Prediction of Neurological Diseases by Using Autoantibodies: Wishful Thinking Come True

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Abstract

Medical screening is not a tangible existent tool in autoimmune disorders as it is in other illnesses. Numerous attempts are made to identify individuals destined to develop an autoimmune disease, including analysis of the genetic background, which along with the immunological profile, may assist in identifying those individuals. If these efforts turn out to be successful they could lead to proactive measures that might prevent the emergence of such disorders. This review will summarize the attempts made to pursue autoantibodies specific for the central nervous system as potential predictors of autoimmune neurological disorders.

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Autoimmune diseases are characterized by the production of antibodies that are directed against native targets. Autoantibodies react with various cellular and extracellular components, bringing forth the activation of the immune system which might eventually cause damage to organs and tissues. It is well established that autoantibodies may be a natural phenomenon present in healthy individuals who never develop disease and presumably play an important role in normal immunological physiology. The disposition to develop autoimmune disorders is influenced by many factors – genetic, environmental, infectious, and dietary. Yet, it is not possible to predict which person will be afflicted by an autoimmune disorder. Nevertheless, continuous research has enabled us to identify several of these risk factors that increase the risk of developing an autoimmune disorder.

Autoantibodies are formed after an erroneous identification of cellular constituents as foreign by the immune system cells. It is currently impossible to state exactly why this process occurs, but molecular mimicry is one of the suggested mechanisms. The structural similarity between normal native and foreign molecules prompts this misidentification.

Since prevention is the best medicine, attempts are made to pick out those subjects who are at greater risk for developing an autoimmune disorder. Obviously not all patients producing autoantibodies will become ill, therefore pursuing those individuals with impending disease is expedient and practical. Thus, from all the people tested, the attention and resources can later be directed to those at greater risk. The foreknowledge may provide physicians with an opportunity to intervene and halt the pathological processes and postpone their manifestations. This may be done by instructing patients about necessary life changes – quitting harmful habits such as smoking, changing diets, or avoiding hazardous occupational exposures. In selected patients the autoimmune condition might be discovered during a subclinical phase and guided therapy would slow the progression of disease, thus reducing future morbidity and mortality. This review will discuss the possible roles that autoantibodies play as predictors of future autoimmune neurological conditions.

Myasthenia gravis

Quintana et al. [1] demonstrated that a strain of laboratory mice (NOD/LtJ) naturally producing anti-acetylcholine receptor antibodies did not manifest symptoms of myasthenia gravis. However, after being challenged by a standard laboratory protocol they did develop the rodent form of experimental autoimmune myasthenia gravis. When compared to a different strain of mice known to be highly susceptible to the disease (C57BL/6), the challenged mice produced similar amounts of autoantibodies.

The classical complement pathway is also thought to participate in the pathogenesis of this disease. Tuzun and co-authors [2] induced experimental autoimmune MG in a strain of mice and were able to show an increase in anti-C1q antibodies. Moreover, the severity of their condition (measured as decrease in grip strength) stood in direct relation to the titer of anti-C1q antibodies. They also tested human patients showing the anti-C1q antibodies to be present only in the MG but not in control patients.

The AchR antibodies may be of two types: those directed against adult muscle and those targeting fetal muscle type. Gardnerova and team [3] succeeded in showing that although the titer of AchR antibodies varies widely before, during and after pregnancy in MG female patients, the ratio of anti-fetal to anti-adult muscle stays much the same for each patient. This ratio is predictive of the risk of a firstborn to develop neonatal MG.

Multiple sclerosis

Berger et al. [4] tested patients who experienced a first demyelinating clinical event for two types of autoantibodies: anti-myelin oligodendrocyte glycoprotein and anti-myelin basic protein. These two antibodies are known to be involved in the pathogenesis of multiple sclerosis. The tested patients also had evidence for

MG = myasthenia gravis
AchR = anti-acetylcholine receptor

demyelination on magnetic resonance imaging and oligoclonal bands in their cerebrospinal fluid analysis. Thus they were tagged as having possible MS. The diagnosis of definite multiple sclerosis requires a second clinically evident event. When the patients harboring these autoantibodies were compared with those who did not in relation to the conversion to definite MS, the authors were able to show an adjusted hazard ratio of 76.5 for those who tested positive for both antibodies and a ratio of 31.6 for those who had only anti-MOG antibodies.

Rauer and colleagues [5] presented different results. In a retrospective study they measured both anti-MOG and anti-MBP in patients who suffered a clinically isolated event. A comparison showed that those who tested positive for both antibodies were not more likely to experience a second event than those who tested negative for the antibodies. Of the patients who did have a relapse, those who tested positive had, on average, an earlier recurrence than those who tested negative (mean 5.5 months vs. 25 months). The authors also tested healthy subjects for the presence of both antibodies and found a prevalence of 21% for anti-MOG and 28% for anti-MBP antibodies. This limited specificity hampers efforts to dub these antibodies as diagnostic tools for the prediction of MS. Antel and Bar-Or [6] stated in their monograph that it is not yet known whether the presence of autoreactive antibodies in the cerebrospinal fluid of MS patients reflects a response to myelin injury or the initial cause for the insult.

Galactocerebroside is a glycolipid derived from central nervous system myelin and has been shown to be a target for autoimmune antibodies in the experimental equivalent of MS, the experimental allergic encephalomyelitis. Menge et al. [7] tested the frequency of anti-GalC in 51 definitely diagnosed MS patients and in 20 healthy controls. While the MS patient group had a 40% frequency, none of the control patients was shown to carry the antibody. Of note was their finding in 14 additional patients who had only one clinical demyelinating event. In this group the frequency of anti-GalC antibodies was about 8%, much lower than among the definite MS patients. This report suggests that the testing for anti-GalC may help predict MS in both healthy patients and in those who had a single clinical event.

Lampasona and co-workers [8] measured the frequency of anti-MOG immunoglobulin G and M antibodies in 87 MS patients and 47 healthy subjects. They detected a low frequency of antibody positivity in both groups, which did not differ in a statistically significant manner from each other. Thus, they concluded that anti-MOG antibodies could not be used to predict MS in healthy patients.

A different approach was taken by Lefranc et al. [9] who compared the immune response of self-antibodies from the sera of MS patients and healthy subjects against antigens derived from brain tissue of both normal and MS patients. They found a distinctive pattern of response for each group as shown by Western blotting assay. Further testing detected 16 brain antigens that had a distinct band on the assay – 9 from control brain tissue samples and 7 from MS brains. When applying statistical analysis to the results the authors found a sensitivity of 96.3% and a specificity of 88.9%.

In a preliminary work conducted by Xiao and team [10], 90 patients were screened for the presence of anti-MOG antibodies. The participants were divided into three equally sized groups according to their chief diagnosis: MS patients, patients suffering from tension headaches, and patients with other neurological disorders. Anti-MOG antibodies were found in 7 of 30 MS patients. However, the antibodies were detected in only two of the patients with other neurological diseases and one patient suffering from tension-type headaches.

Gaertner et al. [11] tested patients with definite MS, patients with a first clinical demyelinating event, and healthy controls for anti-MOG antibodies. They showed that while levels of antibodies did not differ between healthy controls and MS patients during remission, higher levels were found in active MS patients and those having their first event. It was proposed that the presence of antibodies may detect those at greater risk even prior to clinical manifestations.

Haase and associates [12] examined the specificity of anti-MOG antibody response using sera from both MS and normal patients. They found that the epitope specificity of the autoantibody response was heterogeneous in both groups. This may indicate that anti-MOG antibodies may have a role in inducing the disease in some of the definitely diagnosed MS patients. In others these antibodies may appear without a clear pathogenetic outcome.

Epilepsy

The possible role of autoantibodies in epilepsy was recently pursued by McKnight et al. [13] who tested 139 epilepsy patients and 150 healthy controls. A statistically significant difference was found only in two assays. Increased titers for anti-voltage gated potassium channels were found in 11% of patients compared to only 0.5% of controls. High levels of anti-glutamic acid decarboxylase were detected in 3.6% of epilepsy patients but in none of the controls.

Ganor and collaborators [14] compared monozygotic twins and healthy controls after measuring titers of several autoantibodies – anti-peptide B of the glutamate receptor, anti-double stranded DNA, antinuclear antibodies, anti-GAD, anticardiolipin and anti-β2-glycoprotein I. Only one patient from each twin couple suffered from epilepsy. They found higher levels of most antibodies in the twins compared to controls, but the epileptic twin had much higher titers compared to his/her sibling. No single antibody was exceptional in that manner.

In another interesting study, 50 pediatric epilepsy patients were compared with 20 healthy pediatric controls for the presence of various antibodies. The members of the study group had

MS = multiple sclerosis
MOG = myelin oligodendrocyte glycoprotein
MBP = myelin basic protein
GalC = galactocerebroside

GAD = glutamic acid decarboxylase

higher positivity levels than the controls and a higher average number of positive assays per patient. Due to the small size of the cohort only the test for aCL showed a statistically significant difference. While it was detectable in 44% of the epilepsy patients, only 10% of the controls were positive for the antibody [15]. Interestingly, this finding corresponds to the known fact that patients with the antiphospholipid antibody syndrome have higher rates of epilepsy [16].

Peltola et al. [17] conducted a similar study using 152 adult patients with different types of epilepsy. These patients were compared to 83 healthy controls. IgG aCL were more prevalent in the study group (21%) compared to the control group (7%). Moreover, when IgM aCL positivity was compared, the epileptic patients had significantly higher rates than the controls. Depending on seizure type, positivity rates were 33–60%, much higher than the 7% rate among the healthy patients.

Conclusions

The studies cited above provide us merely with preliminary data. Even so, it seems that autoantibodies, some of them suspected to be involved in the pathogenesis of non-neurological ailments, may have a role in neurological diseases as well. The differences in their prevalence may enable us to use them as markers for increased risk. Nonetheless, there is need for further research in this field before clinical application to render prediction of neurological illnesses using autoantibodies is possible.

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aCL = anticardiolipin
Ig = immunoglobulin

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