EDITORIAL

Diagnostic utility of testing for antineutrophil cytoplasmic antibodies

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Antineutrophil cytoplasmic antibodies (ANCA) that target the third neutral serine proteinase (PR3) and myeloperoxidase (MPO) of human neutrophils are associated with primary systemic vasculitis that predominantly affects small and medium blood vessels.[1,2] There is an international consensus that testing for ANCA should specifically be focused on identifying antibodies against those 2 antigenic targets.[3] In this edition of the journal, Wójcik et al[4] discuss the data from the Polish Vasculitis Register (POLVAS) including information from 536 individuals who presented with vasculitis over 27 years, in the demographic context.

The basic premise of their analysis is focused around the need for ANCA testing. We know that there is evidence that distinct genotypes predict the generation of either PR3-ANCA or MPO-ANCA serotypes in individuals with ANCA-associated vasculitis (AAV).[5] There are also genotypes that produce associations for PR3-ANCA and MPO-ANCA in different directions, where an association for increased risk for one serotype is associated with a reduction for another serotype.[6] Observational data tell us that these serotypes have a weak association with distinct phenotypes.[7] Indeed, the POLVAS data demonstrated that most individuals with MPO-ANCA had MPA (n = 86/127), most individuals with PR3-ANCA had GPA (n = 316/338), and most individuals with ANCA-negative vasculitis had EGPA (n = 47/75). This is in line with previous observations. It is slightly surprising that in such a large cohort of individuals with AAV, there were no patients with dual positivity. In a similar size pan-European cohort of 535 cases, 16 patients (3%) were dual positive.[8]

Vasculitis academics have long grappled with the classification of AAV. As in the POLVAS data, GPA is a heterogenous disease and MPA is a homogenous disease. This may purely be a function of the way we classify the disease. We know that AAV is a spectral disorder, ranging from a pure granulomatous end that is typified by indolent inflammation to a pure vasculitis end that is explosive on its onset, and that the 2 ends behave very differently.[9] Using the Chapel Hill nomenclature, we call the pure vasculitis end MPA. The association of MPA with renal involvement and the risk of death is therefore not interesting, as it is circuitous, while the association of MPO-ANCA with the risk of renal involvement is certainly interesting. If we did the same thing to the nomenclature of GPA and only used that term for the pure granulomatous end of the AAV spectrum, we might find the same sort of association of it being a homogenous disorder with PR3-ANCA, associated with indolent but relapsing inflammatory disease. Then, what should we do about all the other cases between the 2 ends of the spectrum, and how do the double ANCA-positive patients fit in?

Diseases should be identified and named after their pathogenetic mechanisms, not phenotypes. A chest infection can be caused by many different organisms and not all of them would respond to the same antibiotics. We therefore strive to identify the microbe involved and treat each person accordingly. If we think PR3- and MPO-ANCA are pathogenic, can we call the AAV simply by its serotypes and discard the GPA, MPA and EGPA descriptors? We probably cannot! EGPA has a strong argument for being classified into the domain of eosinophilic disorders rather than AAV. We also know that the phenotype of a MPO-ANCA–positive GPA is very different to what we might expect from MPO-positive MPA. If the disease phenotype is a function of the ANCA subtype, then we might expect MPO-ANCA GPA to present more like MPO-ANCA MPA. However, MPO-ANCA GPA appears to have a presentation which is less severe and may have a better survival outcome than PR3-ANCA GPA.[7] This suggests that the classification may reflect the disease mechanism as well as the serotype.

Wójcik et al[4] showed that ANCA antibody production may be a function of age. We know that

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the production of antinuclear antibodies rises with age. Could this just mean that as the body gets older, there is a degree of immune senescence that just results in greater antibody production? After all, we do not know precisely what the background ANCA positivity rate in the population is. There are several flaws in that argument, not least because ANCA are known to be pathogenic in vivo and in vitro.[10,11] It is therefore unlikely that these antibodies are innocent bystanders if present in a large fraction of the population. However, if they are pathogenic, we do not understand why 75 out of 536 patients (14%) are ANCA negative. Do they just have a different disease that looks a lot like AAV?

ANCA testing has been around since the 1980s and has been standardized since 1996.[12] The testing to support the diagnosis of a small and medium vessel vasculitis has been recommended since 2009.[13] We know that we cannot rely on serial titers for monitoring the disease and therefore their only utility is in establishing a diagnosis in individuals that have manifestation of a small and medium vessel vasculitis. The POLVAS data helped by filling in a small part of the knowledge gap in understanding the need for ANCA testing. There are very few national registries in the world and the establishment of such a concerted effort is likely to help us understand these rare diseases more than we currently do, and for that it must be commended.

ARTICLE INFORMATION

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