Publication of the Month 2006

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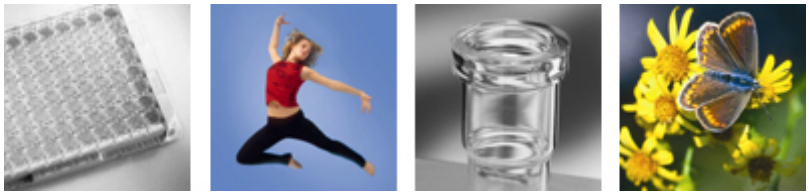
Publication of the Month



December - No. 12, 2006

Guidelines for improving AI diagnostics

At the time when disease criteria were agreed upon decades ago, the laboratory test procedures were quite different from those used in most serological routine settings today, but the criteria are still used as if the technology by which they are detected has little influence on diagnosis. This is far from being true as exemplified in more recent scientific literature. Therefore, it seems more and more important to set up guidelines for autoimmune serology testing to provide optimal support for clinicians in setting a correct diagnosis and estimating a likely prognosis.

The European Autoimmunity Standardization Initiative (EASI) steering group has been working to harmonize different approaches to autoimmunity diagnostics. Initiated and organized by Phadia, the steering group members are independent European laboratory and clinical experts. To give an insight into the aims of EASI, the steering group published the following article in Lupus:

- Wiik A, Cervera R, Haas M, Kallenberg C, Khamashta M, Meroni PL, Piette J-C, Schmitt R, Shoenfeld Y (2006)
  European attempts to set guidelines for improving diagnostics of autoimmune rheumatic disorders
  Lupus 14, 391-396

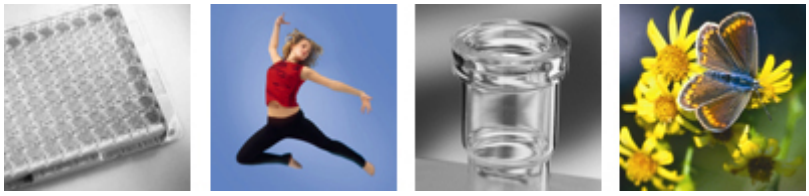
Some of the questions addressed in this article are:

- How can we use results derived from use of new technologies?
- Are such results as valuable for diagnostics as those of classical techniques?
- Do we use serological results rationally in clinical work?
- Where can we make progress in clinical diagnostics?
- Do we need more than one method to ascertain a positive result?
- Who decides which methods are optimal for clinical work?
- Will new technologies help solve our problems in diagnostics?
- Can we limit costs for serodiagnostics by use of algorithms for test ordering?
- Can long-term costs for the patient be limited by early diagnosis and intervention?

The article does not try to answer all these questions but is meant to be a catalogue of issues to be discussed among active partners in the health system.

At the present time, national EASI teams consisting of clinical and laboratory experts are working in many European countries. Several countries, where no national EASI team yet exists, have expressed an interest in joining these activities. High interest was also shown at the 5th International Congress on Autoimmunity in Sorrento on December 1 where the hall for the EASI session was completely overcrowded. The EASI members hope that their efforts will lead to an open dialogue among involved parties all over Europe and possibly beyond.

Publication of the Month



November - No. 11, 2006

Anti-tTg in PBC

It has been reported that patients with primary biliary cirrhosis (PBC) have an elevated risk for celiac disease (CD). On the other hand, it has been shown that the risk for false positive results in anti-tTG tests is very high in PBC patients. In the following study, Bizzaro et al tested six different anti-tTG enzyme immunoassays to verify if the positive results are false positives due to cross reactivity with mitochondrial antigens or if they are correctly positive because of an elevated prevalence of CD in PBC patients.

- Bizzaro N, Tampoia M, Villalta D, Platzgummer S, Liguori M, Tozzoli R, Tonutti E (2006)
  Low specificity of anti-tissue transglutaminase antibodies in patients with primary biliary cirrhosis
  J Clin Lab Anal 20, 184-189

The authors measured anti-tTG antibodies in 105 adult patients affected with PBC. IgA antibodies were measured with six different immunoenzyme assays that use antigen from different sources: human recombinant (Eurospital and Phadia), human placenta (Euroimmun), human erythrocytes (Inova) and guinea pig liver (Eurospital and Inova). Three different kits were used to measure IgG antibodies: human recombinant antigen (Eurospital and Phadia) and human red blood cells extraction (Inova).

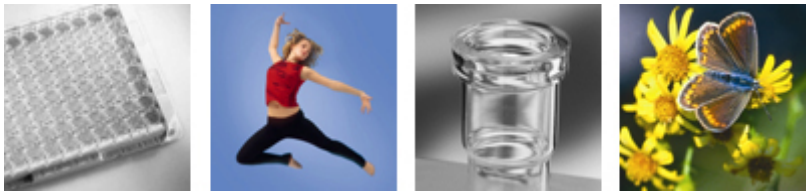
In total, 28 out of 105 PBC subjects tested positive for anti-tTG IgA antibodies in any method, but only 2 were eventually found to be affected by CD. The other 26 were shown to be false positive.

The specificity of the IgA kits using the various antigenic substrates ranged from 82.5% (human erythrocyte substrate) to 97.1% (human recombinant tTG). However, the differences in performance were not only attributable to the substrate origin as, even within the human recombinant antigen group, one test gave more than twice as many false positives as the other.

A further interesting aspect was that whereas in general anti-tTG IgA antibodies are considered a far more specific marker for CD than anti-tTG IgG antibodies, this study supports a previous study in showing a much higher number of false positives in PBC with anti-tTG IgA than with anti-tTG IgG.

Finally, this study shows an association between PBC and CD in 2% of cases which is comparable to that seen in screening studies. It shows that a significant number of subjects with PBC may give false positive results in tests detecting anti-tTG antibodies and that this false positivity is related to the antigen and the test system used. The authors urge care with interpreting the results from this patient group.

Publication of the Month



October - No. 10, 2006

Antineutrophil cytoplasmic antibodies

Testing for antineutrophil cytoplasmic antibodies (ANCA) is a useful serological test to assist in diagnosis of small-vessel vasculitides, including Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and their localised forms (eg, pauci-immune necrotising and crescentic glomerulonephritis). Indirect immunofluorescence and ELISA remain the most widely used techniques for ANCA detection, their combination being the most recommended approach. This summer, a very comprehensive review of ANCA was published in The Lancet:

- Bosch X, Guilabert A, Font J (2006)
  Antineutrophil cytoplasmic antibodies
  Lancet 368, 404-418

The authors searched MEDLINE and PubMed for work on ANCA and ANCA-related diseases published between 1982 and 2005. Their review covers pathogenesis with the pathogenetic role of ANCA, the cell molecular background of ANCA binding and acting, the possible reasons for the development of ANCA-associated vasculitides, methods for the detection of ANCA and of course the clinical usefulness of ANCA.

When talking about clinical usefulness, the authors also discussed disease monitoring. For an even closer look at this interesting field, we recommend another article which was published this year:

- Birck R, Schmitt WH, Kaelsch IA, van der Woude FJ (2006)
  Serial ANCA determination for monitoring disease activity in patients with ANCA-associated vasculitis: Systematic review
  Am J Kid Dis 47, 15-23

Early evidence about the usefulness of ANCA as markers of clinical activity in Wegener's granulomatosis was reported in 1985 by van der Woude and his group and now, 20 years later, the same group has put together a wrap up of today's knowledge on this topic in the attached review. Although 22 studies met the inclusion criteria, including a total of 950 patients, the authors could not come to a final conclusion as to whether or not anti-PR3 or anti-MPO can be used as predictors of relapses. Specificially, this is due to pertaining literature appearing very heterogeneous with respect to, for example, study design, test methods, and definitions of relevant findings of index and reference tests used. A specific problem of diagnostic ANCA research is the difficulty in defining and using an objective reference standard.

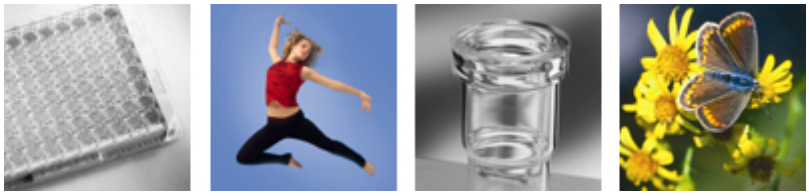
According to the article of Csernok et al, serum standards for PR3-ANCA and MPO-ANCA will very soon be available and these might provide better tools for alignment of ANCA results worldwide.

- Csernok E, Lamprecht P, Gross WL (2006)
  Diagnostic significance of ANCA in vasculitis
  Nature Clin Pract Rheumatol 2, 174-175

In this article, methodologies, disease associations and clinical usefulness of ANCA are discussed. The new EUVAS study, which demonstrated that capture ELISA is superior to direct ELISA for PR3-ANCA detection in Wegener's granulomatosis, is mentioned. There is first evidence that PR3 capture assays in particular may be good predictors of relapses in Wegener's granulomatosis, but here, again, more statistically powerful trials are needed to assess the risk-benefit-balance of pre-emptive treatment.

While the high sensitivity of Phadia's new PR3 capture assay has already been shown, its use for predicting relapses is currently under examination.
i-Jo-1 relating to malignancy.

Publication of the Month



September - No. 9, 2006

Antibodies in idiopathic inflammatory myopathies

Idiopathic inflammatory myopathies are diseases characterised by skeletal muscle inflammation and by a variety of other systemic symptoms. Polymyositis (PM) and dermatomyositis (DM) are the primary clinical variants. The presence of anti-Jo-1 antibodies (or other antisynthetase antibodies) helps to identify a subgroup of patients characterised by systemic clinical manifestations in muscles (myositis), lungs (interstitial lung disease) and joints (chronic polyarthritis), which is referred to as the 1990 described antisynthetase syndrome.

The May edition of "Autoimmunity" was dedicated to idiopathic inflammatory myopathies. Those articles which were especially focussing on serodiagnosis were chosen for this edition of the "publication of the month":

- Ghirardello A, Zampieri S, Tarricone E et al. (2006)
  Clinical implications of autoantibody screening in patients with autoimmune myositis
  Autoimmunity 39, 217-221

- Mielnik P, Wiesik-Szewiczyk E, Olesinska M et al (2006)
  Clinical features and prognosis of patients with idiopathic inflammatory myopathies and anti-Jo-1 antibodies
  Autoimmunity 39, 243-247

- La Corte R, Lo Mo Naco A, Locaputo A et al (2006)
  In patients with antisynthetase syndrome the occurrence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease
  Autoimmunity 39, 249-253

In these articles the autoantibody profiles of all in all 184 patients with inflammatory myopathies were evaluated and compared with the clinical outcome. All authors found that Anti-Jo-1 was the most frequent antibody in myositis patients (30-35%) while antibodies targeting other tRNA synthetases were less frequent and they could confirm that anti-Jo-1 antibodies were related to interstitial lung disease and polyarthritis.

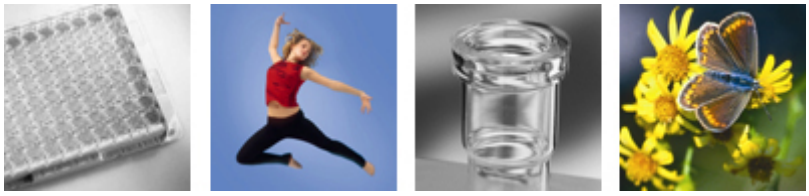
Ghirardello et al. found that anti-Mi2 antibodies were almost exclusively found in dermatomyositis and were never associated with lung involvement. Among the myositis associated (but not specific) antibodies, anti-Ro antibodies, by far the most frequent ones, were more prevalent in patients with antisynthetase syndrome than in those without.

Mielnik et al. looked closer on the clinical features and prognosis of anti-Jo-1 positive patients. They could confirm the association of anti-Jo-1 with interstitial lung disease. Additionally they found an association with Raynaud's phenomenon.

La Corte et al. studied the clinical and serological features of 69 patients (32 PM and 37 DM; 21 of them having antisynthetase syndrome). Anti-Jo-1 were the most frequent antibodies in these patients, followed by anti-Ro. Only one patient with anti-Ro fulfilled the criteria for an associated Sjögren's syndrome. The patients with coexistent anti-Ro antibodies tended to have a more severe form of interstitial lung disease. This does not necessarily mean a more severe prognosis or a more rapid decline of pulmonary function. Anyway, the presence of anti-Ro would alert the clinician to a potentially more severe lung involvement requiring an in-depth observation in those patients. The early diagnosis of rapidly progressive deterioration of lung function from interstitial lung disease is mandatory to a more effective treatment.

9 patients (6 with DM, 3 with PM) had an associated malignancy. Interestingly, none of those patients had antisynthetase syndrome confirming a "protective" role of anti-Jo-1 relating to malignancy.

Publication of the Month



August - No. 08, 2006

Exclusion of IgA deficiency in coeliac disease

Celiac disease is characterised by a life-long intolerance to gluten from wheat, barley or rye. Ingestion of gluten results in a pathogenic alteration of the small instestinal mucosa (villous atrophy) leading to malabsorption of nutrients. It affects as many as about 1 % of the total European population. Diagnosis still relies on duodenal or jejunal biopsy result, but has been helped in recent years by the measurement of IgA antibodies against gliadin and tissue transglutaminase (detected via ELISA or via immunofluorescence, then called endomysium antibodies, EMA).

Specialists recommend that total serum IgA is estimated to exclude coexisting IgA deficiency, which is 10 to 20 times more common in patients with celiac disease than in the rest of the population. Hence, to be sure of finding all celiac patients in serodiagnosis, laboratories include either an IgG-specific assay for tTG or endomysium antibodies, or measure total serum IgA in every sample.

The authors of the following study wanted to evaluate whether it is possible to devise an optical density read-out cut-off value for ELISA, above which there is no IgA deficiency. If this proved possible, it would mean that only those samples with optical densities below a certain level would need to be investigated further for both IgA deficiency and the presence of gut-related IgG antibodies.

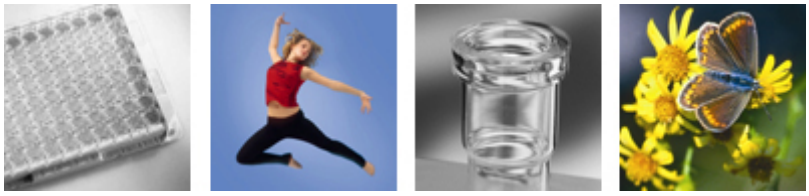
- Sinclair D, Saas M, Turk A, Goble M, Kerr D (2006)
  Do we need to measure total serum IgA to exclude IgA deficiency in coeliac disease?
  J Clin Pathol 59, 736-739

From a total of 608 routine consecutive samples, the authors measured tTG IgA ELISA optical density values ranging from 0.010 to 3.322. The authors found that no patient with an optical density >0.07 had a total IgA concentration <1 g/l. Of the 608 samples studied, four patients were shown to have IgA deficiency (IgA <0.05 g/l). One of these was a patient with known celiac disease, who was compliant on a gluten-free diet and had no IgA or IgG endomysium antibodies; the remaining three had no IgA or IgG endomysium antibodies and were not investigated further. One other patient had an OD of 0.014 in the tTG IgA ELISA, low IgA (0.25 g/l), no IgA endomysium antibodies but positive IgG antibodies, and a subsequent biopsy result suggestive of celiac disease.

This study shows that it is possible to predict those routine screens for people with celiac disease that are likely to require further investigation on IgA deficiency by using the optical density values obtained by tTG ELISA. This removes the need to test for IgA deficiency by estimating the total serum IgA in every case.

The authors suggest that the following algorithm be considered. If tTG optical density <0.05, a total serum IgA concentration should be estimated. If total IgA is within the age-related reference range, the negative tTG antibody can be reported. If IgA is below the reference range, endomysium IgA and IgG should be measured.

Publication of the Month



July - No. 07, 2006

Diagnosis and prognosis of early rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common inflammatory musculoskeletal disease, affecting approximately 1% of the population. Early diagnosis has a high priority due to the availability of effective disease modifying agents which not only improve patient wellbeing but influence the eventual outcome in terms of joint destruction.

The following article is a concise review on today¿s diagnosis and prognosis of early RA:

- Mierau R, Genth E (2006)
  Diagnosis and prognosis of early rheumatoid arthritis, with special emphasis on laboratory analysis
  Clin Chem Lab Med 44, 138-143

The authors start with a brief discussion of the 1987 classification criteria of the American College of Rheumatology emphasising their lack of usefulness in the differential diagnosis of early RA. A flow scheme which includes clinical and several laboratory markers is proposed and the relevance and importance for each of these assays is further detailed and discussed. Naturally, anti-cyclic citrullinated peptide antibodies (anti-CCP) receive some focus and the detailed and well-referenced table showing the prevalence of anti-CCP in several health states provides useful information for clinicians faced with the difficult task of diagnosis or exclusion of early RA.

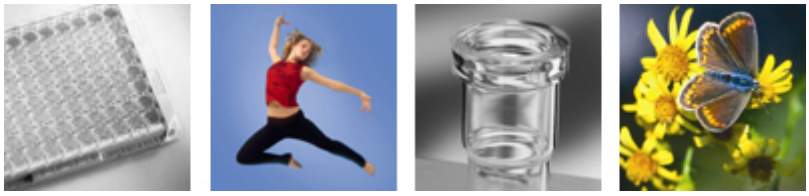
However, anti-CCP is not only used for the first diagnosis but also for prognosis. In the following article, Berglin et al. evaluated the prognostic use for disease activity and progression:

- Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, Rantapää-Dahlqvist S (2006)
  Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset
  Ann Rheum Dis 65, 453-458

93 patients with early RA had donated blood before symptoms of RA (defined as pre-patients). Individuals positive for anti-CCP before the onset of symptoms of joint disease had significantly more joint erosions at the time of diagnosis of RA than individuals negative for these antibodies. Two years after diagnosis the radiological outcome was worse in those positive patients. Anti-CCP predated the onset of signs and symptoms of joint disease by up to several years. In several previous studies, an association between initial inflammation, measured as ESR, C-reactive protein, or number of swollen joints, and radiological outcome or progression has been reported. In this study, and in agreement with multiple regression analysis, however, anti-CCP and rheumatoid factor were shown to be better predictors for radiological outcome and progression than were measures of inflammation.

Anti-CCP titres declined during the study in those patients with a therapeutic response. This is in agreement with the results in other studies showing significant decrease in anti-CCP titres in patients who had a decrease in disease activity. The therapeutic response predicted less radiological progression after two years, in contrast to the presence of anti-CCP at baseline. This suggests that repeated measurements of the anti-CCP titre could be of clinical use for assessing disease activity and severity.

Publication of the Month



June - No. 06, 2006

12th International Vasculitis and ANCA Workshop - Therapy

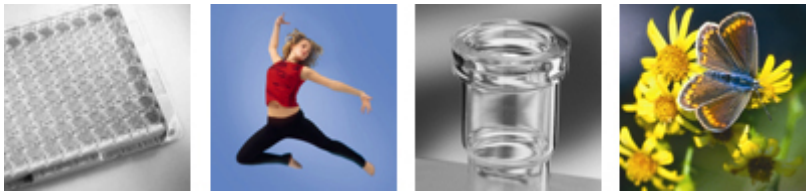
The 12th International Vasculitis and ANCA Workshop was held in Heidelberg from June 15 - 18, 2005 with 240 registered participants. The programme was divided into topics under 7 headings: immunopathogenesis, new therapeutic approaches, proteases, genetics and infection, management of the critically ill patient, advances in clinical and laboratory diagnosis, and therapy of primary vasculitis. In the journal "Clinical Nephrology" Vol. 64 (6), some highlights of this conference are presented including the following article.

- De Groot K, Jayne D (2005)
  What is new in the therapy of ANCA-associated vasculitides? Take home messages from the 12th workshop on ANCA and systemic vasculitides
  Clin Nephrol 64, 480-484

ANCA-associated systemic vasculitides were previously fatal diseases with 80% mortality within the first year after diagnosis. Today, remission is achieved in over 90% of the patients and 5-year survival amounts to about 80% with the use of therapeutic cyclophosphamide (CYC) and prednisolone. However, long-term follow-up of these patients now demonstrates that ANCA-associated systemic vasculitides are relapsing conditions with a high morbidity resulting from the combined effects of treatment toxicity and chronic damage.
As present-day, more sensitive diagnostic procedures allow the earlier diagnosis of these diseases, stage-adapted treatment regimens that reduce the exposure to CYC are required. There is consensus that, at present, CYC remains the drug of choice in patients with generalized vasculitis for the induction of a remission period of between 3 and 6 months.

There are efforts to further minimize the cumulative CYC dose for remission induction in elderly people (because the mortality is highest in this group) and by adding monoclonal anti-B-cell antibodies. Adding Etanercept to the conventional induction regimen has not proven beneficial. For maintenance of remission, a switch from CYC to azathioprine has proven to be safe. Several different studies and planned future trials are reviewed in this article.

Publication of the Month



May - No. 05, 2006

Review on anti-tTg antibodies in celiac disease

In 1984 the detection of IgA class antibody by indirect immunofluorescence to antigens present in monkey oesophagus was shown to have high sensitivity for celiac disease; coupled with remarkable specificity, it proved to be an almost ideal diagnostic test. The antibody stained the structure around the muscle fibre bundles and was therefore named endomysial antibody (EMA). The recognition, in 1997, of tissue transglutaminase (tTg) as the antigen of EMA allowed the development of ELISA tests with human purified or recombinant tTG.

The use of anti-tTG IgA antibodies enables the laboratory to play a full part in the diagnosis and monitoring of this disorder.

In the "Annals of Clinical Biochemistry" of March 2006, Peter Hill and Stan McMillan wrote the following very comprehensive and detailed Review on anti-tTg and their role in celiac disease:

- Hill PG, McMillan SA (2006)

  Anti-tissue transglutaminase antibodies and their role in the investigation of coeliac disease

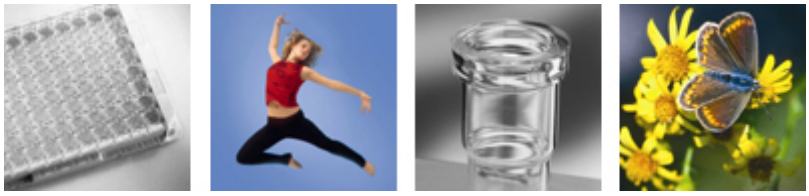
  Ann Clin Biochem 43, 105-117

The authors describe the clinical background of celiac disease with prevalence, clinical presentation, and diagnosis, followed by an overview of the pathogenesis (environmental, genetic, and immunological factors) and the serological tests with background and antigen specificity. Tissue transglutaminase antibodies are described in detail, their diagnostic use, their use for monitoring dietary compliance and an explanation of false-positive and false-negative tTG antibody results. One chapter is about the detection of selective IgA deficiency and its role in diagnosis of celiac disease and last but not least the laboratory strategy for detecting celiac disease in children and adults is described and an algorithm for use of anti-tTg for detecting celiac disease is shown. The algorithm includes suggestions for the interpretation and follow-up of different test result patterns. The authors have based their proposal around the use of anti-tTG testing as the first screening test as they judge that *"human recombinant TGA kits have adequate sensitivity and specificity for the detection of CD in children and adults and can replace EMA as a first-line test"*.

The comparison study of different IgA tissue transglutaminase antibody kits referred to on page 111 actually gives much more information than is able to be presented in the table shown and is worth further reading. The study, from Van Meensel et al, Clinical Chemistry 2004, 50:2125, investigates concordance with mucosal damage classification according to Marsh as well as the use of different kits' antibody titre in the monitoring of patients on gluten-free diets. Unsurprisingly, the full study confirms the excellent performance of Celikey as also shown in Wong et al, J Clin Pathol 2002, 55:488, Blackwell et al, Scand J Gastroenterol 2002, 37:1282; Fernandez et al, World J Gastroenterol 2005, 11:3762 and in several other studies referred to in this review.

Celiac disease is an eminently treatable condition once the diagnosis has been considered and confirmed. Using a highly specific anti-tTG antibody assay can minimise unnecessary biopsies because so few false positive results are generated. Bearing in mind that many patients under investigation for celiac disease are children, we need to remember our responsibilities to all patients so that expensive and invasive investigations can be limited to those in which they are most likely to give a diagnostic benefit.

Publication of the Month



April - No. 04, 2006

Prevalence of anti-CCP antibodies in other diseases than RA

Several studies have shown that anti-cyclic citrullinated peptide antibodies (anti-CCP) show good sensitivity (41-70%) and very high specificity (91-98%) in rheumatoid arthritis (RA), depending on the study population and the ELISA kit used. Anti-CCP now appear to be the most specific markers for the diagnosis of RA, and the easiest to detect.

However, there have been reports on anti-CCP in other diseases than RA. Two of these studies were published recently and are summarized in the following:

- Sène D, Ghillani-Dalbin P, Limal N et al (2006)

  Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjögren's syndrome

  Ann Rheum Dis 65, 394-397

Rheumatological manifestations are common during HCV infection and in some cases may mimic the onset of RA. A definite diagnosis and specific treatment are usually delayed. For investigating the diagnostic reliability of anti-CCP and rheumatoid factor (RF) in distinguishing HCV associated rheumatological manifestations and Sjögren¿s syndrome from RA, both markers were tested in 147 HCV infected patients and 64 patients with definite rheumatoid arthritis in a retrospective study. 35 (23.8%) of the 147 HCV infected patients had rheumatological involvement, 19 (54.3%) of whom were RF positive and 2 (5.7%) were anti-CCP positive. In the 112 HCV infected patients without arthralgia only 30 (26.8%) were RF positive and none of them had detectable anti-CCP. In contrast, 50 of 64 patients with RA were positive for anti-CCP (sensitivity of 78%).

Thus, the specificities of anti-CCP and RF for RA in the differential diagnosis to HCV infection were 94.3% and 46%, respectively.

- Alenius GM, Berglin E, Rantapää Dahlqvist S (2006)

  Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without joint inflammation

  Ann Rheum Dis 65, 398-400

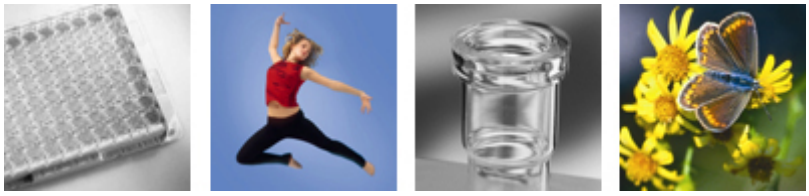
Patients with psoriasis arthritis may have symptoms and signs, such as mild mono-oligoarthritis or very severe, erosive and destructive polyarthritis, which are possibly indistinguishable from those seen in patients with RA. RF is usually absent in these patients, although there are reports of a slightly increased prevalence of RF in patients with psoriasis and inflammatory joint manifestations. The development of tests for antibodies against CCP has enhanced the possibility to distinguishing between RA and other rheumatic diseases.

The authors compare the prevalence of anti-CCP in psoriatic patients with and without joint inflammation, patients with early RA, and controls by measuring anti-CCP in 160 patients with psoriatic arthritis, 146 patients with psoriasis but no arthritic disease, 101 patients with early RA, and 102 healthy controls.

11 (7%) patients with psoriatic arthritis, 75 (74%) patients with early RA, 2 (2%) healthy controls, and 1 (0.7%) patient with psoriasis without arthritis had anti-CCP above the cut-off. 8 of the 11 patients with psoriatic arthritis and positive anti-CCP had a polyarthritic disease, and all fulfilled the ACR criteria for RA at 4 year follow up. 5 of these 8 patients also had manifestations such as dactylitis, DIP involvement, radiological changes associated with psoriatic arthritis, and/or enthesitis.

Anti-CCP and RF significantly distinguished RA from psoriatic arthritis and predicted RA in patients with polyarthritic disease.

Publication of the Month



March - No. 03, 2006

New Classification Criteria for APS

Widespread recognition of the clinical importance of antiphospholipid antibodies (aPL) dates from the seminal work of Harris, Gharavi, and their colleagues in 1983. Their finding indicated that aPL are significantly associated with and may have a causative role in vascular thromboses and pregnancy losses.

Preliminary classification criteria for the antiphospholipid syndrome (APS) were formulated during a post-conference workshop held October 10, 1998 in Sapporo, Japan. Since then, the knowledge on APS has grown enormously and so has the need for an update of these classification criteria. In the following article, the authors appraise the existing evidence on clinical and laboratory features of APS addressed during a workshop in Sydney, Australia, before the Eleventh International Congress on antiphospholipid antibodies. Based on this, the group proposes amendments to the Sapporo criteria and provide definitions on features of APS that were not included in the updated criteria.

- Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RHWM, De Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA (2006)

  International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS)

  J Thromb Haemost 4, 295-306

The Sapporo classification divided the APS criteria into clinical and laboratory; this categorisation was maintained in the current revision.

The high frequency of thromboembolic disease in hospitalised patients may cause classification bias. Thus, in the updated criteria standard definitions of premature cardiovascular disease and conditions conferring risk for thrombosis should be taken into account. Thrombosis may be more frequent when multiple risk factors coexist. Strict exclusion criteria therefore were included. Additional factors contributing to thrombosis should be assessed and APS patients should be stratified according to (a) the presence or (b) the absence of other - inherited or acquired - contributing causes of thrombosis.

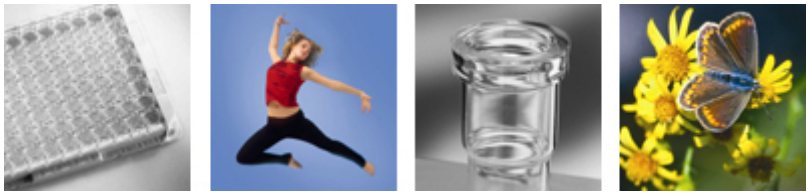
Both lupus anticoagulant (LA) and anticardiolipin (aCL) IgG and IgM are maintained as laboratory APS criteria, and IgG and IgM anti-ß2 glycoprotein-I (anti-ß2GPI) assays are added in the revised criteria. The committee introduces a clear statement on threshold for positive: >40 GPL or MPL units, or >99th percentile.

The revised criteria introduce a concept of subclassification of APS patients into four different categories of aPL assay positivity (specified in table 2 in the article)

APS requires the combination of at least one clinical and one laboratory criterion. A remote test avoids false results from interference with the event. The stability of the laboratory testing over time is reassuring, yet spontaneous variation of aPL in individual patients occurs in a quarter of cases. The committee suggests that researchers should not classify APS if more than 5 years separate the clinical event and the positive laboratory test, and that an allowance of at least 12 weeks between symptom and test will assist assessment of the relationship between clinical manifestations and aPL. These time limits are valid independently of which feature of APS occurs first. On the other hand, persistent positivity of laboratory tests is important. Increasing the interval of at least 6 weeks (Sapporo) to 12 weeks is proposed.

The criteria are listed in detail in table 2 of the article.

Publication of the Month



February - No. 02, 2006

Treatment of RA

The early diagnosis of Rheumatoid arthritis (RA) has become a high priority due to the availability of effective disease modifying agents which not only improve patient wellbeing but influence the eventual outcome in terms of joint destruction.

For this reason the development of the anti-CCP antibody assay has been a great step forward for the physician, who must decide early whether to treat symptomatically or begin immediately with an aggressive treatment strategy.

In the following article Paul Emery gives a comprehensive review of the changes in RA treatment over the last few years:

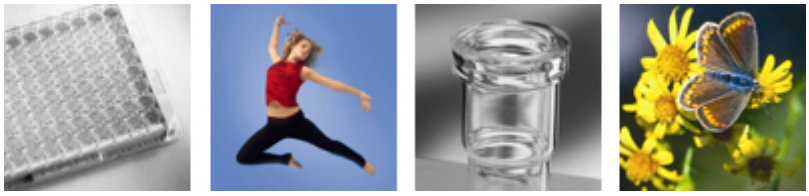
Emery P (2005)
Treatment of rheumatoid arthritis
Br Med J 332, 152-155

The conventional management of RA has included non-steroidal anti-inflammatory drugs which do little to alter the structural progression and long term disability. Further therapy using disease modifying antirheumatic drugs (DMARDs) was only prescribed when there was radiographic evidence of erosions. Patients who develop RA have normal radiographs in 80% of cases at presentation, whereas magnetic resonance imaging can pick up changes in over 80% of such cases. Imaging has allowed the identification of the pathognomonic features of RA. More recently, anti-CCP antibodies have also been associated with persistence and damage. They may be present for years before the development of clinical disease and are, unlike rheumatoid factor, highly specific.

Although statistically only a small proportion of all patients who have inflammatory arthritis will develop RA, evidence already shows that other patients with less well defined disease, such as undifferentiated arthritis, and even those with so called ¿inflammatory¿ osteoarthritis will benefit from appropriate targeted intervention long term. If referral of these patients is doubtful then the level of anti-CCP should be measured as this is a strong predictor of damage.

Meanwhile a revolution has occurred in the therapy of RA with the realisation that the pro-inflammatory cytokine TNF-alpha played a central and hierarchical part in the pathogenesis of the disease, and that its blockade would lead to major improvements in symptoms. It was shown that TNF-alpha antagonists were remarkably effective in patients who had not responded to DMARDs. A recent study of patients with relatively early disease showed that, at two years, half the patients receiving combination therapy (methotrexate combined with anti-TNF-alpha) were in remission. This must now be the goal for patients with early disease. A double-blind randomised control study showed that after a year of therapy, biological agents could be withdrawn and patients left in remission with benefit beyond two years. Another study showed that after treatment with anti-TNF-alpha had produced remission for six months, it was possible to withdraw the biological agent and maintain remission in the second year. Even more strikingly, a proportion of patients were able to successfully stop taking methotrexate. These patients were actually in remission while receiving no therapy representing "cure" at least temporarily.
Early diagnosis and appropriate therapy has the potential to bring this previously crippling disorder under control and gives new hope to patients.

Publication of the Month



January - No. 01, 2006

Longitudinal analysis of CCP antibodies

Most studies on CCP antibodies to date have focused on the initial qualitative anti-CCP status at study inclusion, and compared this status with clinical conditions at one or a few subsequent time points. In the following study the authors used a quantitative and longitudinal approach with parallel investigations of antibody levels and clinical characteristics, including radiological data on multiple occasions and in a very high number of patients. The authors particularly wanted to investigate whether the anti-CCP phenotype was stable or fluctuated with time and whether the antibody level at the time of diagnosis predicted clinical and radiological disease course and response to pharmacological treatment.

- Rönnelid J, Wick, MC, Lampa J, Lindblad S, Nordmark B, Klareskog L (2005)

  Longitudinal analysis of citrullinated protein / peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression

  Ann Rheum Dis 64,1744-1749

279 Patients with rheumatoid arthritis (RA) from a prospective cohort of patients with early RA at Karolinska University Hospital were included between 1995 and 2000. At inclusion, 160 of these 279 patients had anti-CCP antibodies (a level >25 U/ml was considered as positive). Qualitative changes in anti-CCP status with time were rare. Only 11 patients had an altered status (3 initially negative patients became positive, and 8 initially positive patients lost demonstrable antibodies at any occasion during follow up). There was no association between appearance and disappearance of anti-CCP and clinical variables, including drug treatment.

Whereas no difference in disease activity between anti-CCP positive and negative patients was present at baseline, the groups started to diverge from each other after 3 months. Anti-CCP positive patients had a significantly higher disease activity. In all comparisons for which the subgroups differed, anti-CCP positive patients had the least favourable outcome. Likewise, patients who presented with anti-CCP at baseline showed a significantly higher increase in radiological damage during the first 2 years of disease. In other words, the effect of antirheumatic treatment on both the clinical course and on radiographic progression was less impressive for the anti-CCP positive patients than for the anti-CCP negative patients.

Correlation between quantitative anti-CCP levels and disease activity increased steadily over time, being highest at 5 years. This implies that the prognostic importance of quantitative anti-CCP levels at baseline may increase with time and indicate that follow up studies in longstanding RA are warranted.

Use of sulfasalazine, but not other DMARDs, was dose-dependently associated with decreased anti-CCP serum levels during the first year. It appears that sulfasalazine can down-regulate antibody responses in RA, indicating that it may have more profound effects on humoral immunity than other DMARDs.

The authors conclude from their results, that the stability of anti-CCP status and the failure of efficient treatment to eliminate these antibodies from serum strengthens the notion that anti-CCP positive RA may differ from anti-CCP negative RA in several important aspects, and that these two subgroups thus should be evaluated separately in future studies of both aetiology and treatment.