

Aryl hydrocarbon receptor activity may serve as a surrogate marker for MS disease activity

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MS diagnosis and prognosis is based on a combination of clinical criteria, MRI, and CSF findings. However, we still lack the ability to predict disease course, including relapse frequency and disability progression. Thus, reliable biomarkers of MS risk and prognosis are sorely needed. In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Rothhammer et al.¹ suggest that changes in serum agonistic activity of the aryl hydrocarbon receptor (AHR) may be a useful measure of MS activity.

The AHR is a ligand-activated transcription factor that was initially described in response to toxins, but was later found to be activated by a multitude of diverse stimuli, including environmental toxins, microbial toxins, dietary compounds, and endogenous metabolites.² The AHR is found on a host of immune cells, including T cells and B cells, and is found at particularly high levels in barrier tissues such as the gut, skin, and lungs.² A number of endogenous AHR ligands have been reported, including kynurenine (a tryptophan metabolite produced by indoleamine 2,3-dioxygenase), indoles (produced by bacterial metabolism of tryptophan and dietary intake), and 6-formylindolo[3,2-b]carbazole.² Depending on the ligand, AHR stimulation can strongly influence the development of proinflammatory Th17 or anti-inflammatory regulatory T cells, leading to profoundly different outcomes in the MS animal model, experimental autoimmune encephalomyelitis (EAE).^{3,4} The AHR is therefore a putative MS therapeutic target in MS. In this regard, laquinimod can alter the phenotype of antigen-presenting cells and autoreactive T and B cells,^{5–8} and its therapeutic efficacy in EAE is dependent on AHR activation.⁹ AHR stimulation in the CNS also seems to have a neuroprotective effect in EAE.¹⁰ It therefore stands to reason that AHR activity could provide a link between environmental exposures, genetics, and MS risk and disease activity.

In a study by Rothhammer et al.,¹ serum AHR agonistic activity in patients with MS using a reporter

assay driven by an AHR-responsive promoter was measured. They first demonstrated that AHR agonistic activity was reduced in a cohort of patients with relapsing-remitting MS (RR-MS) compared with healthy controls. The authors then measured AHR activity in MS patients with different stages of disease activity. Surprisingly, they found that AHR agonistic activity was lower in patients with MS in remission compared with those with active inflammation (as confirmed by contrast-enhanced MRI), although both groups were still lower overall compared with controls. By contrast, AHR activity levels were higher in patients with clinically isolated syndrome at the time of their first clinical attack compared with healthy controls, whereas no difference was found between patients with benign MS (long-standing RR-MS with minimal neurologic impairment) and controls.

The findings by Rothhammer et al. are the first indication that AHR activity is dynamically modulated at various stages of MS. In addition to representing a potential biomarker of MS activity, the AHR is also a novel therapeutic target for MS, as in the case of laquinimod.^{5,6} The reason why AHR agonistic activity is increased during a first clinical attack, but decreased in subsequent relapses remains unclear. The authors did not identify any association between AHR agonistic activity and patient age, disease duration, or status on approved MS therapies. However, one must recognize that the patient numbers in their cohorts were relatively small. It is possible that AHR agonist levels may be influenced by factors other than MS activity. The reporter assay used by the authors captures the sum of all AHR agonistic activity in the sera but does not measure individual AHR ligands, which can vary markedly in their effects on the immune system.^{3,4} Thus, these findings may represent changes in endogenous AHR ligand levels in response to inflammation, differences in patient microbiota, or other extrinsic environmental sources. As the study by Rothhammer et al. was not longitudinal, it is not clear to what extent AHR levels

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fluctuate throughout the course of individual patients with MS. It is also unknown whether changes in the AHR agonistic activity drive changes in MS activity or represent a compensatory response. Further study into the dynamic changes of specific AHR ligands and fluctuations during different stages of disease activity within individual patients and larger populations as a whole is clearly needed. It is hoped that such studies will shed light on the utility of AHR as a possible biomarker and therapeutic target in MS. The findings by Rothhammer et al. represent an exciting step forward toward realizing this goal.

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