PSYCHIATRIC ASPECTS OF THE MELAS SYNDROME

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Abstract

MELAS (Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes) syndrome is a condition characterized by mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes. It is a rare, inherited, neurodegenerative disorder caused by mitochondrial dysfunction that leads to energy production disturbances. The disease most commonly begins at a younger age, before the age of 40, with episodes resembling strokes, and psychiatric symptoms can also occur in the early stages of the disease. Later on, encephalopathy may develop, which is accompanied by epileptic seizures and/or dementia. Psychiatric disorders in MELAS syndrome are present but insufficiently studied, which should be considered during diagnosis to prevent the disease from going unrecognized. Early diagnosis of any disease, including MELAS, is crucial as timely initiation of treatment significantly contributes to a more favorable course and better prognosis of the disease. When diagnosing MELAS, attention should be paid to the potential presence of psychiatric disorders.

Keywords: MELAS, genetics, diagnosis, psychiatric disorders

Introduction

MELAS syndrome is a disorder characterized by mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes. It is a rare, inherited, neurodegenerative disease caused by mitochondrial dysfunction, leading to disturbances in energy production[1]. At the core of the disorder are point mutations that occur at various genes within mitochondrial DNA (mtDNA), which is inherited through the maternal lineage. If a mother carries mutated mtDNA, she will pass on the mutation to her children, with daughters transmitting the mutation to their offspring while sons do not inherit it[2]. Mutations lead to disruptions in the synthesis of the respiratory chain proteins and oxidative phosphorylation processes, resulting in reduced ATP (Adenosine Triphosphate) synthesis[1]. In 80% of patients, the point mutation occurs at position 3.243 nucleotides (A3243G) in the mitochondrial MTTL1 gene, leading to a deficiency of the enzyme complex NADH dehydrogenase (complex and the respiratory chain).

MELAS affects the central nervous system (CNS) as well as the peripheral nervous system (PNS), musculoskeletal, cardiovascular, urinary, and other systems. The disease typically starts at a younger age, most commonly before the age of 40, and often in childhood (between the ages of 4 and 15). While the prevalence of pathological changes and clinical manifestations can vary significantly, MELAS syndrome is most commonly characterized by stroke-like episodes and encephalopathy, accompanied by epileptic seizures and dementia. The presence of lactic acidosis and a typical histopathological finding of ragged-red fibers in skeletal muscles are important for confirming the diagnosis.

Pathogenesis

In the pathogenesis of MELAS syndrome, the presence of at least 29 specific point mutations is of significance, as established so far[2]. In over 80% of cases, a substitution of adenine with guanine at the 3.243rd base pair (A3243G) of mtDNA is present. This mutation has been found in other clinical phenotypes as well, such as maternally inherited diabetes mellitus and deafness (MIDD)[2], progressive external ophthalmoplegia (PEO)[3], mitochondrial myopathy[4], Leigh syndrome[5], and others. The pathogenic events are driven by a state of chronic cellular energy deficiency, leading to mitochondrial dysfunction and their inability to generate an adequate amount of ATP (through oxidative phosphorylation) for the cell's energy demands. Consequently, the balance between lactate and pyruvate is disrupted, resulting in the accumulation of lactate, leading to chronic lactic acidosis. Pathological changes are present in a large number of organs and organ systems, resulting in disruptions in their function due to reduced production of the energy required for physiological processes to occur. In some mitochondrial cytopathies, compensatory mitochondrial proliferation occurs, as is the case in MELAS. This can aid in understanding the still incompletely understood pathogenesis of this syndrome. Several hypotheses exist: ischemic vascular (mitochondrial angiopathy)[6, 7], metabolic (generalized mitochondrial cytopathy)[8], and neurovascular, non-ischemic mitochondrial hypothesis, suggesting that both vascular and metabolic damage contributes to the pathogenesis of

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stroke-like episodes that dominate the clinical presentation[9].

The clinical presentation

The initial manifestations of the disease can occur very early in life, between the ages of two and twenty years[1]. The early development of these patients is usually normal, but later they begin to experience symptoms such as headaches (migraine-like), epileptic seizures, myopathies, hearing impairment, and episodes resembling strokes (stroke-like episodes). Other symptoms may include speech impairment, various forms of visual disturbances, growth delay, infertility, diabetes, and more. If the clinical picture is fully manifested, it can lead to a fatal outcome in early adulthood, before the age of 20.

In addition to neurological symptoms, which are the most significant, the disease can also present through other neurological and psychiatric symptoms and signs, such as depression, learning difficulties, neuropathy, and more. Of particular diagnostic and prognostic significance is the loss of hearing, which occurs in the initial stages of the disease. Studies by Hiran and Pavlakis have shown that up to 75% of patients with MELAS syndrome had varying degrees of hearing impairment[10, 11].

Dementia is a common characteristic of this syndrome, resulting from the accumulation of cortical damage and neuronal dysfunction. Impairments in cognitive functions of patients with MELAS syndrome have long been observed and described. These often involve speech, perception, memory disorders, as well as executive and other functions. Further deterioration of these functions can lead to dementia[12-15]. Hirano and colleagues[10] found that clinical criteria for dementia were present in 90% of patients with MELAS.

Diagnosis

The diagnosis is established based on laboratory analyses, muscle biopsy, radiological studies, and genetic investigations. In all mitochondrial diseases, including MELAS, an important but not pathognomonic diagnostic criterion is the measurement of lactate levels. Elevated lactate levels are a nonspecific marker of this condition. During stroke-like episodes in MELAS syndrome, radiological diagnostics such as CT and MRI are necessary. These imaging techniques can reveal asymmetric lesions resembling infarctions, most commonly localized in the cerebral cortex and in the subcortical white matter of the occipital, temporal, and parietal lobes[1, 10]. These changes are not associated with the distribution of major cerebral blood vessels, which distinguishes them from typical ischemic changes. These changes are variable and reversible[15]. Additionally, calcifications and partial or complete brain atrophy can be observed. MR spectroscopy of brain tissue and ventricles may show increased lactate levels[16].

Skeletal muscle biopsy reveals ragged-red fibers, which are irregular contours of skeletal muscle cells due to compensatory accumulation of mitochondria, leading to elevation of the muscle cell's sarcolemma. These fibers stain red when using the trichrome Gomori stain, indicating mitochondrial proliferation[17]. Electron microscopy of skeletal muscle biopsy reveals numerous enlarged, irregular mitochondria with altered cristae and the presence of paracrystalline inclusions in their matrix[18-22].

For genetic analysis of mtDNA mutations, peripheral blood leukocytes are most commonly used[23], but alternatively, skin fibroblasts, oral mucosa, and urine sediment can also be used[24]. In the majority of cases, the A3243G mutation is present, while the T3271C mutation is much less common (80% *vs* 8%)[25].

Psychiatric manifestations in MELAS

It is well-known that the brain relies heavily on oxidative metabolism, and primary disturbances at the mitochondrial level can lead to cognitive impairments, including dementia in adults and mental retardation or neuropsychological regression in children. So far, little attention has been given to the association between mitochondrial disorders and psychiatric illnesses. The literature sporadically presents descriptions of individual cases of psychiatric disorders (mostly severe depression), but there are few studies with a large number of patients who have mitochondrial disorders. Kaufman and colleagues[16] conducted a study involving over 100 individuals from 30 families, some of whom had a clinical presentation, some were asymptomatic, and a third group were oligosymptomatic carriers of the mutation. Symptoms of depression were observed in all three groups (42% *vs* 22% *vs* 29%), whereas only 7% of individuals in the control group had depression. In our studies (Lačković et al)[18-20], using the Hamilton Depression Rating Scale (HAM-D) for assessing depression, it was shown that nearly half of the participants (42.8%) exhibited signs of varying degrees of depression. In addition to the most common symptoms of depression[18, 26-29], other psychiatric disorders can also be encountered, such as bipolar disorders[30, 31], obsessive-compulsive disorders[32], episodes resembling schizophrenia, and more[33].

Although rare, psychiatric symptoms in MELAS can be accompanying manifestations and/or initial symptoms of mitochondrial dysfunction. In the study by Fattal and al[34], it was shown that in 75% of cases, psychiatric symptoms were the initial symptoms in the diagnosis of mitochondrial dysfunction, and they could last for several (even up to 10) years. There are indeed several case reports in the literature where psychiatric manifestations preceded the classic symptoms of MELAS. This highlights the complexity and variability of how mitochondrial disorders can manifest and the importance of considering them as potential underlying factors in cases of psychiatric symptoms.

Thomeer and al[35] described a case of a patient with MELAS in whom psychiatric symptoms appeared several years before the diagnosis was established. The patient was hospitalized in a psychiatric ward due to neglect of personal hygiene, aggressive and paranoid behavior. Only years later, the patient's condition worsened with hearing impairment, speech disturbances, movement problems, and the onset of epileptic seizures, leading to the diagnosis of MELAS syndrome, which was confirmed histologically. This case illustrates the challenges in diagnosing mitochondrial disorders, as they can present with psychiatric symptoms that may not immediately lead to the consideration of a mitochondrial disorder as the underlying cause.

Other unusual initial manifestations of MELAS have been described as well[36]. In the case of a 16-year-old boy, psychiatric symptoms such as unwarranted euphoria, excessive talkativeness, grandiose ideas, echopraxia, insomnia, reduced appetite, and subsequent decreased food intake appeared. This was followed by weakness in the left leg and limb rigidity. Although most of these symptoms are characteristic of MELAS, some were atypical, such as nausea and catatonia. Additionally, the absence of a family history of mitochondrial myopathy made the diagnosis challenging, and it took eight months to establish. Electron microscopy of skeletal muscle biopsy revealed an accumulation of mitochondria with abnormal appearance beneath the sarcolemma, confirming the diagnosis. This case highlights the diversity of clinical presentations of MELAS and the importance of considering mitochondrial disorders even in cases with atypical symptoms and lacking a family history of such conditions.

Obsessive-compulsive disorder (OCD) can also occur as the first manifestation of MELAS syndrome, as first described in the study by Lacey and Salzberg[32]. The aforementioned cases suggest that psychiatrists should consider the possibility of mitochondrial dysfunction when making a psychiatric diagnosis, especially in patients with atypical symptoms during psychiatric disorders, as well as in those patients who do not respond as expected to standard therapy.

Treatment options

Conventional pharmacotherapy, such as mood stabilizers, antidepressants, and antipsychotics, has beneficial effects on improving mitochondrial function[37] and psychiatric disorders in MELAS syndrome. Research indicates that the administration of agents with antioxidant and stimulatory effects on mitochondrial function (especially newer therapeutic options such as glutamate, insulin, melatonin, endopeptidases, etc.) also has a favorable impact[8]. Therapeutic regimens that include supplements, such as omega-3 fatty acids, alpha-lipoic acid, L-carnitine, coenzyme Q10, inositol, and melatonin, yield similar (positive) outcomes[37]. Furthermore, supplementation with vitamins (C, E, and B3) has been shown to have favorable effects on depressive symptoms[38, 39].

Given the specificities of the pathogenesis and clinical presentation of MELAS syndrome, as well as the involvement of various organ systems in this disease, it is necessary to make an optimal selection of pharmacological agents, dose them appropriately, and consider their potential adverse effects. The best therapeutic response in comorbid depressive episodes has been achieved with the use of duloxetine, an SNRI antidepressant (Serotonin and Norepinephrine Reuptake Inhibitor), while other antidepressants have potentially serious side effects. The SSRI antidepressant sertraline demonstrates hepatotoxicity, and tricyclic antidepressants like anafranil and imipramine result in extrapyramidal symptoms and memory impairment[40].

Valproic acid, indicated for controlling impulsivity, aggression, and epileptic seizures, can cause hepatotoxicity, steatosis, and encephalopathy. The best control of anxiety is achieved by using clomipramine and pregabalin[35, 40].

Conclusion

The results of previous research have led to several important conclusions. Firstly, it is crucial to pay attention to psychiatric disorders that occur within the context of MELAS syndrome, to apply appropriate therapy for these disorders and improve the quality of life for patients. This consideration is important, especially since the underlying causes leading to typical strokes differ in the pathogenesis of this disease. Furthermore, special attention should be given to psychiatric disorders that may manifest as initial symptoms of MELAS. Such symptoms can play a significant role in diagnosing this condition, which might otherwise remain undiagnosed or misdiagnosed. Early and accurate diagnosis of MELAS is highly important, holds prognostic significance, and prevents patients from unnecessary exposure to potentially harmful, ineffective therapeutic agents, and diagnostic procedures.

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