COMMENTARY

Redefining Acute Relapses in Multiple Sclerosis: Implications for Phase 3 Clinical Trials and Treatment Algorithms

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ABSTRACT

Relapses in multiple sclerosis are defined as periods of clinical worsening and radiological progression. Magnetic resonance imaging data, however, are not always supportive of "clinical worsening," and clinical symptoms of worsening may not always be present in cases of acute relapse. In the pharmaceutical domain, this discordance between "clinical worsening" and "radiological progression" has never been fully elucidated, and no Phase 3 clinical study has addressed this conundrum. Thus, the true number of acute relapse cases enrolled in Phase 3 clinical studies remains unclear.

Breach of the blood-brain barrier solely, as determined by magnetic resonance imaging, may be more a more accurate definition of an acute relapse in multiple sclerosis. Increasingly, magnetic resonance imaging data push the boundaries of science and carry significant advantages in sensitivity, data storage, retrieval, and unbiased analyses, if warranted retrospectively. Magnetic resonance imaging data can also be standardized, shared, and exploited by pharmaceutical companies to develop more effective drugs and therapeutic endpoints. Neurology is awakening to big data concepts and how such concepts are evolving the field. Magnetic resonance imaging data is one of the pillars of this evolution.

In this commentary, the author reviews the current standard of determining acute relapse in both clinical practice and clinical research, and discusses its limitations. The author then proposes a more modern definition of acute relapse in multiple sclerosis and includes a supportive discussion on the current and emerging roles magnetic resonance imaging and "big data" are playing in the prevention, diagnosis, and treatment of multiple sclerosis.

INTRODUCTION

Multiple sclerosis is a chronic disease of the central nervous system (CNS) with a variable clinical course. Outcome measures of disease progression and monitoring of therapeutic efficacy of drugs require more sensitive biomarkers than clinical evaluation for reproducibility and follow-up. Typically, in the relapsing-remitting MS (RRMS) variant, acute relapses, defined as symptoms that occur over a minimum of 24 hours and separated from a previous attack by at least 30 days, accrue.[1] Relapses occur in the absence of fever or infection and are not linked to environmental and systemic triggers;

they denote acute inflammation in the CNS characterized by breach of integrity of the blood-brain barrier (BBB). In the radiological domain, the criteria for relapses are defined as an increase in lesion load/size on T2 imaging or T1 gadolinium enhancement of lesions on magnetic resonance imaging (MRI) in the brain, spinal cord or both.

RRMS is clinically characterized by relapses, pseudo-relapses, paroxysmal symptoms, or indolent changes that can occur over time with variation in severity and complexity and exhibit inter-individual differences. An important objective is to treat relapses, but its definition has been ill-defined and is subjective. Just as the conversion of clinically isolated syndrome (CIS) to clinically definitive MS (CDMS) is predicated upon MRI imaging characteristics, so too must reliance be placed on imaging in determining if clinical suspicion can be validated in evaluating MS relapses. Only then can data be validated across populations, clinical trials, and databases. A relapse diagnosis must be deferred or discarded if clinical data are unsupported by MRI evidence.

DETERMINING RELAPSE IN CLINICAL PRACTICE

In general, patients with MS who experience "mild" symptoms such as pins and needles sensations that are fleeting and/or spasms that persist for a few seconds or minutes may not need much more than close follow-up. Paroxysmal or fleeting symptoms are often the result of a temperature-dependent conduction block in demyelinated axons, triggered by an increase in body temperature.[2] A pseudo-exacerbation is a temporary worsening of existing symptoms secondary to an underlying infection.

For severe exacerbations, such as the occurrence of ataxia or motor weakness of a limb, which interfere with a person's mobility, dexterity, safety, or overall ability to function, most neurologists recommend a short course of high-dose corticosteroids to reduce the inflammation and bring the relapse to an end more quickly. However, severe relapses that are self-reported and observed clinically (even if the clinician cannot ascertain if findings on examination are new or old) should also be linked to MRI changes in the CNS, with or without neuro-anatomical correlates. Lesion topography, size, and magnitude of myelin loss determine the clinical phenotype and relapse severity.[3]

DETERMINING RELAPSE IN CLINICAL TRIALS

More recently, "no evidence of disease activity"—or NEDA[4]—is a new concept that links lack of relapses, among other variables, to a drug's efficacy. A drug's failure, success, or economic viability all hinge on whether relapses can be suppressed, and its fortune depend on how a relapse is defined. This definition also has tremendous implications as an outcome measure, as every clinical MS trial—from the approval of the first drug for MS, interferon beta-1b (Betaseron®, Bayer) in 1993, to the recent United States Food and Drug Administration (FDA) approval of daclizumab (Zinbryta®, Biogen Idec) in 2016— have used relapses in MS as both primary and/or secondary endpoints to test a drug's efficacy. In Phase 3 clinical trials, "relapse" is based on a patient's clinical symptoms and evaluation by a neurologist, and then as a secondary measure, on MRI findings. Since imaging techniques have sharpened our understanding of disease better and can validate BBB integrity or loss, the diagnosis of a relapse ought to be conferred only if MRI data are concordant with clinical evaluation—not when they are discordant. Moreover, MRI evaluation can reveal silent lesions that can be active as well, and could indicate worsening disease status despite lack of symptoms.

It remains unknown if past or ongoing Phase 3 clinical trials in MS included or are including patients deemed to have a relapse by clinical evaluation but with no MRI evidence. Data analytics of Phase 3 clinical trials show that all FDA-approved MS drugs calculate reduction in relapses as a surrogate marker of a drug's efficacy, but what is unclear is if all patients included in these trials had clinical *and* radiological evidence of breakthrough disease.

TO TREAT OR NOT TREAT?

A critical question that remains unanswered is whether a patient should be treated for a "relapse" when evidence is only clinical. Increasing detection of contrast enhancement on MRI scanning may provide earlier and immediate assessment of disease activity as compared to clinical examination,[5] and imaging certainly could be the endpoint in screening for drug efficacy in clinical trials, as it provides a more sensitive marker. In fact, triple-dose gadolinium (0.3mmol/kg) and delayed imaging techniques can increase lesion detection by as much as 235 percent, and they double the number of patients classified as radiologically "active."[6] Investigators have also suggested that a combination of triple-dose contrast, short/long delayed imaging, and MRI with 3T and magnetization transfer offer the best option to increase MRI sensitivity in MS patients.[7] However, no large study, as of yet, has been done using this imaging combination on patients with MS, leaving the clinician with spotty data at best on which to draw conclusions. It also is relevant in the context of this discussion to note that "clinic-radiological paradox"[3] refers to the poor correlation between MRI lesion load and disability but does not apply to acute relapses.

MRI AND "BIG DATA" IN MS RESEARCH AND PRACTICE

Most investigators view MRI measures as the best prospect for a biological indicator—or biomarker—that can help them understand the disease process, diagnose patients, monitor treatment response, and predict prognosis. MRI scans have indeed sped up diagnosis of MS, and they are a ubiquitous tool in clinical drug trials. Radiologists and neurologists agree that MRI research has opened up a visual window into the pathology of MS, and is perhaps the best objective biomarker there is, eliminating or minimizing the bias of subjective symptoms of patients and errors such as inter- or intra-rater differences in clinical findings. Although

MRI findings also suffer from intra- and inter-rater differences, these data are permanent, retrievable, and can be analyzed by unbiased radiologists anywhere in the world. Data can be stored and standardized for longitudinal studies and retrospective analyses are possible. More importantly, the pharmaceutical industry benefits from this deluge of digital data—or "big data"—through sharing and data mining and is ideally positioned to design better therapeutic options for patients based on MRI metrics. A new vision to manage the burgeoning MRI data accumulating in acute MS relapses and transform all this "big data" into "big brain science" is urgently needed. Lastly, high-field MRIs, though only in research use thus far and complicated by artefactual noise, promise to bring more to the MS relapse world, among other brain disorders.

CONCLUSION

A better definition of what constitutes a relapse in MS is urgently needed. From a treatment perspective, the management of relapses, particularly in the emergency department (ED), is highly variable. In general, it is possible that patients are treated with steroids based on symptomatology and an ED physician's evaluation. It is often difficult in the ED to ascertain baseline status or a deviation from it, and an MRI may or may not be performed in the ED owing to cost and availability. However, if objective MRI data are not the singular surrogate biomarker to validate BBB breach, false-positive cases are probably subjected to unneccessary treatment in clinical practice, and false-positive cases may inaccurately "improve" a drug's efficacy in clinical research. As MRI techniques improve, it is only a matter of time before a gold standard based on imaging will emerge. Clinical skills and evaluations, meanwhile, are probably stagnant, at best. It is time to ditch the current definition of an MS relapse. Routine MRIs should be performed on all patients with MS. If the BBB is intact, then the patient should not be diagnosed as having an acute relapse.

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