



Review

Autoantibody diagnostics in clinical practice

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ABSTRACT

Disease associated autoantibodies (AAB) are important biomarkers not only to confirm the diagnosis of the respective systemic autoimmune disease but also to diagnose the disease at very early stages (mono- or oligosymptomatic manifestations) or to diagnose the respective disease without the typical clinical manifestations (atypical forms). A confirmation of the diagnosis in early stages is required, if patients should benefit from early therapeutic intervention. Furthermore, AAB determinations are used for prognostic purposes and for monitoring of disease activity or response to therapy. For the advancement of autoantibody diagnostics in clinical practice the following aspects have to be considered: (i) The search for novel clinically relevant AAB and the identification of autoantigenic targets of AAB broadened the spectrum of autoimmune diagnostics and permit the diagnosis of former idiopathic diseases. (ii) To obtain steady diagnostic variables of clinically relevant AAB, the evaluation studies have to be standardized. (iii) Several special features and novel developments of autoantibody diagnostics make correct interpretation of antibody test results increasingly difficult. (iv) Beside standardization of AAB detection methods and quality management efforts the improvement of autoantibody diagnostics depends on further development of diagnostic algorithms including cost-effective multiparametric analyses.

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Abbreviations: AAB, autoantibodies; AID, autoimmune diseases; CCP, cyclic citrullinated peptide; EIA, enzyme immunoassay; GP2, glycoprotein 2; IIF, indirect immunofluorescence; MCTD, mixed connective tissue disease; NMDAR, N-methyl-D-aspartate receptor; PHT, pulmonary hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSC, systemic sclerosis.

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1. Introduction

The determination of disease associated autoantibodies (AAB) is very helpful in diagnostics, prognostics, and, in some cases, monitoring

of autoimmune diseases (AID). With the growing medical and economical impact of AID and the continuous improvement of treatment possibilities through targeted therapies, the acceptance and relevance of autoantibody diagnostics increases. However, there is a gap between the practical options and the requirements for high quality and cost-efficient serological diagnostics of AID. The reasons for this are manifold and comprise: (a) methodical problems due to the heterogeneity of AAB, inadequate standardization of autoimmune diagnostics, local working conditions and traditions, (b) marginal commercial interests in the development of assays for the detection of rare AAB, (c) cost constraints by medical insurers, (d) limited knowledge and/or little acceptance regarding the relevance of AAB, especially among general practitioners, (e) inability to correctly interpret the results of certain assays, (e) missing cost-effective multiparametric assays of high quality, and (f) no or unsatisfactory standardization of evaluation studies. Due to several unique features, the AAB diagnostics cannot be compared with other laboratory diagnostics in terms of automation, quality assessment, and standardization as well as in terms of interpretation and consequences of the results. Furthermore, there are no “golden standards” for the determination of most, if not all, of the clinically relevant AAB.

2. Special features of autoantibody diagnostics

Several features of AAB diagnostics are more or less different from other laboratory diagnostics such as the biological heterogeneity of autoantibody responses, the broad spectrum of autoantigenic targets even in one defined disease entity, the highly inverse relationship between diagnostic sensitivity and specificity, various factors influencing the expression of autoantibodies, disrupting factors influencing the measurement of autoantibodies, the pre-symptomatic occurrence of autoantibodies, and the interdependency of serological and clinical associations.

2.1. Biological heterogeneity of the serological autoimmune response

Although the autoimmune response in a defined autoimmune disease is characterized by a major molecular recognition pattern to the main autoantigen(s), this response is not uniform among patients with the same disease but may be heterogeneous with regard to the autoantibody isotype, affinity/avidity, and epitope specificity as well as with regard to the intra- and intermolecular epitope spreading. Those variations may be in part responsible for differences in the results obtained by different AAB detection assays and in variations in AAB profiles, in the pathogenicity of autoantibody and in the clinical course of the disease. For example, anti-dsDNA antibodies in sera of patients with SLE are heterogeneous in relation to cross-reactivity with some proteins [1,2]. The cross-reactivity of human SLE anti-dsDNA antibodies with α -actinin may contribute to the pathogenesis of lupus nephritis [2]. Heterogeneity may also occur regarding the recognition of distinctly modified forms of the respective autoantigen(s). An association between recognition of either apoptotically or oxidatively modified forms of the U1-70 kD autoantigen and different clinical disease manifestations has been described [3]. Diagnostically relevant are variances in the fine specificity of autoantibody response due to different intra- and intermolecular epitope spreading. For example, although most of the anti-centromere antibodies (ACA) of patients with systemic sclerosis (SSc) bind the centromere protein CENP-B, there are some cases only detecting CENP-A and therefore are negative in assays using recombinant CENP-B. Other examples are AAB against proteins of the U1-snRNP complex (marker of SLE and MCTD) and AAB against the 2 oxoacid dehydrogenase components of inner mitochondrial multienzyme complexes (marker of primary biliary cirrhosis).

2.2. Ethnic variations in frequency, epitope recognition and clinical relevance of disease-related autoantibodies

Many studies have shown differences in the clinical as well as serological presentation of AID by ethnicity. The distribution of many of the SLE, SSc, and myositis related AAB differs among patients of various ethnic backgrounds. For example, Caucasian SSc patients have the highest frequency of ACA, whereas Afro-Americans have a higher frequency of anti-topoisomerase and anti-fibrillarin antibodies [4]. Anti-Sm antibodies were significantly more frequent seen in Afro-American, Afro-Caribbean and black South-African SLE patients than in Caucasian [5]. Besides such different AAB frequencies striking ethnic differences in epitope recognition have been reported for some disease specific AAB. For example, the frequency of reactivity of anti-topoisomerase antibodies to the region adjacent to amino terminus of DNA topoisomerase I was lower in Caucasian and Afro-American than in Japanese and Choctaw Native American SSc patients. Conversely, the frequency of reactivity to the region adjacent to the carboxyl terminus was lower in Japanese patients compared to patients from other ethnic groups [6]. Furthermore, ethnic variations in clinical presentations may occur even in immunologically similar groups. Anti-Ku antibodies in Japanese patients are strongly associated with scleroderma-polymyositis and SLE-scleroderma-polymyositis overlap syndromes whereas in Afro-American patients these AAB are associated with SLE [7]. In conclusion, those differences between several ethnical groups in the prevalence, epitope specificity and clinical associations of disease-related AAB should be considered if the relevance of a defined AAB will be evaluated in retrospective and/or prospective studies. The ethnical differences may reflect genetic, social, or environmental factors that have yet to be discovered.

2.3. Autoantibodies as predictors of disease development

Most AID are characterized by a subclinical prodrome, during which the only evidence of the developing disorder may be the production of disease specific AAB. Indeed, AAB that are typically produced in defined diseases are detectable months to years before appearance of the respective clinical symptoms [8–10]. This has been shown for systemic and organ specific AID by retrospective (use of stored sera) and prospective (follow-up) studies. Therefore, certain AAB might predict disease development in risk groups or even in the general population. The prediction of AID becomes more and more important as effective novel immune intervention therapies are introduced. Recently, the most important clinical utility of AAB testing is the diagnosis of the respective AID as early as possible or the diagnosis of limited or non-typical forms of the disease, respectively.

2.4. Interdependent relationship between diagnostic sensitivity and specificity

By increasing the sensitivity for AAB detection, the diagnostic specificity decreases and vice versa. Depending on the cut-off used for positivity, the relation between sensitivity and specificity can be influenced. If the AAB assay should be used as a screening test, the sensitivity must be high taking into account of a decreased specificity. On the other hand, if the AAB assay should be used as a confirmatory test, the specificity must be high accepting a higher number of false-negative samples. In general, the higher the titer of a disease-associated AAB, the higher is the diagnostic specificity for the appropriate disease. As a consequence, different reference ranges (e.g., borderline or weakly positive, positive, strong positive) should be defined for the interpretation of the results in clinical practice. For example, a strong positive result may be defined at a cut-off point given a diagnostic specificity higher than 98% (or even 99%).

Taken together, the special features of AAB diagnostics lead to several problems that have to be considered in routine practice: (a) A

uniform technological platform for multiparametric and high quality AAB determination is difficult to realize due to the broad spectrum of autoantigenic targets in some disease entities. For example, the serological diagnostics of SLE requires DNA, DNA/protein complexes (nucleosomes), ribonucleoproteins (core proteins of snRNP complexes), ribosomal phosphoproteins, and phospholipid (cardiolipin) as autoantigenic targets for AAB determination. (b) The results of AAB testing may vary (sometimes dramatically) by using different detection techniques. (c) Methodological aspects, the heterogeneity of the autoimmune response, the ethnic variations as well as the pre-symptomatic production of AAB have to be considered for the correct interpretation of the results.

3. Significance of autoantibodies in clinical practice

Regardless of the pathological role, AAB are used as serological markers if a significant association between their expression (production) and a defined disease and/or special disease features (course, organ manifestations, activity, response to therapy) exists. The traditional role of AAB diagnostics is the discrimination of an autoimmune disease from non-autoimmune disorders. Because many AAB specificities are detectable at early disease stages, their determination is very helpful to make a definite diagnosis of the appropriate AID as early as possible as a prerequisite for improving the treatment success.

For example, it has been shown that treatment with disease modifying anti-rheumatic drugs initiated within only 3 months of symptom onset of rheumatoid arthritis (RA) is beneficial when compared to even short delay of such therapy [11]. Since the clinical picture of early systemic AID is not always characteristic and the classification criteria are frequently not fulfilled at early disease stages, AAB tests with high diagnostic specificity and high predictive values are required. Such assays may also replace more invasive and costly diagnostic techniques. Furthermore, some AAB specificities are predictors of certain organ manifestations and can help in the early recognition of fatal complications of systemic diseases such as pulmonary hypertension (PHT) or renal crisis. For example, anti-U3-RNP antibody is strongly associated with PHT in SSc patients [12]. Since endothelin receptor blocker became available as a successful medication of PHT, AAB together with other risk factor assessment may be helpful in therapy decisions. Early therapy may possibly prevent, delay, or attenuate this severe complication [12]. Apart from diagnostic and prognostic purposes, serial AAB detection may be helpful in monitoring disease activity and therapy response.

4. Demands, challenges and perspectives of autoantibody diagnostics

4.1. Search for novel clinically relevant autoantibodies

The identification of autoantigenic targets of AAB as well as the discovery of novel AAB may not only lead to the improvement of the serological diagnostics of AID but also to define former “idiopathic” diseases as novel autoimmune entities. Recently, the major zymogen granule membrane glycoprotein 2 (GP2) has been identified as the main target antigen of pancreatic AAB in sera of patients with Crohn's disease [13]. The quantification of GP2 AAB could significantly improve the serological diagnostics of inflammatory bowel diseases. Substantial progress in serological diagnostics of autoimmune neurological diseases has been made in the last years by the discovery of several AAB against receptor and membrane channel proteins. For example, neuromyelitis optica (NMO) can be distinguished from multiple sclerosis at an early stage of disease by the presence of autoantibodies against the water channel protein aquaporin-4 [14]. Furthermore, different autoimmune variants of encephalitis have been described by the occurrence of newly discovered AAB such as AAB against the N-methyl-D-aspartate receptor (NMDAR) [15].

4.2. Standardization of evaluation studies

For the interpretation of AAB findings in the clinical practice it is important to evaluate the clinical relevance by determining the diagnostic variables such as sensitivity, specificity, positive and negative predictive values as well as positive and negative likelihood ratios [16,17]. However, the results obtained by different evaluation studies may vary due to methodical aspects and different study designs. For example, if the control group includes patients without a definite diagnosis (in a prospective study design), the diagnostic specificity of anti-CCP antibodies for rheumatoid arthritis is lower than that determined in most other studies, because this control group may include RA patients at very early stages [18]. Therefore, the study design, e.g. the type of study (retrospective, prospective), the size and composition of the disease group (ethnicity, age, gender, stage and activity of disease, duration and kind of therapy) as well as the size and composition of control groups (“healthy” blood donors, more or less defined disease control groups, persons at risk) have to be standardized to obtain comparable results. This is a prerequisite to compare the usefulness of different methods. Therefore, joint bio banks and data banks for autoimmune diseases should be established that also include sera of patients with rare and very rare diseases.

4.3. Diagnostic strategies, quality management and standardization of autoantibody diagnostics

Based on the failure of all efforts to confine autoantibody diagnostics to a multiparametric one-step procedure using microbead or array technologies, the diagnostic algorithms for many AID still imply a stepwise procedure based on indirect immunofluorescence (IIF), enzyme immunoassays (EIA), and blot technologies [19,20]. Novel automation strategies consider these needs and integrate multiple technologies into one platform, accompanied by quality assurance and standardization solutions [21,22]. Such strategies should include an autoantibody profiling in the final steps to get relevant information [18,23].

Regarding the currently employed diagnostic kits, several studies have suggested that there are limitations and concerns in the use and clinical application of test results derived from commercial kits. It has been proposed that a higher level of commitment and partnership between all of the participants (manufacturer, clinical laboratory, physician, patient) is required to achieve an improved quality of patient care through the use of autoantibody testing [24]. Furthermore, IIF techniques as well as blot and immunoassay technologies are subjects to quality assurance and accreditation concerns. Even in well established parameters, age- and gender-adapted reference values are yet to be defined regarding most AAB. Another challenge is the regular use of defined mono- or oligospecific positive control sera of human origin. Frequently, control sera are used in a daily changing manner. External sample exchanges frequently hamper unique specificity based on different specificities of various test kits. Therefore, autoantibody detection should be done by experienced, well educated technicians and scientists. The activities of expert committees and networks such as the Autoantibody Standardization Committee and the European Autoimmunity Standardization Initiative are aimed at solving many of the discussed problems [25–28].

4.4. Interpretation of autoantibody test results

The introduction of novel autoantibody markers, the possibilities of autoantibody profiling and methodological aspects make correct interpretation of antibody test results increasingly difficult. Besides positivity for AAB with significant clinical correlation, an interpretative comment on autoantibody test results is decisive if an unexpected AAB with high diagnostic specificity and high predictive value are found by chance (e.g., antimitochondrial antibody by IIF screening on HEP-2 cells), if discrepant results for the same AAB specificity are obtained with different methods

Table 1
Autoantibody diagnostics in clinical practice – challenges and solutions.

Manufacturer	Challenges	Problems	Solutions
(i) Commercial aspects	High quality assays at justifiable costs for all clinically relevant AAB	Marginal interests in the development of assays for the detection of rare AAB	Integration of rare AAB in multiparametric platforms (e.g., line immunoassay)
(ii) Assay development and production	Optimal presentation of autoantigenic target epitopes for best autoantigen/AAB binding	False negative or false positive results by • Less stability of epitopes • Masking of epitopes • Missing posttranslational modifications • Cross-reactive epitopes	• Change preparation and purification of autoantigens • Modification of assay components (e.g., autoantigen binding, fixation, buffer composition) • Change technological platform
(iii) Technological platform	Uninterrupted high quality	Differences between assay charges	Internal and regulatory quality control
	Cost-effective, high quality and high-throughput multiparametric analyses	• Standardization • AAB profiles of unknown relevance • Automation	Further development with accompanying clinical evaluation
Clinical laboratory	High quality of test results	• Require high quality assays • Different assays for the same AAB may show divergent results	• Accreditation • Quality assurance • Defined diagnostic algorithms (guidelines)
	Interpretation of test results	• Inadequate results from evaluation studies • Based on several methodical and individual aspects • Inadequate knowledge	• Standardized evaluation studies • Knowledge diagnostic accuracy of the assay methods used • Continuing education
Physician	Interpretation of test results	See clinical laboratory	See clinical laboratory
	Consequences for medical care	Mainly depends on interpretation	• Accurate interpretation • Guidelines

(e.g., dsDNA antibody positivity by EIA but negative nuclear staining by IIF using HEp-2 cells), and if further tests are necessary (e.g., determination of anti-dsDNA antibodies in sera showing high titred homogeneous nuclear staining on HEp-2 cells) [29].

5. Conclusion

The importance of AAB determinations, especially for the early diagnosis of AID, increases continuously. To fulfill the requirements of the growing relevance of AAB diagnostics, standardized procedures must be established including disease-targeted stepwise multiparametric testing. The challenges for optimized AAB diagnostics require cooperation and coordination between manufactures, clinical laboratories and physicians as well as expert committees and networks (Table 1).

Disclosure statement

Dirk Roggenbuck is a shareholder of GA Generic Assays GmbH and Medipan GmbH. Both companies are diagnostic manufacturers. The remaining authors declare that they have no competing financial interests.

Take-home messages

- The importance of AAB determinations, especially for the early diagnosis of AID, increases continuously.
- The identification of novel clinically relevant AAB broadened the spectrum of autoimmune diagnostics and permits the diagnosis of former idiopathic diseases.
- The introduction of novel autoantibody markers, the possibilities of autoantibody profiling and methodological aspects make correct interpretation of antibody test results increasingly difficult.

- To meet the requirements of a growing relevance of AAB diagnostics, standardized procedures must be established including disease-targeted stepwise multiparametric testing.
- The challenges for optimized AAB diagnostics require cooperation and coordination between manufactures, clinical laboratories and physicians as well as expert committees and networks.

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Kidney failure in SLE: a cortical problem

Acute renal cortical necrosis (ARCN) is a rare cause of acute kidney injury characterized by the destruction of all elements of the renal cortex, with sparing of the medulla and a thin layer of subcapsular cortex. This severe and potentially fatal event can occur in patients with Systemic Lupus Erythematosus (SLE) due to the possible development of intravascular coagulation, and the interactive effects of immune complex or endotoxin-induced vascular injury, change in platelet dynamics, impairment of fibrinolysis, alterations in the mononuclear phagocytic system, and/or concomitant use of corticosteroids. Till now, only two cases have been reported in the literature, one in 1984 by Baer and Winer (*South Med J*. 1984;77:81–3), and another one more recently by Kim et al. (*Am J Kidney Dis*. 2011;57:945–7).

Interestingly, in this second case the patients, a 16-years old Korean girl, had APS associated with SLE, while there are no data concerning the first patient (we have to remind that in 1984 the studies on APS were at dawn). Antiphospholipid antibodies are related to vascular thrombosis and pregnancy morbidity, and ARCN is typically related with pregnancy. Thus, it could be suspected a major role of these autoantibodies in the pathogenesis of ARCN independently from the presence of SLE and of fully clinically characterized APS.

Nonetheless, although bilateral ARCN is a rare complication of SLE-associated APS, it should be suspected when the sudden onset of anuria is accompanied by a sustained low-grade fever, mild leukocytosis, and high serum lactate dehydrogenase level. The exact pathogenic mechanism by which this event takes place deserves further investigations.

Carlo Perricone, MD