



HOPE. ENERGY. LIFE.

MITO 101 – Psychiatry

Petra Kaufmann, MD

Neurological Institute
Columbia University
710 W 168th St
New York, NY 10032-3726

Key Points:

- Neuropsychiatric problems are relatively common features of mitochondrial disease
- Not all patients with mitochondrial disease develop neuropsychiatric symptoms
- In children, mitochondrial disease can be associated with cognitive delay, regression, and autism spectrum disorders. In adults, mitochondrial disease can be associated with dementia.
- Depression, hallucinations and behavioral abnormalities can be associated with mitochondrial encephalopathies.
- Psychiatric symptoms can be difficult to recognize amidst cognitive impairment and other medical problems associated with a multi-system mitochondrial disorder.
- Recognizing and treating psychiatric disease with pharmacotherapy and behavioral interventions is important, as effective management can improve quality of life.

Clinical Investigation:

- A careful history, specifically eliciting behavioral and depressive symptoms, addiction, and cognitive impairment, are important in recognizing neuropsychiatric disease.
- Neuropsychological testing can uncover a subtle impairment; more precisely assess its extent, and help guide educational interventions in children and management in adults.
- It is important to ascertain what medications a patient with mitochondrial disease is taking, as drug side effects or interactions can exacerbate or cause neuropsychiatric symptoms.
- Magnetic resonance imaging (MRI) can identify potential new lesions underlying behavioral changes.
- Electroencephalography, including continuous monitoring, can identify if epileptiform activity is contributing to the neuropsychiatric symptoms.
- Given that mitochondrial diseases can affect multiple systems, laboratory testing may be indicated to rule out metabolic factors that can contribute to cognitive and behavioral impairment.

Neuropsychiatric features associated with mitochondrial disease (organized by genetic etiology)

- Single, large scale deletions causing Kearns-Sayre syndrome can be associated with visuospatial executive deficits¹, but rarely with psychiatric disease.
- Transfer RNA mutations in the mitochondrial DNA (mtDNA) causing encephalopathies are frequently associated with dementia and psychiatric

- symptoms, including depression, hallucinations, delusions, behavioral abnormalities, and autism spectrum disorders^{24,9,26,12,16,18,13,2,3,25,11,19,20,5}.
- Mutations in mtDNA protein-coding genes causing Leber's hereditary optic neuropathy (LHON) do not seem associated with neuropsychiatric disease.¹⁷ However, mutations causing NARP/MILS (neuropathy, ataxia, retinitis pigmentosa/maternally inherited Leigh syndrome) commonly are associated with mental retardation^{17,27,6,4}.
 - Among nuclear DNA defects, primary coenzyme Q10 deficiency has been associated with often subtle neuropsychological deficits, but also with affective disease and behavioral abnormalities^{8,15,14,10}.
 - Among defects in intergenomic signaling, adenine nucleotide transporter (*ANT1*) gene mutations, *POLG* and *PEO1* mutations have been associated with depression, less commonly paranoia, and personality disorders (avoidant, histrionic, or psychotic)^{28,22,23,21,7}.

Management of mitochondrial psychiatric disease

- Depressive symptoms often respond to one of the newer antidepressants, including SSRI's (selective serotonin re-uptake inhibitors). Older drugs including tricyclic antidepressants can be helpful, but should be used with caution because of their potential autonomic and cardiac side effects.
- Psychotic symptoms and significant behavioral problems respond to antipsychotics. Depending on the type of behavioral disturbance, more activating or more sedating drugs are chosen.
- Supportive counseling and psychosocial interventions are often helpful.
- In children, referral to appropriate early intervention or school special education services is indicated.

Acknowledgments:

The author is supported by NICHD PO1

1. Bosbach S, Kornblum C, Schroder R, Wagner M. Executive and visuospatial deficits in patients with chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome. *Brain* 2003;126(Pt 5):1231-1240.
2. Bruno C, Kirby DM, Koga Y, Garavaglia B, Duran G, Santorelli FM, Shield LK, Xia W, Shanske S, Goldstein JD, Iwanaga R, Akita Y, Carrara F, Davis A, Zeviani M, Thorburn DR, DiMauro S. The mitochondrial DNA C3303T mutation can cause cardiomyopathy and/or skeletal myopathy. *J Pediatr* 1999;135(2 Pt 1):197-202.
3. Campos Y, Garcia A, Eiris J, Fuster M, Rubio JC, Martin MA, del Hoyo P, Pintos E, Castro-Gago M, Arenas J. Mitochondrial myopathy, cardiomyopathy and psychiatric illness in a Spanish family harbouring the mtDNA 3303C > T mutation. *J Inherit Metab Dis* 2001;24(6):685-687.
4. Corona P, Antozzi C, Carrara F, D'Incerti L, Lamantea E, Tiranti V, Zeviani M. A novel mtDNA mutation in the ND5 subunit of complex I in two MELAS patients. *Ann Neurol* 2001;49(1):106-110.

5. Corona P, Lamantea E, Greco M, Carrara F, Agostino A, Guidetti D, Dotti MT, Mariotti C, Zeviani M. Novel heteroplasmic mtDNA mutation in a family with heterogeneous clinical presentations. *Ann Neurol* 2002;51(1):118-122.
6. Crimi M, Galbiati S, Moroni I, Bordoni A, Perini MP, Lamantea E, Sciacco M, Zeviani M, Biunno I, Moggio M, Scarlato G, Comi GP. A missense mutation in the mitochondrial ND5 gene associated with a Leigh-MELAS overlap syndrome. *Neurology* 2003;60(11):1857-1861.
7. Deschauer M, Hudson G, Muller T, Taylor RW, Chinnery PF, Zierz S. A novel ANT1 gene mutation with probable germline mosaicism in autosomal dominant progressive external ophthalmoplegia. *Neuromuscul Disord* 2005;15(4):311-315.
8. DiMauro S, Hirano M. Mitochondrial encephalomyopathies: an update. *Neuromuscul Disord* 2005;15(4):276-286.
9. Feddersen B, Bender A, Arnold S, Klopstock T, Noachtar S. Aggressive confusional state as a clinical manifestation of status epilepticus in MELAS. *Neurology* 2003;61(8):1149-1150.
10. Gironi M, Lamperti C, Nemni R, Moggio M, Comi G, Guerini FR, Ferrante P, Canal N, Naini A, Bresolin N, DiMauro S. Late-onset cerebellar ataxia with hypogonadism and muscle coenzyme Q10 deficiency. *Neurology* 2004;62(5):818-820.
11. Graf WD, Marin-Garcia J, Gao HG, Pizzo S, Naviaux RK, Markusic D, Barshop BA, Courchesne E, Haas RH. Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation. *J Child Neurol* 2000;15(6):357-361.
12. Guillausseau PJ, Massin P, Dubois-LaForgue D, Timsit J, Virally M, Gin H, Bertin E, Blickle JF, Bouhanick B, Cahen J, Caillat-Zucman S, Charpentier G, Chedin P, Derrien C, Ducluzeau PH, Grimaldi A, Guerci B, Kaloustian E, Murat A, Olivier F, Paques M, Paquis-Flucklinger V, Porokhov B, Samuel-Lajeunesse J, Vialettes B. Maternally inherited diabetes and deafness: a multicenter study. *Ann Intern Med* 2001;134(9 Pt 1):721-728.
13. Jaksch M, Lochmuller H, Schmitt F, Volpel B, Obermaier-Kusser B, Horvath R. A mutation in mt tRNALeu(UUR) causing a neuropsychiatric syndrome with depression and cataract. *Neurology* 2001;57(10):1930-1931.
14. Lamperti C, Naini A, Hirano M, De Vivo DC, Bertini E, Servidei S, Valeriani M, Lynch D, Banwell B, Berg M, Dubrovsky T, Chiriboga C, Angelini C, Pegoraro E, DiMauro S. Cerebellar ataxia and coenzyme Q10 deficiency. *Neurology* 2003;60(7):1206-1208.
15. Musumeci O, Naini A, Slonim AE, Skavin N, Hadjigeorgiou GL, Krawiecki N, Weissman BM, Tsao CY, Mendell JR, Shanske S, De Vivo DC, Hirano M, DiMauro S. Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. *Neurology* 2001;56(7):849-855.
16. Onishi H, Kawanishi C, Iwasawa T, Osaka H, Hanihara T, Inoue K, Yamada Y, Kosaka K. Depressive disorder due to mitochondrial transfer RNALeu(UUR) mutation. *Biol Psychiatry* 1997;41(11):1137-1139.
17. Pegoraro E, Vettori A, Valentino ML, Molon A, Mostacciolo ML, Howell N, Carelli V. X-inactivation pattern in multiple tissues from two Leber's hereditary optic neuropathy (LHON) patients. *Am J Med Genet A* 2003;119(1):37-40.

18. Pons R, Andreu AL, Checcarelli N, Vila MR, Engelstad K, Sue CM, Shungu D, Haggerty R, de Vivo DC, DiMauro S. Mitochondrial DNA abnormalities and autistic spectrum disorders. *J Pediatr* 2004;144(1):81-85.
19. Santorelli FM, Tanji K, Sano M, Shanske S, El-Shahawi M, Kranz-Eble P, DiMauro S, De Vivo DC. Maternally inherited encephalopathy associated with a single-base insertion in the mitochondrial tRNATrp gene. *Ann Neurol* 1997;42(2):256-260.
20. Shtilbans A, El-Schahawi M, Malkin E, Shanske S, Musumeci O, DiMauro S. A novel mutation in the mitochondrial DNA transfer ribonucleic acid Asp gene in a child with myoclonic epilepsy and psychomotor regression. *J Child Neurol* 1999;14(9):610-613.
21. Siciliano G, Tessa A, Petrini S, Mancuso M, Bruno C, Grieco GS, Malandrini A, DeFlorio L, Martini B, Federico A, Nappi G, Santorelli FM, Murri L. Autosomal dominant external ophthalmoplegia and bipolar affective disorder associated with a mutation in the ANT1 gene. *Neuromuscul Disord* 2003;13(2):162-165.
22. Suomalainen A, Majander A, Haltia M, Somer H, Lonngqvist J, Savontaus ML, Peltonen L. Multiple deletions of mitochondrial DNA in several tissues of a patient with severe retarded depression and familial progressive external ophthalmoplegia. *J Clin Invest* 1992;90(1):61-66.
23. Suomalainen A, Majander A, Wallin M, Setala K, Kontula K, Leinonen H, Salmi T, Paetau A, Haltia M, Valanne L, Lonngqvist J, Peltonen L, Somer H. Autosomal dominant progressive external ophthalmoplegia with multiple deletions of mtDNA: clinical, biochemical, and molecular genetic features of the 10q-linked disease. *Neurology* 1997;48(5):1244-1253.
24. Suzuki Y, Taniyama M, Muramatsu T, Atsumi Y, Hosokawa K, Asahina T, Shimada A, Murata C, Matsuoka K. Diabetes mellitus associated with 3243 mitochondrial tRNA(Leu(UUR)) mutation: clinical features and coenzyme Q10 treatment. *Mol Aspects Med* 1997;18 Suppl:S181-188.
25. Sweeney MG, Bunday S, Brockington M, Poulton KR, Winer JB, Harding AE. Mitochondrial myopathy associated with sudden death in young adults and a novel mutation in the mitochondrial DNA leucine transfer RNA(UUR) gene. *Q J Med* 1993;86(11):709-713.
26. Thomeer EC, Verhoeven WM, van de Vlasakker CJ, Klompenhouwer JL. Psychiatric symptoms in MELAS; a case report. *J Neurol Neurosurg Psychiatry* 1998;64(5):692-693.
27. Uziel G, Moroni I, Lamantea E, Fratta GM, Ciceri E, Carrara F, Zeviani M. Mitochondrial disease associated with the T8993G mutation of the mitochondrial ATPase 6 gene: a clinical, biochemical, and molecular study in six families. *J Neurol Neurosurg Psychiatry* 1997;63(1):16-22.
28. Van Goethem G, Luoma P, Rantamaki M, Al Memar A, Kaakkola S, Hackman P, Krahe R, Lofgren A, Martin JJ, De Jonghe P, Suomalainen A, Udd B, Van Broeckhoven C. POLG mutations in neurodegenerative disorders with ataxia but no muscle involvement. *Neurology* 2004;63(7):1251-1257.