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INVITED EDITORIAL

MS and autoimmune disorders

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The paper in this issue from Hemminki courageously takes on the thorny question of the co-association of multiple sclerosis (MS) with other diseases, a query which has had more than a few prior attempts at resolution. A priori, this is not an easy question to answer since MS is not all that common, and many of the diseases which have been sought for co-association are even less so. Among ways to attenuate the problems, the most important are ensuring adequate sample size and controlling for ascertainment.

Scandinavian registries are to be envied as on their own they make a strong case for national health delivery. These in particular have been systematically available for study. Hemminki et al. provide a large sample for scrutiny and employ it to conclude that MS is associated with autoimmune and "related" disorders. The dataset is large, the approach is sound, and the investigators are experienced and reliable. The direction of ascertainment, i.e., coming from the autoimmune side, and case-finding for MS is novel and attractive and is complementary to existing studies. There are, however, reasons for misgivings despite my admiration for the authors and their methodology, and this has to do with interpretation of the results.

Ascertainment on the basis of hospital admission may select for more severe cases depending on local custom for diagnostic lumbar puncture with geographic variation. It might be that even these may have changed from the previous generation to the present, but both are included in the study.

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Pooling MS and "related" disorders raises two issues. The first is that adding in cases of familial MS perhaps should not be used to support the argument of co-association as the authors have done. This will surely seem to some a circular argument—increased frequency of MS in the relatives of MS patients is being used to support the thesis that MS is related to autoimmune diseases. Familiality of MS has long been known. The authors, having made a distinction between MS and "related" disorders, perhaps unwittingly merged both into autoimmunity in their discussion. They are so counted in a claimed relative risk of 1.21 for autoimmune disease among the relatives of those with these conditions. Removing MS and amyotrophic lateral sclerosis (ALS) from the numbers subtracts 139 cases or 12.7% of the total of 1,087 cases identified, eliminating the proposed 1.21× excess of "autoimmunity." Taking out the asthma inclusion from the ranks of the "autoimmune and related" as well leaves a *reduction*—not the increase proposed.

The inclusion of ALS and asthma does strain the limits of orthodox contemporary concepts of these disorders. It would help to be reassured these inclusions were not made post hoc when the data were found not to fit a prior hypothesis. There is very little evidence that ALS is autoimmune in nature, and asthma seems primarily more in the allergy line with tenuous connections to autoimmunity. It is possible that the ALS findings result from the inclusion of cases of chronic myelopathy (many of whom had MS) from a previous generation especially when upper extremity atrophy was present or spondylosis coexisted. On the other hand, the one thing that MS and ALS do share is progressive central axonal degeneration.

The many genes involved in axonal transport (e.g., kinesins and dyneins, to name but two families) might contain subtle defects common to both disorders contributing in a small way to axonal loss under unfavorable conditions.

The ability to maintain terminal axonal processes a meter away from the cell body must require all the evolutionary resourcefulness of the neuron. The relative distances between neuronal cell body size and length of axon do rival the ratio between a few circuits of the 400-m oval in Beijing's Birdsnest Stadium and the distance from it to the moon. The fact there are more than two dozen types of hereditary spastic paraplegia bear witness to the number, complexity, and inventiveness of the biological adaptions involved in maintaining the outreaches of the corticospinal tract. So some genetic commonality in outcome determination might be anticipated for axonal loss in degenerative conditions.

The authors dismiss surveillance bias and suggest that this is a short-term phenomenon. The author's excellent and informative studies in cancer diagnosis for the special cases of melanoma and breast cancer are essentially timing biases which are not analogous to the question at hand. It goes without saying that these cancers are rather less likely than MS to go decades before coming to medical attention. For MS at least, knowing one has a relative with disabling MS engenders a life sentence of surveillance of the popular literature about MS. First-degree relatives of MS patients are more informed about MS, about concepts of pathogenesis, and about what the concept of autoimmunity means than are the general populations even if they have not taken part in awareness-enhancing fundraising events. For the innovative approach used here, it is difficult to know if the presence of a variety of autoimmune diseases have a similar effect on MS ascertainment in relatives.

However, it would not be completely unexpected. We only have experience coming at this from the MS side and can say that few close relatives remain unfamiliar with the common early symptoms of MS in a way distinctly different from those lacking an affected relative. We became aware of this phenomenon in our studies of families with MS. For most relatives, any neurological symptom was interpreted in the light of possible MS. This seemed proportional to the degree of relatedness, most evident in twins and sibs but extending out to second- and third-degree relatives. This has basis in fact since the most common diagnosis in first-degree relatives of MS patients presenting to neurology is indeed MS [1]. Far from being a short-term effect, surveillance bias can endure for generations of relatives knowing an ancestor or collateral had a disease. Female interest in and awareness of autoimmune diseases makes them staple features on women's magazine covers, rivaling abdominal muscle preoccupation in magazines for men. Some generalization of this phenomenon might be expected.

The widespread notion that MS is associated with other autoimmune diseases is anything but proven. There are several hurdles to overcome to convince the hardened skeptic repeatedly struck by the fiendishly influential impact of coincidence. As Max Planck wisely said "We are at our most vulnerable when others are confirming our views."

Firstly, the increase should be seen in adequately sized population-based samples. Secondly, it should be detectable in first-degree relatives, who share necessarily many of the same genes. Thirdly, it might be expected that autoimmune diseases would be most common in multiplex families where there are several MS cases, assuming they are more genetically loaded, and fourthly, the association should with the same disease(s) for different populations. If any of these four has been conclusively shown for MS, it has escaped my attention. Finally in MS, with its multiple major histocompatibility associations, there would have to be correction to any proposed association for any major histocompatibility complex (MHC) overlap with MS, and I have also yet to see this done. Co-association might well be present secondary to these, not uninterestingly so, but with implications for how this might be mediated. One thing it clearly has not been shown to mean is a common non-MHC-mediated autoimmune diathesis. Nevertheless, small effects have not been ruled out, and the biology of the tiny influences of some interleukin receptors and other genes turning up in whole genome association studies are which in total barely reach 1% of the genetic risk, still being elucidated.

Limited biological relatedness could be restricted and explainable and with testable corollaries. The case of type I diabetes is a special case in this context since the association with HLA-DRB1*1501 is more negative than the same allele is positively associated in MS. It is entirely possible that the familial similarity in diabetes risk for MS and families vs. controls should be viewed as unexpected. I interpret the evidence to show type I diabetes is actually increased were the MHC associations taken into account. Of course, this increase could be environmentally mediated or even epigenetic.

Here, the association proposed by the authors is entirely dependent on the "related" conditions which are likely not autoimmune in any event and with MS itself. The exclusion of MS, ALS, and asthma leaves no significant overall increase in the other 30 diseases examined and provides no indication that autoimmune diseases are MS associated within the limits of study power. Uveitis warrants further study but the neutral position of rheumatoid arthritis and Crohn's disease should not go unnoticed in the context of the literature.

Studies like this one, even if viewed as negative, do not preclude the possibility of individual families having an autoimmune predilection. However, such families are notable for their rarity if multiple MS cases are a prerequisite. Sadovnick and I have some 50 families with four or more cases in the Canadian Collaborative Study to date, and we

have failed to recognize any with a frequency of autoimmune disease in relatives which supersedes what has been seen in the sporadic MS population. In the latter, we could find no increase compared to spousal controls, but matching for the gender of the information source was critical [2]. This extraordinary gender-specific reporting bias was an order of magnitude greater than the increase in autoimmune disease in either patients or their relatives reported by Hemminki et al. The hospital-record ascertainment method here precludes this kind of bias, a major advantage of the authors' approach.

So with the reservation about type I diabetes which is probably increased in MS relatives compared to that expected when corrected for MHC association, we think the case for a general autoimmune diathesis in MS or an increased incidence of MS in the relatives of probands with autoimmunity remains, at best, unproven. The weight of the population-based evidence is against it even though such studies are outnumbered by methodologically weaker studies claiming association. The vigor with which this notion has been defended suggests that not finding an increase somehow destroys or threatens a cherished idea. In fact, the absence of an increase seems to me near neutral and bears rather little on the notion of MS as an autoimmune disease given the many ways in which autoimmunity can be generated experimentally. This study and the large Canadian study approaching this question from the aspect of autoimmune disease in MS relatives seem both unambiguously negative. This may be a tree up which sufficient barking has been heard. There may yet be room for small effects of individual genes in common, but the genetic epidemiology says not much.

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