Development and neurodegeneration

Turning HD pathogenesis on its head

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The term "neurodegenerative" implies a period of normal development preceding cell death. Determining when decline begins and the selective vulnerability of specific brain regions to the degenerative cascade is key to development of disease-modifying therapies. Huntington disease (HD), an autosomal dominant disease with little contribution from modifier genes, and complete penetrance in individuals with CAG repeat length ≥40 in the *Huntington* (*Htt*) gene, permits the identification of an at-risk population for whom the probability of age at diagnosis can be modeled based on CAG repeat length and age. What if Huntington disease is both a neurodevelopmental disorder and a neurodegenerative disease?

The possibility that mutant *Htt* (*mHtt*) might result in fundamental embryonic developmental abnormalities that correlate with the patterns of regional neurodegeneration has been suggested by a study of a knock-in mouse model of HD. This mouse model exhibits impairments in striatal striosome and matrix functional compartmentalization, alterations in the temporal and spatial profiles of striatal medium spiny neurons (MSN) at birth, and aberrations in the maintenance and maturation of the MSN neural stem cell precursor.[1] Recent evidence suggests that HD is caused by both loss-of-function (LOF) and gain-of-function (GOF) effects, including novel CAG-repeat RNA toxic GOF, and that these distinct pathogenic mechanisms may act synergistically. Studies of normal and mutant *Htt* hypomorph mice suggest that LOF may preferentially compromise essential neurodevelopmental programs, whereas GOF may contribute to disease progression culminating in neurodegeneration.[2]

Htt represents one of a number of proteins with essential roles in centrosome function, including both regulating mitotic spindle orientation and ciliogenesis. Deregulation of these proteins results in alterations in brain size and neuronal organization and gives rise to neurodevelopmental as well as neuropsychiatric disorders. Htt is essential for mitotic spindle orientation and asymmetric cell division of mammalian neural progenitors.[3] Ablation of *Htt* results in depletion of the neural progenitor pool and impaired cortical neurogenesis. Motile cilia are involved in regulation of the neural stem cell niche through modulation of CSF gradients of cytokines and growth factors essential for stem cell maintenance and for neurogenesis and gliogenesis along the entire neuraxis, whereas primary cilia regulate later phases of neuronal maturation. Htt regulates ciliogenesis by modulation of centrosome function through interactions of HAP1 with PCM 1. HD is characterized by dysmorphic, dysfunctional cilia.[4]

Htt is a pleiotropic protein with functional roles in regulating neuronal survival, transcription, and metabolism. mHtt may deregulate the entire process of stem cell–mediated neurogenesis and gliogenesis through impairments in the transcription and nuclear localization of RE1-silencing transcription factor (REST), including the involvement of microRNAs and long noncoding RNAs. mHtt can directly affect metabolic profiles in premanifest HD by altering mitochondrial biogenesis, maintenance, and function at the transcriptional level by inhibiting PGC1α, at the mitochondrial level by increasing the probability of opening of the permeability transition pore and by altering the fidelity of respiratory chain function and at the level of DRP1 by impairing the interplay of mitochondrial fission and fusion events.

In this issue of *Neurology*®, Lee et al.[5] provide a human proof of principle for a developmental etiology for HD, cleverly employing anthropometric measures (head circumference, weight, and height) available to every clinician. Intracerebral volume (ICV), a measure of maximal attained brain volume, is highly correlated with head circumference. By age 6, brain volume is approximately 90% of maximal adult volume and may reflect peak development

See page 668

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rather than neurodegeneration. The authors contend that smaller head circumference in 20 children (ages 7–18) with a CAG expansion, compared to a database of 152 healthy children, reflects a developmental process. This study extends the MRI finding of smaller ICV in premanifest adult men compared to controls in PREDICT-HD,[6] an estimated 3 decades prior to diagnosis. In contrast, smaller striatum and white matter volume on MRI were predictive of diagnosis of HD within 1 to 4 years, in premanifest adults in PREDICT-HD, which may reflect the overlay of neurodegeneration.[7] In Alzheimer disease (AD), with greater levels of cerebral atrophy, cognitive performance was better for individuals with greater head circumference, suggesting cognitive reserve providing "protection" from AD pathology.[8] This study also demonstrates the power of responsible use of genetic testing in children for research and the importance of maintaining investigators and participants blind to individuals' CAG repeat length.

An acknowledged limitation of this study is the small sample size that did not permit between-group comparisons in age- and gender-defined strata with sufficient power to detect meaningful differences. Brain volume trajectories follow an inverted U-shaped curve, peaking at 10.5 years in girls and 14.5 years in boys, encompassing the age range included. Differences in ICV in premanifest adult men compared to men without expanded CAG repeats were not seen in women.[6] Here, no sex-by-group interactions were demonstrated on any measure, but the number of participants within each stratum was small. Given the higher prevalence of neurodevelopmental disorders in males and some evidence of sex differences in age at onset and disease course in HD, study in a larger sample would be optimal. The cross-sectional design makes it impossible to determine whether smaller head circumference and lower body mass index (BMI) reflect a more proximate environmental perinatal insult or whether mHtt drives the association. This study extends the findings of lower BMI in the premanifest state demonstrated in adults[9]; however, caloric intake and energy expenditure were not measured here.

These observations, including the findings that Htt is important for gastrulation and germ layer formation, suggest that HD may represent both a primary developmental disorder of the nervous system and peripheral organogenesis, with early prodromal metabolic impairments representing deregulation of integrated central and peripheral feeding and metabolic circuits. Longitudinal follow-up of a larger cohort with neuroimaging and metabolic profiling may help to elucidate further novel mechanisms underlying HD pathogenesis.[10]

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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