BRAIN
SCIENTIFIC COMMENTARY

Where have prions been all our lives?

This scientific commentary refers to 'Seed amplification and neurodegeneration marker trajectories in individuals at risk of prion disease' by Mok et al. (https://doi.org/10.1093/brain/awad101).

Pathogenic mutations in the prion protein gene (PRNP) cause a neurodegenerative illness that is often shocking in its rapidity, stripping patients of all of their faculties within a few months. This steep decline seems all the more exceptional for the lack of forewarning: despite harbouring the mutations from conception, individuals remain completely healthy for decades before this sudden onset. Do these individuals spend their whole lives in a 'silent incubation' state equivalent to that in acquired prion disease or in animal models? Or, is the period of prodromal pathology as brief as the symptomatic disease course? In this issue of Brain, a longitudinal study of at-risk individuals from Mok and colleagues[1] sheds new light on this mystery.

The authors followed 69 individuals at risk for genetic prion disease—known mutation carriers as well as those at 50% or 25% risk. Sixteen individuals developed active disease, providing a glimpse of biomarker changes on the trajectory to symptom onset. Key findings revolve around three markers: neurofilament light (NfL), a marker of neuronal damage in CSF and plasma; glial fibrillary acidic protein (GFAP), a marker of neuroinflammation in plasma; and prion 'seeds' detected by real-time quaking-induced conversion (RT-QuIC) in CSF.

For individuals with P102L, a PRNP mutation associated with slowly progressive disease (median survival 5 years[2]), plasma and CSF NfL appeared to rise relative to individual baseline—though usually still within the range of normal controls—perhaps 2.5 years before onset. Plasma GFAP kinetics for P102L were similar, with perhaps a whiff of even earlier change in a few individuals. In contrast, for individuals with E200K, a PRNP mutation causing rapidly progressive disease (median survival 0.5 years[2]), prodromal increase in NfL, if any at all, occurred only a few months before onset.

Prodromal periods detectable by increased NfL have been quantified in a handful of other dominant, adult-onset neurodegenerative diseases in recent years.[3-5] Comparison of the data in the current study with these examples suggests that prion disease, even in its exceptional swiftness, may conform to a more general correlation across neurodegenerative diseases: the duration of neuronal damage preceding onset appears to be related to how rapidly fatal each disease is after onset (Fig. 1).

From first principles, neuronal damage should be secondary to derangement of disease-causing proteins. Detection of disease-specific biomarkers more directly tied to the underlying pathological process might be hypothesized to define an even earlier prodromal state. To date, however, neither amyloid-β deposition in early-onset Alzheimer's disease, nor increased mutant huntingtin release into CSF in Huntington's disease, have been detected any earlier than increased plasma NfL.[3,4] In contrast, Mok et al.[1] report that prion seeding activity was detected by RT-QuIC in the CSF of three asymptomatic PRNP E200K individuals. One went on to develop active disease within just a few months, but the other two remained asymptomatic at last follow-up more than 3 years later. This may mirror animal models, where plasma NfL rises only after a period of silent prion replication.[9]

It would follow logically that a lengthy period of prion replication might precede the inflection in NfL in P102L individuals as well. Unfortunately, standard RT-QuIC conditions have very limited sensitivity for prions associated with any PRNP mutation other than E200K, even in the symptomatic phase. In recognition of this need, Mok et al.[1] developed a customized RT-QuIC assay for P102L, which performed more sensitively than standard RT-QuIC conditions. While its identification of four of nine symptomatic P102L patients leaves further room for improvement, this story offers hope that custom RT-QuIC conditions may yet broaden the assay's applicability to additional genetic subtypes.

While the new findings provide a hint of a prion disease prodrome, much work remains. The prognostic value of prion seeding activity in CSF in presymptomatic E200K individuals must be established: by how many years does seeding precede onset, and is this time window dependent upon codon 129 genotype, which modifies disease duration in E200K disease?[2] For the phase of NfL and GFAP increase in P102L, Mok and colleagues[1] note that the prodromal state is most clear in retrospect. Frequent monitoring, and a deeper trove of natural history data, will be needed to improve predictions as to when an 'elevated' reading still within the range of healthy controls counts as a prodromal sign. Importantly, we still lack any ability at all to detect prodromal states in individuals with other PRNP mutations, including D178N and octapeptide repeat insertions (OPRI). The reported efforts did not identify sensitive RT-QuIC conditions for these mutations, nor any clear presymptomatic increase in plasma NfL or GFAP.

The impact on therapeutic development strategy is complex. The new data confirm that, cross-sectionally, a large majority of the presymptomatic at-risk population is negative for pathological biomarkers at any given time.[10] Thus, in this already rare disease, restricting prevention trials to only prodromal individuals is unlikely to enable well powered trials. Age of symptom onset in genetic prion disease is highly variable and currently unpredictable,[2] meaning that following presymptomatic individuals to an end point of disease onset or, by extension, prodrome onset, may be numerically infeasible. In addition, the benefit of therapy in mouse models is maximized with early treatment; intervention after detectable neuropathology confers a more modest benefit.[9] Thus,
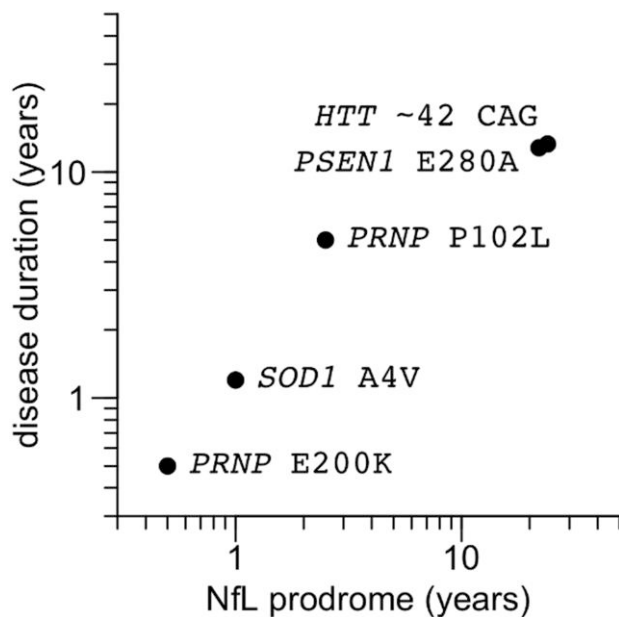
Figure 1 Correlation between prodromal period detectable via NfL and disease duration. Neurofilament light (NfL) data from Mok *et al.*,[1] Quiroz *et al.*,[3] Scahill *et al.*[4] and Benatar *et al.*;[5] and disease duration data from Minikel *et al.*,[2] Bali *et al.*,[6] Ryman *et al.*[7] and Langbehn.[8] Data and source code for this figure are available at https://github.com/ericminikel/mok_commentary.

waiting for prodromal change to begin treatment might not best honour the opportunity for prevention in at-risk individuals. One possibility is that detection of prodromal pathology in presymptomatic carriers could justify compassionate treatment, either as an off-ramp from randomized trials or as an adjunct to trials in symptomatic patients with experimental agents whose safety data do not yet justify testing in non-prodromal presymptomatic individuals. Any changes in prodromal markers, even in a small number of treated individuals, could provide valuable insights to inform clinical development strategy and regulatory decisions.

The time, effort, CSF and blood that at-risk individuals donate to research are precious gifts. We applaud the at-risk community for participation in this study and others like it. For researchers, the mandate is clear: we must extend and expand our efforts to longitudinally monitor at-risk individuals in order to build a deeper understanding of the natural history leading up to genetic prion disease. While it is impossible to repay the gift given by patients who converted to active disease, our shared goal must be to pay it forward to still healthy at-risk people, leveraging these insights as one tool in the effort to prevent this cruel disease from claiming their lives—or their brains.

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