**Psychiatric Disease**

Some patients with primary mitochondrial disease may be at high risk for psychiatric disorders though the literature is not well developed. In addition, some older studies include patients without confirmed genetic diagnoses.

Six studies, four examining adults, one including only children, and one studying both, have examined the prevalence of psychiatric disorders in individuals with primary mitochondrial disease. A US study also noted that among individuals with MELAS due to the m.3243A>G mutation, 32% had depression and 37% had hallucinations, while among mutation carrier relatives, 32% had depression and 6% had hallucination in contrast to controls, who had significantly less depression 17% and none had hallucinations (Kaufmann et al 2009). A Dutch study found that 37% adults with the m.3243A>G mutation demonstrated significant psychiatric symptoms using the Hospital Anxiety and Depression scale, with scores for depression, but not anxiety, significantly higher than controls (Verhaak, de Laat et al. 2016). Italian study found that over half (60%) of adults with MD had psychiatric disease as assessed by the mini-international neuropsychiatric interview, with most having a mood (58%) and/or anxiety disorder (46%) and a lesser number (17%) having psychotic features (Mancuso, Orsucci et al. 2013). A Hungarian study found that 47% of adults with pathogenic mitochondrial DNA mutations had a lifetime psychiatric disorder using the Structured Clinical Interview the DSM-IV with the majority (37%) having mood disorders and fewer having anxiety disorders (5%) and psychotic features (5%) (Inczedy-Farkas, Remenyi et al. 2012). A study examining adults with mitochondrial cytopathies using the mini-international neuropsychiatric interview found that the majority (54%) had a lifetime diagnose of major depressive disorder while fewer had bipolar disorder (17%) and panic disorder (11%) (Fattal, Link et al. 2007). The only prevalence study on children found that 14% of children with MD developed symptoms of major depression before the MD diagnosis (Koene, Kozicz et al. 2009).

One study that systematically reviewed all of the MD cases in the literature that reported psychiatric symptoms found that the most cases (44%) reported major depressive disorder while a lesser number of cases reported psychotic disorder (34%), anxiety disorder (12%), bipolar disorder (4%) and psychosomatic disorder (2%) (Anglin, Garside et al. 2012).

Two studies, one examining adults and one examining adolescents and young adults, looked at psychiatric symptoms rather than diagnosis. Hungarian adults with MD demonstrated higher scores on the Beck Depression Inventory-Short Form and the Hamilton Depression Rating Scale and greater psychopathological symptoms, including obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoia and psychoticism on the Symptom Checklist-90-Revised as compared to the reference group of individuals with sensorimotor neuropathy of similar age, gender, education and disability (Inczedy-Farkas, Remenyi et al. 2012). In another study high-functioning adolescents and young adults from the United States with MD were found to have higher ratings somatization on Behavior Assessment System for Children, 2nd Ed (Schreiber 2012). In addition, those with worse attitudes towards school had higher symptoms of depression and anxiety.

A Hungarian study examined the prevalence of personality disorders in adults with pathogenic mitochondrial DNA mutations. The most common disorders were avoidant personality (16%) and personality disorder not otherwise specified (16%) with fewer individuals (11%) having obsessive-compulsive personality disorder (Inczedy-Farkas, Remenyi et al. 2012).

Other case-series and case-reports have reported psychiatric manifestations in individuals with MD. Several cases of adult-onset progressive external ophthalmoplegia associated with mutations in specific nuclear genes have been reported to have psychiatric manifestations, particularly anxiety and depression (Kiferle, Orsucci et al. 2013, Sommerville, Chinnery et al. 2014). The patients reported had mutations in a variety of genes including *C10ORF2, MGME1, MPV17, OPA1, POLG, RRM2B, SLC25A4, SPG7 and TYMP*.

Interestingly, MD and psychiatric disorders have symptoms that overlap such as fatigue (Gorman, Elson et al. 2015). Whether this represents an overlap in similar biological processes between MD and neuropsychiatric disorders (Streck, Goncalves et al. 2014) or simply a symptom overlap, will require further research.

*Summary*

There appears to be a rather high prevalence of psychiatric disorders in individuals with MD with some studies reporting a prevalence in adults of 60% (Mancuso, Orsucci et al. 2013). However, all but one study used healthy controls as a reference group. Thus, although it is important to screen for psychiatric symptoms in individuals with MD, more research is needed to understand whether psychiatric symptoms are specifically related to MD or to other factors that are common in chronic disease conditions.

Mood disorders, especially major depression, appear to be the most prevalent psychiatric disorder reported across studies with many studies suggesting the prevalence as high as 40%-50% in adults (Fattal, Link et al. 2007, Inczedy-Farkas, Remenyi et al. 2012, Mancuso, Orsucci et al. 2013). Thus, mood disorders are especially important to be aware of in adults with MD.

The prevalence of anxiety disorders varies from study-to-study varying from 5% to 46% in adults with MD (Inczedy-Farkas, Remenyi et al. 2012, Mancuso, Orsucci et al. 2013). Thus, these disorders are also important to recognize when managing adults with MD. Psychotic disorders can be present but appear to be less common. The prevalence of personality disorders has not been evaluated.

Several studies have suggested that psychiatric co-morbidity is associated with older age and more complex medical problems (Fattal, Link et al. 2007, Verhaak, de Laat et al. 2016); so older, medically complicated patients may important patients to have a high-index-of-suspicion for psychiatric problems.

In adolescents and young adults with MD, depression and anxiety appears to be related to school problems, so individuals with MD within this age range with problems in school should be assessed for psychiatric disorders (Schreiber 2012).

Few studies looking at the prevalence of psychiatric disorders have been conducted in children, but one study suggest symptoms of depression predate the diagnosis of MD in a minority of children, so it is important to keep an high index of suspicion for psychiatric symptoms, especially mood disorders, even in children (Koene, Kozicz et al. 2009).

There is no standard screening tool for psychiatric symptoms, but one study found that more symptoms were reported on self-report forms than from interviews, suggesting that symptoms questionnaires may be a reasonable choice for screening patients for psychiatric symptoms.

The quality of the data is less than ideal and prospective assessment of these symptoms is needed.

*Recommendations*

Pediatric and adult patients with primary mitochondrial disease are at a higher risk for a variety of psychiatric symptoms especially depression and anxiety. It is not yet known whether this is due to the underlying mitochondrial disorder alone or a response to chronic disease. Older patient age, increasing medical complexity and a history of ongoing school problems may increase this risk. A standardized screening tool for these symptoms should be routinely used for these patients. Score 4.47

**Additional reader comments:**

The statement “There is no standard screening tool for psychiatric symptoms” is not correct; however, the sentence could easily be re-phrased “There is not universally-agreed upon screening tool…”

Also, the summary focuses on mood disorders, but the body of the text indicates that in some studies up to 1/3 of MD patients have psychotic features. This is exceptionally high, and deserves emphasis.

Finally, the authors DO mention the prevalence of personality disorders in the text (i.e. Inczedy-Farkas, Remenyi et al. 2012), then go on to state this has not been studied.

I agree with the comment about psychosis which in my experience is common in family members of MELAS patients. More information on psychosis features and incidence would be helpful along with some thoughts about drug treatments in mito disease pysychiatric symptoms ie. relative contraindication for tricyclics in cardiomyopathy/conduction defects.

A basal neuropsychology evaluation at diagnosis should be recommended. If psychiatric symptoms arise of depression, adhd, anxiety later on, this will help to rule out cognitive decline as the primary cause of the psychiaric symptoms. As well, this early baseline evaluation will help implant sufficient support early on in school, at home and in the workplace which could potentially prevent some of these co-morbidities. In case of reported psychiatric symptom, reevaluation for increase exercice intolerance, deterioration of condition, seizures, abnormalities of sleep pattern, anemia, or insufficent caloric intake should be recommended as well.

The narrative could be strengthened by giving context to the percentages cited from the studies. For example, in a recent reference (Epidemiol Psychiatr Sci. 2016 May 6:1-1; PMID 27150498) with data collected from the 2012 Canadian Community Health Survey an estimated 5.4% (1.5 million) Canadians aged 15 years and older reported symptoms compatible with a mood disorder. There is a significant amount of data for the general population. Giving context for percentages relative to general population and other chronic diseases would seem most useful for the reader.

An additional reference link is given below from a group of 30,643 individuals. Reference addresses behavioral health conditions (BHC) (depression, bipolar disorder, anxiety, ADD, etc). Compared to individuals without BHCs, adolescents with depression (odds ratio [OR] = 1.16, 95% CI = 1.08-1.26), anxiety (OR = 1.30, 95% CI = 1.20-1.41), and substance use (OR = 1.25, 95% CI = 1.05-1.49) disorders had significantly higher odds of any medical comorbidities; individuals with ADHD and bipolar disorder did not differ from patients without BHCs. BHCs were common and were associated with a disproportionately higher burden of chronic medical disease among adolescents in a large, private health care delivery system.

There are many references that assess the various categories of disorders described in MD in the context of chronic disease and populations without chronic disease.

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