VIEWPOINT

A Mitochondrial Etiology of Neuropsychiatric Disorders

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Enormous resources have been invested in the analysis of neuropsychiatric disorders using powerful genomics techniques, including genome-wide association studies (GWAS), whole-exome sequencing (WES), and whole-genome sequencing, to search for nuclear DNA (nDNA) gene variants associated with these disorders. Yet, no coherent pathophysiological etiology for psychiatric disorders has emerged. For example, after analysis of thousands of autism cases by GWAS and WES, numerous copy number variants and loss-of-function mutations have been identified, but no single variant accounts for a significant proportion of cases. Moreover, the genes that have been found to harbor loss-of-function mutations in patients with autism overlap with those associated with congenital heart disease and metabolic disorders.[1] What do "brain" diseases have to do with congenital heart disease and metabolic disorders?

The likely problem is not with the data but with the perspective from which we are attempting to interpret the data. In Western medical philosophy, it is assumed that if a symptom emanates from an organ, then the "cause" of the problem must be a defect in that organ. Problems with behavior, learning, and memory relate to the brain. Therefore, we assume that to discover the causes of these problems, we must look into the brain.

However, there is an alternative perspective. It is possible that there might be systemic defects to which the brain is uniquely sensitive, thus causing brain-specific symptoms. But how could a systemic defect preferentially affect the brain? The brain is only 2% to 3% of our body's weight but expends 20% of our mitochondrial energy, as measured by oxygen consumption. Therefore, as systemic mitochondrial energy metabolism declines, the brain is the first organ to become limited for energy, dropping below its bioenergetic threshold and resulting in neurological symptoms. The milder the bioenergetic defect, the more brain-specific the symptoms, with hyperactivity or depression being likely examples.

If a 20% reduction in mitochondrial oxidative phosphorylation (OXPHOS) were sufficient to cause depression, the biochemical defect would not be significantly demonstrable in an individual using current technology. By contrast, analysis of cohorts of patients has revealed statistically significant mean differences in OXPHOS relative to control individuals in the brain as well as in peripheral tissues for a variety of neurological diseases.

If mitochondrial dysfunction is a major cause of psychiatric disorders, why haven't the affected mitochondrial genes been found? They have. The mitochondrial genome consists of 1000 to 2000 nDNA-coded genes plus thousands of copies of the maternally inherited mitochondrial DNA (mtDNA). The nDNA component of the mitochondrial genome codes for all of the genes for the anatomical components of the mitochondrion, for mitochondrial intermediate metabolism and mitochondrial biogenesis, and for the regulation of the mitochondrion. The mtDNA component codes for the most critical genes for OXPHOS and for their expression, the mtDNA being in essence the wiring diagram of the power plant. The mtDNA has a very high mutation rate. Hence, new mutations arise regularly, initially giving rise to mixtures of mutant and normal mtDNAs (heteroplasmy). Changes in the heteroplasmy percentage of a mutant can give graded defects and variable phenotypes. Because multiple genes code for each of the enzyme complexes of OXPHOS, multiple different gene alterations can result in similar bioenergetic defects and related phenotypes.

While the brain is the organ most sensitive to mitochondrial dysfunction, the heart, kidney, muscle, and endocrine systems can also be high energy demand tissues. Like the brain, the heart is under chronic energy load and will be one of the first organs to respond to chronic energy deficiency, resulting in cardiomyopathy. Mild mitochondrial dysfunction is also associated with diabetes and metabolic syndrome.[2] Hence, nDNA and mtDNA gene mutations that result in partial mitochondrial dysfunction can cause dysfunction in high energy organs leading to neurological, cardiac, and endocrine symptoms.

There is considerable evidence supporting the hypothesis that mitochondrial dysfunction is associated with neuropsychiatric disorders. For example, an ancient mtDNA single-nucleotide polymorphism (SNP) in the mtDNA $tRNA^{Gln}$ gene at nucleotide 4336A>G is found in about 3% of patients with Alzheimer disease, about 5% of those with Parkinson disease, and about 7% of those with Alzheimer and Parkinson diseases, but only about 0.4% of the European population.[3] Ancient mtDNA lineages harboring function variants (haplogroups) have been associated with predisposition to a broad range of neurological, cardiac, and metabolic diseases.[2] Mitochondrial DNA mutations also accumulate with age in tissues, resulting in the age-related decline in mitochondrial function. The progressive mitochondrial defects resulting from these somatic mtDNA mutations can exacerbate inherited nDNA or mtDNA mitochondrial gene defects, ultimately causing a composite energy deficiency that falls below neuronal bioenergetic thresholds resulting in neuropsychiatric symptoms.[2]

Yet, to my knowledge, mtDNA variation is rarely analyzed in GWAS or WES clinical studies. For GWAS, the problem has been the selection by Illumina of the mtDNA SNPs to be interrogated. Rather than select mtDNA SNPs

based on the universally used revised Common Reference Sequence, Illumina started with an African mtDNA. Hence, the nucleotide numbering of the Illumina mtDNA SNPs does not correspond to that used in virtually all other clinical and evolutionary studies. Whole-exome sequencing can produce off-target mtDNA sequences that can be analyzed, but the mtDNA sequence data are generally contaminated with nDNA-mtDNA pseudogene sequences, complicating the interpretation.

Proof that the same mtDNA variant can cause neuropsychiatric disorders, heart and muscle diseases, or metabolic disorders comes from studies of the heteroplasmic mtDNA $tRNA^{Leu(UUR)}$ nucleotide 3243A>G mutation. Patients harboring 10% to 30% 3243G mutation can manifest as type 1 or type 2 diabetes or autism; 50% to 90% 3243G as multisystem neurological, cardiac, and muscle disease; and 100% mutant as pediatric lethality. In cell lines with the same nucleus but different percentages of the 3243A>G mutation, subtle changes in the heteroplasmy percentage result in phase-like shifts in nuclear gene expression at heteroplasmy levels, which correspond to the changes in patient phenotypes.[4] Therefore, much of the complexity of mitochondrial genetics results from subtle changes in mitochondrial bioenergetics that precipitate abrupt changes in nDNA gene expression.

Evidence that subtle changes in mitochondrial function can cause behavioral, learning, and memory defects comes from mice in which 2 normal but different mtDNAs were artificially mixed. The resulting heteroplasmic mice manifest reduced activity, hyperresponse to stress, and severe memory defects. Yet, their mitochondrial biochemical defect is too subtle to be detected by current methods.[5] Mice with mild mitochondrial defects due to different nDNA or mtDNA mitochondrial gene variants show different physiological responses to short-term stress. Aberrant responses include differential modulation of corticosterone, catecholamines, and serum glucose and amino acid levels, as well as in hippocampal gene expression.[6] Mice with a partial defect in brain mitochondrial export of adenosine triphosphate into the cytoplasm have impaired tangential migration of the embryonic, inhibitory, gamma-aminobutyric acidergic interneurons without affecting the radial migration of the embryonic, excitatory, glutamatergic, pyramidal neurons.[7] This may create the cortical excitation-inhibition imbalance characteristic of the hyperexcitable states associated with autism, schizophrenia, epilepsy, and bipolar disease.

Thus, if we stop attempting to understand neuropsychiatric disorders from the perspective of brain-specific anatomic pathology and mendelian quantized genetics and start thinking in terms of systemic bioenergetics and mitochondrial quantitative genetics, we naturally arrive at a coherent theory for neuropsychiatric diseases. This mitochondrial bioenergetics theory of neuropsychiatric disorders explains the seemingly disparate clinical, physiological, and genetic observations characteristic of these diseases. Thus, neuropsychiatric diseases are not "complex," they just follow different rules.

ARTICLE INFORMATION

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