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Scientific Commentary

A broader view of dementia – multiple co-pathologies are the norm

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Alzheimer's disease and other dementias are defined by hallmark protein abnormalities found in brain tissue post mortem. Despite increasingly accurate diagnosis of primary pathology in life, treatments targeting the underlying protein abnormalities in Alzheimer's disease have so far not worked. Why is dementia proving so hard to treat? One argument is that treatments are given too late in the course of illness – by the time of diagnosis, disease has progressed for a decade or more, has initiated self-perpetuating secondary processes and is no longer modifiable. A related, but distinct argument is presented in this issue by Robinson and co-workers, who demonstrate concurrence of multiple different abnormal proteins in dementias such as Alzheimer's disease, hinting at the likelihood that treatment might require a multi-pronged approach (**REF – Robinson et al**).

Accuracy of clinical diagnosis.

Brains from 766 people who had died with dementia, and age-matched controls, were classified using standard diagnostic criteria as having either a neurodegenerative disease or minimal pathology. As in previous studies, the clinical and neuropathological diagnoses did not always agree. For example, high levels of Alzheimer's disease pathology at post-mortem examination had only a 79% sensitivity and 59% specificity for a clinical diagnosis of Alzheimer's disease. The figures are in keeping with those of other large clinico-pathological studies (e.g. Beach et al. 2012). 14% of brains with high levels of Alzheimer's disease pathology came from patients who had been diagnosed clinically as having frontotemporal dementia. This highlights the complexity and imprecision of clinical diagnosis, even in the best centres, and the importance of moving to molecular markers of disease processes that cause dementia to ensure the right patients enter the right trials.

Ubiquity of tau

A striking finding was that neuronal accumulation of tau protein was almost universal, even in the minimal pathology group, within which neurofibrillary tangles were found in 93% of brains. Neurofibrillary tangles were present in at least 88% of brains with all other primary pathologies, and some of these – frontotemporal dementia and Lewy body diseases in particular – had tau co-pathology in 100% of cases. The prevalence and extent of neuronal tau pathology increased with age and incipient Alzheimer's disease. Robinson et al did not address the relevance of astroglial tau, which also increases with age. One argument is that neuronal tau (i.e. neurofibrillary tangles and neuropil threads) mediates disease whereas tau in astroglial cells is probably incidental, whether age-related or associated with other neurodegenerative processes (Kovacs et al. 2016). However, this remains to be determined and is important if we are to optimise treatments for dementia.

Is co-pathology a significant factor in disease presentation?

Largely, the extent of co-pathology in the disease groups was similar to that in the minimal pathology group, arguing against a significant role for co-pathology in the emergence of disease (**See Table 1 of Robinson et al**). However, in some diseases the frequency of co-pathology significantly exceeded levels expected by chance. Neocortical Lewy body disease, often associated with Lewy body dementia, was accompanied by Aβ plaque pathology in 80% of cases (as opposed to 50% of the minimal pathology cases) and TDP pathology in 22% of cases (compared to 1% in the minimal

pathology group). Co-pathology in Lewy body disease was associated with faster decline in cognitive and motor scores, suggesting that the co-pathology may be important not only in expression of disease but also for effective targeting of treatment. Similarly, Lewy bodies and TDP 43 pathology were more common in Alzheimer's disease. However, as assessments of cognitive function in Alzheimer's disease ceased 3.5 years before death, it is not clear how much co-pathology affected the rate of disease progression.

These findings support a large body of literature on interrelationships between Aβ, tau, Lewy body and TDP pathology. Multiple post-mortem studies have shown that most patients with Lewy body disease have Aβ plaques and over half of Alzheimer's disease patients have some Lewy body pathology (see (Swirski et al. 2014)). The acceleration of cognitive decline in Lewy body disease patients with co-pathology is in keeping with previous observations (Halliday et al. 2008). Other evidence points to an interaction between TDP pathology and clinical severity of Alzheimer's disease (James et al. 2016).

The reasons for the clinical and pathological synergism between Alzheimer's disease and Lewy body disease are not fully understood but there is both circumstantial and experimental evidence of interaction between the Aβ and α-synuclein metabolic pathways. Lewy bodies tend to be more numerous in Lewy body patients who also have Aβ plaques (Pletnikova et al. 2005) and α-synuclein can be detected within some plaque-associated dystrophic neurites (Wirths et al. 2000). The predominant modification of α-synuclein in Lewy body diseases is phosphorylation at Ser129, which is thought to promote the aggregation of α-synuclein to form Lewy bodies. Swirski et al. (2014) found that the concentration of insoluble phospho-Ser129 α-synuclein correlated positively with the levels of Aβ in most regions of cerebral cortex, and aggregated Aβ42 increased the phosphorylation of α-synuclein at Ser129 in vitro. These data suggest that accumulation of fibrillar, plaque-associated Aβ promotes Lewy body formation, causally linking proteinopathies of Alzheimer's and Lewy body diseases.

A missing link?

A striking exclusion from this publication is any reference to vascular disease, whether disease of vessel walls (atherosclerosis, arteriolosclerosis, amyloid angiopathy) or ischaemic and haemorrhagic parenchymal abnormalities. The study also excluded hippocampal sclerosis, an under-recognised contributor to cognitive impairment which may overlap TDP or ischaemic vascular pathology. While incorporating vascular data would have added to the complexity of an already dense dataset, the omission of this information leaves a large gap.

There is increasing evidence that (presumed) ischaemic white matter abnormalities are integral to the progression of Alzheimer's disease, and contribute to the clinical symptomatology (Sarro et al. 2017). In people with mutations causing autosomal dominant forms of the disease, cerebral hypoperfusion and white matter hyperintensities are demonstrable many years before the onset of dementia. The volume of white matter abnormalities is also significantly increased in patients with sporadic Alzheimer's disease (Pietroboni et al. 2018).

Documenting the pathological associations and establishing the mechanisms of white matter damage are clearly critical if we are to develop effective treatments for dementia. At present, it is not clear to what extent different factors contribute to white matter lesions in Alzheimer's disease (**Box 1**). It is also unclear to what extent cerebral hypoperfusion exacerbates the progression of neurodegenerative disease processes such as the accumulation of Aβ, tau and α-synuclein.

Some clinical studies have found white matter damage to relate to Aβ accumulation (or, at least, to reduction of Aβ42 in the cerebrospinal fluid) (Pietroboni et al. 2018), perhaps reflecting altered cerebrovascular responsiveness. Others have found a stereotypical pattern of white matter abnormalities associated with cortical atrophy (Jang et al. 2017), but not in a distribution that would explain the white matter changes simply on the basis of neuronal injury (e.g. tau-mediated) with secondary axonal degeneration.

Robinson et al did not report on white matter damage in Alzheimer's disease, Lewy body diseases or other forms of dementia. Progress on this front is urgently required, as it is critical for treatment, and will require detailed mapping of the topographic and quantitative relationships between white matter demyelination or loss, vascular pathology, ischaemic and degenerative changes, and abnormal protein accumulations, in future large-scale post-mortem studies.

Therapeutic implications

Differential diagnosis in dementia is largely based on identifying a clinical syndrome through history taking, examination and neuropsychology. Dementia mimics are excluded with blood tests and, usually, a CT brain scan. Given the body of neuropathological work that points towards the multiplicity of co-pathologies that can impact on disease progression in dementia, is it time to review the clinical approach? Perhaps we should aim to classify patients clinically according to their spectrum of pathological change, rather than trying to fit them into eponymous syndromes (**Figure 1**). For example, a patient with predominantly Alzheimer's disease pathology could be classified as having dementia associated with amyloid and neuronal tau, with or without α-synuclein, TDP-43 and vessel wall or ischaemic parenchymal disease. We are rapidly acquiring the technology to identify most of these changes in life – such as lumbar puncture for analysis of tau, Aβ and other proteins or peptides in cerebrospinal fluid or amyloid PET. Treatment trials could be targeted to the brain changes in each individual. As we learn more about important pathological factors in dementia evolution, the classification system could be updated to incorporate new knowledge. A shift to a more nuanced, personalised disease classification of dementia at the earliest possible stage of disease might revolutionise therapeutics.

Box 1

Possible mechanisms of white matter damage in Alzheimer's disease include -

- Neuronal pathology in the cortex resulting in secondary axonal atrophy and degeneration
- Vessel wall pathology (particularly cerebral amyloid angiopathy and arteriolosclerosis)
- Extracranial factors such as altered cardiovascular autonomic regulation and associated postural hypotension
- Abnormal regulation of neurovascular coupling, of which possible causes include not only structural disease of arteriolar and capillary walls but also overproduction of vasoconstrictors such as endothein-1 and angiotensin II (both upregulated in Alzheimer's disease). The NIHR-funded RADAR trial is already testing the prediction that an angiotensin receptor blocker, losartan, might delay the progression of Alzheimer's disease.
- Reduced cholinergic innervation of intracerebral blood vessels
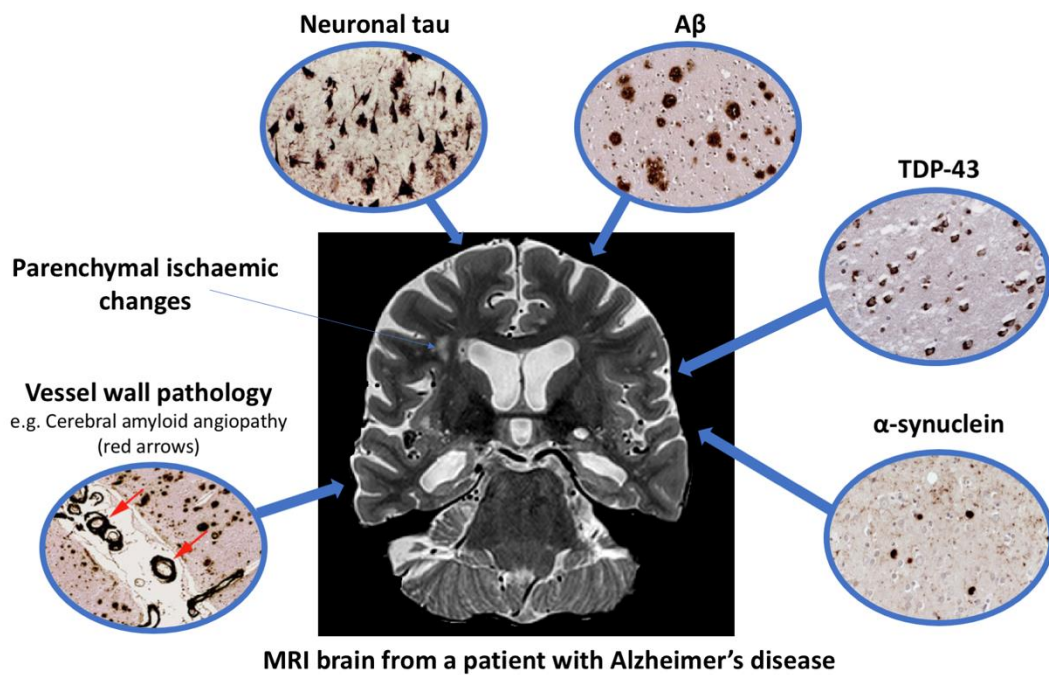- Reduced production of nitric oxide.

Figure 1 Multiple pathologies in the brain in Alzheimer's disease. MRI scan from a patient with Alzheimer's disease shows generalised brain atrophy particularly affecting the hippocampi, parahippocampal gyri and entorhinal cortices and a few white matter hyperintensities (arrow to parenchymal ischaemic changes) suggestive of mild vascular disease (note the distinct hyperintensity in basal ganglia is a perivascular space). Vessel wall changes, parenchymal ischaemic changes, α-synuclein, and TDP 43 may have all contributed to decline in this patient, in addition to the accumulation of Aβ and tau that are the 'hallmark' proteins of Alzheimer's disease.

MRI reviewed by Dr Marcus Likeman, neuroradiologist.

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