

## **The Effect of Colchicine on Apoptosis of Neutrophils from Healthy Donors & Patients with Familial Mediterranean Fever (FMF)**

Mizhir Atallah, Eldad Ben-Chetrit, Inna Verbovetski, Dror Mevorach.  
Hadassah Hospital and the Hebrew University, Jerusalem, Israel.

**BACKGROUND:** FMF is an inherited disorder characterized by recurrent episodes of fever and serositis. The gene associated with FMF (MEFV) encodes a protein named pyrin. Most patients with FMF carry missense mutations in the C-terminal half of the pyrin protein that contain a death domain and thus may be involved in programmed cell death. Colchicine is a medication successfully used in FMF for prevention of attacks and the development of amyloidosis.

**PURPOSE:** To study spontaneous apoptosis of neutrophils and monocytes from healthy donors and patients with FMF that are not in attack, in the presence and absence of colchicine.

**METHODS:** FMF patients, diagnosed both clinically and genetically with no exposure to colchicine were studied and compared to healthy donors. Monocytes and neutrophils were isolated using ficoll and/or magnetic beads. Spontaneous apoptosis was detected using annexin/PI and PI staining of hypodiploid region of cell cycle. Physiological concentrations of colchicine were added to some of the samples.

**RESULTS:** Apoptosis was measured on 0, 4, 8, 16, and 24 hours. Accelerated apoptosis of neutrophils from patients with FMF and no previous exposure to colchicine was documented (Figure 1). Increased annexin-V staining by 10-25% was seen (ten experiments,  $p < 0.01$ , student t-test and  $p < 0.001$ , Kolmogorov-Smirnov test). Patients on colchicine had similar pattern. Colchicine exposure (0-16 ng/ml) clearly accelerated apoptosis of neutrophils from healthy donors with increase in 8-30 % of annexin-V positive cells (Figure 2, five experiments,  $p < 0.03$ , student-t-test and  $p < 0.001$ , Kolmogorov-Smirnov test). Surprisingly colchicine effect on neutrophils from patients with FMF was less dramatic.

**CONCLUSION:** Neutrophils from patients with FMF, between attacks, are more sensitive to spontaneous apoptosis and less sensitive to pro-apoptotic effect of colchicine. This observation supports the concept that in FMF patients neutrophil apoptosis is altered.

## **Cardiac pathology and mortality in patients with systemic sclerosis: Is there a role for Troponin T testing?**

Alexandra Balbir-Gurman<sup>1</sup>, Carol M. Black<sup>2</sup>, Menahem A. Nahir<sup>1</sup>, Jerry J.Cohgan<sup>2</sup>.

<sup>1</sup>The B. Shine department of Rheumatology, Rambam Medical Center, Haifa, Israel

<sup>2</sup>Centre for Rheumatology, Royal College of Physicians, London, UK

### **Background**

Silent myocardial ischemia is supposed to cause myocardial damage in patients with systemic sclerosis (SSc). Second-generation cardiac Troponin T (cTn-T) is a sensitive marker of cardiac damage at the time of myocardial injury. Elevated levels of cTn-T correlated with severity and prognosis in myocardial infarction, congestive heart failure, graft failure in transplanted heart, as well as noncardiac morbidity and mortality in acute stroke, diabetes mellitus, and end-stage renal failure.

### **Aim**

To assess the levels of cTn-T in patients with SSc and its correlation with disease related mortality, disease activity, antibody profile and cardio-vascular morbidity.

### **Methods**

The levels of cTn-T were measured in freeze serum samples of 644 SSc patients attending the clinic before January 1995. In 377 patients the levels of cTn-T were compared to the outcome until March 2000. In subgroup of 204 SSc patients the levels of cTn-T were compared to cardiovascular morbidity.

### **Results**

Elevated levels of cTn-T were found in 18 of 377 patients. Positivity to cTn-T was associated with significantly reduced 5-years survival ( $p < 0.02$ ), SSc related death ( $p < 0.005$ ), short disease duration ( $p < 0.04$ ), diffuse subset of the disease ( $p < 0.002$ ), more active symptomatic disease ( $p < 0.001$ ) with signs of generalized ongoing activity: higher skin score ( $p < 0.002$ ), protein in urine ( $p < 0.001$ ), elevated creatinase levels ( $p < 0.001$ ), elevated sedimentation rate ( $p < 0.002$ ), abnormal cardio-vascular assessment ( $p < 0.001$ ).

### **Conclusion**

Low levels of cTn-T release is associated with an adverse outcome in patients with SSc and can identify patients with ongoing generalized disease activity, poor cardiac reserve and silent myocardial damage.

## **A novel, Persian-Jewish FMF Mutation**

**Yael Shinar, Sophia Menasherow, Irena Kuchuk, Mirit Kolet, Elon Pras, Pnina Langevitz, Avi Livneh.**

Heller Institute and Medicine F, Sheba Medical Center, Israel

**Background** Familial Mediterranean fever (FMF) is an ethnic, recessive episodic inflammatory disease. It is rare and mildly expressed among Persian Jews (PJ). Preliminary data showed no association between the disease and common mutations in the FMF gene (*MEFV*) encoding for pyrin.

**Aim:** To evaluate the role of rare *MEFV* mutations in FMF morbidity in PJ.

**Methods** The tenth exon of *MEFV* was sequenced in registered PJ FMF patients (n=10) and mixed patients (n=10); all *MEFV* exons were sequenced in 10 of these patients. Restriction site analysis was established to screen for a new mutation in individuals seeking genetic diagnosis (n=30), in healthy PJ (n=50) and close ethnic groups. FMF manifestations in patients and mutation carriers were evaluated by interview, physical examination and review of medical files. The secondary structure of pyrin was predicted using the BioInfo.PI structure prediction Meta server.

**Results** One novel mutation, G632S, was identified in a patient of mixed PJ-Ashkenazi family, his two siblings, father and the healthy, PJ grandmother. G632S was also found in two unrelated subjects, seeking molecular diagnosis, of PJ and mixed PJ-Turkish Jewish origin. The G632S carriers that suffered from FMF in these three families (5/8) were males (p=0.02) and distinguished from other FMF patients of PJ origin (n=15) by the sites involved in the attacks (p=0.02) and by sole expression of febrile episodes (p=0.05). Only one G632S carrier was identified among 50 healthy PJ subjects (2%) and none were found in non-Jewish Iranians (of the Baha'i community, n=47). Homologous protein alignments localized the mutation to a conserved region in the B30.2 box of pyrin. Psipred prediction forced a beta strand conformation on a short, wild type alpha helix, adjacent to the mutation site, in the G632S allele. Two known FMF mutations with reduced penetrance, V726A and K695R had the same effect.

**Conclusions** G632S is a newly identified, rare FMF mutation with distribution confined to Persian-Jews and incomplete, male biased penetrance. It may mildly affect pyrin folding. FMF expression in G632S carriers may be limited to recurrent febrile attacks.

## Anti tumor necrosis factor alpha decreases the memory VLA-1+ Th1 subset *in vitro* and *in vivo* while increasing CD4+CD25 high (regulatory) T cells.

Shomron Ben-Horin<sup>1,4</sup>, Itamar Goldstein<sup>5</sup>, Alexander Koltakov<sup>4</sup>, Pnina Langevitz<sup>1,2</sup>, Michael Ehrenfeld<sup>1</sup>, Esther Rosenthal<sup>3</sup>, Leonard Chess<sup>5</sup>, Ilan Bank<sup>1,2,4</sup>

Departments of Medicine<sup>1</sup> Rheumatology<sup>2</sup> and Hematology<sup>3</sup> and Laboratory for Immunoregulation<sup>4</sup>, Chaim Sheba Medical Center, Ramat Gan, Israel, and Medicine<sup>5</sup>, Columbia University, New York, United States, Chaim Sheba Medical Center, Ramat Gan, Israel

**Background:** therapeutic neutralization of tumor necrosis factor (TNF)- $\alpha$  is highly effective in autoimmune arthritis, but the mechanisms are not entirely clear. The  $\alpha 1\beta 1$  integrin, very late activation antigen (VLA)-1, is a collagen receptor induced in a fraction of activated "memory" CD45RO+ Th1 cells localizing to inflamed synovium. Deleting the  $\alpha 1$  integrin gene or blocking its function *in vivo* with monoclonal antibodies (mAb) prevents the development of Th1-cell mediated inflammation, including experimental arthritis.

**Objectives:** Because these data imply an important role of VLA-1+ memory T cells in the pathogenesis of rheumatoid arthritis (RA), it was of interest to study how anti tumor necrosis factor (TNF)- $\alpha$  therapy affects VLA-1+ T cells in RA patients.

**Methods:** Cell-surface membrane molecule expression and cytokine production of T-cells derived from RA patients and controls were assayed.

**Results:** *In vitro* studies showed that neutralizing TNF $\alpha$  with a humanized mAb to TNF $\alpha$  (infliximab, 50ug/ml) during polyclonal activation of VLA-1-depleted (VLA-1-) fresh peripheral blood (PB) lymphocytes (PBL) from RA patients decreases the emergence of VLA-1+ T cells (26.9 $\pm$ 15.7%) compared to control cultures (36.9 $\pm$ 20.3%, n=9, p< 0.011), and secretion of IFN $\gamma$  (60% reduction). In contrast, the percentage of CD4+ T cells expressing a regulatory (CD25 high) phenotype simultaneously increases resulting in a significant increase in the ratio of CD25+/VLA-1+ T cells in the cultures. The clinical relevance of these *in vitro* data was demonstrated by the finding that the percentage of VLA-1+CD3+ T cells in the PB of ant TNF $\alpha$  treated and responsive RA patients was lower (0.26 $\pm$ 0.23%, n=8) than in untreated RA patients (2.5 $\pm$ 3.28%, n=9, p<0.07), non RA controls (1.8 $\pm$ 2.0%, n=8, p<0.04), or patients relapsing after therapy (3.3 $\pm$ 2.3%, n=3, p<0.003).

**Conclusion:** Anti TNF $\alpha$  treatment inhibits "pro arthritogenic" VLA-1+ IFN $\gamma$  producing T cells, while increasing that of regulatory, "anti inflammatory" CD4+CD25+ T cells. These data suggest a novel pathway that may contribute to the therapeutic effect of anti TNF $\alpha$ .

**References:** Goldstein I, Ben -Horin S, Li J, Bank I, Jiang H, Chess L. Expression of the  $\alpha 1\beta 1$  integrin, VLA-1, marks a distinct subset of human CD4+ memory T cells. J. Clin. Invest. 112:1444-1454(2003)

## **Behavior dysfunction upon exposure to anti-ribosomal-P Abs in a mouse model.**

Inna Solodeev<sup>1</sup>, Aviva Katzav<sup>3</sup>, Joab Chapman<sup>2,3</sup>, Miri Blank<sup>1</sup>, Moris Reichlin<sup>4</sup> and Yehuda Shoenfeld<sup>1</sup>.

<sup>1</sup>Department of Medicine B and Research Unit of Autoimmune Diseases,

<sup>2</sup>Department of Neurology, Sheba Medical Center, Tel Hashomer, Israel;

<sup>3</sup>Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Israel, <sup>4</sup>Oklahoma Medical Research Foundation,

Oklahoma City, Oklahoma, USA.

**Background:** Elevated titers of circulating anti-ribosomal-phosphoproteins (anti-ribosomal-P) Abs are associated with CNS involvement in systemic lupus erythematosus (SLE). There is a controversy about the association of anti-ribosomal-P Abs with SLE psychiatric manifestations.

**Aim:** To address the effect of anti-ribosomal-P Abs on the behavior in animal model

**Methods:** C3H female mice were subjected intra-cerebro-ventricularly with anti-ribosomal-P Abs or IgG from healthy donor. Neurological functions of mice were tested in a **passive avoidance**, **plus-maze** and **staircase tests**. In order to examine changes in motor function or physical condition of the mice the **Rotarod test** and **Grip strength test** were performed.

**Results:** In the **passive avoidance** test, immobility time of anti-ribosomal-P Abs injected mice is 3 times higher than that of the control group ( $p < 0.001$ ), that could be interpreted as an increase in depression-like behavior. In **plus-maze** test, anti-ribosomal-P Abs subjected mice showed significant decreased activity in comparison to control IgG injected mice. The results emphasize the passiveness and the mental disorder of the Anti P ribosomal Abs injected mice. Behavioral functions of the mice were tested in a **staircase** test. There was a non-significant reduction in the locomotor (stair-climbing) exploratory activities and the exploratory behavior and anxiety (rearing) found in the Anti-ribosomal-P Abs injected mice in comparison to the control group. **Rotarod test** and **Grip strength test** demonstrated no difference in physical conditions of anti-ribosomal-P Abs injected mice and the mice of the control group.

**Conclusion:** Based on these experiments we can conclude that anti-ribosomal-P Abs injection can cause psychological behavior changes in the mice.

## **Maternal and Fetal Outcome of Lupus Pregnancy:**

### **A Prospective Study of 29 Pregnancies.**

Yair Molad,<sup>1</sup> Tamar Borkowski,<sup>2</sup> Assaf Monselise,<sup>3</sup> Avi Ben-Haroush,<sup>2</sup> Jaqueline Sulkes,<sup>4</sup> Moshe Hod,<sup>2</sup> Dov Feldberg,<sup>2</sup> Jacob Bar<sup>2</sup>.

<sup>1</sup>Lupus Clinic, Rheumatology Unit, <sup>2</sup>Perinatal Division, Department of Obstetrics and Gynecology, <sup>3</sup>Department of Internal Medicine B, and <sup>3</sup>Epidemiology Unit, Rabin Medical Center, Beilinson Campus, Petah Tiqva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

**Background:** Pregnancy and the postpartum period pose a significant risk for women with systemic lupus erythematosus (SLE).

**Aim:** To analyze pre-gestational and pregnancy risk factors for adverse fetal and maternal outcome in lupus pregnancy.

**Methods:** Twenty women with systemic lupus erythematosus (SLE) (29 pregnancies) were prospectively evaluated. Clinical and laboratory variables were obtained at each encounter within 3 month period prior to pregnancy, every month during pregnancy and at the first encounter within 3-month period post-partum, and related to fetal and maternal outcome measurements.

**Results:** Mean patient age was  $29.5 \pm 4.7$  years, and mean disease duration,  $6.3 \pm 6.5$  years. Twenty-two pregnancies (75.9%) ended in live births; preterm delivery occurred in 17.4%, intrauterine growth restriction in 50%, preeclampsia in 3.7%, and gestational hypertension in 8%. Six pregnancies (20.7%) ended in spontaneous abortions. Adverse live-birth outcome was significantly associated with low pregestational serum albumin level, elevated gestational anti-dsDNA antibody, and diabetes mellitus. Spontaneous abortion was directly associated with low levels of pregestational serum albumin, positive anticardiolipin IgA, anti- $\beta_2$ -glycoprotein I IgM, and anti-La antibodies, and inversely associated with number of patient's children. Postgestational lupus flare-up was noted in 6 pregnancies. Risk factors included high pregestational SLE Disease Activity Index, lower serum albumin, elevated serum antibody to dsDNA, proteinuria, and use of prednisone and hydroxychloroquine.

**Conclusions:** This study suggests pregnancy is safe in most lupus patients who conceive while the disease is inactive. Active SLE prior to pregnancy is associated with a less favorable maternal and fetal outcome. Antibodies to cardiolipin and  $\beta_2$ -GPI may increase the risk of fetal loss and adverse outcome. Postpartum flare-ups of SLE are common, although mostly mild. All pregnant patients with lupus must be carefully monitored throughout pregnancy by expert rheumatologists and obstetricians.

## Recurrent transient synovitis (TS) of the hip in childhood. A follow-up study on 39 patients.

Yonathan Butbul-Aviel, Judith Barash, Shai Padeh, Masza Mukamel, Natalia Gorodnitski, Riva Brik, Pinhas Hashkes, Yosef Uziel  
Pediatric Rheumatology Study Group of Israel

**Background:** Transient synovitis (TS) of the hip is a common condition in children between the ages of 1.5-12 years. In most cases TS resolves completely. However some believe TS to be associated with Perthes disease, or other late radiological changes, particularly coxa magna, usually 3-12 months after the first episode. Studies have reported a recurrence rate of TS between 0-17.4%. No predictors of recurrence were found and there are conflicting reports on the outcome of these patients.

**Aim:** To describe the outcome of children with recurrent TS.

**Methods:** We did a retrospective chart review of children with at least 2 separate episodes of TS, diagnosed and registered in our national pediatric rheumatology database between 1986-2003. We examined the work-up and final diagnosis of these patients. A follow-up telephone survey asking for disability and pain scores was done in early 2004.

**Results:** We studied 39 children, 26 boys and 13 girls, from 6 pediatric rheumatology centers. The mean age at the initial episode was  $6 \pm 2.6$  years. There were a total of 107 episodes (mean  $2.9 \pm 1.6$ , range 2 - 10). All children except one had a plain radiographic examination of the hips at presentation or during follow up, (mean  $1.9 \pm 1.7$  years); all were normal. Hip ultrasound was done in 30 children during 53 episodes, revealing joint effusion in 51 episodes. Technetium bone scans were performed on 17 patients (2 patients had 2 studies each); 11 scans were reported as normal, 7 showed a mild increase in hip uptake, consistent with TS, and one patient had a slightly decreased uptake in the femur head, suggestive of sub-clinical Perthes' disease.

All patients were followed by telephone interviewed at  $4.2 \pm 2.5$  years after the first episode. None of them developed clinical Perthes disease or other orthopedic conditions. In 3 (8%) patients TS preceded chronic disease; One patient was diagnosed with familial Mediterranean fever, and 2 patients developed seronegative enthesitis arthritis, 0.5, 2, and 6 years since presentation.

26/36 patients were asymptomatic at follow-up, and 10 reported hip pain after intensive physical effort. These children had more TS episodes than the asymptomatic group ( $4.2 \pm 2.4$  vs  $2.4 \pm 0.7$   $P < 0.005$ ). Five patients continued to have rare recurrent limp episodes.

**Conclusion:** Children with recurrent TS usually have a benign course. However in some patients recurrent TS may be the presenting feature of chronic inflammatory conditions. No progression to chronic orthopedic conditions was found. Larger studies including orthopedic units are suggested.

deep and local musculoskeletal infections.

## Occurrence of antithyroid antibodies in children with juvenile idiopathic arthritis compared to a healthy pediatric population

<sup>1</sup>Liora Harel, <sup>1</sup>Dario Prais, <sup>2</sup>Yosef Uziel, <sup>1</sup>Masha. Mukamel, <sup>3</sup>Pinchas Hashkes, <sup>4</sup>Gideon Harel, <sup>1</sup>Jacob Amir, <sup>5</sup>Yehudit Monselise, <sup>6</sup>Joseph Press  
<sup>1</sup>Schneider Children's Medical Center of Israel; <sup>2</sup>Sapir Medical Center; <sup>3</sup>Ziv Medical Center; <sup>4</sup>Rabin Medical Center, Golda Campus; <sup>5</sup>Rabin Medical Center, Beilinson Campus; <sup>6</sup>Soroka Medical Center, **Israel**

**Background:** The prevalence of acquired hypothyroidism in healthy young populations is about 0.1%. Approximately 2% of hypothyroid patients suffer from juvenile idiopathic arthritis (JIA) concomitantly, raising the question as to whether it might be of value to routinely screen for antithyroid antibodies (ATA) in JIA, in order to detect the disease before clinical decompensation. Reports of coexisting autoimmune rheumatic diseases and thyroid disease are found in adults and also in addition to children with systemic lupus erythematosus. However, in JIA this association is unclear and the prevalence of ATA among patients with JIA compared to healthy controls has as yet not been established.

**Aim:** To estimate the occurrence of ATA in children with JIA and compare it to a matched healthy pediatric population.

**Methods:** Children diagnosed with JIA from 5 pediatric rheumatology centers in Israel were evaluated for the occurrence of ATA including antithyroglobulin (TGAb) and antithyroid peroxidase (TPOAb) using quantitative immunometric enzyme immunoassay (ELISA). The occurrence of ATA was concurrently assessed in an age and gender-matched control group of healthy children without known thyroid or autoimmune diseases. The data was analysed using Analysis of Variance (ANOVA) for continuous variables and Pearson's Chi-Square test for discrete variables or Fisher's Exact test, as appropriate

**Results:** The study group included 66 patients with JIA (50 girls, 16 boys), mean age  $11.7 \pm 4.4$  years (range from 2 to 23). The control group included 89 children (71 girls, 18 boys), mean age  $10.8 \pm 4.2$  years (range 2-18). Mean age at onset was  $7.3 \pm 3.6$  years (range 1-15). The subsets of JIA included polyarthritis 36%, oligoarthritis 39%, systemic arthritis 20%, enthesitis-related arthritis 3%, and psoriatic arthritis 1.5%. Rheumatoid factor was found in 5 of 58 children (8.6%); anti-nuclear antibodies was found in 20 of 62 (32.3%); anti ds DNA antibodies were found in 1 of 47 (2.1%). We have no data regarding the controls. Among the JIA group, TGAb were found in 7 of 62 patients (11.3%) compared with 2 of 89 (2.2%) in the control group ( $p=0.03$ ). TPOAb were found in 5 of 65 (7.9%) of the JIA group compared with 1 of 89 (1.1%) of the control group ( $p=0.08$ ). There was no difference in the incidence of ATA among subsets of JIA. TSH was above normal range (0.4-4mIU/L) in 8 (12%) of the study group and in 3 (3.4%) of the controls ( $p=0.055$ ). TSH levels were higher in the study group (mean  $2.6 \pm 2.3$ ) compared to controls (**mean**  $1.9 \pm 1.0$ ,  $p=0.01$ ). Goiter was found in 3 of 58 children (5.2%) in the study group compared to none in the controls ( $p=0.06$ ).

**Conclusions:** There is an increased incidence of ATA in JIA patients compared to controls, therefore, screening for ATA and thyroid function is recommended in all children with JIA.

## **The diagnostic value of anti-neutrophil cytoplasmic antibody (ANCA) testing in a general hospital setting**

Gabriel S. Breuer, Michal Mates, Gideon Neshet

Shaare-Zedek Medical Center, Jerusalem

**Purpose:** Evaluate the predictive value of ANCA testing for diagnosing Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS), in a general hospital setting.

**Methods:** Results of all ANCA testing performed at Shaare-Zedek Medical Center between 1994-2003 were reviewed. ANCA testing during this period was performed on all requested cases, without applying pre-defined guidelines to increase pre-test probability. Patients' charts were reviewed to sort for relevant clinical data. In addition, the Medical Center's electronic archive of discharge diagnoses was screened looking for possible additional cases of WG, MPA or CSS.

**Results:** 1322 ANCA tests were performed during that period. After excluding children and repetitive testing, tests of 802 adult patients were available. ANCA was positive in 34 cases (4%). P-ANCA was present in 16 cases, C-ANCA in 9 cases and atypical ANCA in 9 cases. Systemic small-vessel vasculitis was diagnosed in 9 of these patients: 5 had WG (all had C-ANCA) and 4 had MPA (all had P-ANCA). 2 more cases with P-ANCA had acute renal failure with pauci-immune glomerulonephritis and another patient had non-specific skin vasculitis, but all 3 patients did not develop involvement of other organ systems, and were not included as WG or MPA in the final evaluation. There were no cases of CSS. No additional cases of WG, MPA or CSS were found by the computerized archive search.

The table shows sensitivity, specificity, positive and negative predictive values (PPV, NPV) for diagnosing WG (by C-ANCA) and MPA (by P-ANCA).

	P-ANCA (for diagnosing MPA)	C-ANCA (for diagnosing WG)
Sensitivity	100%	100%
Specificity	99%	99%
PPV	36%	55%
NPV	100%	100%

**Conclusion:** The NPV of C-ANCA and P-ANCA testing is very high for diagnosing WG and MPA, respectively, even without applying pre-defined guidelines to increase pre-test probability. Applying such guidelines may increase the PPV of ANCA testing for both conditions.

## **Clinical features and etiology of septic arthritis in northern Israel – the prominence of unusual pathogens**

**Authors:** Lih Eder<sup>1</sup>, Devy Zisman<sup>1</sup>, Michael Rozenbaum<sup>2</sup>, Itzhak Rosner<sup>2</sup>

<sup>1</sup> Internal Medicine A, Carmel Medical Center, Haifa, Israel

<sup>2</sup> Department of Rheumatology, Bnai Zion Medical Center, Haifa, Israel

**Aims:** To assess the clinical features and determine the pathogens responsible for septic arthritis in patients admitted to two community hospitals in the Haifa district over a 17 year period.

**Patients and methods:** Retrospective study of the hospital records of patients admitted to "Carmel – Medical Center" and "Bnai-Zion – Medical Center" in Haifa, between 1987 and 2003 with septic arthritis.

**Results** – Of 142 cases identified by discharge summary diagnostic codes only 89 patients met criteria for the case definition of septic arthritis and form the basis for this report. Their mean age was 44.5 years; 25 patients (28.1%) were Arabs; 11 patients were recent immigrants (12.9%), most of them from the former Soviet Union (8 patients) and the rest from Ethiopia. Co-morbidities were recorded in 43 patients: 13 patients (14.6%) with diabetes mellitus while chronic renal failure was diagnosed in 7 patients (7.8%). Past infection with tuberculosis was known in all 8 patients with tuberculosis arthritis. Primary joint disease was reported in only 15 (16.8%) of the cases, osteoarthritis being most prevalent, with 9 patients (10.1%) affected. Knees (42.9%) and hips (24.2%) were joints most commonly involved. Of the infected joints 9 (10.1%) were prosthetic. Staphylococcus aureus was the most common pathogen isolated, making up 39% of all positive cultures. Gram negative bacteria were the second most common group identified, in 14%, with Mycobacterium tuberculosis in third place, with 10%. Another pathogen, unusual in developed countries, was Brucella species – identified in 7.5% of the cases. In four patients more than one bacterial species were cultured. Two thirds of the patients underwent surgical joint drainage while the rest were treated solely by antibiotics. Most frequent complications during hospital stays included: acute renal failure/ dialysis treatment (5.6%), need for ICU care (5.6%), mechanical ventilation (3.3%), and operative wound infection (3.3%). Two patients died of sepsis.

**Conclusions:** Our data, with only 2/3 diagnosed cases meeting case definition, give further impetus to the vital importance of obtaining adequate synovial fluid for analysis and culture before administration of antibiotics. Blood cultures contributed much to the diagnosis in cases of sterile synovial cultures. In our survey population, unlike most developed and technologically advanced countries to which we compare ourselves, tuberculosis arthritis is a growing problem, mainly due to recent immigration waves, and brucella is an endemic and common pathogen. It is important to keep a high level of suspicion for these latter two bacteria, as they require special and unique care.

## **Vaccination against influenza in Rheumatoid Arthritis patients: The effect of disease modifying drugs, including TNF $\alpha$ blockers.**

Fomin I<sup>1</sup>, Shalev Y<sup>2</sup>, Levy V<sup>2</sup>, Mendelson E<sup>2</sup>, Paran D<sup>3</sup>, Litinsky I<sup>3</sup>, Wigler I<sup>3</sup>, Levartovsky D<sup>3</sup>, Caspi D<sup>3</sup>, Elkayam O<sup>3</sup>.

<sup>1</sup>From the Department of Internal Medicine "E" and <sup>3</sup> the Department of Rheumatology, Tel Aviv "Sourasky" Medical Center and <sup>2</sup> The Central Laboratory of Virology, Sheba Medical Center and the "Sackler" School of Medicine, Tel Aviv University, Tel Aviv

**Background:** The safety and immunogenicity of vaccination in patients with rheumatic diseases is controversial.

**Aim:** To assess the effect of disease modifying drugs (DMARD's), including TNF $\alpha$  blockers on the efficacy and safety of influenza virus vaccine in patients with rheumatoid arthritis (RA).

**Methods:** The study population comprised 82 RA patients and 30 age/gender matched healthy controls . Split-virion inactivated vaccine containing 15 mcg hemagglutinin (HA)/dose of each of B/Hong Kong/330 (hk), A/Panama/2007/99 (pan) and A/New Caledonian /20/90 (nc) was used. Disease activity was assessed by No of tender and swollen joints, morning stiffness, evaluation of pain by , Health Assessment Questionnaire and ESR, on the day of vaccination and 6 weeks after. Hemagglutination inhibition (HI) antibodies were tested by a standard WHO procedure. Response was defined as  $\geq$  4-fold rise in HI antibodies 6 weeks after vaccination, or seroconversion in patients with a non-protective baseline level of antibodies ( $<1/40$ ). Geometric mean titers (GMT) were calculated to assess the immunity of the whole group.

**Results:** Six weeks after vaccination, a significant increase in GMT for each antigen was observed in both groups, although the increase was significantly higher in the healthy group for hk ( $p=0.004$ ). The percentage of responders was lower in RA patients in comparison with healthy controls achieving statistical significance for hk : 67%(RA) vs. 87%(healthy), ( $p=0.05$ ) but not for: pan (53% vs. 54%) or nc (53% vs. 68%). Response to  $\geq 1$  antigen was noted in 70% of RA patients vs. 82% of the controls. The percentage of responders was not affected by prednisone or any DMARD, including MTX, Infliximab and Etanercept. Parameters of disease activity remained unchanged.

**Conclusions:** Influenza virus vaccine generated a good humoral response in RA patients, although lower than in healthy controls. The response was not affected by the use of DMARD's. Disease activity was not influenced by vaccination.

## Pulmonary function tests in rheumatoid arthritis, a 5-year follow-up study.

L. Sølling Avnon<sup>1</sup>, F. Manzur<sup>2</sup>, A. Bolotin<sup>3</sup>, D. Heimer<sup>1</sup>, D. Buskila<sup>2</sup>, S Sukenik<sup>2</sup>, M. Abu- Shakra<sup>2</sup>.

<sup>1</sup>Pulmonary clinic, <sup>2</sup>Rheumatology clinic and Epidemiology Department, Soroka University Medical Center.

**Background:** Abnormal pulmonary function testing (PFT) has been observed commonly among patients with rheumatoid arthritis (RA).

**Aim:** the aim of this study was to determine the 5-yrs change in PFT of patients with RA.

**Methods:** PFT was performed on consecutive RA patients and were repeated 5 years later. All patients were assessed according to a standard protocol that included articular and extraarticular features of RA. Linear and multivariate regression analyses were performed to identify associated with change in PFT.

**Results:** Initially in 1998-99, 100 patients agreed to undergo testing and the surviving 80 patients were offered to repeat the study in 2003/04. Thirty-eight patients (8 men and 30 women) agreed to participate and constitute the study group. Their mean age was 58yrs (SD=14) and their mean RA duration was 16.7 yrs (SD=9.7). Drugs given to the patients during their disease included: systemic glucocorticoids (63%) 5; gold: (26.3%); anti-malaria agents (23.7%); imuran: (13.1%); methotrexate:(71%) and salozoprin: (18.4%). Five patients were current smoking, five ex-smoker and 27 were non-smokers. Thirty patients lost height over five years in the range 1-5 cm.

The pulmonary function tests are shown as percentage of predicted were:

	1998/99	2003/04
Age	53.2 (13.6)	57.3 (13.9)
Height cm	159.9 (8)	158.1 (8.3)
Weight kg	67.3 (11.2)	69.1 (11.3)
FVC % predicted	77.1 (15.3)	76.7 ( 15.2)
FEV1 % predicted	83.1 (19.1)	80.5 ( 19.9)
FEV1/ FVC	88.1 (9.3)	84.9 ( 10.6)
FEF <sub>25-75%</sub> % predicted	98.6 (36.2)	86.7 (40)
SCV % predicted	80.9 (14.4)	79.2 (14.3)
IC % predicted	89.1 (19.5)	86.3 (20.9)
FRC % predicted	87.9 (21.5)	94.9 (26.8)
RV % predicted	102.7 (31.7)	112.1 (38.2)
TLC % predicted	88.5 (16.1)	91.3 (15.8)
RV / TLC	39.8 (7.7)	44.6 (12.6)
DL <sub>co</sub> % predicted	86.1 (28.9)	94.2 (23.4)
DL/VA % predicted	97.1 (30.9)	133.4 (25.5)
Saturation %	97.1 (0.8)	96.8 (0.7)

The PFTs are essentially normal and show no changes over the study period of five years.

An obstructive ventilatory defect, defined as a FEV1/ FVC less than 70%, was seen in 2 patients initially and in 3 at 5 years. Small airways disease, defined as FEF<sub>25-75%</sub> less than 70% predicted FEV1/FVC in the normal range, was observed in 8 patients initially and in 11 patients at follow-up. A restrictive ventilatory defect, defined as TLC less than 70% predicted, was seen in 4 patients initially and in 2 patients at five year follow-up. A reduced DL/ VA (less than 70%) was seen in 3 patients initially and in no patient at five year follow up. No link was found between impaired PFT and clinical features or medications given to the patients

**Summary and conclusion:** Although, RA patients have essentially normal mean PFTs and there is no clinically significant mean change over 5 yrs, obstructive and

restrictive patterns are not uncommon. In addition, the change in FEV1 ~ 231 cc over 5 years is equivalent to 46.2 cc/ year and is more than the expected 15- 30 cc/year decline seen in healthy non-smoking adults and more equivalent to the decline seen in smokers (35-60 cc/year).

## ANTI CCP as a predictor to response to anti TNF therapy in rheumatoid arthritis patients

Y. Braun-Moscovici, A. Balbir-Gurman, O. Zinder, D. Schapira, D. Markovits, A. Rozin, M. Ehrenburg, L. Dain, E. Hoffer and A.M. Nahir  
B. Shine Department of Rheumatology and Israel Poison Information Center  
Rambam Medical Center, Haifa, Israel

The treatment of rheumatoid arthritis (RA) has changed dramatically over the past years with the introduction of anti tumor necrosis factor (TNF) agents. Unfortunately, a subset of patients have only a partial response or not at all. No measurements were found to predict the efficacy of this therapy.

Anti-citrullinated protein antibodies (Anti-CCP) are highly specific and sensitive for rheumatoid arthritis and their titer correlate with erosive disease.

**Objective:** To investigate the correlation between the efficacy of infliximab therapy and the titer of anti CCP.

**Methods:** Fifteen consecutive seropositive RA patients were treated with infusion of 3mg/kg Infliximab on weeks 0, 2, 6, and 14. Clinical assessment and blood withdrawal were made before each treatment, i.e. at the minimal concentration of the drug. Disease activity was assessed by DAS28 score and by IL-6 level. Anti CCP titer was measured by a commercial enzyme linked immunosorbent assay at week 0 and week 14.

**Results:** At baseline, all the patients were positive for antiCCP antibodies. In most of the patients there was a significant correlation between the clinical response to therapy and the anti CCP titer. The results were especially noteworthy in those patients who showed a sustained and significant decrease in IL-6 levels through the entire period.

**Conclusion:** Anti CCP titer and IL-6 levels might be early predictors of the efficacy of anti-TNF therapy in rheumatoid arthritis patients.

## Thickened Carotid Artery Intima-Media in Rheumatoid Arthritis Patients is Associated With Elevated Anti-Cardiolipin Antibodies

Yaniv Sherer, Roberto Gerli, Rosita Allegrucci, Andrea Giordano, Boris Gliburd, Gaetano Vaudo, Simona Marchesi, Giuseppe Schillaci, Elmo Mannarino, Yehuda Shoenfeld

Department of Medicine B and Center of Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel-Aviv University, Israel. Section of Internal Medicine & Oncological Sciences, Center for the Study of Rheumatic Diseases, Section of Internal Medicine, Angiology & Atherosclerosis Diseases, Department of Clinical & Experimental Medicine, University of Perugia, Perugia, Italy. Incumbent of the Laura Schwartz Kipp Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel

**Background:** Anti-cardiolipin autoantibody (aCL) which is the hallmark of the antiphospholipid syndrome (APS), is associated with atherosclerosis in animal studies<sup>1</sup>, and it may also be associated with atherosclerosis among patients with APS, as well as in the general population<sup>2</sup>. Rheumatoid arthritis (RA) is characterized by excess cardiovascular morbidity and mortality.

**Objectives:** To determine possible association between presence of aCL and sub-clinical atherosclerosis among RA patients.

**Methods:** Carotid artery intima-media thickness (IMT) was measured in 82 RA patients. The IMT was evaluated on both carotid arteries in the common carotid (CC), bifurcation (BI), and internal carotid (IC) arteries. Three measurements in each site were performed on both carotid arteries allowing calculation of mean IMT for each site and for the carotid artery (C) in general. IMT > 0.9 mm was considered thickened carotid IMT, and IMT > 1.3 mm was considered presence of atherosclerotic plaque. IgG aCL was detected using standard ELISA, and the cut-off level was 15 GPL.

**Results:** Elevated levels of IgG aCL were detected in 17 of 82 (21%) RA patients. The extent of mean CC, BI, IC and C-IMT among these 17 patients was higher than the remaining 65 RA patients who did not have elevated aCL, but this difference was not statistically significant. However, among these 17 patients with aCL, those 7 having the highest levels (> 40 GPL, medium to high levels), had even higher carotid IMT levels. Mean BI-IMT was 1.23 mm in the group of high aCL compared with 1.02 mm in the group negative for aCL (p=0.03). Mean carotid IMT was similarly higher in the high aCL group (1.05 mm versus 0.87 mm, respectively; p=0.02). 6 of 7 patients in the high aCL group had thickened (>0.9 mm) mean carotid IMT.

**Conclusions:** Medium to high levels of IgG aCL are associated with thickened carotid artery bifurcation and mean IMT among RA patients.

1. George J, Afek A, Gliburd B, Levy Y, Blank M, Kopolovic J, Harats D, Shoenfeld Y. Atherosclerosis in LDL-receptor knockout mice is accelerated by immunization with anticardiolipin antibodies. *Lupus* 1997;6:723-9.
2. Sherer Y, Shemesh J, Tenenbaum A, Praprotnik S, Harats D, Fisman EZ, Blank M, Motro M, Shoenfeld Y. Coronary calcium and anti-cardiolipin antibody are elevated in patients with typical chest pain. *Am J Cardiol* 2000;86:1306-11.