

The predictive significance of autoantibodies in autoimmune diseases

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ABSTRACT

Several studies have shown that autoimmune diseases are preceded by a long pre-clinical phase, and that many autoantibodies can be detected in the serum of asymptomatic subjects years before the clinical manifestations become evident.

Three parameters must be carefully quantitated for predictive tests to be clinically useful: sensitivity of prediction, specificity of prediction, and positive predictive values.

Purpose of review is to summarize the evidence for use of autoantibodies in screening asymptomatic individuals.

Long-term large studies of outcome are needed to assess the use of assaying autoantibodies for prediction of disease. Such data could lead to interventional trials to prevent autoimmune disease.

Keywords: autoantibodies, autoimmune diseases, predictors of disease

Many autoimmune diseases are chronic conditions that progress over the course of years, and are characterized by the presence of autoantibodies that precede the overt disease by months or years. The number and variety of preventive medical programmes are constantly increasing and this creates the impression or hope that they help or at least do some good.

The aim of disease prediction is disease prevention. Here, we focus on autoantibodies as predictive markers of disease. While the practical value of autoantibodies has been realized in some clinical conditions, it remains underutilized in the majority of diseases (1).

We can define predictive medicine as the identification of an individual who is healthy, but nevertheless more susceptible to developing a given disease. In fact, predictive medicine

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differs from preventive medicine in that the former is strictly individual, whereas preventive medicine is generally a public health initiative. Predictive medicine can be an individual preventive medicine, if the predictions lead to appropriate preventive measures. The lack of long-term prospective studies is perhaps the single most important reason why the role of autoantibodies as predictors of disease is still in its infancy. Autoimmune diseases result from aberrant activation of T and B lymphocytes which recognize and destroy self-molecules (termed autoantigens) (2).

For years laboratory professionals have been seeking the best screen at the shortest time possible in the most cost-effective way. Screening has the potential to save lives, or improve quality of life through early diagnosis of serious conditions, it is not a fool-proof process. Screening can reduce the risk of developing a condition, or its complications, but it cannot offer a guarantee of protection. No diagnostic test is 100% effective. Screening of population for susceptibility to certain autoimmune diseases is now feasible. The aim of disease prediction is disease prevention.

Screening for autoantibodies may become a routine part of a medical examination. It is essential to use assay methods with high diagnostic specificity, to minimize false positive and obtain a high positive predictive value. These observations hold out the prospect of screening the general population to identify individuals at high risk for some autoimmune diseases. The practical value of screening healthy populations to detect individuals at high risk for a particular autoimmune disease will be enhanced enormously once preventive measures and safe therapy become available. Recognizing the clinical potential of autoantibodies and identifying appropriate populations to screen for such autoantibodies, we argue, could have rich practical rewards (3).

Most autoimmune diseases are relatively rare, and most are not fatal. Therefore, they never appear on the public "radar screen" as a serious health problem requiring more attention and more funding. An autoimmune disease is debilitating for the patient and often destructive of a productive lifestyle of an entire family (4).

Molecules called predictive autoantibodies appear in the blood years before people show symptoms of various disorders. Detection of

specific autoantibodies remains the most practical clinical and research marker of autoimmune disease (5).

The definition of an autoimmune disease is sometimes very hard to pin down. The basic definition of an autoimmune disease is a disorder caused by an autoimmune response. The presence of an autoimmune response is signaled by the appearance of autoantibody in the circulation, and so the demonstration of a particular autoantibody usually constitutes the path to recognize an autoimmune disease. Further, the survey revealed that 45 percent of autoimmune disease patients had been labeled hypochondriacs in the earliest stages of their illnesses. Since symptoms can be vague and not visibly apparent, many doctors don't think to test for autoimmune diseases initially (6,7).

Tests for these autoantibodies could therefore be used in principle in screening studies on unselected populations to identify individuals predisposed to the development of the disease at an early stage and start treatment or adopt preventive measures where possible. Tests vary for different autoimmune diseases, and no single test can ascertain whether a patient has an autoimmune disease (8).

Making an autoimmune diagnosis is an exercise in the art of medicine as well as the science. Many human diseases are the result of autoimmune attack, presumably related to a loss of tolerance to self (9).

Autoimmune disease can be divided into either organ-specific illnesses, such as thyroid disease, type I diabetes, and myasthenia gravis, or systemic illnesses, such as rheumatoid arthritis and systemic lupus erythematosus (10).

Virtually all autoimmune diseases are associated with circulating autoantibodies, which bind self-protein (11).

Autoantibodies can be detected in diseases with a long prodrome during which there are no clinical symptoms. Furthermore, for many diseases these autoantibodies are found in serum samples many years before disease onset. Tests for these autoantibodies could therefore be used in principle in screening studies on unselected populations to identify individuals predisposed to the development of the disease at an early stage, and start treatment or adopt preventive measures where possible (12).

Testing and follow-up of special populations with one autoimmune disease, probably cannot be extrapolated to the general population,

which is at lower risk of disease. However, since disease-associated autoantibodies do not develop simultaneously and since many patients have only one antigen-specific autoantibody, using a panel of different autoantibodies is likely to increase the sensitivity of prediction (13).

The idea that autoantibodies can be used to predict disease comes from extensive studies on type I diabetes. Thus far, all prospective studies on relatives of type I diabetes patients have shown that the combination of two or more autoantibodies gives a higher positive predictive value than any single autoantibody. Apart from the studies on type I diabetes, however, the value of autoantibodies as predictors of disease has not been fully explored, nor has the potential been fully realized. As examples, the presence of two islet cell antibodies (ICA) are associated with a 50% risk of developing diabetes mellitus in 5 years, anticyclic citrullinated peptide (anti-CCP) antibodies are found in the sera of rheumatoid arthritis (RA) patients a median of 4.5 years before the overt disease, and in systemic lupus erythematosus (SLE) patients accrue antibodies throughout a foreseen course during the 3-4 years prior to the clinical symptoms. This ability to predict autoimmune diseases, or rather their clinical manifestations, leads to the prospect of screening healthy individuals for autoantibodies (14).

The early diagnosis of RA has become a priority owing to the availability of effective disease-modifying agents that can improve patient wellbeing and influence the clinical outcome. For this reason, development of the anti-CCP antibody assay, a highly disease-specific serological marker for RA, has been a great step forward for the rheumatologist and the clinical laboratory. The presence of rheumatoid factor (RF) in asymptomatic individuals may predict the subsequent development of rheumatoid arthritis. Anti-topoisomerase I autoantibodies may precede the development of scleroderma. The development of myositis-specific antibodies may be predictive of the development of polymyositis. Celiac disease-associated autoantibodies are now widely used for disease prediction (15,16).

In organ-specific autoimmune diseases such as type 1 diabetes and thyroiditis, autoantibodies can be detected in peripheral blood years

before the destruction of hormone-secreting cells leads to overt clinical symptoms (17).

Many of the diabetes-associated autoantibodies appear by 5 years of age, so screening should ideally be performed at birth and repeated at intervals thereafter. Limiting the screening program to only young children, however, would miss a significant fraction of potential cases (18,19).

Thyroid antibodies, on the other hand, rarely appear before 20 years of age and there would be no value in screening for them until after that age. A number of other diseases not discussed here are associated with the presence of autoantibodies, but there are no large screening studies to determine whether these same autoantibodies can predict the disease; for example, neurological disorders such as myasthenia gravis and Lambert-Eaton syndrome, in which autoantibodies can be diagnostic of the disease. By identifying at birth those infants who are genetically at increased or reduced risk of autoimmune diseases, it might be possible to substantially reduce the numbers in a population who would have to be screened for autoantibodies. This additional step might also increase the predictive value of a positive autoantibody test. Gliadin antibodies, both IgA and IgG, have been used in screening and have a sensitivity and specificity for prediction of celiac disease of 70-100%. IgA endomysial antibodies are also highly predictive of celiac disease. Antibodies against citrulline often appear in the bloodstream before the first symptoms turn up, in some cases more than 10 years earlier. The negative predict value of this test was high, and the positive predictive value in a population with joint symptoms was 62%. It is important to follow patients who have low levels of autoantibodies. Autoantibodies associated with RA may also predict disease in healthy individuals in whom hormonal changes might be a trigger for autoimmune disease. These autoantibodies are a warning sign of impending disease, and it opens the possibility of predicting disease and possibly benefiting patients by early treatment or even interrupting the autoimmune responses. There is the potential in the next few years to identify people who go on to get an autoimmune disease, and that kind of identification may lead to preventive therapies.

The best documented relationship between the presence of specific autoantibodies and the subsequent development of an inflammatory

or autoimmune disease with rheumatic features is the relationship between the presence of autoantibodies to the E2 component of pyruvate dehydrogenase and primary biliary cirrhosis (PBC). The presence of this autoantibody can precede the development of PBC by many years, and many asymptomatic individuals with these autoantibodies subsequently develop PBC. The levels of adrenocortical autoantibodies correlate with the degree of adrenal dysfunction in subjects with preclinical Addison's disease. Autoantibodies, traditionally the hallmark of SLE, are typically present several years prior to diagnosis of SLE and serve as markers for future disease in otherwise normal individuals (2,20-23).

The next most significant advance in characterizing autoantibodies as predictors of disease will be development of standardized tests based on use of specific antigens. Long-term large studies of outcome are needed to assess the use of assaying autoantibodies for prediction of disease. Such data could lead to intervention trials to prevent autoimmune disease.

Conclusion

This review really shows the importance of early screening, particularly in people with early symptoms. Antibodies may reflect the presence, nature, and intensity of the immune response. Thus the presence of autoantibodies in otherwise healthy individuals might be a marker of future autoimmune disease or, alternatively, certain autoantibodies might predict the course in a person with established disease.

Several studies have shown that autoimmune diseases are preceded by a long pre-clinical phase, and that many autoantibodies can be detected in the serum of asymptomatic subjects years before the clinical manifestations become evident.

Novel antigen-specific autoantibodies, once identified, might improve prediction even further. However, as no antibody assay offers 100% specificity, and the results are strongly dependent on the assay method used to measure the autoantibodies.

Long-term prospective studies are needed to more definitively define the value of these autoantibodies in prediction.

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