

# On the Trail of Diseases, Years Before They Strike – Auto Antibodies

Vipla Puri

Auto antibodies are the markers of future disease in presently healthy individuals. Although auto antibodies might not always be directly responsible for many of the manifestations of auto immune diseases, but assaying auto antibodies for prediction of disease could lead to intervention trials to prevent auto immune organ specific diseases like Type 1 Diabetes, Thyroid disease, Myasthenia gravis or systemic illnesses like Rheumatoid arthritis and Systemic Lupus Erythematosus (SLE). Thus predictive autoantibodies are molecules that appear in blood years before people show symptoms of various disorders. Tests that detect these molecules could warn of the need to take preventive action.

## Auto Antibodies as Markers of Disease Activity, Severity and Classification

Antibodies may reflect the presence, nature and intensity of immune response. Since in auto immune diseases the immune response is itself part of the disease process, it is possible to use auto antibodies as markers of disease activity. These auto antibodies can be detected in certain diseases with a long prodrome during which there are no clinical symptoms. The titer or the levels of these auto antibodies can also predict both the likelihood of clinical disease and rate of progression of the disease i.e. the disease activity and the severity of the disease.<sup>1</sup>

---

Consultant Lab Medicine, PD Hinduja Hospital,  
Mahim 400 016.

Many auto immune diseases are chronic conditions that progress over the course of time and are characterized by the presence of auto antibodies that precede the overt disease by months or years.<sup>2</sup> It is now known that the presence of two, Islet Cell Antibodies (ICA) are associated with a 50% risk of developing diabetes mellitus in 5 years; Anti Cyclic Citrullinated Peptide (Anti-CCP) antibodies are found in sera of rheumatoid arthritis patients 4 to 5 years before the overt disease, and in SLE patients accrue antibodies throughout a foreseen course during 3 - 4 years before to clinical symptoms. This ability to predict auto immune diseases, or rather their clinical manifestations lead to the prospect of screening healthy individuals for auto antibodies. This notion will enable to prevent life threatening manifestations, such as Addisonian's crisis and thyroid storm and help to treat or even prevent overt autoimmune diseases.

## Causes of Auto antibody Formation

The causes of auto antibody production are varied and not well understood. It is thought that some auto antibody production is due to a genetic predisposition combined with environmental trigger such as viral illness or a prolonged exposure to certain toxic chemicals. Hormonal component has also been implicated in many auto immune conditions since auto immune conditions are much more prevalent in reproductive age groups.

### **Clinical Utility of Auto antibodies**

Although the incidence and prevalence of individual auto immune diseases are not high, but the population burden of disease is large and under-estimated. A number of broad principles that may apply to auto immune diseases, in general, can be drawn from the observations based on few selected auto immune diseases.

*First*, Auto antibodies reflect the disease process and in those cases where the disease has a long prodrome antibodies can predict clinical disease particularly when the auto antibody itself has the capacity to damage tissue.

*Second*, a number of distinct auto antibodies are associated with any one disease and some are more predictive of progression to clinical symptoms than others.

*Third*, the risk of progression to disease, the rate of progression and the severity of disease can be predicted to a degree by the number of auto antibodies, the type of auto antibody, the titre of antibody and associated features including genetic risk and evidence of target organ failure.

These observations hold out the prospect of screening the general population to identify individuals at high risk for some auto immune diseases. Such cases might be amenable to therapy either to prevent progression to clinical disease or to limit the impact of disease.

However, appropriate strategies have to be devised before screening becomes a reality since predictive value of antibodies will depend on whether we are screening twins, first degree relatives or general population. Also the appropriate or best age at which the screening should be done will vary with the disease in question, for example, many of the diabetes associated antibodies are known to

appear by the age of 5 years, so screening should ideally be done at birth and repeated at regular intervals. Limiting the screening only to young children may miss a significant fraction of potential cases. Thyroid antibodies, on the other hand, rarely appear before 20 years of age and so there will be no value screening for them before this age.<sup>3</sup> Large population based screening studies have been shown to be feasible for diabetes associated autoantibodies, therefore similar studies using a wider panel of auto antibodies associated with other diseases may prove valuable. Due to lack of long term prospective studies, the role of autoantibodies as predictors of disease is still in its infancy.

By identifying infants at birth who are genetically at increased or reduced risk of autoimmune diseases, it might be possible to substantially reduce the numbers who would have to be screened later in a population.

Additional genetic parameters along with autoantibody can increase the predictive value of a positive test e.g., non diabetic relatives with autoantibodies are unlikely to develop diabetes if they have the HLA allele DQB\*10602,<sup>4</sup> whereas individuals with 21-hydroxylase autoantibodies and HLA DRBI\*0404 allele<sup>5</sup> are at high risk of progression to adrenal failure. Maximal predictive sensitivity and specificity may require different sets of autoantibodies at different ages and at different times in the course of a particular disease.

Although, screening of populations for susceptibility to certain autoimmune diseases is now feasible, high throughout cost effective methods should be available for screening healthy populations to detect individuals at high risk for a particular autoimmune disease. The practical value of screening will be enhanced once preventive measures and safe therapy become available.

**Some of the predictive autoantibodies in autoimmune diseases**

Disease	Auto Antibodies
Rheumatoid Arthritis	RA (Anti - IgG) Anti - CCP*
Systemic Lupus Erythematosus (SLE)	Anti - PL Anti - Ro, Anti -La Anti - DNA, Anti - Sm Antinuclear ribonucleoprotein Anti - HS Anti - Nucleosome Anti - Histone Antiribosomal - P - Protein
Sjogren's Disease	Anti - Ro, Anti - La Anti Phospholipid Antibodies (IgG, IgM)*
Anti Phospholipid Syndrome	Anti Cardiolipin (IgG, IgM)*
Pregnancy Induced hypertension	Anti Phosphotidyl - serine
Repeated Pregnancy loss	Anti - Prothrombin Anti - Laminin-1 Anti Beta 2 glycoprotein* (IgG, IgM) Lupus Anticoagulant
Pernicious Anaemia	Intrinsic Factor Blocking Antibodies*
Autoimmune Hepatitis	Parietal Cell Antibodies*
Primary Biliary Cirrhosis (PBC)	Anti LKM-1.*
Chronic Liver Disease	
Pernicious Anemia	
Coeliac Disease	Anti Tissue Transglutaminase Antibodies* (IgG, IgA)
Dermatitis Herpetiformis	Anti - Gliadin Antibodies* (IgG, IgA) Anti - Endomysial Antibodies* (IgG, IgA)
Chronic Active Hepatitis	Anti - Mitochondrial Antibodies*
Primary Biliary Cirrhosis	M2 , M3
Syphilis	Anti - Mitochondrial Antibodies M1
Isoniazid Induced Hepatitis	Anti - Mitochondrial Antibodies M6
Autoimmune Active Hepatitis	Anti - Smooth Muscle Antibodies

Primary Biliary Cirrhosis	
Primary Sclerosing Cholangitis	
Primary Pulmonary Hypertension	
Crohn's disease	Anti - Saccharomyces* Cerevisiae Antibodies (ASCA)*
Type I Disease	Anti Glutamic Acid Decarboxylase Antibodies (Anti GAD)* Anti Islet Cell Antibody* Anti Insulin Antibody*

**Thyroid diseases**

Disease	Auto Antibodies
Hashimoto Disease	Microsomal Antibodies*
Atrophic Thyroiditis	Thyroid Peroxidase Antibodies*
Graves' Disease	
Hashimoto's Thyroiditis	Thyroglobulin Antibodies*
Primary Hypothyroidism	
Primary Hyperthyroidism	
Colloid Goitre	
Adenoma	
Thyroid Cancer	
Addison's disease	
Diabetes Mellitus	
Graves' Disease	Thyrotropin Receptor Antibodies*
Immunological Infertility	Anti - Sperm Antibodies* Anti - Ovary Antibodies*
Autoimmune Addison's Disease	Anti - 21 Hydroxylase Antibodies Anti - Adrenal Antibodies*
Myasthenia Gravis	Acetylcholine Receptor* Antibodies (ACHRAB)* Anti Muscle Specific Tyrosine Kinase Antibodies (MUSK)*
Peripheral Neuropathy	Ganglioside M1 Antibodies
Multiple Sclerosis	Myelin Associated Glycoprotein Antibodies
Good Pasture's syndrome	Anti Glomerular Basement Membrane Antibodies (Anti GBM)*
Glomerulonephritis	Anti - Neutrophil Cytoplasmic Antibodies (ANCA)
Bullous Pemphigoid	Bullous Pemphigoid 180*

Pemphigus Vulgaris and 230 Antibodies\*  
Desmoglein I and III  
Antibodies\*

Pemphigus Foliaceus

\* Done routinely at RIA dept of Hinduja Hospital.

#### References

1. Dayan CM, Daniels, GH. Chronic Autoimmune Thyroiditis. *N Engl J Med* 1996; 335 : 99-107.
2. Leslie RDG, Atkinson MA, Notkins AL. Auto antigens IA – 2 and GAD in Type 1 (Insulin dependent) Diabetes. *Diabetologia* 1999; 42 : 3-14.
3. Leslie D, Lipsky P, Notkins AL. Autoantibodies as predictors of disease. *J Clin Invest* 2001; 108 : 1417-22.
4. Leslie RD, Elliott RB. Early environmental events as a cause of IDDM. Evidence and implications. *Diabetes* 1994; 43 : 843-50.
5. YU L, *et al* DRBI\* 04 and DQ alleles expression of 21- hydroxylase autoantibodies and risk of progression to Addison's disease. *J Clin Endocrinol Metab* 1999; 84 : 328-35.
6. Scofield RH. Autoantibodies as predictors of disease. *Lancet* 2004; 363 : 1544-46.

#### SMOKELESS TOBACCO USE BY SOUTH ASIAN YOUTH IN THE UK

Cancer of the oropharynx constitutes one of the ten commonest cancers, in the world. Important causal agents include the alkaloid content of the habit-forming betel nut (areca) – commonly known as supari among south Asians – and tobacco, whether smoked in cigarettes, bidis or through a hookah or chewed as gutka or paan.

Gutka is made up of tobacco, betel-but fragments, fennel, and other spices, and is marketed in attractive colourful sachets that are appealing to children.

The recent addition of chocolate-flavoured ingredients, may further enhance this appeal. Gutka can be bought by young people from “corner shops” in many UK inner cities for only a few pence.

Paan is believed by many to be an aphrodisiac, which thus further heightens its attractiveness, particularly to young men. Its use is, however, far from benign, as shown by a study among Gujaratis in northwest London, which found that paan chewers in northwest London, which found that paan chewers had cocaine-like dependency with withdrawal symptoms of headaches and sweating.

**Sukhmeet Singh Panesar, Rashid Gatrad, Aziz Sheikh, *The Lancet*, 2008; 372 : 97-98.**