The Significance of Visual Physiology: A Tool with Relevance in Multiple Sclerosis (MS)

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Introduction

The role of Visual Evoked Potentials (VEP) in diagnosing Multiple Sclerosis has been overshadowed by the combined use of magnetic resonance imaging and oligoclonal bands, which effectively demonstrate the characteristic spread of pathology in space and time [1]. These new criteria enhance diagnostic confidence, allowing for earlier deployment of licensed Disease-Modifying Therapies (DMTs). The hope is that early intervention with DMTs will mitigate the initial inflammatory injury, which is directly disabling and likely a precursor to the delayed axonal degeneration that drives the progressive MS phenotype [2].

However, even the most potent licensed therapies show that the majority of patients will eventually experience 'No Evidence of Disease Activity' within a few years [3]. In response to this, attention is now shifting towards actively reparative strategies, including potential Remyelination Therapies (RMTs). In this issue, Barton and colleagues present a timely review that highlights the remarkable sensitivity of multifocal VEP (mfVEP) techniques in understanding the pathophysiology [4]. This review suggests a potential new role for utilizing mfVEP to detect the effects of Remyelination Therapies (RMT) in Multiple Sclerosis (MS).

When employing evoked potential techniques, latency parameters offer good construct validity as they serve as a causally-related index of demyelination and subsequent remyelination. The main challenge in translating RMT into practical application lies not in a lack of potential agents worthy of evaluation but rather in identifying a reliable biomarker against which these agents can be tested.

The utility of the conduction-enhancing agent 4-Aminopyridine supports the idea that correction of conduction delays due to demyelination leads to direct albeit partial alleviation of symptoms [5]. Additionally, empirical observations in vitro and findings from animal models suggest the acute and long-term benefits of remyelination by oligodendrocyte precursors on axonal survival [6,7]. Although pursuing Remyelination Therapies (RMTs) holds a strong biological rationale, there are several crucial considerations to address. Firstly, there is a concern that the more extended testing time required for multifocal VEPs (mfVEPs) might be hindered by the prevalent fatigue experienced by individuals with MS. This fatigue can also limit even shorter standard VEP acquisition.

Secondly, the criterion validity of visual physiology as a surrogate measure of overall clinical disability in MS remains questionable. Barton and colleagues recognize that the relationship between visual electrophysiology and clinical disability outcomes in phase 3 trials is likely to be weak. The goal is to identify RMTs that can benefit overall disability, ensuring that the licensed indications are not limited to addressing visual impairment, which affects only a minority of patients. It is worth noting that many patients may have milder or even subclinical deficits.

The question arises as to whether an improvement in provoked visual conduction would accurately predict an overall enhancement in disability ratings. Unfortunately, although phase 2 trials have shown therapeutically enhanced remyelination leading to recovery of VEP conduction, this improvement has not consistently translated into a clinically significant enhancement in visual function itself [8,9].

Incorporating Multifocal VEP (mfVEP) as part of a Multimodal Evoked Potential (mmEP) battery could enhance the content validity by capturing a more comprehensive representation of disseminated demyelination in Multiple Sclerosis (MS). The use of multimodal approaches has demonstrated a close association with the final phase 3 clinical disability measures [10].

However, it is important to recognize that EDSS (Expanded Disability Status Scale) outcomes seem to be predominantly influenced by myelopathic burden and the integrity of long tracts [11]. Thus, it might be erroneous to assign equal weight to visual and long tract EPs in the current mmEP rating systems or assume that all constituent fibers are equally reparable. There are substantial differences in scale and vulnerability between the human optic nerve and murine spinal cord used in RMT paradigms and the long tracts of the human spinal cord that significantly contribute to disability.

Nevertheless, the sophisticated visual electrophysiological techniques reviewed by Barton and colleagues propose an approach that could potentially help investigators strike a better balance between candidate advancement and rejection in translational efforts. By incorporating mfVEP into a multimodal approach, researchers may gain insights that lead to more favorable outcomes in RMT development and evaluation. Indeed, candidate Remyelination Therapies (RMTs) could be tested in phase 2a paradigms using visual metrics. This approach would involve deploying a standardized visual electrophysiological acquisition alongside structural morphometrics, incorporating Optical Coherence Tomography (OCT) for the eye itself and diffusion tensor imaging for the retrobulbar pathways. Leveraging the strengths of Multifocal VEP (mfVEP), which offers higher sensitivity to subclinical and subradiological changes, may enable the detection of potential RMT effects in the human setting, as envisioned by Barton and colleagues.

By starting with this initial step of an RMT 'screening' paradigm utilizing optic physiological and morphometric OCT data, researchers could potentially require a smaller-scale study compared to the current multimodal Evoked Potential (mmEP) batteries. This approach could identify poorly remyelinating agents without effects on a sensitive system through a small yet adequately powered study. Subsequently, a larger and more resource-intensive cord-based assay could be undertaken before a pivotal phase 3 trial. This two-step phase 2 approach could minimize the risk of failure at phase 3 by testing agents against the higher bar of long tract rescue in around a hundred patients, which would causally relate to the clinical outcome assessed in nearly a thousand.

Having a reliable biomarker surrogate that is accepted by regulatory authorities for use in pivotal phase 3 studies is of utmost importance. The failure of fingolimod in primary progressive multiple sclerosis (INFORMS), partly driven by a positive response against brain volumetrics in earlier

disease during phase 2, might be attributed in part to the lack of a sufficiently meaningful relationship between the biomarker and the desired clinical disability outcome [12].

Failures in phase 3 trials not only result in the loss of financial resources and potential unnecessary risk exposure to enrolled patients but may also discourage further industrial efforts. Visual electrophysiology, with its ongoing advancements, holds promise in accelerating translational endeavors in MS, aiming to achieve what was previously deemed impossible.

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