Patent foramen ovale leading to mismanagement in a mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) patient

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Abstract

We report the clinical, imaging, echocardiography and muscle biopsy findings of a patient presenting by characteristics which have not been reported in previous Melas cases. This is the first reported case of MELAS accompanying with PFO, and the first case of MELAS with the progressive pattern of ischemic lesions.

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Abstract

Introduction: Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is the most common maternally-inherited mitochondrial disorder presenting by stroke-like episodes, seizures, encephalopathy and muscle weakness.

Methods: We report the clinical, imaging, echocardiography and muscle biopsy findings of a patient presenting by unique characteristics which have not been reported in previous cases of MELAS.

Results: The reported case is a 34 year old man with the history of three times hospitalization due to muscle weakness, encephalopathy, progressive cognitive decline and gradual visual loss. Muscle biopsy revealed Ragged Red Fibers concomitant with mitochondrial disorders. PFO was found in echocardiography leading to mismanagement of this patient and MR imaging showed ischemic lesions with a progressive pattern.

Discussion: This is the first reported case of MELAS accompanying with PFO. All previous reported cases of MELAS have mentioned a fluctuating characteristic for the ischemic lesions; hence this is the first case of MELAS with the progressive pattern of ischemic lesions.

Key Words: MELAS, mitochondrial disease, muscle biopsy, clinical features

Declarations

Funding: This study has not received any financial support from any organization

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Ethics approval: This study has been approved by Shahid Beheshti Medical University research ethics committee and informed consent was obtained from the subject in this study. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate: not applicable

Consent for publication: informed consent was obtained from the subject in this study

Introduction

Mitochondrial disorders consist of a number of diseases, which are mostly due to gene mutations of mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). Clinical traits usually demonstrate as symptoms in high energy-consuming organs such as brain, skeletal muscles, myocardium and endocrine systems[1]. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is presumably the most common mitochondrial disorder, which is inherited maternally[2].

MELAS was first introduced in 1984[3], which typically presents with stroke-like episodes, seizures, short stature, encephalopathy, muscle weakness, nausea, vomiting, headaches, diabetes mellitus, exercise intoler-

ance, sensorineural hearing loss, myopathy and lactic acidosis[3,4,5,6]. Magnetic Resonance Imaging (MRI) in company with muscle biopsy and genetic studies is now the foundation of diagnosis in MELAS cases[7].

In this case report, we will review the presentation of symptoms, diagnosis challenges and follow-ups in a patient affected with MELAS. This study has been approved by Shahid Beheshti Medical University research ethics committee and informed consent was obtained from the subject in this study.

Case Report

A34- year old right-handed man was brought to the emergency department with left upper extremity weakness and severe encephalopathy. In his past medical history, multiple hospitalizations were found due to similar symptoms. The patient's first admission dates back to 7 years ago when he was admitted with bilateral visual loss, which had gradually become worsen during 20 days. He also gave history of new onset seizure and was admitted to rule out cerebral venous thrombosis (CVT).

Physical Examination revealed left homonymous hemianopia. Brain Magnetic Resonance Imaging (MRI), Magnetic Resonance Venography (MRV), and Magnetic Resonance Angiography (MRA) were done and although MRV and MRA study were normal, Brain compound tomography (CT) and MRI findings were suggestive of right temporal lobe ischemia. (Figure1) Laboratory tests which were conducted for the patient were all within normal ranges, including screening for vasculitis. Echocardiography was performed and showed Patent Foramen Ovale (PFO).

Visual field was improved, but his seizure like movements persisted and were misdiagnosed as pseudo-seizures.

6 years ago, he was admitted again because of sudden onset visual loss, which was accompanied with nausea and vomiting. Neuro-ophthalmological examinations disclosed homonymous hemianopia of right side. His vision was gradually enhanced during the one month. Other neurological examinations were unremarkable. Complete paraclinical and laboratory studies were performed including cerebrospinal fluid analysis, electrocardiogram (ECG), brain CT scan and brain MRI. All came back negative except brain MRI which demonstrated signal changes in occipital lobe. (Figure1)

Complete laboratory tests including autoimmune encephalopathy panel was done which was negative in the patient. CSF analysis revealed high lactate levels, which along with the high serum lactate level suggested the diagnosis of mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome. Other laboratory tests were normal which are summarized in Table 1.

In his last admission, the neurological physical examination revealed left side hemiplegia, significant cognitive decline (mini mental status examination: 17).

Echocardiography was performed and showed that left atrial appendage (LAA) was filled with clot, ejection fraction (EF) of 60 percent and PFO, and he received warfarin.

To confirm the diagnosis of mitochondrial disorders muscle biopsy was performed and it revealed ragged red fibers (RRF). (Figure2)

Discussion and Conclusion

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is the most common maternally-inherited mitochondrial disorder, which usually becomes symptomatic before the age of 40 years[8]. MELAS is characterized by stroke-like episodes, seizures, dementia, encephalopathy, lactic acidosis and also RRFs on muscle biopsy[9].

Previous studies reporting cases of MELAS have shown specific characteristics on brain MRI imaging of these patients. Transient stroke-like lesions have been reported in these patients, typically affecting gray matter without being restricted to vascular areas. Involvement of white matter has also been observed in MELAS, being more distinguished in periventricular white matter and centrum semiovale. All the previously reported cases of MELAS have reported a fluctuating characteristic for the lesions observed in the brain MRI[10].

The case we report here suffered from progressive cognitive decline, encephalopathy, seizures and stroke-like episodes, being compatible with the previously reported cases of MELAS. Nevertheless, this patient had some unique features, never reported in cases of MELAS so far, leading to mismanagement. Since structural heart diseases are more common in young adults with stroke[11]; to rule out the presence of any heart diseases, echocardiography was performed in our patient and patent foramen ovale (PFO) was discovered and confirmed with trans-esophageal echocardiography (TEE). This finding was first misdiagnosed as the reason for the patient's symptoms, medication was prescribed according to this finding and further investigations were postponed to his next admissions. Despite treatment with anticoagulant, the patient had had another stroke, so investigation was done again to find a cause and led to diagnosis of MELAS.

Our literature review revealed no evidence of existing PFO in MELAS cases. Johnson et al. described a MELAS patient in their case report who was once diagnosed with PFO in echocardiography which was later ruled out with TEE. The only reason they could find for the incidence of stroke in their patient was MELAS syndrome[13].

Another unique presentation in our patient was the pattern of ischemia lesions being different from the previously reported fluctuating characteristic of the lesions on MRI, lesions had a progressive pattern in this patient and every time he was admitted, new lesions were added to the old ones, without disappearing of previous lesions.

In conclusion, this is the first reported case of MELAS syndrome with PFO and progressive pattern of ischemic lesions on brain MR imaging. The presence of PFO has led to mismanagement and late diagnosis in this patient. For this reason further investigations are recommended to rule out PFO in MELAS cases presenting by stroke-like symptoms.

All procedures performed in this study were in accordance with the ethical standards of Shahid Beheshti Medical University research ethics committee and with the 1964 Helsinki Declarations and its later amendments. The study was approved by the Bioethics Committee of the Medical University of the Medical University of Shahid Beheshti.

Abbreviations:

MELAS: Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

MRV: Magnetic Resonance Venography

MRA: Magnetic Resonance Angiography

CT: Compound Tomography

PFO: patent foramen ovale

TEE: trans-esophageal echocardiography

CSF: Cerebrovascular Fluid

RRF: revealed ragged red fibers

EF: Eejection Fraction

ECG: Electrocardiogram

RBC: Red Blood Cell

WBC: White Blood Cell

Hb: Hemoglobin

MCV: Mean Corpuscular Volume

ESR: Erythrocyte Sedimentation Rate

PT: Prothrombin Time

INR: International Normalized Ratio

PTT: Partial Thromboplastin Time

BUN: Blood Urea Nitrogen

Cr: Creatinine

Na: Sodium (from Latin natrium)

K: Potassium (from Latin kalium)

CPK: Creatine phosphokinase

Alk.p: Alkaline Phosphatase

AST (SGOT): Aspartate Aminotransferase (serum glutamic oxaloacetic transaminase)

ALT (SGPT): Alanine Transaminase (serum glutamic-pyruvic transaminase)

PCO2: partial pressure of carbon dioxide

HCO3: Bicarbonate

References:

1. Wang, Y.-X. & Le, W.-D. Progress in Diagnosing Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like Episodes.*Chin. Med. J. (Engl).* **128** , 1820–1825 (2015).

2. Thambisetty, M. & Newman, N. J. Diagnosis and management of MELAS.*Expert Rev. Mol. Diagn.* **4** , 631–644 (2004).

3. Pavlakis, S. G., Phillips, P. C., DiMauro, S., De Vivo, D. C. & Rowland, L. P. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. *Ann. Neurol.* **16** , 481–488 (1984).

4. Hirano, M. & Pavlakis, S. G. Topical Review: Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes (MELAS): Current Concepts. *J. Child Neurol.* **9** , 4–13 (1994).

5. Ciafaloni, E. *et al.* MELAS: clinical features, biochemistry, and molecular genetics. *Ann. Neurol.* **31** , 391–398 (1992).

6. Ito, H., Mori, K. & Kagami, S. Neuroimaging of stroke-like episodes in MELAS. *Brain Dev.* **33** , 283–288 (2011).

7. Hirano, M. & Pavlakis, S. G. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): current concepts.*J. Child Neurol.* **9** , 4–13 (1994).

8. Sinnecker, T. *et al.* Diagnosis of adult-onset MELAS syndrome in a 63-year-old patient with suspected recurrent strokes - a case report. *BMC Neurol.* **19** , 91 (2019).

9. Song, W. J. *et al.* Twenty-one-year follow-up of variable onset MELAS syndrome with heteroplasmic nt3243A>G mtDNA mutation: A case report. *J. Genet. Med.* **16** , 31–38 (2019).

10. Saneto, R. P., Friedman, S. D. & Shaw, D. W. W. Neuroimaging of mitochondrial disease. *Mitochondrion* **8** , 396–413 (2008).

11. Williams, L. S., Garg, B. P., Cohen, M., Fleck, J. D. & Biller, J. Subtypes of ischemic stroke in children and young adults.*Neurology* **49** , 1541–1545 (1997).

12. Katsanos, A. H. *et al.* Recurrent stroke and patent foramen ovale: a systematic review and meta-analysis. *Stroke* **45** , 3352–3359 (2014).

13. Johnson, E. C. B., West, T. W., Ko, N. U. & Strober, J. B. A 41-year-old man with new headache and altered mental status. *The Neurohospitalist* **1** , 48–54 (2011).

Table 1: Summary of Patient's Laboratory results

Laboratory Data	Results
Blood Tests	**Blood Tests**
WBC	9200 /uL
Hb	12.3 g/dl
MCV	87 fL
Platelets	271000 /uL
ESR	26 mm/hr
PT	13
INR	1.3
PTT	42
BUN	21 mg/dl
Cr	1.2 mg/dl
Na	136 mEq/L
K	4.7 mEq/L
CPK	184
Alk.p	273 U/L
AST (SGOT)	17 U/L
ALT (SGPT)	28 U/L
PH	7.31
PCO2	57
HCO3	28.5
CSF Analysis	**CSF Analysis**
RBC	120
Leukocyte	10
Neutrophil	8
Glucose	103
Protein	45

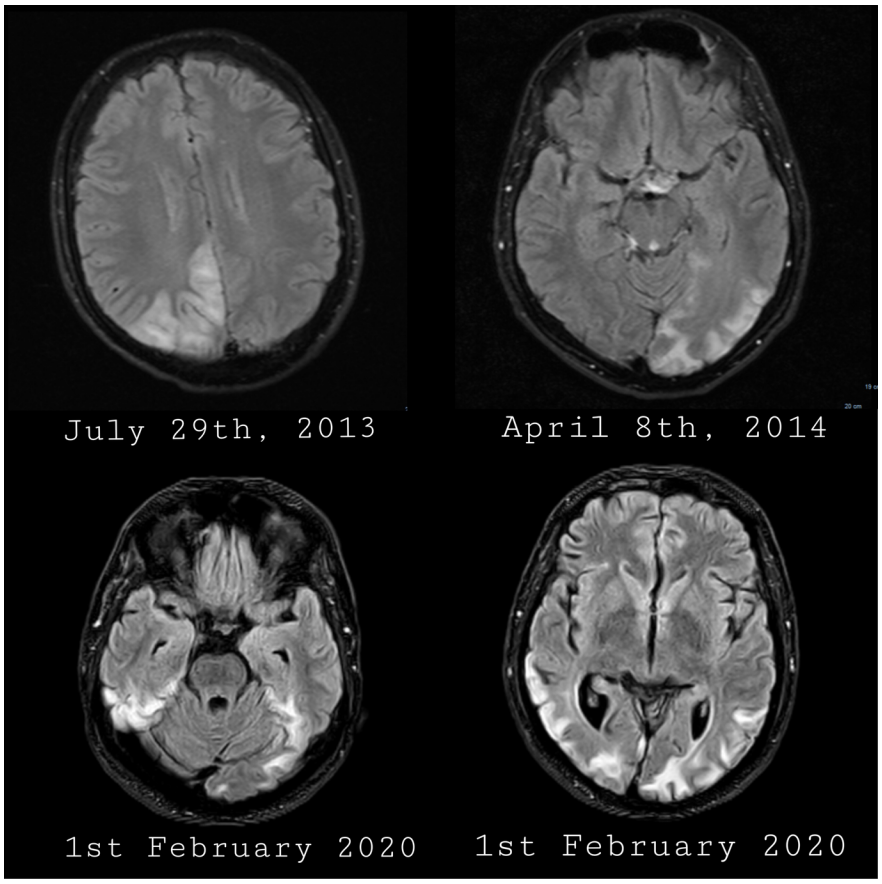

FIGURE 1

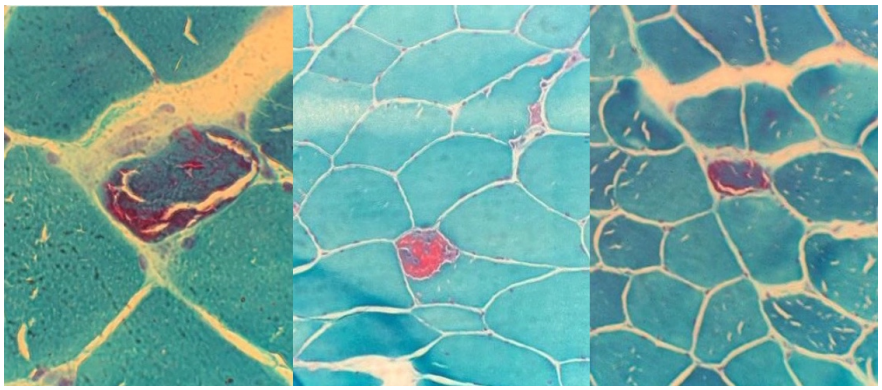

FIGURE 2

Figure captions

Fig.1 Fluid attenuated inversion recovery (FLAIR) images 2013 showing ischemic lesions in the right occipital lobe and posterior parietal regions. FLAIR images in 2014 showing left occipital and posterior parietal lobe ischemia. In 2020 FLAIR imagines revealing bilateral ischemic lesions on occipitoparietal regions and generalized brain atrophy.

Fig.2 Modified Gomori trichrome section of biopsy showed increased mithochondrial staining in the subsarcolemmal and intermyofibrillar region of muscle fibers responsible for Ragged Red appearance.