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Editors Welcome

Ageing and multiple sclerosis

Is premature ageing a driver of late worsening in people with multiple sclerosis?

A few years ago one of us was asked to see a 62-year old woman who had presented in her late fifties with worsening disability, due to secondary progressive MS (SPMS). She was diagnosed originally with MS at the age of twenty-one after three clinical attacks over a period of two years. The last episode left her bed-bound for several months due to a paraparesis. There was a gradual recovery from this relapse over several years, which left her with residual weakness in her right leg and an exercise-inducible foot drop. Despite the inability to run she was fully functional, remaining in remission until her late 50s when there was increasing weakness in the paretic right leg and worsening foot drop.

MRI of the brain and spinal cord, undertaken 3 years apart, showed no active or new lesions. There was overt brain and moderate spinal cord atrophy compatible with a diagnosis of SPMS. CSF analysis demonstrated local synthesis of oligoclonal IgG bands confirming the diagnosis of MS. CSF neurofilament light chain levels were low.

It was explained to her that she did not have 'active MS' and that the diagnosis was now non-relapsing, or inactive, secondary progressive MS. She volunteered that the worsening was not due to MS, but rather ageing. We do not necessarily disagree with her; previous attacks had presumably reduced the number of axons or nerve fibres in the motor pathway to the right leg and with advancing years, she was noticing increased weakness in the leg presumably from dying of surviving nerve fibres. This phenomenon is often referred to as the 'premature ageing theory' of progressive MS. However, is there any proof for it?

We know from other neurological diseases that ageing can cause delayed worsening. The most well known condition is post-polio syndrome (Bartels and Omura, 2005). Thus people who have experienced poliomyelitis notice increasing weakness in previously affected muscles decades later as they age. Similarly, in HIV age-related neurodegenerative diseases present decades earlier than one would expect (Rosenthal and Tyor, 2019). The theory is that HIV brain infection reduces its reserve or resilience and triggers premature ageing mechanisms that bring forward the age of presentation of other comorbid neurodegenerative diseases (Rosenthal and Tyor, 2019). In Alzheimer's disease factors, such as vascular comorbidities, that are associated with reduced brain reserve result in an earlier age of onset of dementia (Pettigrew and Soldan, 2019).

The brain and spinal cord were not necessarily designed by evolution to last longer than approximately 35 years (Opfer et al., 2018). It is only relatively recently that as a species we have extended our lifespans. Once there is survival beyond approximately 35 years there is a gradual loss of nerve cells and axons (Opfer et al., 2018). This explains why as we mature, the effects of ageing occur such as reduced vision, loss of hearing, poor balance and, sadly, age-related cognitive impairment. In short, life after 20 or 30 years is an age-dependant neurodegenerative disease. If we all live long enough we will all develop cognitive impairment. What protects us from age-related changes is so-called brain reserve, i.e. the size of the brain and spinal cord, and cognitive reserve, which relates to education level and environmental enrichment (Sumowski et al., 2016). We know that MS reduces both brain and cognitive reserve and as a result people with MS, and reduced reserve, experience the impact of ageing much earlier (Sumowski et al., 2016).

With advancing years, the DNA at the tips of chromosomes (telomeres) shortens. Telomere length may be used as a crude biomarker of biological but not chronological age. By using telomere length instead of chronological age one may be able to unpick the impact of ageing on disease worsening. In a recent study by Krysko and colleagues, there was a clear inverse correlation between disability worsening and telomere length (Krysko et al., 2019). Thus, shorter telomere length was associated with disability independent of chronological age, suggesting that biological ageing contributes to neurological injury in MS (Krysko et al., 2019). An earlier cross-sectional study had shown significantly shorter telomere length in subjects with primary progressive MS, but not relapse-onset MS, compared to age-matched controls (Guan et al., 2015).

There are biological observations to support the premature ageing hypothesis. Age-related failure to produce oligodendrocytes from oligodendrocyte progenitor cells (OPCs) has been proposed to contribute to progressive MS. Neural progenitor cells (NPCs) from people with progressive MS have been found to express cellular ageing markers when compared with age-matched controls implying that cellular ageing or senescence may be an active process in progressive MS and may contribute to limited remyelination and recovery (Nicaise et al., 2019). The differentiation potential of adult rodent OPCs decreases with age; aged OPCs are unresponsive to pro-differentiation signals, which in turn, is associated with markers of cellular ageing (Nicaise et al., 2019). Interestingly, caloric restriction or fasting, or treatment with metformin reversed these changes and restored the regenerative capacity of aged OPCs (Nicaise et al., 2019). Such findings indicate that ageing-associated remyelination failure and hence age-related worsening MS may be modifiable.

We know from studies in the general population there are many activities that people with MS can undertake to maximise brain and cognitive reserve. This initiative is called Brain Health and involves lifestyle factors such as exercise, diet, sleep, avoiding smoking and excessive alcohol consumption. It is important to screen people with MS for comorbidities and initiate treatment; e.g. hypertension, diabetes, obesity and abnormal lipids.

Data from animal models indicate provisionally that calorie restricted, intermittent fasting and ketogenic diets have most promise

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with regard to brain health (Moreno and Mobbs, 2017; Fontana et al., 2018; Di Francesco et al., 2018).More evidence of potential benefits of these diets in humans is required before promoting them for MS.

In summary, ageing is a biological process and as we decode the molecular programmes that cause ageing we may be able to develop treatments that reverse or slow it down. Metformin, the example given above, is only one of many drugs with putative anti-ageing effects that will need to be tested in MS. We envisage a future of anti-ageing medications and lifestyle strategies, in particular, diet as add-on therapies to treat MS.

To maximise the outcome for MS we need to treat MS holistically. That means encouraging people with MS to live a Brain Healthy life and for healthcare professionals to offer brain health and wellness programmes (Giovannoni et al., 2016). We are entering the era of combination therapies that goes beyond the era of the anti-inflammatory monotherapies.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Gavin Giovannoni: In the last 5 years, Gavin Giovannoni has received compensation for serving as a consultant or speaker for or has received research support from AbbVie, Actelion (Jansens), Atara Bio, Biogen, Canbex, Celgene, Sanofi-Genzyme, Genentech, GlaxoSmithKline, Japanese Tobacco, Merck-Serono, Novartis, Roche, Synthon BV and Teva.

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