The measurement of autoantibodies is an essential part of medical investigation and diagnostics, and, in turn, the prognostics of organ specific autoimmune diseases. Since practically all organs and tissues can be affected by autoimmune processes, nearly all medical disciplines will be confronted with autoimmune diseases. The remarkable spectrum of autoantibodies with confirmed or potential diagnostic and/or pathogenetic relevance to organ specific autoimmune diseases is ever increasing. Considerable progress has also been made in the development and optimization of autoantibody detection methods. Therefore, more and more autoantibodies are detectable in the normal routine laboratory. The diagnostics and differential diagnostics of neurological diseases in particular have profited from the knowledge gained and discoveries made in recent years. Through this progress however, the demands for serological tests as well as the interpretation of laboratory results has also increased. This reference book supplies useful information intended for all physicians active in the field of diagnostics, who are confronted with autoimmune diseases in their daily work. This volume covers not only the autoantibodies occurring in organ specific autoimmune diseases, but also the diseases themselves and their symptoms. In addition to those autoantibodies known to be diagnostic markers, the user will also be presented with autoantibodies of former but not current diagnostic relevance. Numerous newly described autoantibodies with confirmed or potential clinical relevance, which are currently not accessible for routine diagnostics, are also described so that this volume is also of interest to scientists active in the field of autoimmunology.

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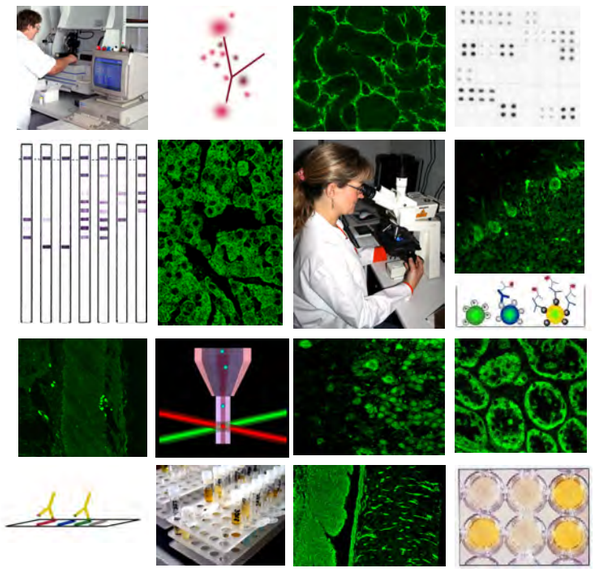
Autoantibodies in Organ Specific Autoimmune Diseases

A Diagnostic Reference



AUTOANTIGENS, AUTOANTIBODIES, AUTOIMMUNITY
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Autoantibodies in Organ Specific Autoimmune Diseases

A Diagnostic Reference

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Contents

Part 2
Organ specific autoimmune diseases — symptoms, entities, syndromes

Foreword

Autoimmune diseases, after heart and circulatory disorders and cancer, are the most common diseases in industrialized nations. Their prevalence, which is in addition increasing, is around 5 %. This means that in Germany alone more than four million people suffer from an autoimmune disease. Therefore, due to the high costs of treatment, hospital stays and early retirement, autoimmune diseases have both medical and economic importance.

Autoimmune processes can affect practically all organs and systems, meaning they concern almost all medical disciplines. In the last years it has been clearly demonstrated in some autoimmune diseases that early and targeted treatment improves disease management and avoids late effects. As a result, long-term healthcare costs can be reduced and, not least, patient's quality and length of life can be increased.

With the reference book 'Autoantibodies in Systemic Autoimmune Disease — a Diagnostic Guide'; the authors had initially faced the field of autoantibody diagnostics in systemic autoimmune disease. Due to the positive response to this book, within a few years the third German, second English and the first Spanish edition were published. Thanks to the suggestions of many readers and colleagues, it is now the time to present the sequel covering autoantibodies in organ specific autoimmune disease.

As the boundaries between systemic and organ specific autoimmune diseases are not always clearly defined, the guide to systemic autoimmune disease is referenced in respective places.

The following work, as the previous diagnostic guide, is addressed to all physicians and scientists who are confronted with autoimmune disease in their daily work. It is dedicated to both the autoantibodies occurring in autoimmune disease, as well as the diseases themselves and their symptoms. In addition to autoantibodies currently more or less well known as diagnostic markers, some which are no longer diagnostically relevant are included on historical grounds. Numerous newly described autoantibodies with proven or potential diagnostic and/or pathogenic relevance, which are so far not available for routine diagnostic use, are also

included so that this work is also of interest to scientists working in the field of autoimmunity.

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Notes on the use of this book

This guide to the serological diagnosis of organ specific autoimmune diseases consists of two alphabetically organized sections. The first deals with autoantibodies, the second with autoimmune or potential autoimmune diseases as well as symptoms related to particular organ specific autoimmune diseases. Appropriate cross-references (marked with ➢) allow quick and easy navigation (from symptom to disease, from disease to relevant autoantibodies). The dark arrow (➤) refers you to the relevant chapter in the book 'Autoantibodies in Systemic Autoimmune Disease — a Diagnostic Guide'.

Due to the diversity of the subject matter, the authors decided against including comprehensive literature references. Only in some cases the first author of important historical or current publications is mentioned. Original and review articles, as well as results and experiences used as sources for this guide, can be requested from the authors.

To allow for better orientation, the 'anti-' prefix in the alphabetical listing of autoantibodies is omitted. When relevant, alternative names and synonyms are also given. In cases where these are still in use, the description favored by the authors is given in the alphabetical listing and cross-reference.

Introduction

Autoantibodies – Definitions and Characteristics

Autoantibodies, in terms of their specificity, induction, effectiveness and clinical relevance, are a very heterogenic group of immunoglobulins:

- Autoantibodies are directed against self antigens (autoantigens). Autoantibody targets can be proteins (e. g. intracellular enzymes, receptors, structural proteins), glycoproteins (e. g. β2 glycoprotein I), nucleic acids (e. g. dsDNA, tRNA), nucleic acid protein complexes (e. g. nucleosomes), phospholipids (e. g. cardiolipin) or glycolipids (glycosphingolipids, e. g. gangliosides).
- Autoantibodies are detectable in serum, and in some cases in other body fluids (e. g. synovial or cerebrospinal fluid) too. Depending on the recognized target structure, they can also be bound in tissue (e. g. autoantibodies in autoimmune blistering diseases).
- Autoantibodies can be induced through specific antigen contact (non-natural or pathogenic autoantibodies), or be present in the natural repertoire without such induction (natural autoantibodies). Whereas the natural antibodies rather have a physiological role (e. g. a first defense against infection, immune regulation), non-natural autoantibodies can have a pathological effect (e. g. blocking or stimulating of receptors).
- Regardless of whether a pathogenic effect occurs or not, a large number of non-natural autoantibodies have great diagnostic relevance. They may display significantly higher prevalence and titers in disease groups when compared to local age and sex matched control groups. The titer of pathogenic autoantibodies often correlates with disease activity.

In organ-specific autoimmune diseases, diagnostically relevant autoantibodies are predominantly directed against autoantigens of the organ addressed (e. g. TSH-receptor autoantibodies in Graves' disease). Clinically significant autoantibodies in

organ-specific autoimmune diseases are almost always of IgG type, and rarely IgA (e. g. in autoimmune intestinal disease) or IgM (e. g. in autoimmune hemolytic anemia).

Autoantibodies in the Diagnosis of Autoimmune Diseases

About 5 % of the population of industrialized nations suffer from autoimmune diseases. The most commonly occurring organ specific autoimmune diseases are the group of autoimmune thyroid diseases, followed by gluten-sensitive enteropathy (celiac disease) and autoimmune liver diseases. The prevalence of most other organ specific autoimmune diseases is comparatively lower. As autoimmune processes can involve practically all organs, the presence of organ specific autoimmune diseases should be considered in all cases of idiopathic inflammation or dysfunction, of any type and location. The measurement of autoantibodies often points the way ahead in the diagnosis of such diseases.

In the majority of the up to now described autoimmune entities, autoantibodies with high disease-specificity are detectable. This is true even for those diseases that are predominantly cellular (autoreactive T-lymphocytes) mediated (e. g. diabetes mellitus type 1). The number of newly described autoantibodies with proven or potential diagnostic and/or pathogenic relevance in organ specific autoimmune disease is ever increasing. Considerable progress has also been made in the development and optimization of autoantibody detection methods. Therefore, autoantibody measurement is increasingly in demand in the routine diagnostic laboratory. In particular, the detection and differential diagnosis of neurological diseases has profited significantly from the insights and developments in this area of recent years. For example, neuromyelitis optica can be distinguished as a separate entity from multiple sclerosis due to the discovery of aquaporin 4 antibodies. Also, more and more diseases previously considered to be idiopathic can now be classified as having autoimmune etiology, following the discovery of new disease specific autoantibodies. In turn, it is not uncommon that particular diseases are found to have a much wider clinical spectrum (e. g. celiac disease, ganglioside and GAD associated diseases) or to occur much more frequently (e. g. autoimmune encephalopathies) than previously thought.

Part 1

Autoantibodies in organ specific autoimmune diseases

17α-hydroxylase antibodies

17α-hydroxylase is the main target antigen of antibodies directed against steroid-producing cells (➢ steroid producing cell antibodies).

21-hydroxylase antibodies

21-hydroxylase is the target antigen of ➢ adrenal cortex antibodies.

AADC antibodies

See ➢ aromatic L-amino acid decarboxylase antibodies.

Acetylcholine receptor antibodies, general

Acetylcholine receptors (AChR) are transmembrane receptors, which bind the neurotransmitter acetylcholine (Ach). Two forms exist, the nicotinergic or nicotinic (nAChR, nicotine receptors) and the muscarinergic or muscarinic AChR (mAChR, muscarine receptors). Clinically relevant, or potentially relevant, antibodies can be directed against various nAChR or mAChR:

- The 'classic' ➢ AChR antibodies (**α1-nAChR antibodies**) in ➢ myasthenia gravis are directed against α1 and other nAChR subunits in the **neuromuscular junction**.
- The ➢ ganglionic AChR antibodies (**α3-nAChR antibodies**) in autoimmune ➢ autonomic gangliopathy bind the α3 nAChR subunit in the **sympathetic and parasympathetic postganglionic fibers.**
- In one form of autoimmune encephalopathy (Baker 2009), and also in ➢ Rasmussen's encephalitis (Watson 2005), autoantibodies directed against the α4 and/or α7 nAChR subunit in the central nervous system (**cortex and hippocampus**) have been described (**α4-nAChR antibodies, α7-nAChR antibodies**).
- Autoantibodies against the muscarinic type 3 AChR (**M3mAChR antibodies**) are detectable in patients with ➢ Sjögren's syndrome, ➢ systemic sclerosis and gastrointestinal dysmotility (Singh 2009).

- Autoantibodies against the muscarinic type 2 AChR (**M2mAChR antibodies**) have been described in ➢ Chagas disease, in idiopathic ➢ dilated cardiomyopathy (in 40 % of cases) and in idiopathic atrial fibrillation (23 %) (Baba 2004; Fu 2002).

Acetylcholine receptor antibodies, classical type

Synonym: AChR antibodies.

Autoantigen

The nicotinic acetylcholine receptor (nAChR) of the neuromuscular junction is a glycoprotein with a molecular weight of 300 kDa and is comprised of five subunits: α1, β, δ, γ/ε. Autoantibodies are predominantly directed against the α1 subunit.

Pathologic relevance

AChR antibodies influence nicotinic acetylcholine receptors in three ways: (1) Influencing the neuromuscular function of these receptors through binding and cross-linking, accelerating their internalization and degradation. (2) To a small extent blocking acetylcholine binding sites. (3) Activating complement locally, leading to destruction of the postsynaptic membrane, with the consequence that neuromuscular stimulus transmission is wholly or partially inhibited.

Detection methods

Radioimmunoprecipitation with ^{125}I-α-bungarotoxin labeled native acetylcholine receptor.

Note: Other methods, such as enzyme immunoassays or indirect immunofluorescence, are not currently popular due to their low sensitivity and specificity. An immunofluorescence test utilizing transfected AChR cells is under development.

Clinical relevance

- Acetylcholine receptor antibodies are pathognomonic for ➢ myasthenia gravis (MG) and are detectable in 80–90 % of patients with generalized MG. AChR antibodies are found in only ~50 % of ocular MG cases. A positive AChR antibody test is seen as proof of MG due to the high specificity (almost 100 %), however a negative result does not exclude MG ('seronegative' MG).
- In healthy individuals and patients with an inherited form of MG, as well as ➢ Lambert-Eaton myasthenic syndrome (LEMS) which has a very similar clinical picture, AChR antibodies are not detectable.
- Low titers of AChR antibodies can be found, for example in ➤ rheumatoid arthritis patients taking penicillamine therapy, ➢ primary biliary cirrhosis and thymoma. These patients have an elevated risk of suffering from MG.
- AChR antibody titers do not correlate with the severity of myasthenic symptoms. However, the follow-up of AChR antibody levels can allow conclusions to be made on the prognosis of individual patients. A 50 % reduction in antibody titer is often (but not always!) associated with a marked improvement in condition.

Indications

1. Suspicion of myasthenia gravis.
2. Monitoring of myasthenia gravis patients.

Actin antibodies

Autoantigen

Actin is a component of smooth muscle microfilaments, and one of the target structures of autoantibodies against smooth muscle cells (➢ SMA). Polymeric F-actin, with a molecular weight of 41 kDa, has been identified as the relevant antigen in the diagnosis of autoimmune hepatitis.

Detection methods

- Indirect immunofluorescence on cryostat sections of rat stomach, liver and kidney. The typical immunofluorescence picture shows staining of the smooth

muscle layer of the stomach and blood vessels, as well as the septa of stomach interparietal cells. Depending on the recognized autoantigen target structures, numerous other structures may also be stained.
- Indirect immunofluorescence with HEp-2 cells or fibroblasts. The typical immunofluorescence picture shows fibrous cytoskeletal staining.

  Note: The detection of actin antibodies on rodent tissue sections is more sensitive than detection with HEp-2 cells.

- Enzyme immunoassay with F-actin.
- Line/dot immunoassay with F-actin.

  Note: According to the consensus report of the International Autoimmune Hepatitis Group, indirect immunofluorescence on multi-organ rodent sections (kidney, stomach, liver) is the method of choice for the detection of AIH relevant autoantibodies (Vergani 2004). Larger studies are needed to evaluate the diagnostic value of F-actin antibodies as the basis of enzyme or line/dot immunoassays. So far, commercially available immunoassays (ELISA, line/dot immunoassays) for the detection of actin antibodies have mostly displayed specificities too low to serve as a diagnostic of AIH.

Clinical relevance

- High concentrations (titers) of actin antibodies are largely specific for ➢ autoimmune hepatitis (AIH) type 1. The sensitivity ranges from 52–85 %, although (usually low titers of) actin antibodies have also been observed in healthy individuals (3–18 %), primary biliary cirrhosis (PBC) (22 %), hepatitis C (7 %), connective tissue diseases and celiac disease (IgA antibodies).
- In about 19 % of ➢ SMA positive patients, no actin antibodies are detectable.
- Patients with actin antibodies have an earlier disease onset and a more severe prognosis than actin antibody negative patients with ➢ anti-nuclear antibodies (ANA).

Indications

1. Suspicion of autoimmune hepatitis type 1.
2. Differential diagnosis of autoimmune hepatitis.

ADAMTS13 antibodies

ADAMTS13 ("**a** **d**isintegrin **a**nd **m**etalloprotease with **t**hrombo**s**pondin-1 like domains **13**") is a von Willebrand factor (vWF) cleaving protease, which strongly

regulates the size of the high molecular weight vWF, and thereby its biological activity. In patients with acquired ➢ thrombotic thrombocytopenic purpura (TTP), autoantibodies against ADAMTS13 are detectable in most cases. These antibodies can inhibit the protease function of ADAMTS13 (Furlan 1998; Tsai 1998), or induce the elimination of ADAMTS13 from the circulation (Scheiflinger 2003; Rieger 2005). Therefore, the high molecular weight vWF complexes remain uncleaved, leading to formation of microvascular thrombi. Patients with ADAMTS13 antibodies have a more severe disease progression and higher mortality rates than TTP patients without these antibodies.

Adrenal cortex antibodies

Synonyms: ACA, 21-hydroxylase antibodies.

Autoantigen

21-hydroxylase (21-OH), an enzyme with a molecular weight of 55 kDa involved in the synthesis of steroid hormones (cortisol), has been identified as the main target antigen. The conformation-dependent epitope is localized in the C terminal region of hemoproteins.

Detection methods

- Indirect immunofluorescence using cryostat sections of human adrenal cortex (preferably from patients with Cushing syndrome). The immunofluorescence picture shows cytoplasmic staining of the hormone producing cells of the adrenal cortex (Fig. 1).
- Radioimmunoassay with recombinant ^{125}I labeled 21-hydroxylase.
- Radioimmunoprecipitation with ^{35}S labeled 21-hydroxylase.
- Western blot with native or recombinant 21-hydroxylase.

Note: The concurrence between immunofluorescence and immunoassays is relatively good, although discrepant results can be obtained in some cases. Immunoassays have a somewhat higher sensitivity.

Clinical relevance

- ACA are markers of autoimmune ➢ adrenalitis (idiopathic Addison's disease). Autoimmune adrenalitis can manifest as a solitary disease or as part of an

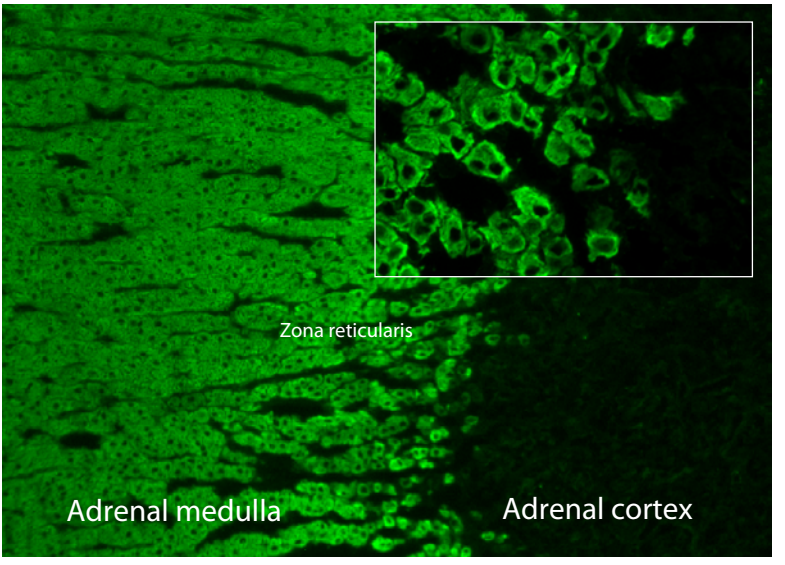

Figure 1. Indirect immunofluorescence using cryostat sections of human adrenal cortex. Adrenal cortex antibodies show a strong cytoplasmic staining pattern in the hormone producing cells of the adrenal cortex. The cells of the adrenal medulla are negative.

➢ autoimmune polyglandular syndrome. In solitary diseases, ACA are detectable in 65–81 % of cases with a specificity of 98–100 %. With autoimmune polyglandular syndrome these autoantibodies are found in 86–92 % (type 1) and 89–100 % (type 2), respectively.

- The prevalence of these antibodies may decline as disease progresses.
- ACA/21-hydroxylase antibodies have a predictive role, as they can precede disturbed adrenocortical function and disease manifestation. Children in particular with autoantibodies against the adrenal cortex have an increased risk of being diagnosed with Addison's disease (on average after 2.7 years). It is recommended that children with an organ specific autoimmune disease (especially idiopathic hypoparathyroidism and ➢ diabetes mellitus type 1) are tested annually for adrenal cortex antibodies.

Indications

1. Suspicion of Addison's disease.
2. Differentiation between Addison's disease from tuberculous adrenal insufficiency or necrosis of the adrenal glands (Waterhouse-Friderichsen syndrome).
3. Suspicion of autoimmune polyglandular syndrome (APS type 1 or type 2).

4. Evaluation of the risk of developing Addison's disease, particularly in children with organ specific autoimmune diseases.

Adrenoceptor antibodies

Adrenoceptors are adrenergic receptors, that are responsible for adrenalin and noradrenalin mediated effects. Autoantibodies can exert an agonistic or antagonistic influence on the corresponding adrenoceptor, and therefore have a pathogenic effect. Pathologically relevant or potentially relevant autoantibodies can be directed against various adrenoceptors:

- Stimulating ➢ beta-1 adrenergic receptor antibodies are a pathologically significant marker of idiopathic ➢ dilative cardiomyopathy, as well as the cardiopathy of Chagas disease.
- Autoantibodies against beta-2 adrenergic receptors were found in patients with asthma, myasthenia gravis and Chagas disease (Eng 1992; Wallukat 1991).
- Beta-3 adrenoceptor antibodies were found in patients with heart failure (Li 2005).
- Agonistic alpha-1 adrenoceptor antibodies have been described as potential pathogenic factors in refractory hypertension (Wenzel 2008).

Alpha enolase antibodies

Autoantigen

The ubiquitously occurring glycolytic enzyme α-enolase. It has 82 % homology with the two other isoforms β- and γ-enolase, as well as homology with the soluble lens protein tau (a crystalline).

Detection methods

Enzyme immunoassay or immunoblot with purified α-enolase.

Part 2

Organ specific autoimmune diseases — symptoms, entities, syndromes

Achalasia

Achalasia is a motility disorder of the oesophagus characterized by aperistalsis with inadequate lower sphincter relaxation. Etiologically, achalasia can be classified as primary (idiopathic) or secondary to another disease. In primary achalasia inhibitory nitrergic myenteric plexus neurons are lost. The cause of these neuronal degeneration is not known, but mononuclear and lymphocyte infiltration in the myenteric plexus, the association with class histocompatibility complex haplotypes, and the presence of autoantibodies support autoimmune mechanisms for idiopathic achalasia. In some studies, autoantibodies binding the myenteric plexus were found by indirect immunofluorescence on rat digestive tissue sections (Ruiz de Leon 2002). However, it has been discussed that at least a part of this binding is attributable to non-organ specific autoantibodies. In a recently published study, ➤ GAD antibodies were detected in 21 % of patients with primary achalasia (Kraichely 2010). Therefore, primary achalasia may be added to the growing list of GAD antibody positive neurological disorders.

Acquired angioedema type II

A form of ➤ angioedema caused by ➤ C1 inhibitor antibodies.

Acute disseminated encephalomyelitis (ADEM)

Synonyms: Perivenous encephalomyelitis, Hurst's encephalitis.

ADEM is a rare, monophasic inflammatory demyelinating disease of the CNS. The neurological symptoms, as with other forms of ➤ encephalitis, are variable depending on the location of the lesions. The manifestation spectrum ranges from minimal disturbances to fulminant, progressive symptoms with seizures and coma. A characteristic symptom is ➤ optic neuritis. Very severe (fulminant) courses can be fatal. It is postulated that ADEM is a post-infective autoimmune disease, usually triggered by a viral infection in which autoreactive T-lymphocytes are directed against proteins of the white matter. So far, specific autoantibodies have not been found.

Acute inflammatory demyelinating polyneuropathy (AIDP)

AIDP is the classic and most common form of acute ➤ Guillain-Barré syndrome. In AIDP ➤ ganglioside antibodies against GM1 of mainly IgG, and rarely IgM class, are detectable. In addition to GM1 antibodies, IgG autoantibodies against GD1a, GD1b and GT1b are found.

Acute motor axonal neuropathy (AMAN)

AMAN is a rare variant of acute ➤ Guillain-Barré syndrome (primary axonal GBS), characterized by the acute onset of paralysis with particularly rapid progression, but without sensory disturbance. Some patients show a rapid remission. The disease is associated with IgG autoantibodies against the gangliosides GM1, GM1b, GD1a and GalNAc-GD1a. IgG autoantibodies against GD1b and/or GT1b are rarely detectable (see also ➤ ganglioside antibodies).

Acute motor sensory axonal neuropathy (AMSAN)

AMSAN is a rare variant of acute ➤ Guillain-Barré syndrome (primary axonal GBS with sensory involvement) characterized by severe paralysis, sensory disturbances, rapid progress and incomplete recovery. The disease is associated with IgG autoantibodies against the gangliosides GM1, GM1b and GD1a. Rarely, IgG autoantibodies against GD1b and/or GT1b are also present (see also ➤ ganglioside antibodies).

Acute pandysautonomia

Acute pandysautonomia was originally considered to be a special form of ➤ Guillain-Barré syndrome with manifestations exclusive of the vegetative nervous system. With the discovery of ➤ ganglionic nAChR antibodies, pandysautonomy is now regarded as a separate entity (➤ autoimmune autonomic gangliopathy).

Addison's disease

Synonym: Primary adrenocortical insufficiency.

Addison's diseases (named after the physician Thomas Addison from London) is the result of progressive destruction of the adrenal cortex. Whereas previously tuberculosis was responsible for most Addison's disease cases, currently autoimmune reactions against the tissue of the adrenal cortex (➢ autoimmune adrenalitis) are the most common cause of ➢ adrenocortical insufficiency. Disease symptoms first occur when ~90 % of the adrenal cortex (AC) tissue is destroyed, causing a pathological deficiency of hormones produced by AC (predominantly cortisol and aldosterone). The diverse symptoms (weight loss, abdominal discomfort, nausea, vomiting, diarrhea, anemia, collapse after physical exertion, muscle weakness, hyperpigmentation ('bronzing') of the skin and mucous membranes, loss of libido, appetite for salt, low pulse rate and low blood pressure) essentially result from the deficiency of cortisol and aldosterone. Addison's disease can occur in isolation or as part of an ➢ autoimmune polyglandular syndrome (APS).

Autoantibodies

➢ Adrenal cortex antibodies directed against 21-hydroxylase are markers of the autoimmune form of Addison's disease. These antibodies are predictive because they are detectable even in the preclinical stage. With increasing disease duration the prevalence of adrenal cortex antibodies can decrease. As Addison's disease is often (mostly as part of an APS) associated with other autoimmune diseases, the autoantibodies typical of these conditions (e.g. ➢ autoimmune thyropathy, ➢ diabetes mellitus type 1, ➢ celiac disease) should be measured.

Adenohypophysitis

Lymphocytic adenohypophysitis (LAH) is the classic and most prevalent form of ➢ autoimmune hypophysitis.

Adrenocortical insufficiency

Adrenocortical insufficiency (AC insufficiency) refers to all forms of adrenal cortex hypofunction. Primary (➢ Addison's disease) and secondary forms can be differentiated. Whereas the somewhat more common primary AC insufficiency results from the absence or deficiency of all AC hormones as a result of adrenal cell destruction (e.g. in autoimmune adrenalitis, sepsis, tuberculosis, adrenal cortex metastases), in the secondary form the basis is a disturbance in the area of the pituitary gland (e.g. ➢ autoimmune hypophysitis) or the hypothalamus with consecutive deficiency of adrenocorticotropic hormone (ACTH, which controls hormone production in the adrenal cortex) and/or corticotropin releasing hormone (CRH, stimulates the distribution of ACTH). AC insufficiency is associated with a deficit in glucocorticoids, adrenal androgens and — in primary AC insufficiency — mineralocorticoids in addition. The most common cause of AC insufficiency is an autoimmune related inflammation of the AC (➢ autoimmune adrenalitis), either as a solitary disease or as part of an ➢ autoimmune polyglandular syndrome.

Autoantibodies

For the diagnosis of autoimmune related primary AC insufficiency, ➢ adrenal cortex antibodies (➢ 21-hydroxylase antibodies) should be measured.

AIH-PBC-overlap syndrome

Overlap syndrome with the characteristics of ➢ autoimmune hepatitis (AIH) and ➢ primary biliary cirrhosis (PBC); see also ➢ overlap syndromes of autoimmune liver diseases. According to Chazouillères (1998), an AIH-PBC overlap can be diagnosed when at least two of the following AIH and at least two of the PBC criteria are fulfilled:

AIH Criteria	PBC criteria
(1) Alanine aminotransferase (ALT) elevation (5 times the normal limit).	**(1)** Alkaline phosphatase (2 times the normal limit) or gamma glutamyltransferase (5 times the normal limit) elevation.

AIH Criteria	PBC criteria
(2) Serum IgG elevation (2 times the normal limit) or ➤ SMA positive.	**(2)** ➤ Anti-mitochondrial antibody positive.
(3) Histology: Moderate to severe portal or periportal lymphocytic piecemeal necrosis.	**(3)** Histology: florid bile duct lesions.

Autoantibodies

➤ Anti-mitochondrial antibodies, ➤ anti-nuclear antibodies, ➤ SMA (should display an anti-actin specificity), ➤ SLA/LP antibodies.

AIH-PSC overlap syndrome

Overlap syndrome with characteristics of ➤ autoimmune hepatitis (AIH) and ➤ primary sclerosing cholangitis (PSC) usually appears in children, adolescents and young adults. In contrast to AIH, AIH-PSC overlap primarily affects males. Similar to PSC, a link can be made to ➤ chronic inflammatory bowel disease. AIH-PSC overlap-syndrome usually reacts well to immunosuppressive therapy. See also ➤ autoimmune sclerosing cholangitis (ASC).

Autoantibodies

Atypical ➤ anti-neutrophil cytoplasmic antibodies, ➤ anti-nuclear antibodies, ➤ SMA. See also ➤ autoimmune sclerosing cholangitis (ASC).

Alkaline phosphatase increase

The increase of alkaline phosphatase of hepatic origin is a sign of cholestatic liver disease, and is, among others, characteristic of ➤ primary biliary cirrhosis (PBC) and ➤ primary sclerosing cholangitis (PSC).