Accelerated Cure Project for MS

March 2018

Accelerating research towards a cure for multiple sclerosis

Why we still need to talk about smoking in MS

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"We already know smoking is bad, and we tell patients to stop smoking – this is not an interesting question," wrote a grant reviewer in response to a proposal I submitted in 2009 to investigate genetic variants mediating tobacco-smoke-related MS risk. A few years earlier I may have agreed – but in the interim I realized the opportunities to study smoking in MS. In response to the reviewer, I wrote "Yes, I do agree that we know smoking increases the risk for MS, however, we do not know *how*. Tobacco smoke is one of a few environmental factors influencing the risk for MS, and therefore if we can identify the mechanisms through which smoking is *bad* then we might uncover novel targets for drug development." The grant was funded, and it is an argument I still champion. Today, it is still unclear how smoking influences risk. The simplest explanation is that it is a pro-inflammatory agent. It is now generally accepted that smoking also accelerates the progression of MS – though studies investigating progression have varied in their findings for two reasons: the measure of progression used (e.g. relapse activity, walking speed, comorbidity burden, etc.) and how smoking was measured (ever versus never smoker, current versus never non-smoker, average number of packs smoked per day, etc.). Nonetheless, there is a valid reason to continue supporting research investigating the impact of tobacco smoke on MS as demonstrated by two studies from last month.

Multiple Sclerosis Journal published a German study of 263 persons with MS (PwMS) who were untreated and recently diagnosed with relapsing-remitting MS or clinically isolated syndrome.[1] The researchers' goal was to identify factors contributing to very early brain volume loss in the study participants. In recent years it has become apparent that there is brain volume loss in those with MS, and this occurs very early in some individuals – therefore it is an active area of research. In this study, data on smoking and body mass index (BMI) was collected. Then two genetic variants were genotyped from blood samples – *HLA-DRB1*15:01* (the strongest MS genetic risk factor) and *APOE* ε4 (the strongest Alzheimer's disease genetic risk factor). MRIs were performed on all participants to calculate brain volume and other related measures. BMI and the genetic variants were not associated with brain volume. However, current smokers had greater atrophy in total brain volume (specifically in gray matter) than non-smokers. The smoking result is consistent with a few other studies in non-MS populations. But *why* does smoking impact brain volume, and *why* the gray but not white matter? Is it because nicotine increases the permeability of the blood-brain-barrier that sequesters our brains from the rest of our bodies? Is it an increase in oxidative stress in the brain? Would e-cigarettes have the same impact? This study is intriguing, particularly considering these are very early in MS, and the lack of association of brain volume with BMI and genetic variants.

The second study, published in *Neurology*, was a Danish study of 834 relapsing remitting PwMS who were all treated with interferon beta (IFN-β).[2] The study participants completed a survey on their smoking habits at baseline; there was also genetic data for *HLA-DRB1*15:01* and two other variants of interest. Study participants underwent a neurologic examination at baseline and then every three months for one year. As part of each neurologic examination, a physician would ask the participant to report the number of relapses occurring since the last clinical visit. Well, none of the genetic variants were associated with relapse activity. Unfortunately, smokers had a 20% increase in relapse activity than non-smokers, and the more a PwMS smoked, the greater the relapse activity. Remember, all these individuals were on IFN-β therapy, which is supposed to reduce the number of relapses. Thus, the authors concluded that smoking reduced the effectiveness of IFN-β for treating relapses in PwMS. I personally think this is a big deal – but of course, these findings need to be replicated. Nonetheless, erring on the side of caution, these findings suggest promoting smoking cessation for those who are active smokers.

Back in November, I published a paper on a study of 950 PwMS. My findings showed active smokers had worse physical and mental quality of life, and greater overall disability than non-smokers.[3] The results did surprise me, as smoking negatively affected all measures we looked at in the paper. So, okay, we know smoking is bad, really bad… but why do some continue to smoke? Is it their coping strategy? Is it a lack of health promotion by healthcare professionals? Is it a lack of smoking cessation resources? Maybe it is a little bit of everything, we all have a part in continuing this conversation. I will continue to study the role

of smoking in MS. I want to get at the *how* and *why*, and strengthen the argument for MS-tailored smoking cessation programs.

1. https://www.ncbi.nlm.nih.gov/pubmed/29532745
2. https://www.ncbi.nlm.nih.gov/pubmed/29343473
3. https://www.ncbi.nlm.nih.gov/pubmed/28059618