Clinical Case Reports International

Case Report
Published: 07 Jun, 2023

Melas Syndrome in the Differential Diagnosis of Encephalopathies in Older Adults: A Case Report

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Abstract

MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke) is a syndrome characterized by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes. Although usually diagnosed in the first decades of life, it is possible that manifestations are not recognized at older ages. This article aims to report the case of a 70-year-old female patient, admitted to the emergency department with delirium, and who, after ruling out organic causes, was diagnosed with a rare mitochondrial syndrome. The detailed evaluation of the case allowed the diagnosis of MELAS syndrome, with symptoms manifesting late. In this report, the importance of possible differential diagnoses regarding encephalopathies of atypical course is highlighted, even in patients with advanced ages.

Keywords: MELAS; Delirium; Mitochondrial Diseases; Older adults

Introduction

MELAS (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke) syndrome is one of the most common mitochondrial diseases, although its prevalence is rare (0.18 cases per 100,000 population/year) [1,2]. There are reports of more than 30 pathogenic variants related to this syndrome, as the m.3243A>G mutation is known as the most commonly found. It is a mitochondrial DNA pathogenic variant, and maternal relatives of patients with the syndrome may carry this mutation without showing symptoms [3]. The prognosis of patients with MELAS is quite unfavorable, with rapid and aggressive progression; thus, patients hardly ever reach advanced ages and only 1% to 6% of cases occur after the age of 40 years [4,5].

Especially for patients at older ages, MELAS syndrome manifests as cumulative multi-organ disease with broad manifestations that are relatively common to aging population including stroke-like episodes, dementia, hearing impairment, muscle weakness and diabetes. Such impairments, evaluated separately, would hardly be attributed to a rare genetic syndrome, especially in an older patient and could possibly be undiagnosed. Similarly, the syndrome may course with cognitive deterioration in different degrees, and its manifestations may mimic an acute confusion condition, that could be attributed to other cause or even and undefined etiology [1,2].

This case report aims to describe a patient with an initial clinical manifestation of delirium, which, after extensive investigation, led to a late diagnosis of MELAS syndrome. Previous cognitive alterations, history of familial migraine, neuroimaging exams, and a positive family history with the pathogenic variant m.3243A>G helped in the diagnostic conclusion.

Case Presentation

A 70-year-old white female patient was admitted to the emergency room with a history of psychomotor agitation and worsening of disorientation that began the day before admission. Her comorbidity history was referred by a son and consisted of systemic arterial hypertension, type II diabetes mellitus not properly controlled, visual and auditory impairment since the age of 50, and no history of smoking. During her medical history, it was also reported that, approximately a year before, the patient had a stroke, manifested with aphasia and transient motor deficit (right hemiparesis). Since then, she had been apathetic, with periods of disorientation and psychomotor agitation, associated with tonic-clonic seizures. She presented a neuroimaging exam that showed previous ischemic insults. In the first 24 h of hospitalization, the patient presented with decreased level of consciousness associated with generalized tonic-clonic seizures, with gasping respiratory pattern, being submitted to orotracheal intubation in the emergency room and referred to the intensive care unit for neurological monitoring and hemodynamic control.

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Received Date: *23 May 2023*
Accepted Date: *02 Jun 2023*
Published Date: *07 Jun 2023*

Citation:
Ramos RR, Matchil NL, de Oliveira BD, Kohatsu SB, Wederman D, Gattás-Vernaglia IF. Melas Syndrome in the Differential Diagnosis of Encephalopathies in Older Adults: A Case Report. Clin Case Rep Int. 2023; 7: 1556.

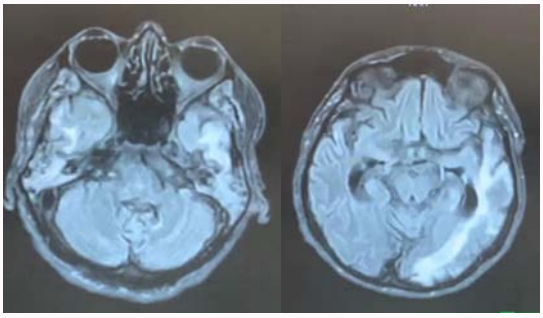

Figure 1: Skull MRI showing altered cortical-subcortical intensity of the temporal lobes, hyperintense on T2 and FLAIR, notably on the left.

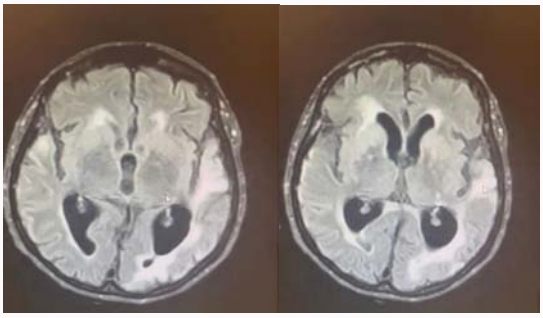

Figure 2: Contrast enhancement in thalamic capsular vascular lesion, left. Lentiform nucleus has hypersignal on FLAIR, hypoxic-ischemic lesion, dilation of the ventricular system.

During the investigation, Computed Tomography (CT) of the skull demonstrated cortical-subcortical hypodensities in the left temporal and occipital region with liquor density, suggesting encephalomalacia due to a previous ischemic event, and another temporal cortical-subcortical hypodensity on the right, suggesting another area of ischemia. Laboratory testing showed elevated blood glucose, with no evidence of bacterial infection and negative viral serological markers. Electrocardiogram showed sinus rhythm and repolarization alteration; transthoracic echocardiogram with preserved cardiac function and mild mitral insufficiency; doppler of carotids showed no obstructions. Sedation was discontinued a couple of days after but the patient did not recover consciences.

Furthermore, an electroencephalogram was performed, which showed no epileptiform seizure pattern, as well as a control CT scan of the skull, with no evidence of acute ischemic or hemorrhagic events. Thus, it was decided to collect Cerebrospinal Fluid (CSF), which showed elevated lactate (58 mg/dl - RV: 9-19 mg/dl), with no other alterations. During hospitalization, the patient underwent skull Nuclear Magnetic Resonance (MRI) due to clinical worsening, demonstrating an alteration in the cortical-subcortical intensity of the temporal lobes, hyperintense on T2 and FLAIR, notably to the left (Figure 1). Contrast enhancement in the thalamic capsular vascular lesion, on the left. Lentiform nucleus has hypersignal on FLAIR, hypoxic-ischemic lesion, dilatation of the ventricular system (Figure 2). Cranial arterial and venous angioresonance was also performed, which showed no evidence of aneurysmal dilatation or stenosis (Figure 3).

Regarding clinical evolution, the patient underwent treatment for subsequent infectious conditions, required dialysis therapy with recovery of renal function and, due to the indispensability of

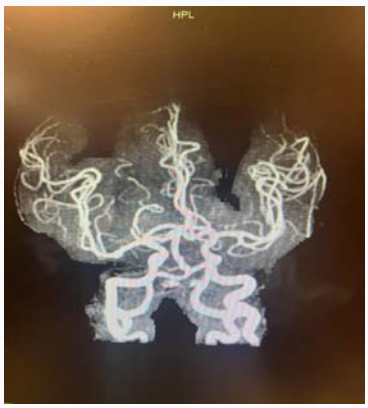

Figure 3: Cranial arterial and venous angioresonance with no evidence of aneurysmal dilatation or stenosis.

mechanical ventilation without neurological recovery, needed a tracheostomy. Approximately 90 days after admission, the patient evolved with refractivity to the instituted treatments, with progressive clinical worsening and death in the intensive care unit.

Discussion

Genetic diseases involving pathogenic variants are more prevalent in young patients, rarely developing symptoms after the age of 65. Among the diseases caused by pathogenic variants, one of the most frequent is MELAS syndrome. The manifestations of MELAS are typical in childhood, with a prevalence of 65% to 76% of affected individuals presenting symptoms until the age of 20 [4,5]. Although the onset of MELAS manifestations is more typical in young patients, this case report shows a later onset of symptoms.

MELAS syndrome is a neurodegenerative disease caused by the decreased ability of cells to produce sufficient energy in the form of Adenosine 5′-Triphosphate (ATP) [5,6]. Dysfunctional mitochondria are unable to generate enough ATP to meet the energy needs of various organs, particularly those with high energy demands, including the nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine system [4].

MELAS involves multiple organ involvement with diverse clinical manifestations, including neurological symptoms, lactic acidosis, myopathy, recurrent headaches, hearing impairment, psychiatric, renal, gastrointestinal, and endocrine disorders [7]. Symptoms develop when the metabolic demands of the body exceed the available energy supply of the defective mitochondria [8]. The most common manifestations of MELAS include altered level of consciousness, stroke-like episodes, focal or generalized seizures, migraine headaches, and dementia. Stroke-like episodes are so described because they do not present an ischemic etiology, and the affected areas do not correspond to the classical vascular distributions [6,9].

The reported patient initially presented with two important clinical manifestations: Acute onset disorientation and psychomotor agitation, attributed at first to a delirium possibly superimposed on a previous neurodegenerative condition. Acute changes in the emergency department have a high prevalence in patients over 65 years of age. Commonly, these patients are rashly diagnosed with delirium, and the organic cause is often not identified. Delirium is defined as an acute neuropsychiatric syndrome marked by cognitive and behavioral changes. It comprises a brain dysfunction, with

multifactorial etiology, of abrupt onset and fluctuating course. Delirium is a common disease, but 55% to 80% of cases are not recognized and are not documented by the clinical team treating the disease [7,10]. Initially, the management involves identifying several etiologies, such as: Psychoactive drugs, hydroelectrolytic alterations, severe pain, hypoxemia, severe anemia, infections, and significant immobility [11-14].

In the present case, after excluding the most common etiologies that trigger delirium, the presence of clinical manifestations, such as seizures, decreased level of consciousness and behavioral changes, associated with a history of recurrent headaches, psychiatric alterations and maternal family history, and neuroimaging exams, stimulates clinical reasoning focused on differential and uncommon diagnoses of other encephalopathies. After a joint investigation of the clinical, family, laboratory, and imaging history, it is concluded to be a rare mitochondrial syndrome.

As a genetic disease with hereditary characteristics, MELAS is a progressive neurodegenerative disease associated with polygenic mutations, inherited from the mother, of the mitochondrial DNA [15]. Thus, a rigorous review of family history is of great importance, especially in relation to maternal antecedents, including a history of migraine, exercise intolerance, and psychiatric alterations. In the clinical case reported here, the family history proved to be of enormous magnitude to hypothesize MELAS as a possible diagnosis.

As well as the clinical history, the radiological examination is extremely important to aid in the diagnosis, since the lesions are similar to stroke in the temporal, occipital and parietal regions. The affected areas do not correspond to the classical vascular distributions, presenting an irregular distribution, well associated with metabolic or small vessel etiology [13]. In the reported case, neuroimaging exams showed cortico-subcortical alterations in temporal and occipital regions, on the left, and thalamus, justifying the symptoms presented, such as migraine and neuropsychiatric alterations.

The management of MELAS syndrome involves a multidisciplinary approach, with lifestyle modification by means of diet and physical exercises, in addition to symptomatic treatment and treatment of complications. There is no drug therapy approved by the Food and Drug Administration or therapeutic protocol established to date for the treatment of MELAS [16-18]. Affected individuals need to be evaluated globally, with assessment of the organs most affected by the disease and should be followed up at regular intervals to monitor progression, with screening for possible complications [17]. One of the most important behavioral measures is smoking cessation since it can worsen mitochondrial dysfunction [19]. Among the treatments, supplements, such as antioxidants and cofactors, are being used in MELAS syndrome based on limited clinical trials, for example, L-arginine and citrulline, which aim to increase the availability of nitric oxide, leading to an improvement in vasodilation and, consequently, blood flow [20,21]. More studies are still needed to effectively establish a drug therapy that can interfere with the prognosis and improve the quality of life of patients with MELAS, especially those with a later diagnosis.

The case reported here demonstrates the importance of screening and initial evaluation of older patients with delirium or acute encephalopathy, reinforcing the concept of the need to perform a detailed review of the clinical history of these patients, including family history. It is emphasized the importance of expanding the range of differential diagnoses when the most prevalent and common etiologies are discarded or when the evolution of the case presents clinical manifestations that do not confirm the context of delirium. The present report also emphasizes that MELAS disease, although rare, may be diagnosed in older patients and it is possible that the incidence is underestimated due to underdiagnosis.

Conclusion

Acute neurological conditions are highly prevalent in patients over 65 years of age in the emergency department; therefore, detecting their etiology might be challenging. In cases that present with unusual clinical manifestations and atypical evolution, less prevalent diagnostic hypotheses should be considered. Mitochondrial pathologies, although more common in young people, can mimic an acute neurological condition in older adults. Although there is an unfavorable and progressive evolution, without therapeutic possibility, the diagnosis of MELAS is fundamental for the planning of patient comfort care and support in the face of unfavorable evolution. The diagnosis also allows genetic counseling of family members and its better recognition and investigation in future studies, contributing to the understanding of the causative mechanisms of this disease and therapeutic possibilities.

Acknowledgment

We thank the family members for consenting to conduct this report and Doctor friends Luciana Miranda, Luiz Abelardo and Romilson and for their support in carrying out this report.

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