

Psychiatric disturbances in five patients with MELAS syndrome

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Summary

Objectives: Mitochondrial disorders of energetic metabolism (MD) represent a heterogeneous group of diseases manifesting at any age with a broad spectrum of clinical symptoms, including psychiatric disorders.

Methods: The aim of the study was to characterize psychiatric symptoms and diagnoses in five patients with MELAS syndrome between the ages of 17 and 53 years.

Results: Four of MELAS patients then harbored the prevalent mitochondrial DNA (mtDNA) mutation 3243A>G, and one patient had the mtDNA mutation 12706T>C. Three patients had positive family histories for MELAS syndrome. In one patient, depression was diagnosed as the first symptom of MELAS syndrome. Depression also preceded a stroke-like episode in one patient. Four patients had disturbed cognitive functions, confusional states occurred in three patients. One patient manifested psychotic (schizophrenia-like) symptoms.

Conclusion: Mitochondrial disorders deserve consideration as part of the differential diagnosis, especially if there is suspected involvement of other organ groups or positive family history of MD.

Key words: MELAS, depression, confusional state

Introduction

Mitochondrial disorders (MD) of energetic metabolism represent a heterogeneous group of diseases with a broad spectrum of clinical symptoms; tissues with the highest energetic demands, including the brain, muscles and heart, are most frequently affected [1, 2]. Disease causing mutations for MD have already been recognized in more than 130 nuclear or mitochondrial genes [3].

The manifestation of psychiatric disturbances occurs more frequently in patients with MD than in the general population. For example, in one group of 36 patients with MD and fatty acid oxidation disorders, the lifetime prevalence of psychiatric diagnosis was 69% [4]. In another study including 24 patients with mitochondrial myopathy in Italy, psychiatric problems developed in 60% of patients in comparison to 20% of individuals in the general Italian population [5]. A recent study in Hungary showed that, for 19 patients harboring various mitochondrial DNA mutations, the prevalence of psychiatric diagnosis was 47%, whereas similarly affected patients without mitochondrial disease only had a 30% prevalence of psychiatric diagnosis [6].

Psychiatric disturbances also are more common in patients with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) than in the general population [7,8]. Anglin et al. [9] published the comprehensive review of literature of 50 patients with MD and psychiatric symptoms, at least one half had MELAS syndrome. The aim of this study was to share our experiences with this specific syndrome and characterize psychiatric disturbances in five patients with MELAS syndrome.

Methods

Patients

Five patients with MELAS syndrome, aged 17 to 53 years, were included in this study. Four patients harbored the prevalent mitochondrial DNA (mtDNA) mutation 3243A>G, and one patient had the mtDNA mutation 12706T>C. All patients had been repeatedly examined and interviewed by senior psychiatric and metabolic specialists at our centres during their follow-ups. Retrospective clinical and laboratory data were summarized and analyzed with an emphasis on the psychiatric symptomatology. ICD-10 diagnostic criteria were used. The study was conducted in accordance with the Helsinki Declaration.

Lactate levels and enzymatic and genetic studies

To measure lactate levels, samples were deproteinized immediately by the addition of two volumes of 8% (v/v) perchloric acid. A spectrophotometric method based on the lactate dehydrogenase-catalyzed oxidation of lactate to pyruvate, in which NADH is formed, was used [10]. The respiratory chain enzyme activities and the activity of the control enzyme citrate synthase were determined spectrophotometrically [11,12]. DNA was isolated from muscle, blood, hair follicles or a buccal smear by a phenol extraction method. The presence of a prevalent mutation was analyzed by PCR-RFLP, and mitochondrial DNA genes were studied by the method of direct sequencing using the ABI 3100 Avant Analyzer (Applied Biosystems). The heteroplasmy

level of mtDNA mutations was determined by PCR-RFLP in all available samples. Corresponding mtDNA regions were amplified by PCR (Plain PP Master Mix, Top Bio, Czech Republic). After restriction of the PCR products, mixtures were loaded on an Agilent High Sensitivity DNA Chip and run in the Agilent 2100 Bioanalyzer. In each sample, intensities of individual fragments were determined by the Agilent 2100 Expert Software (all Agilent Technologies, USA). The level of heteroplasmy was calculated as a percentage of fragment intensity corresponding to the mutated mtDNA molecule.

Results

The clinical and laboratory data for the five patients with psychiatric disorders and MELAS syndrome are presented in Table 1, including age at the onset of the disease, first symptoms, complications, age at diagnosis and results of the molecular analyses. The interval between the appearance of the first symptoms and the diagnosis of MD ranged from 5 months to 28 years. Three patients had positive family histories. Two patients had epilepsy, and four experienced one or more stroke-like episodes (additionally documented by MRI or CT scan). Hypertrophic cardiomyopathy was present in two patients, visual impairment in three patients and hearing impairment in three patients. Elevated lactate levels were present in 4 patients. Psychiatric symptomatology is described in Table 2. Depressive symptomatology developed in three patients: in one as the first symptom of MELAS syndrome, in another it was associated with anxiety. Depression preceded a stroke-like episode in the third patient. Three patients suffered from cognitive decline. Three patients experienced single or recurrent episodes of confusional states (which were associated with stroke-like episodes for two of these patients). Social functioning impairments were common in a majority of our patients. One patient manifested psychotic (schizophrenia-like) symptoms, and one died due to suicide.

Case studies

Patient 1

MELAS syndrome manifested in a 16-year-old girl with migraine-like headaches and vomiting, followed by epilepsy, repeated stroke-like episodes, paleocerebellar syndrome, intermittent nystagmus and tingling sensations. Her cognitive functions declined (i.e., mild cognitive disorder). Blurred vision, hearing impairment and dizziness occurred in the course of the disease, as well. She was admitted to the psychiatric department at age 29 due to a rapidly progressive state of disorientation with hallucinations. The course of symptoms was fluctuating in severity over a 24-hr period. Her communication was not productive, and she replied to questions inadequately. Her

mood was labile; she was dysphoric most of the time and cried frequently, but sometimes she smiled unnaturally. Her behavior was infantile. She refused to open her eyes. The episode diminished gradually and was diagnosed by the attending psychiatrist as an organic schizophrenia-like disorder (F06.2). Even the chronic medication with pregabalin, olanzapin and citalopram has not prevented the need of further hospitalization in psychiatric ward. The level of heteroplasmy of the mtDNA mutation 3243A>G was 40% when measured in her hair follicles, 47% in urothelial cells, 51% in buccal cells and 11% in her blood. The laboratory analyses revealed increased creatine kinase at 8,6 μ kat/l (controls < 2,5), myoglobin at 154 μ g/l (controls < 76) and lactate in the blood at 3,12 mmol/l (controls < 2,2).

Patient 2

This patient was the mother of Patient 1. She was followed for recurrent depressive disorder (F33.2) since her fourth decade of life and was unmedicated. She committed suicide at the age of 53 years. The level of heteroplasmy of the mtDNA mutation 3243A>G was 2% in muscle, 5% in blood, 31% in urothelial cells, and 40% in hair follicles. The activities of respiratory complexes in a muscle biopsy were within the normal range.

Patient 3

This woman developed chronic fatigue syndrome, myopathy, cerebellar symptomatology, unilateral ptosis, strabismus and external ophthalmoplegia during the second and third decade of life. Deafness, cardiomyopathy and dependent diabetes mellitus type II manifested in the fifth decade of life. Her cognitive functions, hearing impairment and articulation deteriorated gradually. She did not go out and could no longer dress herself without assistance. Closer to the time of the study, she manifested a stroke-like episode marked by an acute confusional state and a loss of orientation. Organic amnesic syndrome (F04) was diagnosed. Levels of lactate in the blood were intermittently elevated (2,3-3,0 mmol/l, controls < 2,2), and creatine kinase was mildly increased (3,4 μ kat/l, controls < 2,5). The level of heteroplasmy of the mtDNA mutation 3243A>G was 50% in a muscle biopsy, 20% in hair follicles and 12% in blood. Numerous malatic lesions and cerebellar atrophy were documented by MRI. The activity of the respiratory chain complex IV in a muscle biopsy was decreased (complex IV: 5,4 nmol/min/mg protein, controls 25-120).

Patient 4

This boy failed to thrive and experienced exercise intolerance from the age of 5 years. His condition was characterized by stroke-like episodes with severe

headaches, fatigue with excessive sleepiness, hemianopsia, nystagmus, aphasia, dysarthria and word-finding problems since 13 years of age. He also developed severe depressive symptoms (F06.3) with a loss of interest and communication problems. At the age of 17 (i.e., the time of the study), four stroke-like episodes had resulted in peripheral and central hearing impairment and secondary epilepsy, external ophthalmoplegia, hypotonia, hyporeflexia, mixed polyneuropathy and myopathy and cerebellar syndrome. The patient's hypertrophic cardiomyopathy did not improve with beta blocker therapy. On therapy with citalopram, he continued to be depressed with periods of improvement. The level of heteroplasmy of the mtDNA mutation 3243A>G was 42% in his hair follicles, 30% in his blood, 78% in muscle biopsy and 93% in urothelial cells. The lactate level in his blood varied between 3 and 5 mmol/l (controls < 2,2).

Patient 5

This patient experienced the sensation of sparkling in his right visual field during adolescence along with hearing impairment and fatigue starting at age 18. One year later, epilepsy developed with variable partial and global motoric and sensory seizures with only partial response to therapy. After a stressful period, the patient withdrew from therapy, resulting in status epilepticus. An MRI revealed mild brain atrophy. Chronic depressive symptoms appeared (F06.3) with no effect of paroxetine treatment. During next three years, he experienced several ischemic stroke-like episodes accompanied by headache, aphasia, right-sided homonymous hemianopsia and central facial nerve paresis. At the age of 24, organic personality disorder (F07.0) was diagnosed. He suffered from inverted circadian rhythms and confusional states. He lost the ability to understand spoken words. Laboratory tests revealed an elevation of lactate in the blood (2,7 mmol/l, controls < 2,2) and in the cerebrospinal fluid (3,3 mmol/l, controls < 2,1 mmol/l). The activities of the respiratory chain complex I and complexes I+III in a muscle biopsy were decreased (complex I: 99 nmol/min/mg protein, controls 110-290; complex I+III: 12 nmol/min/mg protein, controls 126-316). Mutation m.12706T>C of the mtDNA was found in the *MTND5* gene encoding complex I subunit mtnd5. The level of heteroplasmy in muscle was 83% but only 3% in blood.

Discussion

MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) syndrome is a maternally inherited mitochondrial disorder with very broad clinical variability, ranging from severe forms with early manifestation, unfavourable prognosis to milder and incomplete late-manifesting forms [7,8]. Mutation 3243A>G of the mtDNA is prevalent with a surprisingly high incidence (1 in 424 in Australian

population), but other mutations may also be present [13]. The concept of heteroplasmy with varying proportions of mutant and wild-type mtDNA molecules in different tissues plays an important role in the interindividual and intergenerational variability [14]. Psychiatric symptoms are less common but are an important but often overlooked part of the clinical manifestation of MELAS syndrome [9].

MELAS syndrome and depression

The most common psychiatric symptom in patients with mitochondrial disorder (MD) is depression (e.g., 20 in a group of 71 MELAS patients [15]; 54% in a group of 36 MD patients [4]). Depression in MD patients is more common than in the general population (15-20% [16]) or in other chronic illnesses (e.g., 10-30% patients with diabetes, 35% patients with Parkinson disease) [17,18]. Recurrent depression was even a prominent psychiatric symptom in one of our MELAS patients. This presentation is possible even in children; an early study found five patients from a group of 35 children with MD suffering from depression [19]. Organic brain disorder is the most probable cause of this presentation: the onset and development of depression may be related to stroke-like episodes in some MELAS patients. Post-stroke depression was found in 36% of 1064 patients following an ischemic or hemorrhagic stroke, but the majority of these patients (80,17%) had only minor depression [20]. Eight patients manifested stroke-like episode in our group of 29 MELAS patients. As only two of them suffered from depression, which preceded the strokes for one of the patients, stroke-like episodes cannot fully explain depression in our MELAS patients. This supports the hypothesis that decreased mitochondrial respiratory rate probably participates in pathophysiology of depression [21]. Psychological factors can also be considered to be the sequelae of difficult family situations, family breakdowns or feelings of culpability in mutation-carrying mothers of affected children, as in the case of Patient 2.

MELAS syndrome and psychotic symptoms

MELAS syndrome may also include manifestations of psychotic symptoms, as in the cases of Patients 1 and 3. In the literature, there are few examples pertaining to MELAS patients (e.g.[22,23]) or other patients with various mutations in mitochondrial DNA [24] that include descriptions of similar states of psychosis, characterized by delusions, hallucinations, confusion, disorganized speech, exaggerated or diminished emotions, bizarre behavior or psychomotor excitation or stupor.

The diagnostic obstacles

The average delay from the clinical onset of the disease to the time of diagnosis confirmation in our group was 12,5 years. Demanding diagnostic testing relies on several factors: 1) a need for cooperation between clinicians and specialized biochemical and molecular laboratories; 2) an unspecific manifestation of MD during acute psychic or physical stress, often through muscle weakness or exercise intolerance (Patients 3, 4, 5), chronic fatigue (Patients 3,4,5), or head pain (Patient 4, 5), back pain, hypersomnia (Patient 4), inefficiency or vertigo [4]; 3) an often mild and incomplete form of MD – e.g., only 4% of patients from the Dutch MELAS group manifesting stroke-like episodes [15]. Even a normal lactate level in blood does not exclude the possibility of MD, especially in case of milder and lately manifesting forms [25].

A suspicion of MD with psychiatric symptomatology should be investigated particularly in patients with combined multisystemic symptoms (4/5 of our patients), patients with visual impairment or sight visual loss (3/5), hearing impairment (3/5) or cardiomyopathy (2/5). MD patients often manifest some degree of cognitive impairment (4/5). In the case of MD caused by mtDNA mutations, as in the case of MELAS syndrome, confirmation of a family history subject to the typical maternal inheritance pattern may help to hone the diagnostic approach. In case of suspicion of MELAS syndrome, it is important to analyse the prevalent mtDNA mutation not only in blood sample, where the mutation can be even missed due to low heteroplasmy, but also in other tissues (urothelial cells, buccal cells, or hair follicles).

Conclusion

Mitochondrial disorders deserve consideration as part of the differential diagnosis applied to patients with psychiatric disturbances, especially if combined with multisystemic symptoms or positive family history. Even a normal lactate level in blood does not exclude the possibility of mitochondrial disease.

Table 1. **Clinical and laboratory data in five patients with MELAS syndrome and psychiatric disturbances**

Patient	1	2	3	4	5
mtDNA mutation (the level of heteroplasmy*)	3243A>G (40% in hair follicles, 11% in blood; 47% in urothelial cells, 51% in buccal cells)	3243A>G (5% in blood, 6% in buccal cells, 31% in urothelial cells, 40% in hair follicles)	3243A>G (50% in muscle biopsy, 20% in hair follicles, 12% in blood)	3243A>G (78% in muscle biopsy, 60% in buccal cells, 93% in urothelial cells, 42% in hair follicles, 30% in blood)	12706T>C (83% in muscle biopsy, 3% in blood)
gender	♀	♀	♀	♂	♂
Age of onset (years)	16	4 th decade	17	5	18
age of diagnosis (years)	16	37	45	9	36
present age (years)	30	died at 53	60	17	36
first symptom	migraine, vomiting	depression	ptosis	failure to thrive	visual and hearing disorder
family history	positive	positive	negative	positive	negative
epilepsy	-	-	-	+	+
stroke-like episode	+	-	+	+	+
external opthalmoplegia	-	-	+	+	-
visual impairment	+	-	-	+	+
hearing impairment	-	-	+	+	+
speech impairment	-	-	-	+	+
hypertrophic cardiomyopathy	-	-	+	+	-
elevated blood lactate	+	-	+	+	+
MRI/CT changes	+	n.d.	+	+	+

* heteroplasmy represents the ratio between mutated and wild type molecules of mitochondrial DNA

Table 2. Psychiatric symptoms in five patients with MELAS syndrome

Patient	1	2	3	4	5
mtDNA mutation (the level of heteroplasmy*)	3243A>G (40% in hair follicles, 11% in blood; 47% in urothelial cells, 51% in buccal cells)	3243A>G (5% in blood, 6% in buccal cells, 31% in urothelial cells, 40% in hair follicles)	3243A>G (50% in muscle biopsy, 20% in hair follicles, 12% in blood)	3243A>G (78% in muscle biopsy, 60% in buccal cells, 93% in urothelial cells, 42% in hair follicles, 30% in blood)	12706T>C (83% in muscle biopsy, 3% in blood)
present age (years)	35	53	60	17	36
cognitive functions impairment	+	-	+	+	+
depression	-	+	-	+	+
anxiety	-	-	-	-	+
psychotic symptoms	+	-	-	-	-
confusional states	+	-	+	-	+
social functions impairment	+	-	+	+	+
suicide	-	+	-	-	-

* heteroplasmy represents the ratio between mutated and wild type molecules of mitochondrial DNA

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