



● INVITED REVIEW

Multiple sclerosis: integration of modeling with biology, clinical and imaging measures to provide better monitoring of disease progression and prediction of outcome

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Abstract

Multiple Sclerosis (MS) is a major cause of neurological disability in adults and has an annual cost of approximately \$28 billion in the United States. MS is a very complex disorder as demyelination can happen in a variety of locations throughout the brain; therefore, this disease is never the same in two patients making it very hard to predict disease progression. A modeling approach which combines clinical, biological and imaging measures to help treat and fight this disorder is needed. In this paper, I will outline MS as a very heterogeneous disorder, review some potential solutions from the literature, demonstrate the need for a biomarker and will discuss how computational modeling combined with biological, clinical and imaging data can help link disparate observations and decipher complex mechanisms whose solutions are not amenable to simple reductionism.

Key Words: multiple sclerosis; modeling; integration; disease progression; disease prediction

Introduction

Multiple sclerosis (MS), received its name in 1955, is an inflammatory disorder of brain and spinal cord where in body's immune system incorrectly attacks its own central nervous system (CNS), causing variable and unpredictable symptoms (some examples including slurred speech, blurred vision, loss of balance, poor coordination, tremors, numbness, extreme fatigue, problems with memory and concentration, paralysis, and blindness). Even though a lot of advances have been made in past few decades, exact causes of this disorder remains unknown (environmental factor combined with genetic predisposition). There is a high cost associated with this disorder and it reduces life expectancy as well as quality of life.

Unfortunately, there is no cure for MS, and most of the current drugs available in the market help treat the symptoms. MS is not the same in any two people who have it, since the underlying cause is demyelination (along with axon degeneration), which can target any brain area, resulting in a broad range of clinical symptoms (Compston and Coles, 2002; Alastair Compston et al., 2005; Trapp and Nave, 2008). In addition, brain lesions can sometimes outnumber the clinical symptoms by as much as 10:1, and

lesions in noncritical areas may not result in obvious functional deficits, even if brain function is in fact altered. This leads to clinically silent cases of MS. There are four subtypes of the disease-relapsing-remitting MS, primary progressive MS, secondary progressive MS and progressive relapsing MS, which differ in relapse rate, clinical symptoms, trajectory, underlying causes and approaches to disease management. Combined all these aspects of the disease (various locations for demyelination, clinically silent timeline, and a highly variable disease course) make the approach to care and treatment complex (Compston and Coles, 2008; Trapp and Nave, 2008). Current behavioral and imaging methods used to assess disease severity are insufficient by themselves to allow confident prediction of disease progression. The addition of functional modeling (modeling that correlates the functional loss to disease progression) and objective functional measurements (imaging as well as other assessments combined with disease status) may greatly improve such prediction.

Current Diagnostic Measures

Currently, magnetic resonance imaging (MRI) along with clinical manifestation of the disease are used as clinical tools

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for diagnosing MS (Filippi and Grossman, 2002). The 2010 revision to the McDonald diagnostic criteria (Polman et al., 2011) uses a combination of lesion and clinical attacks for the most confident diagnosis of MS. Lesions must be disseminated in time or space or have positive identification from cerebral spinal fluid (CSF) measure (Lublin et al., 2014). Unfortunately, discrepancy still exists between clinical symptoms and structural measurements, because of the poor correlation between the presence of lesions and symptoms. The two common measures used for diagnosis and monitoring with MRI are hyperintense lesions on dual-echo MR, which is a nonspecific measure of macroscopic tissue injury, and enhanced abnormalities on T1 lesion weighted images, which is a measure of lesions. However, neither of these measures do provide extent and severity of inflammation, cellular component, or resultant tissue damage information (Filippi and Grossman, 2002). Thus, there is a need for supplemental information from alternative techniques to have a more holistic approach. There are emerging techniques that hold promise to quantify the brain imaging data, and relate that with clinical outcomes. Some promising examples include magnetization transfer MRI (quantitative and continuous measure of loss of myelin and reduction in axonal density), diffusion weighted MRI (quantitative measure of size, shape, geometry, and orientation of tissues), proton magnetic resonance spectroscopy (MRS, provides measure of two major pathologic aspects of MS—the active inflammatory/demyelinating process and axonal injury), functional MRI (provides functional information about brain activation during motor, sensitive, and cognitive tasks), high field strength imaging (ex 7T MRI, leads to improved signal-to-noise ratio, speed, and resolution in both MRI and MRS) and transcranial magnetic stimulation (TMS, highly sensitive technique to evaluate cortico-spinal conduction abnormalities in MS). Since T1 scan is transient, it should be only used in patients that have frequent MRI, and should not be used for comparison between subjects. Instead, T2 scan (although technically demanding and time consuming) should be considered. Given the availability of multiple brain imaging modalities, the need still exists for creating a combined assessment tool.

Integration of Biology, Clinical and Imaging Measures

Quite a few studies have attempted to combine various measures (Petzold et al., 2006; Daumer et al., 2007, 2009; Castro-Borrero et al., 2012; Sormani, 2013; Giffroy et al., 2016). Multiple Sclerosis Severity Scale (MSSS) was developed to relate Expanded Disability Status Scale (EDSS) to the disease duration. It has been shown that MSSS correlates with axonal biomarkers but not with glial biomark-

ers (Petzold et al., 2006). This scale was tested on 195 MS patients to predict accrual of disability over time to see if current therapies have impact on disease severity over time. Pachner and Steiner (2009) concluded that the current disease modifying drug therapies lack emphasis on disease severity.

An online analytical processing tool was developed that can be used for prognosis of near term future course of an individual patient (Daumer et al., 2007). This tool is based on matching algorithm (using statistical analysis) and contains data of 1,059 patients. Outcome was to show the probable progression over time which can be useful for subjects, physicians, researchers and other professionals who counsel the patients.

In an attempt to test the developing treatment methods, Sormani (2013) explored the use of various biomarkers that can be used to predict the clinical response to interferon beta (IFN- β) treatment. He concluded with the need for precise, meaningful measures of disease progression, integrated with clinical measures to help with personalized treatment for MS.

A computational classifier was modeled that can be used for predicting short term course of MS (Bejarano et al., 2011). It combined clinical data, with MRI and motor evoked potential (MEP), and it was found that the model did good job on predicting short time scale disability.

A description of the use of various potential biomarkers with their pros and cons was created. It ranges from markers for immunological activation, as well as markers for demyelination, axonal damage, oxidative stress, remyelination, glycoses, and details of specimen such as blood, urine, tears and CSF (Bielecki et al., 2010). Bielecki et al. (2010) concluded with a need for unification and standardization of results of various measurements and techniques.

There have been many advances in modeling and designing tools and predictive capabilities for MS. Tintore et al. (2015) studied 1,959 patients from 1995–2013 with clinically isolated syndrome and found that demographic and topographic characteristics had a low effect on prognostic factors for MS, while the presence of oligoclonal band (oligoclonal bands are proteins called immunoglobulins and their presence indicates inflammation of the central nervous system) had medium effect, and the number of lesions had the highest impact. In another study, Ruet et al. (2014) recruited 652 patients and studied them for prediction factors that can be classified as Disseminated in Time (DIT), Disseminated in Space (DIS), or both, and concluded that there is a need of more predictive factor combinations to help risk for MS. An analysis of 598 MS patients was performed in Norway to determine factors responsible for life expectancy, and the conclusion was that high age at the onset was correlated with unfavorable prognosis (Riise et al., 1988). In another study on early prognostic features on the late course for MS in

world war veterans, it was found that pyramidal and cerebellar scores are the best predictors (Kurtzke et al., 1972). Wang et al. (2015) performed a study to combine *in vivo* biomarker using electrical vestibular stimulation and eye movement recording to measure evoked vestibular-ocular reflexed (eVOR) in 18 subjects with MS (Wang et al., 2015). The goal was to measure the axonal conduction velocity to understand the myelin process and provide a way for assessing efficacy of novel reparative therapies in MS.

Need for Biomarker

All above examples have attempted to combine multiple modalities to help with this disorder. There still exists a need to for quantification, combination of various results from studies, and longer longitudinal studies. Lastly, a computational approach will be necessary for various biological, clinical, imaging findings to form an integrative modeling system that encompasses grey matter pathology, myelin sheath aqueous layers, energy metabolism, and perhaps most importantly, multi-scale or integrated modeling.

MS is the disease which results primarily from demyelination of axons. My recent paper (Chaubey and Goodwin, 2016) is a computational modeling study which makes it possible to make quantitative predictions about the degree to which electrical signals will move more slowly through axonal pathways as a function of how much of their myelin sheath they have lost as a result of MS (using data from diffusion tensor imaging (DTI), and other modalities). The paper identifies a new biomarker for network failure in MS that should improve our ability to predict and track loss of sensory, motor and cognitive function in the disease and a better way to measure the efficacy of new treatments. The potential also exists to relate this “slow down” to disease progression, and eventually, to disease prediction, in which we could use the existing model to predict the disease symptoms in subsequent years.

A study in my research center (Brain Sciences Center, VA Medical Center) used magnetoencephalography (MEG) resting state recordings as a functional biomarker to classify MS and various other patient populations to their respective groups, by assessing synchronous neural interactions at high temporal resolution as a measurement of the dynamic synchronous neural interactions, an essential aspect of brain function (Georgopoulos et al., 2007). Another study used similar analysis in 50 MS patients (31 RRMS, 15 SPMS, 4 PPMS) and 214 healthy controls (Carpenter et al., 2011). ANCOVA was performed at each of the 30,628 sensor pairs (PCCs) using group (MS, control) as a fixed factor and age, gender and handedness as covariates. Similar analyses were done using each MS phenotype (RRMS, SPMS, etc.) as a factor and 300 (out of 30,628) sensor pairs were found to have a significant group differences after correction for multiple

comparisons. These results demonstrate use of MEG as a potential biomarker.

There is a need to combine such objective measures of brain function with modeling techniques to improve assessment and prediction of the disease over what is possible using established methods. To list few direct advantages of these predictions: 1) these predictions can identify high-risk patients who require early and more aggressive therapies, 2) they can help patients with clinically isolated syndrome (CIS, one of the MS disease courses, refers to a first episode of neurologic symptoms, but it is not alone enough to have diagnosis of MS, as there needs to be two episodes disseminated in time or space) to predict how likely and at what time frame the MS diagnosis is likely, 3) they can provide an individual plan for various subjects depending on their current status and symptoms (Bergamaschi and Montomoli, 2016).

Conclusion

There is a need for modeling to help direct research using testable predictions and fixing the current gap in knowledge. There is enormous amount of data available, a lot of which is open access, and it is important to make sense of it all. Computational modeling can be an essential tool to help make use and sense of all this data and lead to better understanding, diagnosis, prediction of various diseases, especially MS.

As there is no cure for MS, most treatments typically focus on slowing the progression of the disease and managing symptoms. There is a large body of research on new therapies and treatment methods. Since tissue destruction and disease onset begins much earlier than the actual clinical symptoms appear, it will be important to test future therapeutics to detect early axonal loss, axonal dysfunction and efficiency of these treatment methods. Advances in imaging technology and use of new techniques need to be established and validated to determine the success of remyelination and cessation of old damage. Finally, a combination of modeling will allow for prediction and better quality of life for people with MS.

There is a huge need for a reliable and personalized disease prediction model of MS. It would benefit patients with MS, as they can plan and select the best individualized treatment option. It would be helpful to the clinician working with patients, especially early stage patients, to help with selection of the best therapeutic treatment options. Integration of modeling, biology, clinical and imaging data can help provide more personalized and reliable monitoring of disease progression and in turn lead to better disease prediction.

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