Is mitochondrial oxidative metabolism the right therapy target in early Huntington disease?

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Huntington disease (HD) is a progressive and fatal autosomal dominant neurodegenerative disorder characterized by extrapyramidal motor signs often preceded by cognitive and behavioral disturbances, with a prevalence of 5–10 cases per 100,000 people worldwide[1]; expanded CAG repeats within the coding sequence of the *HTT* gene on chromosome 4p[2] are the cause. The gene encodes huntingtin (HTT), a ubiquitously expressed protein associated with most intracellular organelles. CAG repeats of 40 or more are associated with nearly full penetrance by age 65 years with a mean age at onset of 40 years and death 15–20 years later.[3] Although the function of HTT remains incompletely understood, HD likely arises from gain of function caused by the abnormal conformation of the mutant protein.[3]

Over the last 2 decades, many lines of evidence, from both patients with HD and HD transgenic mouse models, have suggested impairment of mitochondrial energy production in HD.[4] In vivo magnetic resonance spectroscopy has shown abnormalities suggestive of impaired mitochondrial ATP production in the brain[5] and skeletal muscle[6] of patients with HD and in presymptomatic CAG repeat expansion carriers. Impaired activity of mitochondrial enzymes involved in cellular respiration contributes to defective energy metabolism in HD. Brain and peripheral tissues from patients with HD and animal models demonstrate reduced complex I, II, III, and IV activity.[4] Increased free radical production, abnormal mitochondrial calcium homeostasis, and the influence of mutant HTT on transcription factors regulating the expression of genes involved in mitochondrial biogenesis and respiration, documented in several studies of patients with HD and animal model tissues, all point to widespread cellular energy metabolism impairment associated with mutant HTT.[4]

Currently, besides symptomatic treatments, no therapy modifies the natural history of HD. In this issue of *Neurology*®, McGarry et al.[7] report on the safety and efficacy of a chronic pharmacologic treatment targeted to reverse the energy metabolism impairment in HD. The Huntington Study Group 2CARE performed a multicenter randomized, double-blind, placebo-controlled trial on 609 patients with early-stage HD treated with high-dosage coenzyme Q10 (2,400 mg/d) over a follow-up period of 60 months.[7] Coenzyme Q10 is a component of the mitochondrial electron transport chain, as well as a potent free radical scavenger in lipid and mitochondrial membranes, whose concentration increases in brain (and in brain mitochondria) following oral administration.[8] Coenzyme Q10 oral administration enhances mitochondrial oxidative phosphorylation in the brain of patients with HD in vivo[5] and has clinical and pathologic beneficial effects in HD transgenic mice.[9]

Despite the strong physiopathologic rationale and encouraging preliminary data, the present multicenter study, the largest ever performed and with the longest duration, failed to show any substantial effect of oral high-dose coenzyme Q10 administration in modifying HD disease course; the study was concluded early on the basis of an interim analysis for futility (34% of patients with HD completed the month 60 visit). Changes in Total Functional Capacity score, combined with time to death, the primary outcome variable, and secondary outcome variables derived from the other Unified Huntington's Disease Rating Scale subscale scores, were similar in the 2 groups of patients with HD treated with coenzyme Q10 and placebo, with the exception of a smaller mean decline in Word reading score in the coenzyme Q10 group, possibly related to a multiple testing effect. On the other hand, oral administration of high doses of coenzyme Q10 proved generally safe and well-tolerated throughout the study.

The results of the present trial do not support the administration of coenzyme Q10 for reducing the functional decline in patients with HD (Class I evidence), and suggest that the mitochondrial oxidative metabolism impairment found in HD may be the endpoint of a variety of altered molecular pathways contributing to HD pathology. A number of abnormalities have been implicated in HD pathogenesis, including reduced brain-derived neurotrophic factor,

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impaired corticostriatal pathways due to glutamate-mediated excitotoxicity, caspase-mediated cleavage of pathologic HTT, accumulation of aggregates of mutant HTT, abnormal autophagy pathways, and transcriptional and posttranscriptional dysregulation, all suggesting alternative or better treatment targets for HD other than oxidative metabolism.[4]

As discussed by the authors, the lack of benefit of coenzyme Q10 in HD is unlikely due to insufficient study power to detect an effect, an insufficiently high daily coenzyme Q10 dosage, insufficient treatment duration, or low sensitivity of the selected outcome measures. More sensitive biomarkers, such as neuroimaging, may have demonstrated differences between coenzyme Q10 and placebo HD groups, but in the absence of coenzyme Q10–related functional changes these would not support the use of coenzyme Q10 in the clinic, at least in patients with manifest HD.

This is a critical issue for pharmacologic trials. Brain pathology clearly precedes clinical onset. In presymptomatic HD carriers, quantitative brain MRI detects reduced tissue volumes for striatum, thalamus, and white and cortical gray matter more than 15 years prior to the estimated onset of motor symptoms.[10] This observation, together with the negative results of the coenzyme Q10 trial in patients with early-stage HD reported in this issue,[7] suggests that future studies testing the efficacy of a putative neuroprotective agent for slowing neurodegeneration in HD should target one or more pathologic pathways identified in HD besides oxidative metabolism impairment[4]; further, it bears consideration to include presymptomatic HD carriers. Hopefully, there will be adequate funding for such research.

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DISCLOSURE

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