Cognitive trajectories in rare neurogenetic diseases: minding the gaps and filling the potholes

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Rapid progress in recent years in the neurobiology of rare genetic conditions affecting the brain, and in translational work with preclinical treatment models, has led to a critical need for translation of disease-directed treatments to humans with these diseases. While placebo-controlled, short-term clinical trial designs for rare disease are needed for regulatory approvals, these trials will not last long enough to measure long-term treatment effects.

For this purpose one must demonstrate how the natural history of the disease has been changed post-regulatory approval, necessitating detailed studies of the natural history of the disorder. This must take place in a setting of standard of care management prior to the new intervention, with development of tools with which to perform such studies. Such tools have been created for a number of diseases with disease-specific rating scales,[1,2] but the rating scales are often heavily focused on motor function and other physical, medical, and behavioral symptoms. They do not include detailed assessment of cognition or developmental function, obviously a key symptom domain in which to demonstrate long-term neurological disease stabilization or reversal.

Few natural history studies mapping cognitive function over years in rare disease exist, largely because of the difficulty in funding and carrying out such studies. Thurm et al.[3] studied cognitive and adaptive trajectory in an ultra-rare disease, Niemann–Pick type C (NP-C), to define natural history and relate decline trajectories on cognitive measures to those on the disease-specific NP-C Clinical Severity Scale.[1] This kind of data is badly needed to assess long-term treatment impact, particularly given several disease-targeted agents are entering clinical trials for NP-C. The paper represents an important first attempt to collect longitudinal cognitive data in NP-C, presents a relatively large cohort given the rarity of the condition, and provides new valuable pilot data and methodology that can be used for design of future ongoing longitudinal studies.

However, as the authors are careful to point out, the study is fraught with many problems and limitations, including: (1) difficulty with sample size and missing data points because of difficulty recruiting and retaining a large longitudinal cohort due to disease rarity, travel to a single site, and discontinuous funding; (2) broad age and cognitive ranges over which testing had to be performed, requiring use of multiple different cognitive tests or versions, both cross-sectionally within the cohort and longitudinally for individual patients as they became older and gained cognitive skills or regressed, resulting in discontinuity in data interpretation due to lack of studies mapping performance on measures for a given level to that on measures for adjacent levels; (3) substantial floor effects that limit interpretation or derivation of a true trajectory of change due to lack of adequate validation or normalization of cognitive tests for individuals with significant intellectual impairment; and (4) lack of existence of tests designed to be done by individuals with moderate to severe intellectual impairment.

Recognition of these gaps in the field is important for further research designed to overcome current hurdles and support the needed longitudinal studies in rare diseases. Research needed includes: (1) formation of consortia with centers at multiple locations to minimize travel burden for patients thus allowing for less missing visits and more complete data sets and, for data reported by patients or families (e.g. completion of standardized forms or scales), use of systems for electronic data entry from home to minimize burden and increase data completeness; (2) systematic evaluation of overlap between tests when patients with intellectual disability go from one testing level or version to the next (e.g. Mullen or Bayley to WISC or Stanford–Binet); (3) studies normalizing cognitive tests for individuals with ID so they can be scored meaningfully without dramatic floor effects and thus allow actual levels of function to be tracked without dilution of assessment of relative performance over time by floor effects; and (4) efforts to develop tests that can be done meaningfully by individuals with significant intellectual disability.

Some efforts in these areas are underway. A number of disease consortia have been developed through special federally funded programs in the USA (examples include Rett syndrome, fragile X syndrome [FXS], tuberous sclerosis complex, and Phelan–McDermid syndrome). Online data entry is beginning to be used for families to reduce missing data, and the WISC and Stanford–Binet have undergone normalization using z-deviation scores for ID populations with FXS[4,5] and autism spectrum disorder.[5] Studies and development efforts have been initiated to address the other issues described above, but there is a paucity of published data (mostly on very small cohorts) and much more work is needed to fill holes in the path to optimal natural history studies for rare disorders affecting cognitive function.

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