Friday May 12, 2000 Lectures

Imaging technic in rheumatology — Connective tissue diseases

Advances in Thermal Imaging for Rheumatology

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Modern infra red imaging systems have reached a high level of accuracy and reproducibility, & provide and objective and non-invasive means of recording the temperature distribution over joints and soft tissues. In a cool environment typically 20°C inflammed joints show localised areas of increased heat according to the severity and distribution of inflammatory foci. In Raynaud's Phenomenon and some sympathetic dystrophies a decrease in temperature of the affected extremities can be found. We have developed a standard protocol for quantifying the reaction to a cold stress test with a numerical index showing severity based on studies with over 200 controls and 140 Rheumatoid Raynuaud's and Connective Tissue Diseases. These measured indices are from +4 - -3.5 in normals and from -4 to -14 in Raynaud's according to severity. This measurement can repeated to assess the effects of treatment or disease progression.

A new generation of silent uncooled infra red cameras are now available which are easily interfaced to a computer for image capture analysis and storage. Focal plane array imagers provide continuous thermograms at video rates, which are ideal for dynamic studies, such as mechanical exercise, chemical or thermal stress tests. Ten years ago this could be achived with expensive thermal imagers, but the necessary computing power for analysis was expensive and complex. This new technology supported by the present facilitues for image processing provides efficient images of arthritis at different anatomical sites at high resolution. Using a wide angle Infra red lens it is possible to image the whole or half of the human body in a fraction of a second. This can show the distribution of inflammed joints. Closer images of for example the dorsal hand shows the thermal patterns relating to the larger veins, the presence of MCP inflammation, and the overall perfusion of individual fingers. For this reason it is of interest in the monitoring of Connective Tissue Diseases, since skin temperature and blood perfusion are closely related. The technique has previously been used to quantify response to anti-inflammatory drug therapy, and is now applied to experimental doses of new biological agents by intra-articular injection.

MAGNETIC RESONANCE IMAGING OF THE HIP

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A limited number of conditions only will be discussed.

Avascular necrosis is demonstrated very early and with great sensitivity. Images combine a low subchondral signal area, surrounded with a low signal band.

Algodystrophy images are different with a higher T2 signal. Difference is not always clear and very early the T1 low signal area can be poorly defined, and T2 weighted images can be variable, mainly in chronic and subacute cases. MRI is the best mean for avascular necrosis diagnosis at the hip level, and elsewhere and also for the detection of bone infarcts. For the detection of avascular necrosis MRI is 96 % accurate when compared with pathology findings whereas only 71 % of isotope studies and 54 % of CT scans correlate with biopsy results.

In villonodular synovitis cases, with T1 weighed images the pattern is always an heterogeneous mass, globulous, well defined with a low signal when compared to the fat, and an isosignal when compared to muscles. Gadolinium injection increases the signal level. With the T2 weighted sequences the mass remains heterogenous with a lowered signal and areas without signal (hemosiderin depositis). This pattern is of high specificity especially with gradient echo sequences but other diagnosis can be concerned : synovial chondromatosis, synovial sarcoma and even rheumatoid arthritis.

In other conditions : rheumatoid arthritis, postoperative painful hip, stress fractures, septic arthritis, abcesses, bursitis, MRI is also of good value.

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HIP JOINT ULTRASONOGRAPHY

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Compared to great interest in the hip joint examination in children, this examination is not so popular in adult ultrasound diagnostics.

Diagnostics of the hip joint effusion is important since it appears in different conditions (arthritis, transient synovitis, osteomyelitis, fracture, total endoprosthesis -TEP loosening). Detection of the effusion can lead towards diagnostic or therapeutic puncture. In our centre, linear probe of 5 – 7,5 MHz frequency is used most frequently. Pronounced echo is obtained from the front area of femoral head and neck bone. Joint capsule lies above front joint recessus, parallelly with femoral neck. Standard ultrasound findings include joint capsule with concave contour, the distance of joint capsule from the outer rim of the femoral neck surface is 2 to 5 mm. Definite pathological finding for the joint capsule distension is the distance bigger than 7 mm or the difference between sides bigger than 1 mm. Ultrasound findings most frequently include hypo-echogenous content. Ultrasound character of effusion to be non-specific and state that, septic effusion can be non-echogenous as well. In the hip joint examination, continuity of bone surface of both head and neck are assessed. Discontinuity of the surface or the fragmentation suggests osteonecrosis or osteomyelitis, erosions are of irregular shape with dorsal strenghtening, present osteophytes may deform the ultrasound projection of the head. This examination presents high sensitivity for detection of effusion in joint location. In experimental conditions, detection of less than 1 ml of liquid was proven. In symptomatic patients after hip joint total endoprosthesis implantation, ultrasound examination to detect changes in surrounding soft structures in limiting CT or NMR factors (presence of metal parts) is useful. As for bursae, the attention is concentrated to trochanteric bursa, which, if it is full, is projected as hypo-echogenous object. Otherwise hard to examine full iliopsoatic bursa is well projected via ultrasound - as an hypo-echogenous object between joint capsule and the tendon m. iliopsoas. When examination is done via hind approach, the probe with 3.5 MHz frequency is used and gluteal muscles are projected.

"The last frontier of the Connective Tissue Diseases: the SATELLITE CONNECTIVE TISSUE DISEASES (SAT-CTD)"

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When a patient shows the classical clinical picture of a well definite Connective Tissue Disease (CTD) with typical auto-antibodies, together with other auto-antibodies characteristic of other CTD, that makes things embarassing.
That may show whether a mistaken overlap syndrome or the coexistence, beside a clear and complete CTD, of another CTD under-tone", that is with oligosymptomatic clinical picture, that is just a SATELLITE CTD (SAT-CTD).
So we have studied 53 patients that showed in the serum the contemporary presence of antibodies markers of several CTD and that at first time were clinically diagnosed, according to respective International Criteria as SLE (25), SS (14), SjS (5), DM (3), PM (1), Unclassifiable CTD (UCTD)-(5-). All autoantibodies were showed with ELISA-test.
The anti-dsDNA and anti-Sm antibodies were showed only in SLE, but every other autoantibody marker was showed in more than one CTD, apparently without specificity.
Reviewing the clinical cases, and taking into account the degree of positivity of every marker, resulted that the positivity from 2 to 4 times the threshold value allowed to identify: 7 overlap syndromes, 31 patients with mere presence of "other markers" (without respective clinical symptoms) and 9 patients with SATELLITE-CTDs, that is with "other markers" with contemporary presence of oligosymptomatic "other CTD".
In conclusion, the hypothesis of the SATELLITE-CTDs (SAT-CTD) appears true and helpful, and confirms the diagnostic specificity of the autoantibodies in the connective tissue diseases.

COMPLICATIONS AND CAUSES OF DEATH IN PROGRESSIVE SYSTEMIC SCLEROSIS

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Objective: The *basic* and *associated diseases*, the major *complications* and *causes of death* were determined and histologically confirmed in a randomized autopsy population of 11 in-patients (female 10, average age: 53.6 years; male 1, age of 65 years at death) with *systemic sclerosis (SSc)*, who died at the National Institute of Rheumatology between 1961 and 1997.
Methods: The tissue blocks were fixed in 8% formaldehyde at pH 7.6 and embedded in paraffin. Serial sections were cut and stained with H-E, Ziehl-Neelsen stain, PAS reaction, and Congo red according to Romhányi. The (AA) amyloid was determined and characterized histochemically.
Results: Mortality data of SSc are summarized in table I.

n	Basic disease	Complication(s)	Cause of death	Associated disease
1.	SSc	Complex nephropathy	Uremia	-
2.	SSc	Complex nephropathy	Uremia	-
3.	SSc	Honeycomb lung	Bronchopneumonia	-
4.	SSc	Complex nephropathy	Uremia	-
5.	SSc	Complex nephropathy	Uremia	Tuberculosis
6.	SSc	Endo-myocardisl fibrosis	Circulatory failure	Meningeoma
7.	SSc	Complex nephropathy	Uremia	-
8.	SSc	Complex nephropathy	Uremia	-
9.	SSc	Myocardiocytoslysis	Circulatory failure	-
10.	SSc	Myocardiocytoslysis	Circulatory failure	-
11.	SSc	Nephropathy - Amyloidosis	Uremia	Renal adenoma

Discussion: In all of our cases *SSc* was the basic disease leading to death. It was complicated with a wide spectrum of vascular changes, such as: fibromuscular intimal proliferation of medium size, and small arteries (with, or without linear fibrinoid necrosis of the vessel wall), total fibrinoid necrosis of small arteries and arterioles (with, or without thrombosis), especial in the kidney, lungs and heart. Complex nephropathy was characterised by fibromuscular intimal proliferation of the vessels (with, or without fibrinoid necrosis, and/or thrombosis), by interstitial nephritis (with, or without fibrosis), by mesangiopoliferative, or membranous glomerulonephritis (in exsudative, proliferative, or sclerotic stages), and by multifocal cortical (tubular) necrosis. Complex nephropathy led to uremia in 7 of 11 Ssc cases. Histopathological changes of the heart included: vasculogenic multifocal endo-myocardial fibrosis, or myocardiocytolysis, leading to circulatory failure in 3 of 11 Ssc cases. Complex alteration of the lungs were characterized by vascular changes, interstitial pneumonitis, fibrosis or 'honeycomb'-lungs.
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PRECURSOR OF ENDOTELIN-1 IN NECROTIZING VASCULITIDES

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Objective. Endotelin-1 is the strongest vasoconstrictory factor and is synthesized by the endothelial cells. Its precursor big endotelin-1 (BET-1) is biologically inactive. The aim of our study was to assess plasma levels of BET-1 in patients with primary and secondary necrotizing vasculitides and to corrrelate the obtained data with acute.phase reactants.
Patients and methods. Total 6 patients with polyarteritis nodosa, 3 with giant cell arteritis, 6 leukocytoclastic vasculitis, 4 with rheumatoid vasculitis, 4 with lupus vasculitis, 4 with vasculitis in undifferentiated connective tissue disease were examined. As a control group 10 blood donors were tested. BET-1 concentrations were assayed by ELISA using a commercial kit.
Results. The plasma concentrations of BET-1 were significantly increased in all patients in comparison with healthy controls ($p=0.01$). Because of small numbers of patients in all subgroups no correlations with acute phase could be calculated.
Discussion. Our preliminary data suggest that high levels of BET-1 in necrotizing vasculitides induce an increase of vascular tone which is probably due to the inflammatory process.

AUTOANTIBODY PROFILE IN SLE - A LONG-TERM EVALUATION

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Different views concerning the utility of different autoantibody profiles in SLE are rarely supported by long-term studies.

We analyzed a cohort of 202 SLE patients (of these were 16 males) aged 16-72 y. (median 38 y); the minimal follow-up period was 2 years (2-10, mean 4,3 y) and at least 3 serum samples were analyzed (3-16, median 5) for autoantibodies against: DNP (ELISA), dsDNA (ELISA, Farr, Crithidia IF), ENA (RNP, Sm, Ro, La), ribP, ELISA, INNO-LIA, CIE) a kardiolipínu (IgG, IgM - ELISA).

Anti-DNP were found in 74 % patients, anti-ENA in 81 % and anti-CL in 53 %. The individual prevalences were concordant with the published data. All combinations of specificities occurred. Anti-ENA profile was remarkably stable in most cases and did not reflect the clinical situation of patients although some relations to the clinical parameters existed. On the other hand anti-DNP (anti- nucleosomal) antibodies in the majority of cases correlated with clinical activity of the diseases better than anti-dsDNA. Anticardiolipin antibodies correlated with APLS only if the antibodies were present for a longer period of time.

Our study confirmed the correlation of anti-DNP antibody levels with clinical activity of SLE while the other specificities were related to some SLE subgroups.

CURRENT EXPERIENCES WITH THE USE OF CYCLO-SPORINE IN TREATMENT OF LUPUS NEPHRITIS IN CZECH REPUBLIC AND IN THE WORLD

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Immunomodulators represent a special group therapies that are not biologics, but mostly occur as natural compounds. They exert relatively specific but noncytotoxic effects on the immune response. Cyclosporine has been the most extensively investigated drug from the group of these immunomodulatory agents. Since 1984, patients with various autoimmune diseases have been succesfully treated with this drug. As long as cyclosporine was given for life-threatening disease, nephrotoxicity and hypertension was not a major concern. However, when cyclosporine was used in non-life threatening diseases, such as nephrotic syndrome, rheumatoid arthritis, psoriasis and many others, its nephrotoxic adverse effect then became an important issue. The active lupus nephritis as classified in III and/or IV class/VHO by biopsy is situated somewhere betwenn. To date, the data available seem to support the use of cyclosporine not only in severe nephritis refractory to other types of immunosuppression but also in cases of severe lupus nephritis as a drug of first choice. From 1989 to 1999 thirteen clinical trials with cyclosporine have been performed in 138 pts suffering with lupus nephritis class III-V: complete renal remission reached in 60 to 100 %, mean treatment duration 10 to 48 months, therapeutical dosage of cyclosporine between 2 to 5 mg/kg bwt/day - in 12 trials together with steroids. Three trials compared the therapeutical effect of cyclosporine versus cyclophosphamide. Unfortunately, only one study was based on randomised patients recruitment. No nephrotoxic adverse events were observed even not in four studies with repeated renal biopsies (Favre et al. 1989, Radhakrishnan et al. 1994, Dostál et al. 1998, Tam et al. 1998).

LONG-TERM FOLLOW-UP OF PATIENTS WITH PRIMARY SJÖGREN´S SYNDROME.

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Sjögren´s syndrome is an autoimmune disease of exocrine glands, involving in particular the salivary and lacrimal glands. It may occur alone (primary Sjögren´s syndrome), or in association with a variety of connective tissue diseases (CTD) and autoimmune disorders (secondary Sjögren´s syndrome). Signs of xerostomia and keratokonjunktivitis sicca are developing in most cases in the course of systemic connective tissue disease.

In a long-term following of 325 patients with primary Sjögren´s syndrome over a period of 3 to 25 years (median value 13.0 years) a diagnosis of another connective tissue disease, i. e. of secondary Sjögren´s syndrome was established in 20 patients. 13 patients fulfilled the diagnostic criteria of rheumatoid arthritis (RA), 5 of systemic lupus erythematosus (SLE) and 2 of systemic sclerosis (SS). The interval between the onset of ocular and oral involvement and the diagnosis of rheumatoid arthritis was 5-25 years (mean value 7.1). In SLE patients it was 4-10 years (mean value 6 years) and in systemic sclerosis 6 and 7 years.

Four patients with primary Sjögren´s syndrome developed malignant non-Hodgkin lymphoma and in other 5 patients the diagnosis of lymphoepitelial lesion was established after histological examination.

Long-term follow-up of patients with primary Sjögren´s syndrome is very important from the viewpoint of possible development of another systemic connective tissue disease (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis) and especially of malignant lymphoproliferation.

Clinical spectrum and aPL s/anti - β_2 GP1 antibodies in Polish PAPS and SAPS patients

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Objective: To compare clinical and immunological features in patients with primary antiphospholipid syndrome (PAPS) and patients with secondary antiphospholipid syndrome in the course of systemic lupus erythematosus (SAPS-SLE).

Methods: 16 patients with PAPS and 39 patients with SAPS were studied. Patients with SLE fulfilled the ACR 1982 revised criteria for SLE. PAPS and SAPS-SLE diagnosis was made according to Harris criteria modified by Asherson and Cervera in 1994. Anticardiolipin antibodies (aCl) and anti-β_2 GP1 antibodies were tested by ELISA. Lupus anticoagulant was measured by method described by Barry and Triplett.

Results: PAPS (F:M=11:5) and SAPS (F:M=38:1) patients slightly differed in respect to the age (x=45,9 vs 37,2).The age at the onset was younger in SAPS group in comparison to PAPS (x=8,1 vs 2,2 and x=8,1 vs 2,7 years, respectively). In both groups clinical features of APS as leg ulcers, recurrent fetal loss were present with the same frequency. Patients with PAPS had increased frequency of arterial thrombosis (31,5% vs 20,5%) and pulmonary embolism (25% vs 2,6%) when compared to patients with SAPS. Patients with SAPS showed higher frequency of livedo reticularis, (46,2% vs 37,5%), cardiomiopathy and TIA (7,7% vs 0).They also showed higher incidence of hematologic disorders: leucopenia (64,1% vs 12,5%),thrombocytopenia (56,4% vs 31,3%),lymphopenia (48,7% vs 0),hemolitic anemia (12,8% vs 6,3%). In both groups serological features of APS: false positive biologic test (VDRL), IgG and IgM anticardiolipine antibodies were present with the same frequency. PAPS patients had more often LAC (90% vs 47,6%) and IgG anti-β_2 GP1 antibodies (62,5% vs 23,3%) as compared to SAPS patients. SAPS patients were more often positive for antinuclear antibodies (100% vs 12,5%). Anti-double-strended DNA and anti - Sm antibodies were present only in patients with SAPS (30,8% and 7,7%, respectively).

Conclusion: PAPS was more often diagnosed in male patients as compared with SAPS. Clinical and immunological discrepancies between PAPS and SAPS-SLE were shown.

Anti-β_2 GP1 antibodies are more relevant in PAPS than in SAPS diagnosis.