The TRACK to clinical trials in Huntington’s disease

Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder classically described as a triad of motor cognitive and psychiatric features. Given the monoclonal nature of this disease and the availability of suitable animal models, finding potential therapies or even a cure should be theoretically feasible particularly since a number of treatments have shown preclinical promise. However, a major challenge facing such clinical trials is the longitudinal assessment of disease progression. Defining tests that are sensitive enough to detect a longitudinal decline over a short period of time in this slowly progressive disease is of utmost importance as it is likely that initial therapies developed for HD will aim to slow down the pathological process and hence hinder decline rather than restoring pathology.

The aim of TRACK-HD, a multicentre longitudinal observational natural history study, is to identify a battery of potential outcome measures to be used in future therapeutic trials. Over the past few years, they have followed up a group of 366 participants divided into groups of premanifest gene carriers (preHD), early manifest HD patients, and controls. In a recent paper in Lancet Neurology, Tabrizi and colleagues reported findings from the 298 participants that completed the 36 month follow up period of the TRACK-HD study. The study was specifically extended beyond 24 months due to the paucity of findings in the preHD cohort. However, by the 36 months visit they were able to demonstrate longitudinal changes in several imaging, quantitative motor and cognitive measures in the preHD group that were close to manifesting disease. In contrast, despite striatal and white matter loss, very little change could be seen clinically in the preHD group estimated to be far from disease onset. In addition, the authors also noted a variety of changes in early HD in accordance with the 12 and 24 month report of the TRACK-HD study. Several baseline imaging and cognitive measures could also predict disease progression in preHD, and functional decline in manifest disease.

HD is unique in the respect that a population which will almost certainly develop disease can be identified prior to the onset of clinically meaningful symptoms. This has led to the ambitious goal of developing a preventative therapy for this disease. However, despite the longitudinal changes in the preHD group estimated to be close to onset in this study such trials will certainly face many practical challenges in the preHD population, including identification of a ‘close to onset’ group, lengthy follow up and large sample sizes. Such trials may be more feasible in manifest HD where TRACK-HD has shown that disease progression can be detected reliably at 24 months, with some measurements showing changes as early as 12 months, which will prove useful in planning future clinical trials in HD.

Consider Earlier Surgical Intervention in people with intractable Frontal Lobe Epilepsy

Frontal lobe epilepsy (FLE) is the second most common type of focal-onset epilepsy treated surgically. Seizure outcomes reported from cohort studies are generally inferior to those reported from temporal lobe surgery, and in particular compared with outcomes from those with mesial temporal lobe epilepsy. A recent paper from the Cleveland Clinic examined potential prognostic factors following frontal lobe surgery. Simas and colleagues reviewed 158 people who underwent FLE surgery between 1995 and 2010 with the primary outcome being complete seizure freedom at last follow-up. The mean age at surgery was 20.8 years (SD 1.2) with a mean age of epilepsy onset of 8.4 years (SD 0.7) and mean epilepsy duration of 12.0 years (SD 0.9). The mean duration of follow-up post-operatively was 4.3 years. The predominant underlying pathology identified was malformations of cortical development (MCD) in almost 60% of cases overall. Non-lesional resections (normal MRI) were performed in 36 patients (24%). Overall, half of the people who underwent surgery for FLE were seizure free at last follow-up. The probability of being seizure free was 66% (95% CI 62-68) at 1 year post-operatively, 52% (95% CI 48-56) at 2 years and 44% (95% CI 39-49) at 5 years and beyond. The majority (70%) of seizure recurrences occurred in the absence of any provoking factors.

The study highlights the importance of early consideration and referral for evaluation of surgery in people with established intractable FLE. It may be that the poorer outcome associated with FLE surgery compared to TLE surgery may be in part explained that TLE surgery, is perhaps considered earlier in people with refractory TLE (given it’s longer surgical pedigree and also the increased number of procedures performed in a typical epilepsy centre) compared to people with refractory FLE.

IST-3: Live not longer, but better?

The third International Stroke Trial (IST3) was designed to test alteplase administered to a wide range of patients, including those aged over 80, and up to six hours after stroke onset. Most previous trials assessing IV alteplase versus control within 6 hours of ischaemic stroke were limited to reported outcomes at 90 days, with none reporting outcomes beyond one year. The Lancet Neurology recently published useful long term clinical data regarding patient outcomes in this cohort at eighteen months post thrombolysis.

3035 patients were originally randomised to receive either alteplase or standard care alone. At 18 months, outcomes from 2348 patients were analysed, revealing there was no significant difference in mortality between treated patients and controls (35%). The number of patients alive and independent, as assessed by an Oxford Handicap Scale (OHS) score of 0 to 1, had not been significantly improved at the 6-month time point in the trial published last year. At 18 months however, this endpoint was significant. Furthermore, there were statistically significant and clinically relevant improvements in the health related quality of life of treated survivors as assessed by the Euro Qol instrument, with them having better functional outcomes, and requiring less help with ADLs, Mobility self-care, ability to perform usual activities, and pain and discomfort were all improved. However, this did not translate into a difference in the proportion of patients living at home as opposed to in care facilities post stroke.

Limitations in study design conceded by authors were that the patients weren’t blinded as to whether they had received thrombolysis...
Can Sudoku save your marbles?

Iris Murdoch is one of many towering intellects who sadly succumbed to the ravages of dementia in their later years. Yet the mass media is replete with headlines exhorting us to “use or lose it” claiming that everything from crossword puzzles to Nintendo games can stave off “The Big D.” With no disease modifying medications available to treat dementia, the idea of being able to modify our lifestyle factors in this way to prevent it, seems like an enticing yet somewhat implausible one.

Wilson et al sought to determine whether childhood (6–12 years), young adulthood (age 18), middle age (age 40), and late-life (current) engagement in cognitively stimulating activities delays late-life cognitive decline and if it is not linked to common neuropathologic measures of amyloid, tangles, cerebral infarcts and Lewy bodies. Utilising neuropathologic assessments on 294 individuals followed clinically every year on average 5.8 years before death, they were able to test the cognitive reserve hypothesis. Interestingly, their results supported the cognitive reserve hypothesis as people with current and early-life engagement in cognitively stimulating activities showed slower decline in cognition, despite the presence of underlying pathology. This raises the intriguing question of how cognitive reserve actually exerts an effect, if not through ameliorating the burden of pathology.


Is ALS a prion-like disorder?

Neurodegenerative diseases are characterised by pathological protein inclusions. The age-old question remains as to whether these inclusions are mechanistically involved in disease or not. In the case of ALS, the hallmark protein in 95% of cases is TDP-43. There has been much interest in the possibility that a prion-like process could explain the pathogenicity of this promiscuous RNA/DNA binding protein. A self-templating, prion-like process is attractive given that patients with ALS initially develop symptoms/signs at a single locus, and that the disease appears to ‘spread’ to contiguous anatomical regions. Such spread might also explain the clinicopathological overlap with FTLD-TDP: the primary motor cortex is of course part of the frontal lobe. Indeed, recent evidence has implicated axons as potential conduits for the spread of TDP-43 pathology (Brettschneider et al 2013). Furthermore, TDP-43 does have modest prion-like domains in hnRNPA2B1 and hnRNPA1. What is far less convincing is their ‘self-templating’ capacity. If the brain solution was first treated to remove TDP-43, it no longer print seen in the brain samples they add. If the disease appears to ‘spread’ to contiguous anatomical regions. Such spread might also explain the clinicopathological overlap with FTLD-TDP: the primary motor cortex is of course part of the frontal lobe. Indeed, recent evidence has implicated axons as potential conduits for the spread of TDP-43 pathology (Brettschneider et al 2013). Furthermore, TDP-43 does have modest prion-like domains in hnRNPA2B1 and hnRNPA1. What is far less convincing is their ‘self-templating’ capacity. If the brain solution was first treated to remove TDP-43, it no longer cause TDP-43 aggregation, demonstrating a specific effect of ALS brains in causing TDP-43 aggregation. What is far less convincing is their ‘self-templating’ capacity. If the brain solution was first treated to remove TDP-43, it no longer cause TDP-43 aggregation, demonstrating a specific effect of ALS brains in causing TDP-43 aggregation.

Prion-like Properties of Pathological TDP-43 Aggregates from Diseased Brains


Further experiments conducted by Nonaka et al (2013) showed that TDP-43 aggregates can ‘seed’ further TDP-43 aggregation. Similar experiments with brain extracts from Pick’s disease and DLB did not cause TDP-43 aggregation, demonstrating a specific effect of ALS brains in causing TDP-43 aggregation.

What is far less convincing is their ‘self-templating’ capacity. If the brain solution was first treated to remove TDP-43, it no longer cause TDP-43 aggregation, demonstrating a specific effect of ALS brains in causing TDP-43 aggregation.

Prion-like Properties of Pathological TDP-43 Aggregates from Diseased Brains


Further experiments conducted by Nonaka et al (2013) showed that TDP-43 aggregates can ‘seed’ further TDP-43 aggregation. Similar experiments with brain extracts from Pick’s disease and DLB did not cause TDP-43 aggregation, demonstrating a specific effect of ALS brains in causing TDP-43 aggregation.

What is far less convincing is their ‘self-templating’ capacity. If the brain solution was first treated to remove TDP-43, it no longer cause TDP-43 aggregation, demonstrating a specific effect of ALS brains in causing TDP-43 aggregation.