By 12 months after injury, the deposits had spread widely through the brain, including the hemisphere contralateral to the original injury.

To find out whether the TBI-induced P-tau exhibited self-propagating 'prion-like' behaviour, the researchers injected brain homogenates from the injured hemisphere into the brains of wild-type mice. At 12 months post-inoculation, widespread P-tau deposition, accompanied by evidence of synaptic loss, was observed in the brains of the recipient mice. In addition, these mice displayed persistent memory deficits.

"The observation that TBI generates a neurotoxic self-propagating form of tau indicates that blocking tau propagation may have therapeutic effects," comments Zanier. "We are planning a series of collaborative studies to test candidate agents with the potential to interfere with progression of tau pathology."

Heather Wood

> we sought evidence of … self-propagating tau pathology in wild-type mice subjected to severe TBI

ORIGINAL ARTICLE Zanier, E. R. et al. Induction of a transmissible tau pathology by traumatic brain injury. *Brain* https://doi.org/10.1093/brain/awy193 (2018)

by the presence of AD pathology. "We also demonstrated that the independent link between *APOE**ε4 and TDP43 proteinopathy contributes to the worse cognitive trajectory associated with *APOE**ε4," says Yang. "Our results imply that TDP43 proteinopathy is another *APOE*-related neurodegenerative proteinopathy."

The analysis also revealed that TDP43 pathology explained a large proportion of the association between *APOE**ε4 and hippocampal sclerosis. "This result strongly suggests that TDP43 proteinopathy has a causal role in hippocampal sclerosis," concludes Yang.

The researchers say that their findings demonstrate a need to consider TDP43 pathology when investigating AD and other neurodegenerative diseases. "Our findings will hopefully contribute to the development of disease-modifying therapies in AD and other age-related neurodegeneration," remarks Yang.

Ian Fyfe

> TDP43 proteinopathy is another *APOE*-related neuro-degenerative proteinopathy

ORIGINAL ARTICLE Yang, H.-S. et al. Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to *APOE* ε4 haplotype status: a community-based cohort study. *Lancet Neurol.* https://doi.org/10.1016/S1474-4422(18)30251-5 (2018)

MULTIPLE SCLEROSIS

A new subtype of multiple sclerosis?

A novel subtype of multiple sclerosis (MS) called myelocortical MS (MCMS), in which cortical neuronal degeneration is independent of cerebral white matter demyelination, has been proposed on the basis of new findings. The observations have implications for our understanding of MS and its pathomechanisms, and for the design of future clinical trials.

Demyelination of cerebral white matter is considered to be the hallmark of MS, whereas neuronal degeneration is the main cause of disability. Demyelination is often assumed to lead to neuronal degeneration, but evidence that supports this link is lacking and the causal relationship between the two processes remains unclear.

In their new study, Bruce Trapp and colleagues at Cleveland Clinic investigated this relationship by examining pathology in post-mortem brains of people with MS. "This project was initiated by the observation that one post-mortem MS brain did not have visible lesions of the brain white matter but did have spinal cord demyelination," explains Trapp. "We looked for additional similar cases."

The researchers retrospectively analysed the brains and spinal cords of 100 patients with MS who died between 1998 and 2012. Inspection of 1 cm slices identified 12 brains in which no cerebral white matter lesions were visible. These brains were classed as being from patients with MCMS. The pathological features of these brains were compared with 12 brains that contained typical MS cerebral white matter lesions. Both sets of brains were compared with eight post-mortem brains in which there were no signs of neurological disease.

The comparison confirmed that cerebral white matter lesions per brain hemisphere were fewer in the brains from people with MCMS than in brains from people with typical MS. However, demyelination was prominent in the spinal cord in both sets of patients and neuronal density in cortical slices was significantly lower in both sets of brains from patients than that in brains from controls. In MCMS brains, neuronal density was reduced in cortical layers III, V and VI, whereas density was low only in layer V in typical MS brains.

"MCMS is a new variant of MS that was present in 12% of our post-mortem MS cohort," says Trapp. "Our findings show that neurodegeneration and demyelination can be independent events in MCMS."

The researchers also assessed post-mortem MRI scans that had been taken before the brains were removed. The scans revealed cerebral white matter MRI abnormalities even in brains with no visible cerebral white matter pathology. "This finding suggests that the white matter MS lesions as we know them are not necessarily demyelinated and that some other process, perhaps in the axon itself, is at play," says Trapp.

This observation has implications for previous clinical trials because the patient groups are likely to have included subgroups with different extents of demyelination that could not be distinguished by MRI. "There is an important need for more specific MRI modalities that reliably delineate myelinated and demyelinated white matter," says Dan Ontaneda, the neurologist who clinically characterized the patients with MCMS. "We are using the pathological samples from patients with MCMS and typical MS to identify MRI measures with specificity for myelin content that may allow future identification of MCMS in vivo."

Ian Fyfe

ORIGINAL ARTICLE Trapp, B. D. et al. Cortical neuronal densities and cerebral white matter demyelination in multiple sclerosis: a retrospective study. *Lancet Neurol.* https://doi.org/10.1016/S1474-4422(18)30245-X (2018)