Eurasian Journal of Analytical Chemistry
ISSN: 1306-3057 OPEN ACCESS 2025 20 (1): 170-172

A Case Of MELAS Syndrome In A Young Male Presenting With Acute Bilateral Cerebral Infarction: A Case Report

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Abstract
We presented the case of a 19-year-old male who arrived at the emergency department with sudden-onset involuntary movements, uprolling of eyeballs, and frothing at the mouth, suggestive of an acute neurological event. The patient was stabilized with intravenous levetiracetam and midazolam, and neuroimaging revealed bilateral acute infarcts without hemorrhagic transformation. Despite an exhaustive workup for autoimmune diseases and hypercoagulable states, no significant findings were observed. A neurology opinion and 2D echocardiography further ruled out conventional etiologies. Suspecting a mitochondrial disorder, genetic testing confirmed MELAS syndrome through exon sequencing. This case emphasizes the importance of considering mitochondrial disorders like MELAS in young patients with unexplained strokes and neurological symptoms.

Keywords: MELAS syndrome, mitochondrial disorders, young adults, bilateral infarcts, genetic testing, case report.

Introduction

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome is a rare mitochondrial disorder caused by mutations in mitochondrial DNA (mtDNA)with an estimated incidence of 1 in 4000.[1] It is characterized by multisystem involvement, including neurological deficits, metabolic derangements, and recurrent stroke-like episodes, which are hallmarks of the condition. The pathogenesis of MELAS stems from mitochondrial dysfunction, resulting in impaired energy production and tissue-specific vulnerability.[2]
MELAS syndrome is typically inherited maternally, as mtDNA is exclusively transmitted through the maternal lineage. The clinical manifestations often vary due to the heteroplasmic nature of mtDNA mutations, which leads to variable expression in different tissues.[3] The MT-ND5 gene, a component of the mitochondrial respiratory chain complex I, is among the genes frequently implicated in MELAS, contributing to the wide phenotypic spectrum of the disorder.[4]
The primary focus of treatment is symptom management through a multidisciplinary team approach, with therapeutic agents such as L-arginine, carnitine, and coenzyme Q10, selected for their potential effects on mitochondrial function.
Nevertheless, only about half of the patients exhibit typical clinical features, with considerable variability in both genetic and clinical presentations.[6] This heterogeneity makes diagnosis challenging and increases the risk of misdiagnosis. Early identification of such cases is crucial for appropriate management and genetic counseling.
This report presents a unique case of MELAS syndrome in a young male with acute bilateral cerebral infarction. It highlights the role of genetic investigations in uncovering rare mitochondrial disorders and underscores the importance of recognizing this condition in atypical presentations of stroke.

Case presentation

A 21-year-old male presented with a history of recurrent strokes. The patient belonged to a consanguineous family, raising suspicion of a genetic etiology. There was no documented history of systemic illnesses, and a family history revealed consanguinity but no similar neurological conditions among relatives. Initial neuroimaging with MRI demonstrated an acute infarct in the left occipital lobe, with no evidence of hemorrhagic

transformation. MR venography was unremarkable. Routine laboratory and immunological investigations, including 2D echocardiography, ANA, LKM, and ASMA, were within normal limits.

Given the recurrent strokes and the absence of conventional risk factors, whole-exome sequencing (WES) was performed. This revealed a heteroplasmic pathogenic variant in the *MT-ND5* gene (c.1178A>G), resulting in the amino acid substitution p.Asp393Gly, with a heteroplasmy level of 9.17%. This variant is associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome), a mitochondrial disorder. The inheritance pattern of MELAS is maternal, due to mitochondrial DNA involvement. An incidental heterozygous variant in the *LMX1B* gene (c.706G>A; p.Ala236Thr) was also identified, linked to focal segmental glomerulosclerosis 10 (FSGS10), an autosomal dominant condition. Although the *LMX1B* variant does not correlate with the current phenotype, it carries implications for future renal health.

The clinical and genetic findings established a diagnosis of MELAS syndrome. This disorder is characterized by mitochondrial dysfunction and is associated with recurrent stroke-like episodes, multisystem involvement, and metabolic derangements such as lactic acidosis. The *MT-ND5*variant identified in this case is recognized as pathogenic and has been previously reported in MELAS and Leigh syndrome. The phenotypic variability observed in mitochondrial disorders is influenced by heteroplasmy levels and tissue-specific expression.

Discussion

MELAS syndrome, though rare, is a significant cause of stroke-like episodes in young individuals, particularly in those without traditional stroke risk factors. In this case, the young male presented with acute bilateral cerebral infarction, a rare yet characteristic manifestation of MELAS syndrome. The diagnosis was confirmed by whole-exome sequencing (WES), revealing a pathogenic mutation in the MT-ND5 gene. This highlights the crucial role of genetic testing in cases of recurrent stroke without identifiable vascular risk factors, as shown by similar reports in the literature.

Several case studies have described the association between MELAS syndrome and stroke-like episodes. According to **Yatsuga S, et al**[7] stroke-like episodes are one of the cardinal features of MELAS syndrome that occur in 84-99% of affected individuals. A study by **Iizuka et al.**[8] described the involvement of the cerebral cortex in 13 of 14 episodes of stroke-like events in MELAS patients, with variable subcortical edema, particularly in the temporal, occipital, and parietal cortex. Repeated MRI scans in two episodes revealed the progressive spread of cortical lesions for weeks after the onset of symptoms. Additionally, focal epileptiform discharges on EEG and focal cortical hyperperfusion on SPECT studies were observed in many of the episodes. These findings reflect the diverse and progressive nature of stroke-like episodes in MELAS, supporting the variability of presentation seen in our case, where the left occipital lobe was affected.

The presence of a heteroplasmic MT-ND5 mutation (c.1178A>G) was pivotal in confirming the diagnosis. This variant has been previously documented in various MELAS cases, including studies by **Koga et al.**[9]and **Henry, Caitlin et al.**[10] where the MT-ND5 mutation was shown to cause phenotypic manifestations ranging from stroke-like episodes to multisystem involvement. These reportthe pathogenic nature of the identified mutation in this patient, emphasizing its role in both the neurological and systemic symptoms characteristic of MELAS syndrome.

Comprehensive management of MELAS syndrome extends beyond the acute stroke episodes to include long-term monitoring and education. As suggested by the literature, patients and their family members should receive genetic consultation and education regarding the unpredictable and fluctuating clinical course of the disease. This education is essential for understanding the potential for disease progression and fostering active participation in the management plan. In addition to periodic follow-up for detecting new symptoms or disease progression, annual assessments for cardiologic, ophthalmologic, and endocrinologic complications are recommended. These evaluations are crucial given the multisystem involvement of MELAS and the potential for complications in these domains.

The identification of a second incidental variant in the LMX1B gene (c.706G>A) highlights the complexity of genetic testing in mitochondrial disorders. Although this variant does not directly contribute to the patient's current phenotype, it warrants monitoring for potential future renal involvement, as seen in the association with focal segmental glomerulosclerosis (FSGS10). Similar incidental findings in mitochondrial disease patients have been reported, suggesting the importance of comprehensive genetic analysis in uncovering concurrent, potentially significant, conditions.

Our case underscores the challenges in diagnosing MELAS syndrome due to its clinical and genetic heterogeneity. The wide range of manifestations and varying degrees of severity based on heteroplasmy levels make early diagnosis particularly difficult. Similar to the case reported by **Sinnecker, Tim et al.,**[1] where the patient's MELAS syndrome was initially misdiagnosed as a stroke, the importance of considering mitochondrial disorders in atypical stroke presentations cannot be overstated. Genetic counseling and regular follow-ups are critical to ensure comprehensive care and to address the variable disease trajectory effectively.

Conclusion

This case emphasizes the importance of considering mitochondrial disorders, particularly MELAS syndrome, in young patients presenting with recurrent, unexplained stroke-like episodes. Genetic investigations, including whole-exome sequencing, play a crucial role in confirming the diagnosis, especially in cases where traditional risk factors for stroke are absent. The identification of pathogenic mutations in the MT-ND5 gene offers critical insights into the molecular underpinnings of MELAS syndrome and reinforces the necessity of a high index of suspicion. Clinicians should adopt a multidisciplinary approach that includes genetic counseling, patient education, and regular monitoring for multisystem complications to improve outcomes and provide appropriate care for affected families.

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