

How far can biomarkers take us in neurodegenerative disorders?

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It is difficult to miss. The rise and rise of biomarkers in neurodegenerative disorders is seemingly like a juggernaut, unstoppable in its momentum, sweeping all aside in its path. In Alzheimer's disease (AD), where the project is at its furthest, it has undoubtedly made significant contributions (Frisoni *et al.*, 2017). Biomarker research has galvanized interest in attempts to detect patients at an earlier, prodromal stage; provided selection criteria for clinical trials to reduce heterogeneity within study populations; and potentially begun to assist clinicians in making a diagnosis.

In some academic centres, structural MRI and FDG PET (fluorodeoxyglucose positron emission tomography) is combined with CSF measurements of tau and amyloid α -beta as routine practice. In addition, patients undergoing investigation for possible AD may be offered amyloid or tau PET imaging. In other conditions too, e.g., dementia with Lewy bodies (McKeith *et al.*, 2017) or frontotemporal dementia (FTD) (Meeter *et al.*, 2017), there is a surge of interest in using combinations of biomarkers to assist particularly in early diagnosis. But even in the Alzheimer's field the validity and utility of fluid and imaging biomarkers remain to be properly defined and established, with some clinicians questioning how much these investigations add – both to diagnostic certainty and health care costs. Hence the publication of a recent strategic roadmap of how to take this endeavour forward (Frisoni *et al.*, 2017).

Perhaps less to the forefront in current debates is the question of the scientific value of biomarkers. Put simply, what do they explain? This might be considered a harsh question, given unquestionable needs to develop better tools for ante-mortem diagnosis in clinical care, prognostic stratification and inclusion in treatment trials. Nevertheless, this might be an appropriate moment to reflect on such issues. Because biomarker research is increasingly likely to define the direction of travel of clinical research in neurodegenerative conditions, we should be questioning what it might help to explain.

Can biomarkers account for the diversity of clinical phenotypes associated with a disease? It is now very evident from post-mortem studies that one particular pathology

can map to many different phenotypes. In AD, in addition to the more typical amnesic presentations, there can be a wide range of different phenotypes, including prominent disturbances in vision (posterior cortical atrophy), language (logopenic primary progressive aphasia), behaviour and executive function (frontal variant) or even a movement disorder (corticobasal syndrome). In FTD too, it has become clear that the same underlying pathology can lead to a variety of different clinical syndromes with different patterns of regional brain atrophy (Mann and Snowden, 2017). While biomarkers might improve confidence in clinical diagnoses, especially in difficult, atypical cases, can they account for the diversity of presentations of the same pathology?

This really requires some relationship between biomarker, brain region and behaviour. Fluid biomarker levels, of course, would be hard pressed to capture variation in regional brain atrophy and therefore are very unlikely to account for variations in AD phenotype. Until recently, only conventional structural MR imaging would be considered to present a means of doing this, since amyloid PET imaging has also failed in this regard. But two reports have now presented evidence that tau PET imaging can demonstrate regional variations consistent with the type of atypical AD syndrome observed in individual cases (Ossenkoppele *et al.*, 2016; Xia *et al.*, 2017).

A new study in this edition of *Brain* also examined relationships between performance in different cognitive domains and regional variations in tau (18F-AV-1451) or amyloid (11C-PiB) ligand uptake, but this time in more typical presentations of mild cognitive impairment (MCI) and AD (Bejanin *et al.*, 2017). The findings suggest that the pattern of regional variation on tau PET imaging has a strong relationship to cognitive performance, whereas this is not the case for the amyloid ligand. If verified, these results obtained *in vivo* would point to a far more causal role for tau than amyloid deposition in cognitive impairment.

These reports therefore suggest that perhaps one biomarker – tau PET imaging – might have potential to account for variations of phenotype associated within a disease (AD). But what about the converse? Can biomarkers account for the fact that different pathologies can present with the same phenotype? For example, a large study of behavioural variant FTD in this issue of *Brain* presents findings that show how diverse pathologies and genetic mutations can all lead to the same clinical diagnosis (Perry *et al.*,

2017). Indeed, structural MR imaging revealed also that these patients share similar patterns of brain atrophy. Again, it is difficult to imagine how fluid biomarkers might ever explain how different pathologies could lead to the same phenotype. Although tau pathology occurs in some types of FTD, and therefore tau PET imaging might potentially be able to assist in distinguishing between molecular aetiologies, two recent papers have raised concerns on this front.

Both of them report data on 18F-AV-1451 PET imaging in the semantic dementia (SD), which is the one variant of FTD that consistently has *not* been associated with tau pathology. Instead it is predominantly a TDP-43 (TAR DNA-binding protein-43) disease (Bevan-Jones *et al.*, 2017; Makaretz *et al.*, 2017). However, both groups show elevated tau ligand binding, largely co-localised with atrophy, in SD. These findings call into question the specificity of tau PET imaging, but further investigations will be required before any definitive conclusions can be made. Until then, physicians have no reasons to be concerned that the combination of clinical – including neuropsychological – assessment, structural MRI, FDG PET and perhaps genetics has now been surpassed in the diagnosis of FTD (Foster *et al.*, 2007; Meeter *et al.*, 2017).

One final question on scientific value: Is it possible to track the trajectory of pathology *in vivo* with biomarkers in order to obtain a better understanding of the sequence of events that occurs in a neurodegenerative condition? Earlier this year another paper in *Brain* offered a glimpse of this possibility (Tosun *et al.*, 2017). The authors reported a combined tau and amyloid PET imaging study on a group of healthy people and those with MCI. Although this was not a fully longitudinal study for both imaging modalities, it showed that over a period of two years, an increase in amyloid in the precuneus and lateral temporal cortex was associated with greater levels of tau in temporoparietal regions. Moreover, the latter showed a strong relationship to episodic memory performance, whereas amyloid levels did not. These important findings are suggestive of a sequence of events in which amyloid deposition might come before tau, which in turn has the major impact on cognitive function. But they also should be interpreted with caution. It is to be anticipated that further data using dual PET imaging are likely to emerge over the next few years to help in evaluation. Until that stage we have to conclude that biomarkers have yet to show us *in vivo* evolution of disease in a manner that sheds new light on pathophysiology.

Both the clinical and scientific roles of biomarkers in neurodegenerative diseases are clearly at interesting stage. It would be impressive if research in the next few years is able to build in terms of scientific contribution on the enormous amount that has already been achieved from a methodological point of view. As should be plain, this is not going to be easy, particularly when it is now abundantly clear that many patients who present with progressive cognitive and/or movement disorders actually have not one, but several underlying brain pathologies. Nevertheless, challenging though the prospects are, there is both momentum and desire to drive the enterprise forward. We just need to keep a sense of perspective as the juggernaut rolls on.

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