Stop inflammation and you stop neurodegeneration in MS - No

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Neuroinflammation is present at all stages of multiple sclerosis. It is an important driver of the loss of tissue and function. Acute lesional inflammation is highly correlated with early axonal disruption as well as subsequent degeneration of chronically demyelinated axons. Relapses - the clinical presentation of episodic inflammation - are correlated with long-term accumulation of disability. It is therefore tempting to attribute the full extent of clinical and pathological deterioration in MS to inflammation as its sole aetiological factor. One could end this 'controversy' here if it was not for the imperfections in the above statements. But devil is in the error and the reasons behind these imperfect associations between inflammation and neurodegeneration may hide the key to the question of the assumed primordial role of inflammation in MS.

There is a little doubt that MS relapses are associated with disability accrual, but it is worth noting that the strength of this association diminishes with time. While relapses recorded within the initial 5 years of the clinical onset of MS had the greatest impact on reaching disability milestones or converting to secondary progressive disease in the short-term, the association between later relapses and disability accrual was less apparent.

It is also of interest that in the randomised controlled settings, the effect of immunotherapies on disability lags behind their usually strong effect on relapse frequency. For example, natalizumab led to a striking 68% relative reduction in relapse frequency accompanied by 42% relative reduction in 3-month sustained progression of disability when compared with placebo. This is mirrored by the differential effect of high-efficacy therapies on acute cerebral inflammation and tissue loss. For instance, in the CARE MS 2 trial, alemtuzumab was associated with a relative reduction of new or enlarging cerebral lesions by 32% and of brain atrophy by 24% when compared with interferon β.

Even more compelling evidence against the complete causal relationship between inflammation and neurodegeneration consists in the clinico-radiological paradox. Inflammatory lesions of the brain explain at best 40% of neurological disability and 47-81% of global brain atrophy. Spinal cord lesions are relatively more closely associated with motor performance, however, this association also fails to completely explain MS-related disability. As to the treatment effect, therapeutic reduction of the number of new or enlarging lesions explains only about 61% of the effect of immunotherapies on disability accrual.

Later stages of MS are characterised by slowing of inflammation in the presence of more pronounced progression of disability, heralding conversion to secondary progression. Importantly, most of the immunotherapies used in relapsing-remitting MS, including fingolimod, natalizumab and rituximab, did not modify disability accrual during the progressive disease forms. Only ocrelizumab and siponimod ameliorated progressive MS. Ocrelizumab was studied in a cohort enriched for younger patients and those with contrast-enhancing lesions. One may speculate that the limited efficacy of immunomodulation in progressive MS is due to compartmentalisation of inflammation behind the intact brain-brain barrier; however, lack of involvement of inflammation in late axonal loss is an equally plausible explanation. Interestingly, a third agent that showed a promising result in secondary progressive MS was high-dose biotin. It was associated with a higher rate of recovery from disability, presumably by stimulating myelin repair and protecting against axonal degeneration.

A possible explanation for the disconnect outlined above could be a delay in the effect of inflammation on neurodegeneration. For example, while brain atrophy rates during the initial two years of treatment
with alemtuzumab improved partially, they have normalised (0.07-0.20%) to the general population
rates during the subsequent 3 years. This observation is suggestive of a ‘therapeutic lag’ between the
effects of immunotherapies on inflammation and brain atrophy that may potentially indicate causation.
However, not even the hypothesis that takes into account therapeutic lag allows us to explain the origin
of neurodegeneration in MS in full. For instance, the rate of disability progression during the later
disease stages can not be fully explained by the intensity of inflammatory activity during the early MS.12
The effect of highly potent anti-inflammatory drugs, which almost completely abolish clinical and
radiological CNS inflammation, on disability accrual and conversion to secondary progressive disease
is yet to be studied.

It is worth noting that in a proportion of patients cognitive performance is impaired at the time of
clinically isolated syndrome, in the absence of substantial T2 lesion load.13 Such preclinical cognitive
decline is therefore unlikely to be secondary to prior subclinical focal inflammatory activity. On the other
hand, diffuse, low-intensity inflammation may play a role as a causative factor here.

Neurodegeneration in MS can occur independently from inflammation. This is a common phenomenon
in chronically demyelinated axons, where immune mediated demyelination remains unopposed by
subsequent remyelination.1 However, the role of other mechanisms, such as oxidative stress and
mitochondrial dysfunction has been recognised. Finally, an inside-out hypothesis has been postulated,
suggesting that inflammation in MS is secondary to neurodegeneration, implying the role of microglial
activation, which is under the control of intact neurons. This view, however, requires further evidence.

In summary, there is a little doubt that neuroinflammation plays a central role in the pathogenesis of
MS. In fact, it is most likely causal to the evolution of MS. However, to test the hypothesis that
inflammation is the sole causal factor of MS-related structural and functional loss, experimental work
studying long-term impact of early and complete elimination of inflammation is needed. This proves to
be an extremely difficult task, as subclinical inflammation is often present during the pre-clinical disease
stages. The apparently imperfect association between inflammation and neurodegeneration (and their
clinical correlates) provides an intriguing food for thought, suggesting that additional pathognomonic
factors may be involved. If this proves to be true, then no sooner will MS be conquered than we learn to
control all of its multiple causative factors.

Conflict of interests
Tomas Kalincik served on scientific advisory boards for Roche, Genzyme-Sanofi, Novartis, Merck and
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