Psychosis as a manifestation of cerebral involvement in mitochondrial disorders

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Abstract: - Introduction: Cerebral manifestations in mitochondrial disorders (MIDs) not only include neurological abnormalities, cognitive impairment, or dementia, but in single patients also psychiatric abnormalities, in particular psychosis. Problem formation: Is there a difference between mitochondrial and non-mitochondrial psychosis? How can mitochondrial and non-mitochondrial psychosis be delineated? Which is the prevalence of mitochondrial psychosis? Which is the therapy of mitochondrial psychosis? Problem solution: Clinically, there is often no difference between mitochondrial and non-mitochondrial psychosis. In such cases mitochondrial psychosis can be delineated from non-mitochondrial psychosis only by additional clinical and instrumental neurologic investigation and investigations for visceral abnormalities. Mitochondrial psychosis is most prevalent in MELAS syndrome, and rarely occurs in KSS, CPEO, or non-syndromic MID. The prevalence of psychosis in MELAS syndrome, the MID most frequently associated with psychosis, is 7-17%. Therapy of mitochondrial psychosis is not at variance from therapy in patients with non-mitochondrial psychosis, but mitochondrion-toxic drugs, particularly haloperidol and risperidone, should be avoided. Conclusions: MIDs should be included in the differential diagnoses of psychoses. Mitochondrial psychosis should be suspected if there is multi-system involvement and if there are structural abnormalities on cerebral imaging.

Key words: - encephalomyopathies, metabolic disease, respiratory chain, bipolar disorder, mood disorder, psychosis schizophrenia

1. Introduction

The cerebrum is the second most frequently involved organ in multi-system mitochondrial disorders (MIDs) [1]. Cerebral manifestations in MIDs include not only neurological abnormalities, cognitive impairment, and dementia, but in single patients also psychiatric abnormalities [1], in particular organic psychosis (organic mental syndrome). Nevertheless, mitochondrial psychosis is frequently misdiagnosed as non-organic psychosis, which is currently classified into two main categories, schizophrenia and bipolar disorders [2].

Schizophrenia is a devastating mental disorder characterised by disturbed thoughts and perception alongside cognitive and emotional decline and associated with severe reduction in occupational and social functioning and in coping abilities [3]. Bipolar disorder is characterised by alternating episodes of mania and depression. Subtypes include major depression and mania. An additional entity, atypical psychosis, includes those patients, who present with acute confusional state without systemic delusions, emotional instability, or psychomotor excitement or stupor [4]. Since atypical psychosis resembles organic mental syndrome, delineation between the two is often difficult and patients with mitochondrial psychosis may be easily misdiagnosed.

2. Problem formation

This study wants to highlight organic psychosis in patients with MIDs as a differential of non-organic, particular atypical psychosis, by addressing the following points: 1. which is the difference between mitochondrial and non-mitochondrial psychosis? 2. how can mitochondrial psychosis be delineated from non-mitochondrial psychosis? 3. which is the prevalence of psychosis among patients with

MIDs? 4. which is the optimal treatment of mitochondrial psychosis?

3. Problem solution

To address these questions a literature search was carried out using the search terms "psychosis", "bipolar disorder", "schizophrenia", "atypical psychosis", and "mood disorder" in combination with "mitochondrial disorder", "encephalomyopathy" and all known acronyms used to describe prominent syndromic MIDs.

3.1 Difference between mitochondrial and non-mitochondrial psychosis

To address this point, descriptions of psychiatric abnormalities in the literature were collected and opposed to the definitions of typical and atypical psychosis according to the DSMIV catalogue [4]. The main obstacle to reach this goal is the paucity of details in the description of psychiatric abnormalities in patients with MIDs. In the majority of the cases it is only mentioned that a patient presented with or developed psychosis, without providing any further details about the psychiatric presentation and conditions. This is usually the case if the study was carried out by physicians not specialised in psychiatry. Only few studies, usually carried out by psychiatrists, provide detailed description of the psychiatric abnormalities in MID patients [5]. In the following part these studies are discussed with regard to the underlying mitochondrial syndrome.

3.1.1 Mitochondrial encephalopathy, lactacidosis and stroke-like episode (MELAS) syndrome

MELAS syndrome is the most frequent of the mitochondrial syndromes and in 80% of the cases due to the 3243A>G mutation in the tRNA(Leu) of the mitochondrial DNA (mtDNA). Among syndromic and non-syndromic MIDs psychiatric abnormalities were reported most frequently in MELAS patients.

3.1.1.1 Case series

In a study on 45 patients with MELAS due to the 3243A>G mutation psychiatric symptoms were frequently found [6]. In a study on 14 MELAS patients a schizophrenia-like psychosis was reported in one of them (7%) [7]. The 3243A>G mutation was also found in the cerebrum of two patients with schizophrenia and one with bipolar disorder [8]. Functional psychosis was also a feature of a group of diabetic patients carrying the 3243A>G mutation in a Japanese study [9]. In two patients with MELAS due to the 3243A>G mutation obsessive-compulsive disorder was diagnosed, which responded only poorly to standard therapy [10].

3.1.1.2 Case reports

A 55yo female carrying the 3243A>G mutation developed progressive cognitive decline, seizures, stroke-like episodes, cortical blindness, recurrent falls, severe dementia, episodes of agitation, and acute psychosis [11]. MRI showed T2-hyperintensities involving the temporal, parietal and occipital lobes bilaterally, and mild atrophy of the brainstem and cerebellum [11]. In a 53yo female, the 3243A>G mutation manifested phenotypically as psychosis and myopathy during 10y [12]. Autopsy showed an Alzheimer-like brain pathology with diffuse senile plaques and neurofibrillar tangles in the parahippocampal gyrus [12]. In a 47yo female with schizophrenia, migraine, deafness, ischemic stroke, and intestinal pseudo-obstruction requiring hemicolectomy, the 3243A>G mutation was detected. Brain autopsy showed mild diffuse atrophy, diffuse cortical gliosis, bilateral basal ganglia calcification, and atherosclerosis [13]. Psychosis was also a phenotypic feature in another MELAS patient carrying the 3243A>G mutation. Cerebral MRI typically showed lesions in the parieto-occipital grey matter involving the adjacent white matter and deep white matter in a watershed distribution [14]. In another MELAS patient schizophrenia-like symptoms preceded the diagnosis for years [5]. At age 22y she presented for the first time with temper tantrums, paranoid ideation, and behavioural disinhibition with vague ideas of reference [5]. During the following years she developed paranoid delusions, affective instability, disturbed impulse control with aggressive incidents, auditory hallucinations, and sometimes suicidal behaviour necessitating a closed ward [5]. Additionally, she developed epilepsy, hypoacusis, aphasia, apraxia and

bradyphrenia but never muscular manifestations [5]. CT scans of the cerebrum showed hypodensities in either the right or left temporo-occipital region. In a patient with MELAS due to the 3243A>G mutation, manifesting as deafness, myopathy, syncope, sensory neuropathy, dysgeusia, tremor, and upward gaze palsy, a first psychotic episode with hallucinations and delusion developed not before age 53y [15]. In a 17yo girl with MELAS due to the 3243A>G mutation depressed mood, loss of interest in activities, and catatonic features developed together with psychomotor retardation and hypersomnia [16].

3.1.1.1.3 No mutation reported

In a patient with MELAS syndrome, a schizophrenia-like mental disorder developed in addition to myopathy, SLE, and dementia [17]. Autopsy showed a SLL, white matter fibrillary gliosis, focal demyelination, spheroid bodies within the spinocerebellar tracts, and degeneration of the posterior columns [17]. A patient with a typical MELAS phenotype additionally presented with encephalopathic psychosis [18]. Autopsy in a patient with MELAS syndrome and schizophrenia-like psychosis revealed widespread infarct-like lesions over the entire cortex, diffuse fibrillary gliosis of the entire cerebral and cerebellar white matter, and marked degeneration of the posterior columns and spinocerebellar tracts [17]. In a 32yo patient with MELAS syndrome transient visual hallucinations occurred and were not attributable to epileptic activity [19].

3.1.2 Kearns-Sayre syndrome (KSS)

Psychosis was also reported in a single patient with Kearns-Sayre syndrome, without providing detailed description of the psychiatric abnormalities [20].

3.1.3 Chronic progressive external ophthalmoplegia (CPEO)

Mood disorder is a characteristic manifestation in several families with autosomal CPEO, caused by mutations in the POLG1, ANT1, or twinkle genes [21].

3.1.4 Non-syndromic mitochondrial disorders

In a single patient with non-syndromic MID, mania was the initial manifestation of the disease [22]. In a 37yo male with muscle biopsy proven non-syndromic MID, schizophrenia and dementia were present during 8y [23]. Psychotic symptoms completely resolved after some months upon discontinuation of haloperidol and administration of coenzyme Q and idebenone [23]. In a 39yo patient with a mtDNA deletion psychiatric abnormalities were the only clinical manifestations of the disease at onset [24]. A 16yo girl with MID received risperidone for mood liability and impulsivity [25]. Shortly afterwards she developed paranoid ideation, profound psychomotor retardation, depression and fatigue [25]. Discontinuation of risperidone resulted in complete resolution of the problems within 48h [25]. Psychosis and dementia were also the presenting feature in another MID patient [26]. Psychiatric symptoms were the predominant manifestation of a patient with MID due to a mtDNA point mutation, who additionally developed diabetes [27]. In a Spanish family harbouring the mtDNA 3303C>T mutation, mitochondrial myopathy and cardiomyopathy was associated with psychiatric abnormalities [28].

3.1.5 Mitochondrial abnormalities in patients with psychosis

There is growing evidence that there is mitochondrial dysfunction in patients with schizophrenia, bipolar disorder, or major depression [8,21,29,30]. This evidence comes from imaging, electron microscopy, genotyping, gene expression, and sequencing studies [30].

Impaired oxidative phosphorylation (OXPHOS), which supplies 95% of the total cellular energy requirement [3], has been reported in several cerebral regions and also in platelets of patients with schizophrenia [3]. In patients with bipolar disorder there is frequently maternal inheritance, abnormal P-MR spectroscopy, or increased frequency of the 4977bp deletion. Also reported were abnormal morphology, size and density of mitochondria in the brain of patients with schizophrenia [3,29]. Other studies showed an association between bipolar disorder and the 10398A mtDNA polymorphism, the 3644C

mtDNA mutation and mutations in the FDUFV2 gene [21]. In patients with bipolar disorder mRNA of the FDUFV2 gene was up-regulated and down-regulated in patients with schizophrenia [31]. In post-mortem brains increased levels of the 3243A>G mutation and altered expression of mtDNA genes have been reported [21]. In a study on 77 patients with schizophrenia, bipolar disorders, and major depression the frequency of mtDNA polymorphisms in the dorsolateral prefrontal cortex was 22% higher in patients with schizophrenia as compared to controls [29]. In a study on 16 patients with schizophrenia and 15 patients with bipolar disorder CSF lactate was elevated [32].

3.2 Diagnosis of mitochondrial psychosis

Because of the similarities between mitochondrial psychosis and atypical psychosis delineation between the two entities is often difficult. Helpful for the differentiation is, in addition to the psychiatric investigations, a clinical neurologic investigation. If indicative of a MID, comprehensive diagnostic work-up is indicated, which also depends on the organs affected in addition to the cerebrum. If the cerebrum is affected, imaging, particularly cerebral CT, MRI, MR-angiography, H-MR spectroscopy, or SPECT, and EEG may be helpful. If the skeletal muscle is involved, investigations for mitochondrial myopathy should be carried out. If organs other than the cerebrum or the muscle are affected, appropriate investigations are necessary.

Features, which may delineate atypical psychosis from mitochondrial psychosis are CNS abnormalities other than psychosis, an MRI showing structural abnormalities, an abnormal EEG showing paroxysmal activity, or affection of organs other than the cerebrum. Psychosis in MID may be accompanied by cognitive impairment, hemisyndrome, visual impairment, speech and swallowing problems, ataxia, dystonia, spasticity, or Parkinson syndrome [1]. Cerebral MRI may show stroke-like lesions, focal or diffuse demyelination, laminar cortical necrosis, focal or diffuse atrophy, microbleedings, ischemic lesions, cysts, or focal calcifications [1]. If there is mitochondrial psychosis in the absence of evident morphological abnormalities on MRI, H-MRS or investigations for visceral involvement may be helpful. The EEG may be normal or may show focal or diffuse slowing, or focal or generalised paroxysmal activity.

3.3 Prevalence of mitochondrial psychosis

Though psychosis has been repeatedly reported in patients with MIDs, there is hardly any information available from the literature concerning the prevalence of psychosis in patients with MID. Particularly prospective studies concerning the frequency of psychotic episodes in MIDs are lacking. In a study on 18 MELAS patients, three presented with psychosis (17%) [26]. Among a group of 14 MELAS patients, schizophrenia-like psychosis was reported in 7% of them [7]. What else can be depicted from the literature is that MELAS syndrome is the MID most frequently associated with psychotic episodes. In a study on diabetic MID patients carrying the 3243A>G mutation ambiguous psychiatric symptoms of functional psychosis were frequently described in several of them [9].

3.4 Therapy of mitochondrial psychosis

Therapy of psychosis in patients with MID is principally not at variance from treatment of psychosis in non-mitochondrial patients. However, mitochondrion-toxic medication should be strictly avoided if possible. These include valproic acid, phenytoin, barbiturates, halothane. isoflurane, sevoflurane, bupivacain, articain, fibrates, statines, biguanides, thiazolidinediones, amiodarone, β-blockers, chloramphenicol, tetracyclines, zidovudine, carboplatin, doxorubicin, ifosamide, interferon, acetyl-salicylic-acid, and dichloracetate. Neuroleptics to which adverse reactions have been reported in MID patients or which are mitochondrion-toxic, include haloperidol [23], risperidone, chlorpromazine, and quetiapine [25]. There is no general agreement on the therapy of psychosis in patients with MID. However, patients with MID and psychosis may profit from coenzyme Q, idebenone, L-arginine, L-carnitin, edaravone, dichloracetate [33], and riboflavin [34].

In a 37yo male with an 8y-history of schizophrenia and dementia, administration of haloperidol resulted in hyperpyrexia and cataplectic rigidity [23]. MID was diagnosed

upon muscle biopsy. Concerning the psychosis, the patient profited significantly from discontinuation of haloperidol and administration of coenzyme Q and idebenone, such that after some months psychotic symptoms completely resolved [23].

4. Conclusion

Mitochondrial psychosis needs to be differentiated from non-mitochondrial psychosis in terms of diagnosis and therapy. Though there is clinically hardly any difference between mitochondrial and non-mitochondrial psychosis, there may be abnormal clinical and instrumental neurologic investigations and investigations for visceral abnormalities, which are frequently present in multi-system MIDs with psychosis. Mitochondrial psychosis should be particularly suspected if there are additional CNS abnormalities on clinical investigation or MRI or if the phenotype presents with visceral involvement. When applying anti-psychotic therapy, mitochondrion-toxic medication should be avoided.

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