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COMPLEX-IV DEFICIENCY MANIFESTING AS CEREBRAL-DOMINANT MITOCHONDRIAL MULTIORGAN DISORDER SYNDROME (MIMODS)

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1. Introduction

Recently, Arilla et al. presented a 36 years old Caucasian female, who was misdiagnosed as a pure psychiatric disorder (somatisation and conversion disorder, maniac episode, affective psychosis, "special" personality) during years until at age 35y the suspicion of a MID was raised [1] . We have the following comments and concerns.

Psychiatric abnormalities are frequently found in patients with affection of the central nervous system (CNS) as part of a mitochondrial disorder (MID) [2] . Psychiatric abnormalities have been particularly reported in patients with MELAS (table 1) [2] . The most frequent psychiatric abnormalities in MIDs include depression, cognitive impairment, anxiety, and psychosis (table 1) [2] .

The patient had obviously epilepsy [1] . Which were the results of the electroencephalography? Was ever paroxysmal activity recorded? The patient received levetirazetam as the first line antiepileptic drug (AED) [1] . From levetiracetam it is well known that it carries the greatest psychiatric and behavioural side effects (PBSE) [3] . Was the antiepileptic treatment modified after the last seizure? Was the patient ever recommended to take a ketogenic diet?

The patient obviously also had Parkinson syndrome. When were manifestations of Parkinson syndrome first recognised? Which drugs were applied? Did she ever receive dopamine-agonists? Was there a temporal content between the maniac episode and the intake of dopamine-agonists?

The authors mention persistent sensory deficits in the index patient [1] . Do they mean the hearing loss or did the patient develop a sensory deficit on the skin? In case she had hypoesthesia we should know the distribution and the quality of the deficit.

When was lactic acidosis diagnosed for the first time? At age 35 years or already earlier? Was lactate determined also in the cerebrospinal fluid (CSF)? Was ever a magnetic resonance spectroscopy (MRS) carried out to see if lactate was elevated in the brain? Was the NAA-/Cr ratio reduced on MRS? A second consequence of the case could be that patients with psychiatric disturbance should undergo neurological work-up. Most likely, lactic acidosis was already present at age 32 years during the episode of abdominal pain and vomiting.

Is it conceivable that elevated creatine-kinase (CK) was due to recurrent unwitnessed seizures? The patient obviously underwent muscle biopsy where a complex-IV deficiency was diagnosed. Were also histological, immune-histological, or ultrastructural investigations carried out?

The patient obviously had a mitochondrial multiorgan disorder syndrome (MIMODS) [4] affecting the cerebrum (epilepsy, Parkinson syndrome, psychosis, aseptic fever), intestines (nausea, vomiting, abdominal pain), and ears (hypoacusis).

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Were other organs prospectively investigated to see if there were other mild or subclinical manifestations of MIMODS? Particularly affected in addition to the brain, ears, and intestines are the eyes, heart, the endocrine organs, and the kidneys.

Since the family history was positive for hypoacusis (brother), exercise-intolerance (sister) and migraine-like headache (sister), these relatives should be investigated for MIMODS as well. Since MIDs are transmitted in the majority of the cases, we should know if any of the parents or grandparents were affected.

Overall, this case confirms that each psychiatric patient requires the neurologist and vice versa. Furthermore, the suspicion of a MID should be raised as soon as a patient develops hypoacusis without sufficient explanation and if the individual and family history is positive for key "mitochondrial" features [5] . Suspecting a MID in a "psychiatric" patient is particularly indicated if multiorgan involvement is present.

Table 1: Specific and nonspecificMIMODS presenting with psychiatric abnormalities

Disorder	Type of psychiatric abnormality	Reference
MELAS	Depression, confusion	[Magneer 2014]
MERRF	Not specified	[Altmann 2016]
Leigh syndrome	Schizophrenia-like	[Satogami 2017]
CPEO	Depression	[Smits 2011]
KSS	Impaired cognitive performance	[Bosbach 2003]
POLG1-related	Psychosis	[Hopkins 2010]
MIMODS	Malingering disease	[Finsterer 2016]
MIMODS	Autism	[Patowary 2017]
MIMODS	Psychosis	[Kytövuori 2017]

2. Author contribution

JF: design, literature search, discussion, first draft,

SZ-M: literature search, discussion, critical comments

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