mellitus, depression, bipolar disorder, gastrointestinal problems and kidney problems.

CT features :

• Multiple infarcts
– involving multiple vascular territories
– may be either symmetrical or asymmetrical
– parieto-occipital and parieto-temporal involvement is most common
• Basal ganglial calcification
– more prominent feature in older patients
• Atrophy

MRI features :

• **Acute infarcts :**
– Swollen gyri with increased T2 signal
– Mass effect
– May enhance
– Subcortical white matter involved
– Increased signal on DWI (T2 shine through) with little if any change on ADC: thought to represent vasogenic rather than cytotoxic oedema
• **Chronic infarcts:**
– Involving multiple vascular territories
– May be either symmetrical or asymmetrical
– Parieto-occipital and parieto-temporal most common

MR spectroscopy :

• May demonstrate elevated lactate peak at 1.3 ppm in otherwise normal appearing brain parenchyma or in CSF
• Decreased NAA spectrum and decreased NAA/Cr ratio
• Choline/Cr ratio was normal.

Complications :

• Cardiac failure
• Pulmonary embolus
• Renal failure
• Aspiration pneumonia

Treatment:

• Coenzyme Q10
• Riboflavin
• L-arginine
• Dichloroacetate
• Menadione (vitamin K-3), phylloquinone (vitamin K-1), and ascorbate have been used to donate electrons to cytochrome *c*
• Sodium succinate and Creatine monohydrate can be used
• Anti convulsants for seizure control
• Valproic acid – Not to be used
• Cochlear implant for deafness
• Supportive care - moderate treadmill training may result in improvement of aerobic capacity and a drop in resting lactate and postexercise lactate levels. Concentric exercise training may also play an important role because after a short period of concentric exercise training a remarkable increase reportedly occurs in the ratio of wild type–to–mutant mtDNAs and in the proportion of muscle fibers with normal respiratory chain activity

Conclusion :

The rarity of this disorder and the complexity of its clinical

presentation make MELAS patients among the most difficult to diagnose. Brain imaging studies require a wide differential diagnosis, primarily to distinguish between MELAS and ischemic stroke. MRI and MR spectroscopy techniques are particularly helpful in the diagnosis of this disorder.

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