Beyond the Frontotemporal Dementia Umbrella: Time for a Biological Definition?

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INTRODUCTION: THE MYTH OF A SINGLE FTD

The reader will permit the author to introduce this letter with a digression: to mark the release of a Hollywood film based on Homer's 'The Odyssey', I recently undertook a rereading of the epic poem. I also revisited the long-standing debate surrounding Homer himself and found that, despite centuries of scholarship and enduring uncertainty, two assertions are still commonly repeated: on one hand, many experts argue that Homer was not a single person, but rather the product of a long oral tradition involving generations of storytellers. On the other hand, he is frequently described as having been blind. Taken together, these two notions appear contradictory, yet both continue to coexist in the popular and academic imagination.

A similar phenomenon can be observed in frontotemporal dementia (FTD). Over the last two decades, genetic, pathological, and molecular research has provided overwhelming evidence that FTD is not a single disease entity. The deposition of distinct proteins in the brain, including tau, transactive response DNA binding protein of 43 kDa (TDP-43), and group of FUS, EWS, and TAF15 (FET) proteins, and the observation that diverse genetic mutations acting through different pathogenic mechanisms can lead to comparable clinical syndromes strongly support this conclusion.[1] Nevertheless, a huge amount of the current literature (including papers authored by the present writer) continue to draw conclusions about FTD as if it were a single disease. The following are a few examples extracted from manuscripts from this work's author (selected in order to not offend other authors): "the inexistent correlation with Mini-Mental State Examination (MMSE) scores in patients with FTD could be due to the fact that MMSE is not a sensitive cognitive measure in these patients"[2] or "the scale was not able to discriminate Alzheimer's disease from FTD."[3] These sentences consider FTD as a single entity when it is now evident that it is not. These conclusions might be valid for some forms of FTD but not for others. Another example: in recent years, it has been repeatedly stated that FTD and amyotrophic lateral sclerosis are part of the same continuum. While this is undoubtedly true for some forms of FTD, it is not true for all of them; patients with tauopathies, for example, do not develop amyotrophic lateral sclerosis as part of the natural

history of their disease. In this context, continuing to group fundamentally different biological entities under a single label risks becoming the equivalent of comparing apples and oranges.

LOOKING BENEATH THE FTD UMBRELLA

The reason why we continue to make such generalisations is obvious: our ability to distinguish these diseases during life remains limited. Current diagnostic frameworks still rely primarily on clinical syndromes rather than underlying biology. However, the emergence of disease-modifying therapies is exposing the limitations of this approach. A syndrome-based classification that was entirely appropriate a decade ago may no longer be sufficient in the era of precision therapeutics. Even the major clinical syndromes included under the FTD umbrella, the behavioural variant of FTD and semantic variant primary progressive aphasia, and non-fluent/agrammatic primary progressive aphasia, have repeatedly been shown to be associated, albeit with varying degrees of overlap, with different underlying neuropathological processes. As therapeutic strategies increasingly target specific proteins or molecular mechanisms, the need to identify these biological substrates *in vivo* becomes paramount. Clinical trials directed against tau pathology, for example, require participants with tau-related disease, not simply patients fulfilling clinical criteria for FTD. The continued use of FTD as a biologically nonspecific category may therefore become an obstacle to therapeutic development.

A similar paradigm shift has already taken place in Alzheimer's disease, where biological definitions based on biomarkers have progressively complemented and, in some contexts, surpassed purely clinical definitions. FTD research is now approaching a comparable turning point. Although molecular classification remains imperfect and many patients cannot yet be assigned with confidence to a specific pathology during life, the scientific evidence accumulated over recent years is sufficient to begin building biologically informed diagnostic frameworks.

The current diagnostic criteria for FTD syndromes, established in 2011, have proven enormously valuable for the syndromic diagnosis of thousands of patients worldwide.[4,5] However, their capacity to predict the underlying molecular pathology remains limited, particularly in behavioural variant of FTD. Advances in the treatment of neurodegenerative disorders now call for a new generation of diagnostic criteria aimed not merely at identifying syndromes, but at estimating the biological disease process driving them. Future efforts should focus on the development of diagnostic criteria for specific molecular subtypes, such as 3-repeat tauopathies, 4-repeat tauopathies, TDP-43 subtype A, B, and C proteinopathies, among others. These criteria should adopt a multimodal approach, integrating clinical features, genetics, neuroimaging, and fluid biomarkers. Importantly, this effort does not start from a position of ignorance. The scientific community has already accumulated substantial knowledge regarding clinicopathological associations. For example, the presence of progressive supranuclear palsy-like features may increase the likelihood of an underlying 4-repeat tauopathy, whereas isolated and asymmetric anterior temporal lobe atrophy may suggest TDP-43 Type C pathology. While no single feature is likely to provide sufficient diagnostic certainty, combining multiple sources of evidence could enable the development of biologically informed diagnostic frameworks capable of predicting the underlying disease process during life.

The discovery and validation of fluid or neuroimaging biomarkers will undoubtedly accelerate this transition. A significant amount of research is currently being conducted with the aim of identifying biomarkers that will enable clinicians to differentiate between tau, TDP-43, and FET forms of FTD. In the last few years, some biomarkers have shown promising results.[6-8] In parallel, large collaborative initiatives such as the Horizon Europe-funded PREDICT-FTD consortium are expected to play a key role in validating existing biomarkers and discovering new ones.[9]

CONCLUSION

The question is no longer whether FTD represents a single disease or a collection of distinct disorders; the evidence has largely answered that question already. The challenge now is to translate this knowledge into diagnostic criteria, research strategies, and therapeutic trials that reflect the biological heterogeneity of the disease. As the field moves towards precision medicine, reliance on syndromic definitions alone is becoming increasingly insufficient.

The future of FTD research and treatment will depend on our ability to identify the molecular pathology underlying each clinical presentation and to develop biologically informed frameworks for diagnosis and patient selection. Just as the figure of Homer conceals a more complex reality than traditionally assumed, the term FTD encompasses a range of distinct diseases that must be recognised and studied individually if truly targeted therapies are to become a reality.

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