

MELAS syndrome mimicking somatoform disorder – a case report

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Abstract

Background: Mitochondrial disorders are underdiagnosed and the variable symptomatology 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 syndrome.

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

Keywords

Mitochondrial Diseases; MELAS Syndrome; Somatoform Disorders; Disability Evaluation

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 location and severity. Due to clinical heterogeneity, mitochondrial disorders are underdiagnosed, patients typically see multiple specialists and have several parallel diagnosis [2]. Somatoform disorder is a common stigmatizing misdiagnosis as it was the case for the woman described.

Case presentation

The 50-year-old female patient had normal childhood development. She came through common childhood infections and at age 6 had a few months period of frequent vomiting. Lab results showed acetonemia 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 concussion of the head. After the second accident, the patient complained of hearing impairment. X-ray revealed block formation of the C5/C6 vertebrae and the hearing impairment was assumed to be part of a post-concussion syndrome. Nootropics were administered without effect. She also complained of severe episodic headaches, associated with vertigo and nausea. CT scan detected calcification of the basal ganglia, slightly decreased levels of parathyroid hormone and serum calcium. An abnormality in calcium metabolism was suspected but was not further explored. Although the patient achieved secondary level education she was unable to keep even undemanding jobs due to 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 hypothesised but got challenged by a negative sweat test. The patient also complained of dysmenorrhoea. Endocrinologic profile was normal except for an elevated prolactine level that normalized spontaneously. Multiple adnexitis was found and – despite hydrotubation and abrasion of the occluded tubes – total amenorrhea 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 found hypotrophic limb muscles, mild truncal ataxia, and decreased deep tendon reflexes on the lower extremities.

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

A few years later, apraxia and resting tremor of the hands developed and an extensive workup took place. A CT scan showed progression of the calcification in the basal ganglia with confluating ischemic lesions periventricularly on both sides. 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 found elevated levels of albumin and IgG both in the serum and the CSF, but oligoclonal bands were not present. EEG examinations revealed theta-beta paroxysms with frontal lobe dominance and occasional spikes, provoked by hyperventillation. Based on these findings, the possibility of Fahr-syndrome and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts

and leukoencephalopathy) arised. The patient was put on long-term disability status and was referred to our center for further investigations.

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), CK (creatine kinase, 305 U/l) and LDH (lactate dehydrogenase, 490 U/l) were found. Neurological examination depicted bilateral ptosis, dysarthria, diffusely hypotrophic muscles, latent paresis of the right arm, distal hypoesthesia in all limbs, generalized areflexia and marked truncal ataxia. Psychiatric assessment showed subclinical depression with the Beck Depression Inventory-Short Form and Hamilton Derpession Rating Scale (8 and 9 point, respectively), structured clinical interviews (SCID-I and SCID-II) detected no psychopathology. Neuropsychological assessment measured an IQ of 92, a PQ (performance quotient) and a VQ (verbal quotient) of 93 which is a balanced but subnormal profile. Task performance was slowed, short- and long-term memory were both impaired. Family anamnesis was positive for head tremor of the 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. Muscle biopsy showed histological alterations characteristic of mitochondrial disease such as typical ragged blue and COX (cytochrome oxidase) negative fibers. Electron microscopy detected intramitochondrial paracrystallin inclusions 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 (myoclonus epilepsy, lactic acidosis, stroke-like episodes), explaining the diverse nature of the patient's symptomatology.

Discussion

Multisystemic conditions are often mistaken for somatization while patients with true somatoform disorder often present to general medical settings rather than mental health settings and undergo multiple workup, pharmacological treatments and even surgeries [3]. Diagnostic subcategories of somatoform disorder are being radically reviewed for the DSM-V [4] in order to make them more reliable [3, 5-9] as there is currently a great heterogeneity in how physicians identify and manage affected patients [10]. 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. Psychiatric diagnosis in general and somatoform disorders themselves are known to cause high perceived stigma to the patients [11] even from healthcare workers [12]. 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 has yet been long cited as the sole manifestation of a variety of conditions which feature prominently among claims for incapacity benefits and long-term disability [13]. The establishment of a comprehensive and reasoned approach to judging the functional impact of 'subjective' impairment is an issue of great importance [13].

Objective findings in the presented case were ignored possibly due to the clinician's frustration of 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 disorder. Keeping in mind a possible mitochondrial dysfunction and a holistic view can make the proper and early diagnosis of multisystemic diseases a reality.

Conclusion

This case report suggests that in multisystemic cases where the signs of a somatoform disorder are combined with laboratory abnormalities - like elevated resting lactate and CK levels - and a positive family anamnesis, mitochondrial workup is warranted to avoid misdiagnosis.

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.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

GIF carried out the psychiatric evaluation of the patient and wrote the manuscript. VR and AG carried out molecular genetic studies. AM performed neuropsychological testing of the patient. GyB referred the patient to our center. BB performed muscle biopsy and reviewed the manuscript. MJM performed neurological examination, supervised mitochondrial workup and reviewed the manuscript. All authors read and approved the final version of the manuscript.

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