CAN WE JUDGE THE EFFICACY OF DISEASE MODIFYING MEDICATIONS BASED ON THEIR EFFECTS ON MRI BRAIN ATROPHY? YES, WE MAY, IF ...

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Neurodegeneration is an early feature in the pathogenesis of multiple sclerosis (MS) that may occur independent and potentially prior to relapses. Its relationship with many long-term clinical symptoms of disability is well established, based on the concept of irreversible neuronal loss and consequent brain atrophy. However, the underlying molecular mechanisms of neurodegeneration in MS are less well understood, and their histopathological investigation remains limited. Quantification of CNS atrophy by volumetric brain and spinal cord MRI is believed to be the best biomarker correlate of neurodegeneration. Three factors drive the interest in CNS atrophy measurement by MRI: a) the long-term clinical outcome in MS is mainly a result of neurodegenerative mechanisms, while relapses, and lesion history as their MRI correlate, are less impactful, b) current disease modifying therapies (DMT) have limited efficacy on the course of neurodegeneration, and c) the clinical tools to measure the effect of candidate drugs on disability are too inaccurate to reliably detect treatment effects in the typical time window of clinical trials (2-3 years).

There is accumulating evidence that MRI measures of CNS atrophy correlate with clinical disability in MS, specifically in studies using high efficacy DMT that last longer than 2 years. The enormous technical progress in MRI technology now allows reliable volumetry of the entire brain and in specific tissue compartments on a longitudinal and cross-sectional basis. However, there are important limitations to the use of brain atrophy as surrogate marker of disability, and hence as an endpoint to judge drug efficacy. Conventional MRI provides only *structural* data. Hence, brain atrophy is a retrospective measure, and its predictive capacity on the future course is based on extrapolation. Beyond neuronal loss, 'atrophy' may result from a mixture of additional components, like myelin damage and inflammatory oedema that are difficult to discern with standard MRI. The lack of prospective MRI studies on the course of atrophy outside of clinical trials further limits the interpretability of measurements with regard to their correlation to clinical disability. The acquisition of such non-interventional long-term data is now limited to primary progressive MS for ethical reasons, putting up a further hurdle.

In conclusion, yes, we can judge the efficacy of DMT based on CNS atrophy in clinical trials, provided that they have a sufficiently long observation time. Given the conceptual and technical (standardisation of image acquisition, hydration state, interference with inflammatory state (pseudoatrophy)) limitations of brain volumetry, the formulation of a well-defined question (e.g., to define atrophy in a specific tissue compartment and how it correlates with a particular feature of disability) may allow one to better link MRI volumetry with the clinical course of disease. A prerequisite to increase the validity of brain atrophy measures as a biomarker of drug effect on disability is the acquisition of long-term data in clinical trials during and after application of study drug. It is also important to be transparent that brain atrophy measurement is unlikely to become a tool for individual therapeutic decision making in the foreseeable future.