

# MELAS syndrome mimicking somatoform disorder

## Case Report

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**Abstract:** Background: Mitochondrial disorders are underdiagnosed and the variable symptomatology, which is not always explained by the medical test results and often includes mental symptoms, can mimic somatoform disorder.

Method: Case report of a woman with multisystemic symptomatology arising from mitochondrial dysfunction diagnosed as somatoform disorder, which impaired her eligibility for incapacity benefit.

Result: Longitudinal follow-up, the synthesis of clinical symptoms, and laboratory data of the reported case suggested mitochondrial disease. Genetic testing proved the presence of the A3243G base substitution, the most common mutation of the mitochondrial DNA, presenting as MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes) syndrome.

Conclusion: The authors wish to demonstrate the importance of multidisciplinary approach in the diagnostic process when symptoms of somatoform disorder are present.

**Keywords:** Mitochondrial Diseases • MELAS Syndrome • Somatoform Disorders • Disability Evaluation

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## 1. Background

Mitochondrial dysfunction was first described in a patient who was losing weight despite normal thyroid function [1]. Mutations of the mitochondrial DNA (mtDNA) compromise oxidative phosphorylation and cause ATP deficiency, affecting multiple organs in varying locations and with varying severity. Clinical heterogeneity makes mitochondrial disorders difficult to diagnose: patients typically see multiple specialists and have several parallel diagnoses [2]. Mitochondrial dysfunction has been proven to play a crucial role in systemic disorders such as fibromyalgia [3] and juvenile idiopathic arthritis [4], in which a high rate of depressive and somatoform

symptoms have also been described. Gardner et al [5] hypothesized mitochondrial etiology for the psychiatric symptoms in these disorders. Somatoform disorders – conversion, somatization, pain disorders and hypochondriasis – fit the definition of a physical symptomatology that mimics physical disease and may be a stigmatizing misdiagnosis for mitochondrial disorders, as it was in the case of the woman we describe.

## 2. Case presentation

The 50-year-old female patient had normal childhood development. She survived common childhood infections and at age 6 had a few months' period of frequent

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vomiting. Lab results showed acetonaemia and iron-deficiency anemia. In her teenage years, she was treated for arthritis. Around the age of 20 she had two car accidents, both resulting in multiple limb fractures and a head concussion. After the second accident, the patient complained of hearing impairment and seizure-like episodes consisting of severe episodic headaches associated with vertigo and nausea. An X-ray revealed block formation of the C5/C6 vertebrae. A computer tomography (CT) scan detected calcification of the basal ganglia; slightly decreased levels of parathyroid hormone and of serum calcium were also found. An abnormality in calcium metabolism was suspected but was not further explored, and the hearing impairment was assumed to be part of a post-concussion syndrome. Nootropics were administered without effect. Although the patient achieved secondary level education, she was unable to keep even undemanding jobs because of fatigue and headache, for which the adrenergic vasopressor pholedrine proved to be the only effective treatment. The patient was found eligible for an incapacity benefit.

A few years later, still in her twenties, inflammation of multiple organs was observed, including pyelonephritis, chronic hepatitis, pancreatitis, jejunitis and terminal ileitis resulting in the atrophy of the intestinal mucosa. She was losing weight due to lactose intolerance and malabsorption. Results of routine blood, liver, and kidney function tests were normal. The heterozygotic form of cystic fibrosis was hypothesized but was challenged by a negative sweat test. The patient also complained of dysmenorrhoea. Her endocrinologic profile was normal except for an elevated prolactin level that later normalized spontaneously. Multiple adnexitis was found and—despite hydrotubation and abrasion of the occluded tubes—total amenorrhoea and postmenopausal osteoporosis developed. Dysthymia was also diagnosed but was not treated. In her thirties, progression of the conductive hearing impairment, as well as transient paralysis of the right arm was observed. Neurological examination revealed hypotrophic limb muscles, mild truncal ataxia, and decreased deep tendon reflexes on the lower extremities.

When the patient was 40, the incapacity benefit was reevaluated and the revising physician gave her the summarizing diagnosis of somatoform disorder. No psychiatric treatment was offered, but the patient's incapacity benefit was reduced.

A few years later, apraxia and resting tremor of the hands developed and she underwent an extensive work-up. A CT scan showed progression of the calcification in the basal ganglia with confluating ischemic lesions periventricularly on both sides. A magnetic resonance

imaging (MRI) scan found multiple demyelinating lesions in the occipital lobe, the semioval center, at the side, the frontal horn, and the trigone of the lateral ventricles. Immunological investigation revealed elevated levels of albumin and immunoglobulin G (IgG) both in the serum and the cerebrospinal fluid, but oligoclonal bands were not present. Electroencephalography (EEG) revealed theta-beta paroxysms with frontal lobe dominance and occasional spikes, provoked by hyperventilation. Based on these findings, the possibility of Fahr-syndrome and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) arose. The patient was put on long-term disability status with financial support and was referred to our center for further investigation.

On assessment in our center, sequence analysis did not find alteration in the NOTCH3 gene. However, an elevated level of resting serum lactate (4 mmol/L), creatine-kinase (CK, 305 U/L) and lactate dehydrogenase (LDH, 490 U/L) were found. A neurological examination depicted bilateral ptosis, dysarthria, diffusely hypotrophic muscles, latent paresis of the right arm, distal type of hypoesthesia in all limbs, generalized areflexia and marked truncal ataxia. Psychiatric assessment showed subclinical depression with the Beck Depression Inventory-Short Form (BDI-SF) and Hamilton Depression Rating Scale (HDRS, scores of 8 and 9, respectively), structured clinical interviews for the DSM-IV (SCID-I and SCID-II) detected no psychopathology. Neuropsychological assessment measured an intelligence quotient (IQ) of 92, a performance quotient (PQ) and a verbal quotient (VQ) of 93, which is a balanced but subnormal profile. Task performance was slowed, short- and long-term memory were both impaired. Her family history was positive for head tremor in her mother, beginning at the age of 70.

Revision of the patient's medical history, the clinical picture together with laboratory data suggested mitochondrial dysfunction. The diagnosis was confirmed by myopathological and genetic investigation. A muscle biopsy showed histological alterations characteristic of mitochondrial disease such as typical ragged blue and cytochrome oxidase (COX) negative fibers (cc. 15% of all muscle fibers). Electron microscopy detected intramitochondrial paracrystallin inclusions and intermyofibrillary enlarged pleioclonal mitochondria with pathological structure. Genetic analysis of the mtDNA revealed the A3243G nucleotide substitution (with a heteroplasmy rate of 35%). This is the most common mtDNA mutation, resulting in MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes), which explains the diverse nature of the patient's symptomatology.

### 3. Discussion

Multisystemic conditions are often mistaken for somatization, whereas patients with true somatoform disorder often present to general medical settings rather than mental health settings and undergo multiple workups, pharmacological treatments, and even surgeries [6]. In our case some of the symptoms – transient paralysis of an arm or leg, hearing loss and seizures – are characteristics of conversion disorder. Others, like headache, fatigue, digestive symptoms, could be signs of somatization disorder. The initial symptoms of our patient – hearing impairment, fatigue – occurred after the motor vehicle accident when the patient was in her twenties. Based on an X-ray that showed block formation of the cervical vertebrae, and a CT scan that detected basal ganglia calcification but no other morphological alteration, hearing loss was attributed to post-concussion syndrome. Yet, this symptom, together with other transient neurological signs and with the history of multiple organ inflammation, is highly suggestive of mitochondrial dysfunction; a mitochondrial workup should have been done at that time. Not only the physicians, but also the patient, failed to seek further investigation, which could be considered as ‘belle indifference’ and might have contributed to the later misdiagnosis of somatoform disorder. The diagnostic categories of somatoform disorders are being radically reviewed for the DSM-V [7] to make them more reliable [6, 8-12], as there is currently a great heterogeneity in how physicians identify and manage this patient population [13]. Current descriptive features such as the symptoms’ relatedness to psychological factors [14] and the presence of ‘la belle indifference’ [15] have been challenged based on systematic reviews and should be weighted accordingly in the diagnostic process.

Psychiatric diagnosis in general and somatoform disorders themselves are known to cause high perceived stigma for the patients [16] even from healthcare workers [17]. For our patient the (mis)diagnosis even resulted in evident negative discrimination in the evaluation process for incapacity benefit. Headache and fatigue, the most debilitating symptoms, were considered an insufficient basis for chronic, total incapacity. ‘Subjective’ impairments are yet increasingly cited as the sole manifestation of a variety of conditions that feature prominently among claims for incapacity benefits and long-term disability [18]. The establishment of a comprehensive and reasoned approach to judging the functional impact of ‘subjective’ impairment has become an issue of great importance [18]. Objective findings in the present case were ignored, possibly due to the clinician’s frustration with not being able to understand and

integrate the symptomatology. Teamwork, consultation between different specialists in complicated multisystemic diseases, is essential.

Given the high energy demand of the central nervous system, neurologic and psychiatric symptoms are common in mitochondrial disorders. In cases misdiagnosed as somatoform disorder or when a psychiatric symptom is the first presentation of the mitochondrial disease, it is the psychiatrists’ responsibility to initiate a mitochondrial workup. An early diagnosis is essential to slow the progression of the disease and to provide proper genetic counseling to patients. Keeping the possibility of mitochondrial dysfunction in mind is important not only from the diagnostic viewpoint but also for the longitudinal follow-up of these patients to recognize mitochondrial disorder in the background of somatoform symptoms – an association that needs to be clarified by further, large-scale studies. Only a holistic view can make the proper and early diagnosis of multisystemic diseases a reality.

### 4. Conclusion

This case report suggests that in multisystemic cases where the signs of somatoform disorders are combined with laboratory abnormalities and a positive family history, mitochondrial workup is warranted to avoid misdiagnosis.

### 5. Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### 6. Competing interest

The authors declare that they have no competing interests.

### 7. Authors’ contributions

GIF carried out the psychiatric evaluation of the patient and wrote the article. VR and AG carried out molecular genetic studies. AM performed neuropsychological testing of the patient. GyB was the patient’s physician for many years and made her referral to our center. BB performed muscle biopsy and managed myopathological

analysis. MJM performed neurological examination, supervised mitochondrial workup, and has been the patient's physician since the diagnosis of MELAS was made and also helped draft the manuscript. All authors read and approved the final version of the manuscript.

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