How Autoantibody Tests Can Help to Diagnose Endocrine Disorders*

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INTRODUCTION

Organ specific autoimmunity (AI) has been demonstrated in all the defined endocrine organs except the pineal gland and is now being studied in the paracrine systems of the gastrointestinal tract and the hypothalamus. The autoimmune endocrine disorders are characterized by the presence of antibodies in the patients' serum which may be detected years before the onset of clinical symptoms and are useful monitors of the lesions well before hormonal deficiencies can be measured by metabolic tests. In the case of stimulating antibodies that produce hormone excess, and hormone receptor antibodies generally, the situation is far more complex.

In this review we will describe the present range of tissue antibodies helpful in early diagnosis and try to show that substantial morbidity could be avoided by preventive autoimmune screening in selected individuals.

Who are the susceptible individuals?

Screening for tissue antibodies has been carried out on a population basis in several countries[1,2] and showed a similar distribution of autoantibodies in most continents except Africa where autoimmunity is rare due to the overriding takeover effects of parasitic infections upon the resources of the immune system.

The AI endocrine diseases all have a strong genetic element. For instance in Graves' thyrotoxicosis, in Hashimoto's disease and in juvenile onset diabetes, the concordance rate of the clinical conditions is about 50% in monozygotic twins. This contrasts strikingly with the non-organ-specific collagen disorders such as SLE and rheumatoid arthritis, where only 10% of identical twins are both affected. The frequency of the endocrine immunopathies varies tremendously from common conditions such as the thyroid autoimmune diseases and AI gastritis through to insulin dependent diabetes, AI adrenalitis and gonadal atrophy to the rare autoimmune hypophysitis and parathyroid atrophies. The more common the disease, the greater the frequency of antibodies to that particular organ in the population, and more so in close relatives of the affected patient. In addition, many of these diseases have a predilection for the female sex and tend to be expressed in adult life, so that antibodies are most likely to be found in middle-aged women especially those belonging to autoimmune families. To a certain extent, the prevalence and titres of autoantibodies also go with the size of the endocrine organs, presumably in relation to the total amount of antigenic material made available to the regulating networks of autoreactive immunocytes.

A most important feature in this group of disorders is the striking overlap between them. At the extreme end we have the rare polyendocrine syndromes where all the endocrine organs may be involved in the same patient. These cases have been recognized clinically for over 60 years and have received growing attention since the discovery of islet-cell antibodies in insulin dependent diabetes (IDDM) and the identification of pituitary autoimmunity.[3,4]

The classical polyendocrine syndromes include Schmidt's syndrome (thyroiditis and adrenalitis with or without IDDM) and the candida-endocrinopathy or C-E syndrome mostly seen in paediatric practice.[5] There are also far more complex mixtures. Endocrine autoimmunity may be associated with diseases such as chronic active hepatitis or myasthenia gravis; with AI haemolytic anaemia or thrombocytopenia and with malabsorption syndromes. In these cases the immune defects are of a wider scope and include immunoglobulin deficiencies, commonly of the IgA class, severe allergies and various thymus dependent-(T)-lymphocyte defects. These abnormalities can be identified in various members of the family as well

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Table 1. Diagnostic antibodies for endocrine autoimmune disorders.

Disease	Antibodies* react with	Frequency in normal population
Graves' thyrotoxicosis	TSH receptors (Table 2)	nyd
Some nontoxic nodular Sporadic goitres	Thyroid microsomes (HA)	F>M; 0-20% according to sex and age
Primary myxoedema Hashimoto's goitre	Thyroglobulin (HA)	F>M; 0-20% according to sex and age
Endocrine exophthalmos	Extraocular muscle (ELISA) retroorbital tissues	nyd
Pernicious anaemia	Intrinsic factor (RIA) Gastric parietal cell	0.1% F>M; 0-16% according to sex and age
Fundal (type A) gastritis	Gastric parietal cell	F>M; 0-16% according to sex and age
Antral (type B) gastritis	Gastrin cell	0.1%
Addison's disease	Adrenal cortex	0.1%
Premature menopause with adrenalitis	Adrenal cortex Steroid cells, gonadal and placental	0.1% 0.01%
Primary gonadal deficiency	Sperm and ovum	7%
Idiopathic hypoparathyroidism	? parathyroid chief cells	nyd
Insulin-dependent diabetes	Pancreatic islet cells: 1. 'Common antigen' 2. Insulin cell 3. Glucagon cell 4. Somatostatin cell 5. Anterior pituitary cell	 0.5% nyd 0.2% 0.5% nyd
Partial pituitary deficiency	Prolactin cell Growth hormone cell	0.1% 0.01%
Idiopathic central diabetes insipidus	Hypothalamic vasopressin and/or oxytocin cells	0.01%
Vitiligo	Melanocyte	nyd
Myasthenia gravis	Acetylcholine receptors (RIA)	1%
Autoimmune liver disorders (overlap with endocrine AI)		
Chronic active liver disease Lupoid variant	Nuclei (mostly diffuse)	F>M; 0-20% according to sex and age
	Smooth muscle (mostly actin)	12%
'Liver and kidney microsome' variant (LKM)	Endoplasmic reticulum	0.3%
Cholestatic variant	Mitochondria	0.4-0.7%
Primary biliary cirrhosis	Mitochondrial inner membranes	0.4-0.7%

* Detected by immunofluorescence unless otherwise stated.
nyd = not yet determined; HA = Haemagglutination with antigen coated red cells; RIA = Radioimmunoassay; ELISA = enzyme-linked-immunosorbent assay

as in the patients themselves.[6]

Much more common are the 'thyrogastric' syndrome, i.e. a combination of thyroid and gastric autoimmunity. Usually the patient presents clinically with one or other of these common conditions i.e. a thyroid disease or pernicious anaemia. Their serum often contains a number of relevant and interesting mixtures of organ-specific antibodies, some of which are indicative of a subclinical lesion that can be followed and prevented from becoming troublesome or dangerous to the patient's well being. It is in this category of 'serological polyendocrinopathy' that our best chances of preventive measures will gradually emerge in coming years. The difficulty today is that for most of the organs except thyroid, it is not known what proportion of patients with circulating antibodies eventually express the corresponding clinical disorder. There is an urgent need to test predisposed subjects for all available specificities in relation to the endocrine system. At the same time it is advisable to look for the non-organ-specific markers as the overlap which extends towards the other end of the autoimmune spectrum is not well understood.

We can now define the susceptible groups:

1. Patients with recognized autoimmunity to one organ.
2. Their first degree relatives, especially sibs and offspring of both sexes.
3. Patients with non-endocrine disorders known to overlap or be connected with the AI endocrinopathies (for instance PA, RA, coeliac/malabsorption syndromes, AI liver diseases, vitiligo and alopecia).
4. The relatives of group (3).
5. Detailed family histories are most important in relation to autoimmunity and any patient with a positive FH should be screened.
6. Patients with disorders of unknown aetiology. The presence of autoantibodies may give a clue for new interpretations or fresh discoveries, (e.g. hypothalamic antibodies in diabetes insipidus).
7. Middleaged women generally, especially those presenting in out patient departments with fatigue, depression or other ill defined symptoms.

Detection of organ antibodies

The range of autoantibodies that can be detected for the early diagnosis of endocrine diseases are shown in Tables 1 & 2. The most suitable method is still the indirect immunofluorescence test (IFT) done on unfixed cryostat sections of human organs obtained at operations, or soon after death, from renal transplant donors. For anterior pituita-

Table 2. Recognized 'receptor antibody diseases.'

Disease	Receptor reacting with antibodies	Action of antibodies
Graves thyrotoxicosis	TSH-R (TSI)	Stimulation of T3/T4 synthesis
Graves' with goitre	? TSH-R (TGI)	Stimulation of cell division
Sporadic/familial non toxic nodular goitre	? TSH-R (TGI)	Stimulation of cell division
Primary myxoedema	TSH-R (TSI-block)	Blocking of c-AMP stimulation
	(TGI-block)	Blocking of cell division
Atrophic fundal gastritis	Gastrin-R on parietal cells	Blocking of carbonic anhydrase
		? blocking of parietal cell regeneration
Myasthenia gravis	Acetylcholine-R	Blocking of neuromuscular transmission
Bronchial Asthma	Beta-adrenergic-R	Impaired sensitivity to beta-adrenergic drugs
Insulin resistent diabetes	Insulin-R	Blocking of insulin secretion
		Insulin-like action on adipocytes
Gonadotrophin resistant gonadal deficiency	Gonadotrophin-R on ovarian cells	Blocking of oestrogen responses
		? blocking of steriod cell regeneration
Renal failure	Parathormone – R	Blocking of parathyroid hormone action on target organs

TSH = thyroid stimulating hormone; R = hormone receptors on cell surface; TSI = thyoid stimulating autoantibodies or immunoglobulins; TGI = thyroid growth immunoglobulins

ry, ovarian and hypothalamic antibodies fresh baboon glands or brain tissue have proved easier to obtain and convenient to handle. The cross-reactivity of human antibodies with primate organs is high compared with guinea-pig, rat or mouse tissues, which cannot be used for this type of work. Fixatives are not recommended as they often inactivate the cellular autoantigens. The test can be done on several organs at once and requires only a few drops of serum from the patient. Semiquantitative tests are obtained by repeating positive results of undiluted serum on suitable dilutions to endpoint. The old-established tests with thyroid, stomach or adrenal and more recently pancreatic islets are available in many laboratories but for the more recent endocrine cell antibodies such as pituitary, gonadal and hypothalamic, the test are at present only done in specialized research units. These organs should be easier to obtain in future, since an American firm (Biodex, New Jersey) sends monkey organ sections ready processed to any country on request at a reasonable cost. For thyroglobulin and thyroid microsomal antibodies, immunofluorescence has been superceded by passive haemagglutination (HA) performed with commercial kits of sheep or turkey red cells coated with the purified human antigens (Welcome Reagents, London, and Fujizoki, Tokyo). The older complement fixation tests have been abandoned in favour of immunofluorescence done with anticomplement (C3) serum conjugated with fluorescein (green) or rhodamine (red). It is now clear that only a proportion of any organ antibodies fix complement and that this subset is more pertinent to the pathogenesis of autoimmune lesions such as pancreatic insulitis in diabetes. This probably applies equally to other endocrinopathies so that the standard IFT with anti-immunoglobulin conjugates should be combined with the complement fixing immunofluorescent test (ICFT) for predictive studies. Radiometric assays become possible when purified antigens are available. Receptor antibody tests will be discussed separately. A method which will be of great value in future is the enzyme linked immunosorbent assay (ELISA). This is at present being used to detect ocular muscle antibodies as a test for endocrine exophthalmos.[7] The 'monoclonal antibody revolution' is being applied in this work and in the analysis of hormone receptor structure.[6] Monoclonal antibodies are a useful tool for the purification and separation of endocrine autoantigens.

EARLY DETECTION IN SPECIFIC DISEASES

Adrenalitis

There are clinical circumstances where autoantibody tests done at an early stage can actually be lifesaving. These are the cases of subclinical adrenal deficiency who develop an adrenal crisis during infection or acute appendicitis. There are descriptions in the literature of young patients with unsuspected Addison's disease who come in as emergencies and die before a diagnosis can be reached. Some of these are known to have had thyroid disease in the past or they suffer from insulin-dependent diabetes. Some have secondary amenorrhoea associated with steroid cell gonadal antibodies. Others have an undiagnosed hypophysitis. Screening for adrenal and pituitary antibodies would be of particular benefit in these circumstance.

Infertility and amenorrhoea

A proportion of patients with no clinical signs of anterior pituitary failure except for absence of periods and inability to become pregnant, were found to have antibodies to prolactin cells. The percentage of positive sera appears to depend mainly on the selection of cases and varied between 5% and 30%. Further studies are urgently needed in this interesting field. For instance it is not yet known if any of the patients with microadenomas of the prolactin cells ever have autoantibodies. Cases are now appearing in the literature where a prolactinoma is diagnosed but where pituitary histology showed enlargement of the anterior lobe with lymphocytic hypophysitis, reminiscent of the appearances in the thyroid gland in Hashimoto's goitres.[8]

Some girls with primary or secondary amenorrhoea have no indication of adrenal failure, yet their sera contain adrenal antibodies and steroid cell antibodies reacting with Leydig cells in the testis and ovarian steroid cells. It is not known how many such cases will eventually develop clinical Addison's disease. Early detection and careful follow up of these young people will teach us a great deal about polyendocrine autoimmunity in its milder forms.

Pancreatic insulitis

Patients with autoimmune thyroiditis, gastritis or adrenalitis have an increased risk of developing insulin dependent diabetes at any age. Islet cell antibodies of the complement fixing variety (CF-ICA) are more closely associated with the presence of an active insulitis because among the mixture of different serum antibodies, some CF-ICA are directed specifically to the pancreatic beta-cells that secrete insulin. Only the beta-cells are destroyed in diabetes, and it is this specific subset which is cytotoxic and relevant. At present it looks as though about half of the subjects with CF-ICA in their sera develop diabetes. This is based upon a 4-year follow-up of 'unaffected' first degree relatives of diabetic children and a 6 year observation of 'endocrine' patients who happened to have a positive CF-ICA when screened for various tissue reactions.[9]

It is regretable that we do not yet know how to reverse an ongoing insulitis. However, it is obvious that before a suitable form of treatment can be discovered it is necessary to know exactly who is liable

to develop diabetes in future years. Extensive glucose tolerance testing in past research schemes has not led to reliable predictions because the tests remain normal until some 80-90% of the beta-cells are lost, much as in the case of atrophic thyroiditis.

The recent finding that cyclosporin-A can prevent diabetes in the BB rat model makes it likely that the drug will be tried in diabetic families. The BB rat develops insulitis and thyroditis and has strong resemblance to the human disease.[10]

Atrophic thyroiditis

Myxoedema often comes on so insiduously that it is easy to miss it unless one is constantly on the look out for early signs. Routine screening of middleaged women shows a 20% prevalence of thyroid antibodies but only 10-20% of the positive reactors eventually lose some of their thyroid function. Because of the much greater frequency of thyroiditis compared with insulitis or adrenalitis, even this low figure represents a substantial number of patients. The TRH/TSH test offers the best chance of selecting hypothyroid cases prospectively, because antibody tests by themselves do not distinguish between the progressive form of thyroiditis and the harmless focal variety. In our clinic we give thyroxine replacement to any patients with a raised basal serum TSH (i.e. higher than 6 mU/l). When this is normal but the value rises above 30 mU at 20 minutes after 200 μg TRH/iv, then we give a trial of T4 for 6 months and see if the TRH returns to normal 3 months after stopping the replacement.

It is still hoped that future studies with thyroid-growth-blocking antibodies will help us to select the progressive cases more accurately but we need an easier method than the cytochemical bio-assays used so far.[11]

Autoimmune gastritis

Atrophic fundal gastritis is known to exist in one thrid of all patients with autoimmune thyroiditis but as in the case of thyroid atrophy, many remain totally subclinical during the whole of the patient's life and neither the presence of parietal cell antibodies nor their titre are reliable indices of progression. Pernicious anaemia occurs 5-8 times more frequently than expected in patients with thyroid disease and the easiest way to monitor this possibility is by measuring the serum B_{12} level at intervals. The radioimmunoassay with labeled vitamin B_{12} for intrinsic factor antibodies should also be carried out as it is positive in over half the cases of latent pernicious anaemia. The presence of these antibodies in the gastric juice would probably be more reliable for prediction but since the antibodies are combined with intrinsic factor it is difficult to extract them from the immune complexes and symptomless patients are not willing to have gastric intubations.

Atrophic gastritis can contribute to iron deficiency anaemia by blood leakage from the injured gastric mucosa, and parietal cell antibodies are often found in women presenting with this common condition.

AUTOIMMUNITY TO HORMONE AND OTHER CELL RECEPTORS

The best known autoimmune 'receptor' disease is Graves' thyrotoxicosis. TSH-receptor antibodies have been demonstrated in the serum of these patients for over 25 years by numerous methods (Table 2) and are thought to cause the hypersecretion of triiodothyronine and thyroxine (T3/T4). As a generic term 'thyroid stimulating antibodies' or TSAb is suitable but the autoimmunity is always polyclonal and each patient responds differently to a range of epitopes or antigenic sites on the complex structure of the hormone receptor so that some antibodies 'bind' to it, some transmit a message to synthesise hormones, some give signals for cell division and goitre formation and some block the receptors and prevent them from responding to TSH or to other TSAb.[12] Many of these antibodies can coexist in a single patient or come and go at different timess of life. This is the reason for the great variety of clinical signs and symptoms seen in Graves' disease and in other autoimmune 'receptor' disorder.[13] It is likely that endocrine exophthalmos is a separate autoimmunization to eye components but the fact that 90% of cases are somehow related to past, present or future thyroid dysfunction, suggests that there is an immunological relationship. It is of special interest that one of the monoclonal antibodies produced by a mouse hybridoma after immunization with eye muscle antigens cross-reacted with the principal antigen of human thyroiditis, i.e. the microsomal antigen.[7] Another hybridoma made with lymphocytes from a patient with pretibial myxoedema has the property of stimulating fibroblast growth.[14] To add further complexity these antibodies cross-react with different affinities with the TSH receptors of other animal species that are used for detecting TSAb.

New simplified assays for the early diagnosis of thyrotoxicosis are being developed using a continuous line of rat thyroid cells immortalized with intact function. There is hope of combining c-AMP stimulation and radioiodine uptake with thymidine incorporation in the same cultures. This will measure both hormone stimulating and growth stimulating antibodies in a reproducible manner. Thyroid growth-stimulating antibodies are detected in some sporadic non toxic nodular goitres[11] and this may represent a new form of thyroid autoimmunity despite the usual absence in this disease of conventional thyroglobulin or thyroid microsomal antibodies in the serum, or lymphocytic thyroid gland infiltrates.[15] When the tests become easier to perform they will prove of help in deciding whether or not to operate on any given patient and how much of the gland to remove as high titres of the

'Growth-antibodies' (TGI) are associated with postoperative recurrences in nontoxic nodular goitres.[16] Also, if TGI are present it is probably ineffective to treat the patient with thyroxine replacement as pituitary TSH is suppressed by the receptor antibodies.

Other receptor antibodies have been identified and are used for early diagnosis. An important radioimmunoassay using radioactive bungarotoxin is regularly used for the early diagnosis of myasthenia gravis. The test is quite sensitive and very specific. Another publicized receptor disease is the rare insulin resistant diabetes with acanthosis nigricans, where insulin receptor antibodies can be detected on the patient's circulating monocytes and in the serum with labelled insulin in a radioreceptor assay. At present only the most severe form of this disease is recognized but already there are reports of cases where hypoglycaemia was the presenting feature rather than insulin resistance and it can be anticipated that more chronic cases will be found. Nearly all the patients with insulinreceptor antibodies have ribonucleoprotein precipitating antibodies and 'speckled' anti-nuclear antibody patterns in the immunofluorescence tests for ANA. Many of the cases have evidence of Sjogren's sicca syndrome. Other less well characterized receptor antibodies are those found in some cases of asthma which are directed to the beta-adrenergic receptors and antibodies to the parathormone receptors found in chronic renal failure. In relation to endocrine disorders[17] it is of interest that antibodies to the gonadotrophin receptors on ovarian cells account for some cases of ovarian atrophy in patients with coexisting myasthenia gravis giving rise to gonadotrophin resistant hypogonadism.[17a]

Full discussion of these autoimmune 'receptor' diseases are found in the recent Ciba Symposium on 'Receptors antibodies and disease'[13] Radioreceptor tests are available commercially for TSAb but most of the other methods are still in the research stage and are difficult to apply in clinical practice.

FUTURE PROSPECTS

Autoimmunity to the anterior pituitary and hypothalamus and antibodies directed to endocrine cells of the gut such as GIP-and secretin-cells, are at present being studied and their significance for early diagnosis is being worked out. One of the remarkable findings is that in diabetic families, some relatives who had islet-cell antibodies without being diabetic, reacted with several of the anterior pituitary cells (multicell pattern).[18]

These antibodies were still present in newly diagnosed IDDM but disappeared with time. This could indicate that pituitary autoimmunity of a distinct kind from the known lymphocytic hypophysitis, could play a role in the initiation of the pathogenic events that eventually lead to breakdown of glucose homeostasis in some forms of diabetes. Gut endocrine cells also appear involved in diabetes mellitus and in coeliac disease and other malabsorption syndromes.[19] Exploration of the hypothalamus with its numerous endocrine cells has only recently been undertaken due to the known clinical association of central idiopathic diabetes insipidus with other autoimmune disorders. Nearly 40% of such cases proved to have cytoplasmic autoantibodies that could be detected by IFT on section of the supraoptic nuclei and paraventricular nuclei. This could be of diagnostic help in distinguishing the 'functional' and 'secondary' cases of diabetes insipidus from those due to destruction of vasopressin cells in the hypothalamus.[20]

The future will reveal many more autoimmune reactions connected with receptors to hormones and neurotransmitters. With the help of monoclonal antibodies it will be possible to purify specific receptors and develop sensitive radiometric or other technologically advanced methods that will make it possible to diagnose early stages of endocrine diseases.

The DR region of the major histocompatibility HLA complex is involved in regulating lymphocyte networks and the endocrine immunopathies are more prevalent in subjects with DR3, DR4 and DR5. HLA typing helps to predict recurrences in thyrotoxicosis[21] and has been used to select susceptible relative in diabetic families.[22]

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