CRCP Case Reports in Clinical Practice

Case Report

Journal Homepage: http://crcp.tums.ac.ir

A Rare Heteroplasmic MT-ND5 Mutation (m.13094T>C) in an Iranian Patient with Adult-Onset MELAS: Diagnostic Challenges and Therapeutic Implications

Hamed Amirifard, Mojtaba Shahbazi, Ghasem Farahmand, Maryam Kaeedi, Sanaz Heydari Havadaragh*

Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online

Citation Amirifard H, Shahbazi M, Farahmand Gh, Kaeedi M, Heydari Havadaragh S. A Rare Heteroplasmic MT-ND5 Mutation (m.13094T>C) in an Iranian Patient with Adult-Onset MELAS: Diagnostic Challenges and Therapeutic Implications. Case Reports in Clinical Practice. 2025; 10(2): 83-89. DOI:10.18502/crcp.v10i2.19903

Running Title Rare MT-ND5 (m.13094T>C) Mutation in an Iranian Adult-Onset MELAS

Article info:
Received: March 19, 2025
Revised: April 1, 2025
Accepted: April 15, 2025

Keywords:
MELAS syndrome; MT-ND5 mutation; Heteroplasmy

ABSTRACT

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS] is a rare multisystem mitochondrial cytopathy that is highly heterogeneous in severity and clinical presentation, mostly caused by diverse mutations in the mitochondrial DNA. While m.3243A>G is the most common variant, rare mutations like m.13094T>C in MT-ND5 are increasingly recognized but poorly characterized.

This report documents the case of a 37-year-old Iranian woman diagnosed with MELAS. Her clinical manifestations include recurrent episodes of stroke-like events, focal seizures, and elevated serum and CSF lactate. Mitochondrial DNA analysis [mtDNA] was positive for a very rare pathogenic point mutation [mtDNA; m.3243A>G] in the MT-ND5 gene, with a heteroplasmy level of 8.2%.

This case highlights: 1. Adult-onset MELAS with MT-ND5 mutations is underdiagnosed. 2.Low heteroplasmy (8.2%) may still cause severe phenotypes, suggesting tissue-specific effects. 3.Ethnic diversity in mtDNA mutations warrants broader genetic screening in non-classical cases.

Introduction

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS] is a rare multisystem mitochondrial cytopathy that is highly heterogeneous in severity and clinical presentation, mostly caused by diverse mutations in the mitochondrial DNA.

MELAS may appear either sporadic or familial, as an inherited disease from maternal pedigrees. Mitochondria, and subsequently the mitochondrial DNA [mtDNA], have a separate replicating system, with its genome containing about 37 genes some of which play a role in respiratory chain enzymes and aerobic respiration, affecting key cellular functions. Cells with high metabolic activity are more prone to damage. There are at least 30 gene mutations linked to MELAS syndrome [1].

A point mutation with an adenine-to-guanine transition at position 3243 of the mitochondrial DNA [mtDNA; m.3243A>G] in the mitochondrially

* **Corresponding Author:**
Sanaz Heydari Havadaragh
Address: *Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran.*
E-mail: *sanazheydari400@gmail.com*

encoded tRNA leucine 1 [*MT-TL1*] gene is responsible for approximately 80% of affected patients, and is associated with a wide phenotypic variety. This is followed by mutations in mtDNA genes coding for mitochondrial complex I, such as the *ND5* gene [2].

The level of heteroplasmy [the mixture of mutated and normal mtDNA] and the distribution of mutated mtDNA in various tissues [including skin, fibroblasts, and muscle] have been correlated with severity and phenotypic variability. This results in a range of presentations, from asymptomatic carriers to severe disease. Such heterogeneity also affects patients with the same mutation or within the same family. Leigh syndrome and early mortality are presentations seen with high levels of heteroplasmy or mutated DNA load [2].

MELAS has high overall morbidity and mortality rates and may affect individuals at any age, with the vast majority of patients experiencing their first symptom before the age of 20 years and over 90% before age 40 [3]. Despite normal early development, mitochondrial dysfunction later in life leads to multi-organ damage, including neurological (partially reversible stroke-like episodes, epilepsy, dementia, migrainous headaches, psychiatric illnesses, sensorineural hearing loss, peripheral neuropathy, ophthalmologic involvement) and non-neurological systems (cardiac, gastrointestinal, endocrine, renal, and muscle systems), with manifestations such as myopathy, exercise intolerance, cardiomyopathy, Wolff-Parkinson-White syndrome, diabetes mellitus, short stature, hypothyroidism, cyclic vomiting, etc. The pathogenesis of brain lesions in patients with MELAS differs from that seen in acute ischemic strokes and is not fully understood, but mitochondrial cytopathy and angiopathy are suggested.

Regarding this broad and nonspecific presentations it makes a diagnostic challenge that may lead to decades of delay in diagnosis and treatment [4]. Diagnostic criteria for MELAS include typical manifestations of the disease: encephalopathy, stroke-like episodes, laboratory or histological evidence of mitochondrial dysfunction and known mitochondrial DNA gene mutations [2]. Neuroimaging performed during the stroke-like episodes reveals high T_2-weighted signal areas that do not conform to the classic vascular territories (so called “stroke-like”). Most lesions are seen at the cortical region of the cerebral hemispheres less commonly at the cerebellum or basal ganglia [5]. Lactic acidemia is commonly seen and muscle biopsies show characteristic pattern of ragged red fibers due to proliferation of abnormal mitochondria.

Hereby, in the present paper, we report a case of MELAS in a middle-aged woman whose clinical course includes multiple stroke-like episodes and focal seizures. Genetic testing of blood mtDNA revealed a heteroplasmic (8.2% of total NGS reads) confirmed pathogenic mutation in the *MT-ND5* gene (m.13094T>C, p.Val253Ala), previously reported only in pediatric cases. This is the first report in an adult Iranian patient, expanding its phenotypic spectrum.

Case presentation

A previously healthy 37-year-old Iranian woman presented to our neurology department with a 6-month history of progressive neurological deterioration. Her symptoms began acutely following treatment for a dental infection (including analgesics and antibiotics), manifesting initially with episodes of confusion, visual hallucinations, and psychomotor agitation. Within 72 hours, she developed left homonymous hemianopia, which partially improved over 4 weeks.

Her initial brain MRI revealed T2/FLAIR hyperintensities in the left frontal and occipital cortices with restricted diffusion, inconsistent with vascular territories (Figure 1). Cerebral vasculature assessments, including brain MRA, MRV, and TCCD, were reassuring, excluding stenosis or occlusion of intracranial and extracranial arteries. Transthoracic

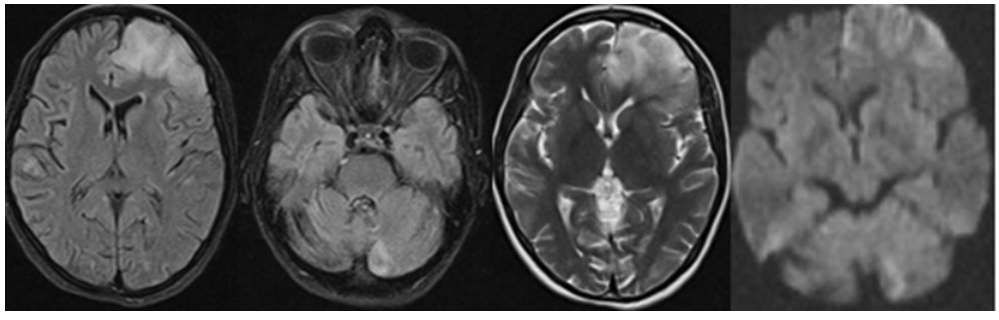

Fig. 1. First brain MRI showed hyper-intense areas in left frontal and occipital lobes, the possibility of juvenile CVA considered due to restriction pattern.

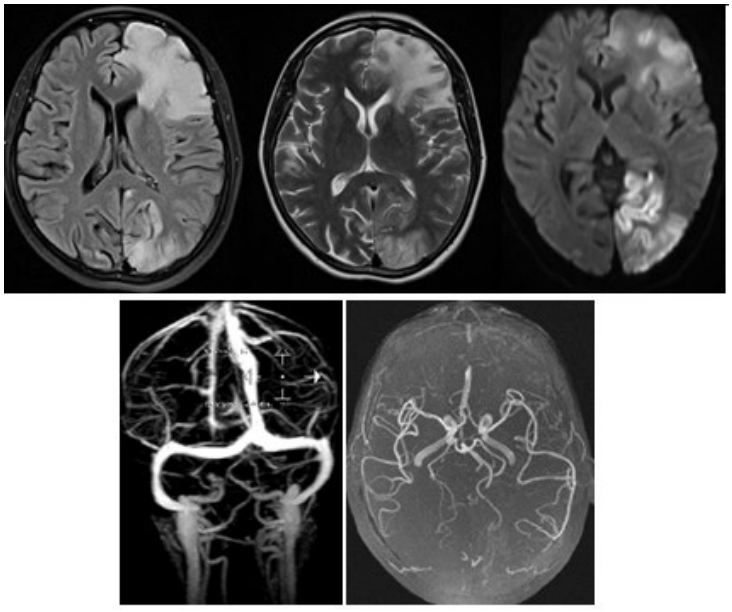

Fig. 2. Following worsening of symptoms, the second MRI done which in comparison with previous imaging revealed progression and enlargement of the brain lesions in left frontal and occipital. Normal brain MRA and MRV excluded possible large vessel occlusion or CVST.

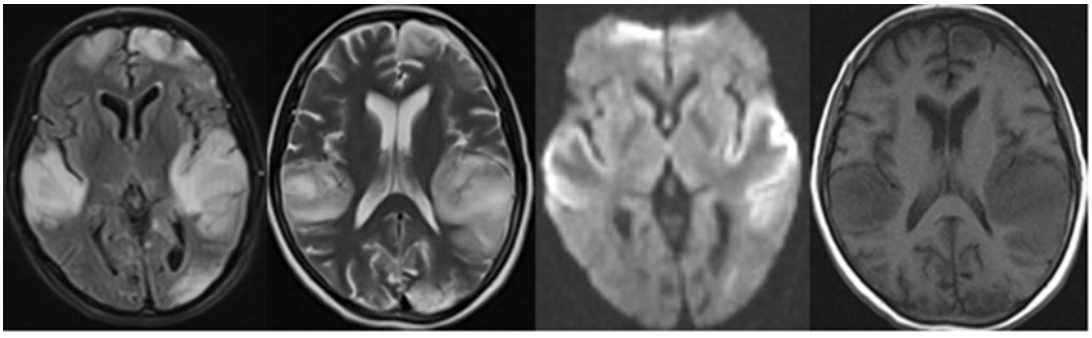

Fig. 3. Following hearing problem and Wernicke's aphasia the next brain MRI showed new bi-temporal hyper signal areas with partial restriction.

echocardiography revealed no pathological findings, and EKG monitoring showed no evidence of transient atrial fibrillation or arrhythmia. Vasculitis markers were all reported negative.

Following worsening of symptoms, follow-up MRI demonstrated enlargement of the brain lesions in the left frontal and occipital regions, associated with choline elevation relative to N-acetyl aspartate (NAA) on brain Magnetic Resonance Spectroscopy (MRS) (Figure 2). Digital Subtraction Angiography (DSA) was performed, with no abnormal findings.

Ten days later, the patient developed new-onset hearing impairment and Wernicke's aphasia over a four-day period, with subsequent partial improvement. Repeat MRI at this time revealed new bitemporal T2 hyperintense lesions with partial diffusion restriction (Figure 3). Biopsy of the brain lesions showed spongiform vacuolation of gray and white matter with reactive proliferation of astrocytes and microglia. No evidence of amyloid plaques or vasculitis was seen.

Over the subsequent six months, the patient experienced a relapsing-remitting course with progressive neurological deficits. One month prior to admission, she developed worsening dysarthria and dysphagia. On presentation to our hospital, she exhibited increasing frequency and duration of left facial twitching progressing to hemifacial clonus, without loss of consciousness during these episodes, which eventually evolved into focal status epilepticus.

The patient's history was negative for in-utero and birth complications. She was under treatment with levothyroxine and escitalopram for hypothyroidism and depression, without any history of drug abuse

or oral contraceptive use. ASA, Plavix, levetiracetam, azathioprine, L-carnitine, and Co-Q10 were recently added to her medications following recurrent stroke-like episodes, with consideration of atherosclerotic, autoimmune, or metabolic pathophysiology.

Regarding family history, she had consanguineous parents, but no similar problems were reported in her family. Her only child had died a few years earlier due to a probable metabolic disease at 22 months of age (developmental delay, developmental regression, hypotonia, elevated lactate, bilateral brainstem lesions), suspicious for Leigh syndrome, although no genetic testing was documented.

On physical examination, she had relatively short stature and was a slim woman, agitated and restless in the emergency department, with frequent and increasing focal seizures of the right side of her face and limbs. She was aphasic and had swallowing difficulty. Mild, diffusely reduced muscle bulk with generalized hyporeflexia was noted. Her resistant focal seizures were controlled with multiple antiepileptic drugs.

On admission brain MRI with and without contrast revealed multiple non-territorial bi-hemispheric and left cerebellar cortical grey and white matter-based lesions with some foci of diffusion-restriction. Same lesions at right side of medulla and bilateral midbrain were seen. Also, there were left frontal geliomalacic changes and hyper signal lesions in previous areas of injury (Figure 4). Cervical and thoracic MRI revealed no pathologic finding. In brain MRS, mild increase in Choline peak, mild decrease in N-acetyl aspartate (NAA) peak with increase Lactate in left cortex was reported. Chol/Cr ratio was up to 1/38 and this finding could rule out neoplastic lesions and suggested destructive brain lesions. CSF examination revealed normal cell count, normal protein, elevated CSF lactate concentration with normal pyruvate but the level of lactate and pyruvate was mildly increased in simultaneous blood sample. The EEG study after controlling focal seizures showed no obvious epileptiform discharge. EMG-NCS showed symmetric axonal distal sensory polyneuropathy (Figure 5).

Treatment began with metabolic cocktail including vitamins and antioxidants. Long term supplementation considered with L-arginine and L-carnitine, Co-Q10, Vit C, Vit E, B complex vitamins, alpha lipoic acid besides anti-epileptic drugs (AEDs) (Levetiracetam 1000mg BD, Phenytoin 100mg TDS, Carbamazepine 200mg TDS). Her neurological deficits subsided partially after treatment and her speech and swallowing

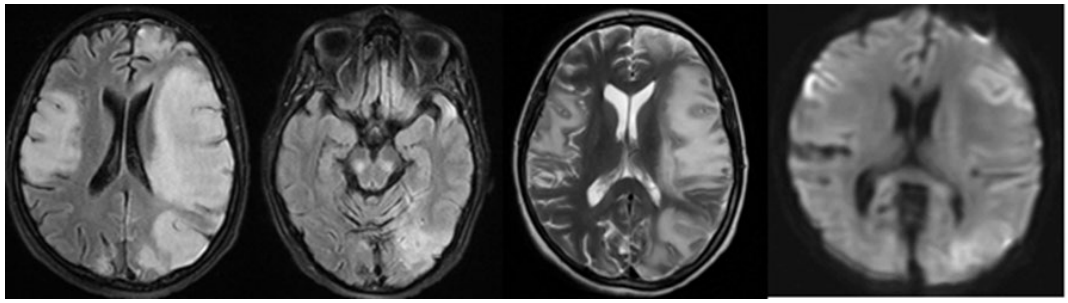

Fig. 4. Multiple non territorial bi-hemispheric and left cerebellar cortical based lesion with some foci of restriction are visible. Similar lesions at right medulla and bilateral midbrain are also visible.

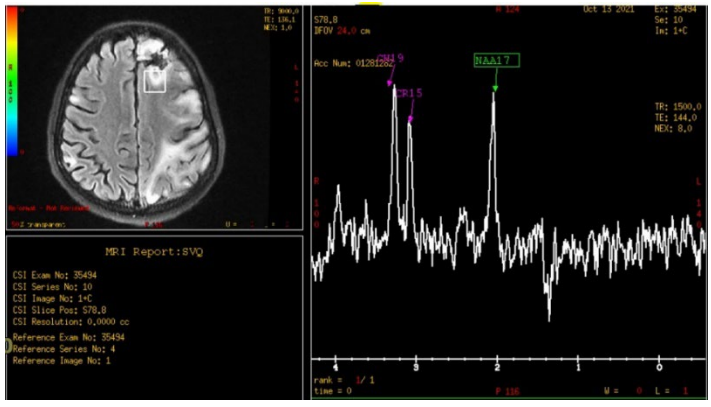

Fig. 5. In brain MRS mild increase in Choline peak, mild decrease in N-acetyl aspartate (NAA) peak with increase Lactate in left cortex reported. Chol/Cr ratio was up to 1/38 and this finding could rule out neoplastic lesions and suggested destructive brain lesions.

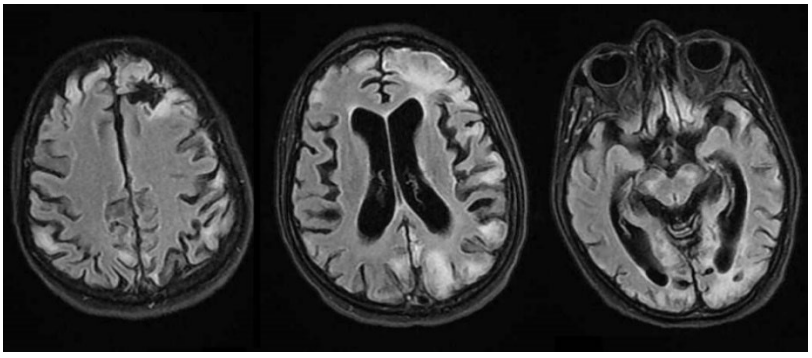

Fig. 6. Follow-up brain MRI study showed significant brain atrophy.

problems were improved dramatically. Also, avoiding dehydration and drugs like valproate, statins, ASA that could worsen her condition by interfering with mitochondrial function was considered.

The next generating sequencing (NGS) analysis was performed on whole blood revealed a heteroplasmic pathogenic variant (8.2% of total NGS reads) in the MT-ND5 gene (m.13094T>C p. Val253Ala).

During follow up the patient experienced another acute neurologic decompensation with visual object agnosia and prosopagnosia probably due to her low drug adherence which led to another admission and supportive treatment.

After 12 months of taking the medications, she needs family care but fortunately she had not any new obvious clinical attack and is still under observation. In follow-up imaging, diffuse brain atrophy incompatible to her age was detected (Figure 6).

Discussion

MELAS is an important differential diagnosis for juvenile strokes and must be considered in cases of recurrent events with atypical imaging findings, particularly when multiple areas are involved without respecting arterial territories even among middle-aged patients with vascular risk factors or concurrent macroangiopathic lesions [3,6].

Although MELAS is diagnosed with the previously mentioned criteria, the whole picture of the disease may take several years to complete. Episodes of neurologic dysfunction in a normally developed child are the classic course of the disease and are usually seen before the age of 20. In the case of late-onset disease, a febrile illness or other injuries could precipitate or hasten the clinical course. The disease course usually takes form in a relapsing and remitting pattern, with gradual neurological decline and dementia [7].

The patient and family members should receive genetic consultation and education about probable deterioration, given the unpredictable and fluctuating clinical course. In addition to periodic follow-up for detecting new symptoms or progression of the disease, MELAS patients should be assessed for cardiologic, ophthalmologic, and endocrinologic complications annually [8].

In our patient, the first symptoms began at the age of 37 years with encephalopathy and serial episodes of neurological deficit with partial improvement (aphasia, cortical visual problems…), initially investigated for vascular and cardioembolic etiologies. Eventually, the riddle was solved by reassessment of her history, alongside distinct findings on brain MRI, paraclinical evaluations, and genetic testing.

The number of molecular causes of MELAS and Leigh syndrome (LS) has steadily increased. Among these, mutations in the ND5 gene (OMIM 516005) of mitochondrial DNA are considered important [9]. Pathogenic variants in the MT-ND5 gene are associated with several mitochondrial disorders, such as Leber optic atrophy and Leigh syndrome due to mitochondrial complex I deficiency syndrome. Given the low heteroplasmy detected for the variant in our patient, testing a sample from different (ideally affected) tissues is recommended but has not been performed to date.

The MT-ND5 variant m.13094T>C (p.Val253Ala) causes an amino acid sequence change from valine to alanine at the 253rd amino acid site. This mutation has been reported in a 10-year-old boy with bilateral and painless visual loss. Gene expression varied among patient tissues. The mentioned mutation was only found in his mother's urine sample at a low percentage but was not detected in the blood or

urine of his younger brother [10]. The same variant has been observed in two other patients. One of them was a 7-year-old boy who presented with ataxia and progressive external ophthalmoplegia (PEO). Muscle biopsy did not disclose any abnormality at the histological or biochemical level. Fibroblasts were also biochemically normal but showed a significant reduction in complex I (CI) in-gel activity and other analyses [11]. This pathologic change was also reported in a 34-year-old woman who was initially suspected to have Kearns–Sayre syndrome; however, further evaluations led to a diagnosis of MELAS/Leigh syndrome.

Based on the MITOMAP database, the mentioned very rare mutation has been reported in association with MELAS/Leigh disease, LHON, ataxia plus progressive external ophthalmoplegia (PEO), myoclonus, and fatigue. In light of previous evidence and the last three cited articles, the m.13094T>C change is strongly suggested as a pathogenic variant for PEO, MELAS/LS (KSS), or LHON, according to the recommendations of the ACMG (American College of Medical Genetics) [12]. Possibly, differential gene expression and heteroplasmy in various tissue cells underlie the phenotypic diversity.

The clinical spectrum of MELAS is broadening as atypical presentations and accumulating knowledge continue to emerge. There is no specific known treatment for this progressive disease; however, metabolic cocktails have been used to improve ATP production.

To date, no definitive pharmacologic therapy has been established for the treatment of mitochondrial disorders, but several medical treatments have been suggested, including cofactors of the respiratory chain, antioxidants, and secondary biochemical correctors. The typical regimen for adults and adolescents includes coenzyme Q10 (400 mg daily), riboflavin (100 to 400 mg daily), thiamine (50 to 100 mg daily), creatine (10 g daily), and L-carnitine (990 mg daily in three divided doses). Additionally, α-lipoic acid, vitamin E, and vitamin C are antioxidants used in mitochondrial disease cocktails, although clinical data remain sparse.

Conclusion

The clinical spectrum of MELAS is broadening as atypical presentations and accumulating knowledge continue to emerge. There is no specific known treatment for this progressive disease; however, metabolic cocktails have been used to improve ATP production.

The aforementioned discoveries propose that a comprehensive analysis of the mitochondrial DNA genome should be taken into account for individuals displaying intricate neurological manifestations and suspected of having mitochondrial disease. This meticulous examination would enable the identification of more than 300 recognized pathogenic variations, such as the m.13094T>C variant.

Ethical Considerations

Ethics approval and consent to participate

The authors have no ethical conflicts to disclose. The patient's legal guardian has provided written informed consent to publish this case report and any accompanying images.

Consent for publication

Informed consent was obtained from the patient's legal guardian for publication of identifying information in an online open-access format.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due the nature of the study but are available from the corresponding author on reasonable request.

Funding Sources

The authors received no financial support for the search, authorship or publication of this manuscript.

Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for the manuscript, take responsibility for the integrity of the work as a whole, and gave final approval to the version to be published.

Acknowledgements

We would like to express our sincere gratitude to our attending physicians and our principal for providing us with the opportunity to undertake this project. Their support was instrumental in

enabling us to explore new concepts and deepen our understanding. We are truly thankful for their guidance and encouragement.

References

[1] FFan HC, Lee HF, Yue CT, Chi CS. Clinical Characteristics of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes. Life (Basel). 2021 Oct 20;11(11):1111. https://doi.org/10.3390/life11111111

[2] Lorenzoni PJ, Werneck LC, Kay CS, Silvado CE, Scola RH. When should MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes) be the diagnosis? Arq Neuropsiquiatr. 2015 Nov;73(11):959-67. https://doi.org/10.1590/0004-282X20150117

[3] Sinnecker T, Andelova M, Mayr M, Rüegg S, Sinnreich M, Hench J, Frank S, et al. Diagnosis of adult-onset MELAS syndrome in a 63-year-old patient with suspected recurrent strokes - a case report. BMC Neurol. 2019;19(1):91. https://doi.org/10.1186/s12883-019-1306-6

[4] Windpessl M, Muller P, Wallner M. Truth is a daughter of time: a case of MELAS diagnosed 25 years after initial manifestation. Oxf Med Case Rep. 2014;2014(2):24-5. https://doi.org/10.1093/omcr/omu004

[5] Tschampa HJ, Urbach H, Greschus S, Kunz WS, Kornblum C. Neuroimaging characteristics in mitochondrial encephalopathies associated with the m.3243A>G MTTL1 mutation. J Neurol. 2013 Apr;260(4):1071-80. https://doi.org/10.1007/s00415-012-6763-4

[6] Sun X, Jiang G, Ju X, Fu H. MELAS and macroangiopathy: A case report and literature review. Medicine (Baltimore). 2018 Dec;97(52):e13866. https://doi.org/10.1097/MD.0000000000013866

[7] Sunde K, Blackburn PR, Cheema A, Gass J, Jackson J, Macklin S, et al. Case report: 5 year follow-up of adult late-onset mitochondrial encephalomyopathy with lactic acid and stroke-like episodes (MELAS). Mol Genet Metab Rep. 2016 Nov 18;9:94-97. https://doi.org/10.1016/j.ymgmr.2016.08.002

[8] El-Hattab AW, Almannai M, Scaglia F. MELAS. GeneReviews® [Internet]. 2001 Feb 27 [updated 2018 Nov 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1233/

[9] Shanske S, Coku J, Lu J, Ganesh J, Krishna S, Tanji K, et al. The G13513A mutation in the ND5 gene of mitochondrial DNA as a common cause of MELAS or Leigh syndrome: evidence from 12 cases. Arch Neurol. 2008;65(3):368-72. https://doi.org/10.1001/archneurol.2007.67

[10] Emperador S, Vidal M, Hernández-Ainsa C, Ruiz-Ruiz C, Woods D, Morales-Becerra A, et al. The decrease in mitochondrial DNA mutation load parallels visual recovery in a Leber hereditary optic neuropathy patient. Front Neurosci. 2018;12:61. https://doi.org/10.3389/fnins.2018.00061

[11] Valente L, Piga D, Lamantea E, Carrara F, Uziel G, Cudia P, et al. Identification of novel mutations in five patients with mitochondrial encephalomyopathy. Biochim Biophys Acta. 2009;1787(5):491-501. https://doi.org/10.1016/j.bbadis.2009.01.002

[12] Zhao D, Hong D, Zhang W, Yao S, Qi X, Lv H, et al. Mutations in mitochondrially encoded complex I enzyme as the second common cause in a cohort of Chinese patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. J Hum Genet. 2011;56(11):759-64. https://doi.org/10.1038/jhg.2011.96