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The early biomarker challenge in neurodegenerative disorders

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Commentary

The early biomarker challenge in neurodegenerative disorders

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Strapline

Biomarkers sensitive to a longer 'compensated' presymptomatic phase of neurodegeneration are needed for preventative therapy development.

Main text

MRI studies have reported structural (2) and functional (3) changes in asymptomatic carriers of highly-penetrant genetic mutations associated with frontotemporal dementia (FTD) and the clinicopathologically-related neurodegenerative disorder amyotrophic lateral sclerosis (ALS). The interpretation of data from cross-sectional studies is hampered by the varying age of participants at the time of testing and the penetrance of the genotype, with inconsistent approaches to statistical modelling (4). In this issue, Feis and colleagues applied a combined structural and functional MRI protocol longitudinally to a cohort of 55 asymptomatic carriers of genetic mutations (*GRN*, *C9orf72* or *MAPT*) associated with FTD (1). Significant MRI changes

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emerged in the months prior to symptom onset in the small sub-group of converters arising during the study period.

A criticism of the study (acknowledged in the discussion) is that a behavioural variant FTD (bvFTD) classification model was applied to a heterogeneous group in which *C9orf72* hexanucleotide expansion carriers (the most relevant to bvFTD) represented only 20% with no converters. Whether an alternative MRI-based classification model might be more sensitive to earlier changes requires the study of larger, genotypically homogeneous groups. However, single-centre longitudinal studies are unlikely to generate sufficiently large converter numbers over a practical time frame. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is the exemplar of what might be possible through international sharing of asymptomatic carrier data.

Intuitively there is a large functional reserve in the human nervous system, so that the emergence of symptoms in neurodegenerative disorders represents a very late stage of neuronal loss that may have been underway for many years. The very existence of highly-penetrant single gene mutations associated with late-onset

neurodegenerative disorders is a core conundrum. Such genes influence (and sometimes directly encode) ubiquitously-expressed molecules with apparently fundamental cellular roles, such as the DNA binding protein TDP-43 found as cytoplasmic aggregates in 97% of all ALS and 50% of all FTD cases, yet such mutations are not embryonically lethal. The latency of decades in terms of overt clinical presentation suggests that neurodegeneration may fundamentally involve a loss of tolerance to congenital cellular perturbations. The dipeptide repeat hallmarks of *C9orf72* expansion-related neurodegeneration (the commonest cause of hereditary ALS and FTD) are detectable in asymptomatic carriers likely to be decades away from symptom onset (8, 9).

There might be a gradual depletion of mitigating cellular resources over decades (with independent genetic determinants), or a more abrupt decompensation through accumulation of a final 'hit' in a multi-step model of pathogenesis. Either way, delicately-poised and 'compensated' cellular equilibria are then pushed into a runaway phase which may be associated with an apparently abrupt onset of symptoms in the most aggressive of the neurodegenerative disorders.

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Neurophysiological studies have noted an apparently sharp drop in motor unit number estimates (5), and an increase in cortical excitability (6), in the few months prior to the emergence of weakness in presymptomatic carriers of ALS-causing gene mutations. At the molecular end of the spectrum, neurofilament levels (thought to be a surrogate marker of neuronal degradation) also appear to rise just prior to symptom onset (7). To assume that everything was ‘normal’ prior to *per-* symptomatic observations of change may be erroneous. Neuronal loss in the months before symptoms may simply have reached the threshold of sensitivity for the investigative tools currently available, including MRI, whether or not the preceding trajectory of loss was gradual over decades or more abrupt.

Understanding the molecular to systems-level functional underpinnings of what might be a lengthy ‘compensated’ phase of neurodegeneration may be essential to developing preventative strategies. Importantly, this period is likely to involve biomarkers entirely different from those that define the late, symptomatic phase of neurodegeneration. The emergence of psychiatric symptoms in those at high risk of, or going on to develop FTD (10) and ALS (11, 12) offer a clue to the existence of

much earlier changes in cerebral function. Metabolic pathways are another area of intense interest as a source of much earlier biomarkers (13, 14). Developments in the application and analysis of encephalographic imaging sensitive to neuronal oscillatory and network dynamics currently have the greatest potential to detect subtle systems-level changes (15, 16). Such biomarkers will be needed to build proof-of-benefit confidence in any vision of applying rapidly-emerging genetic therapies, such as antisense oligonucleotides, to presymptomatic individuals over potentially decades. These biomarkers might ultimately be applicable to mass population screening, providing evidence of early rescuable loss of synaptic integrity, towards the goal of prevention in neurodegenerative disorders more widely.

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