Selected publications from peruvian rheumatologists

Graciela S. Alarcón, MD, MPH
Luis R. Espinoza, MD

Introduction
The contribution to medicine of the rheumatologist whose bios have been described in the previous chapter of this book span different aspects of the practice of medicine in general and of rheumatology in particular; some of these rheumatologists have played important roles in the development of teaching programs at their respective medical schools while others have done it at the medical school level. Still others are recognized for their research efforts which can be attested in refereed publications. In this section, we are presenting a selection of the best articles that these Peruvian rheumatologists have published. This compilation has been done utilizing PubMed the electronic search engine of the National Library of Medicine in the US; although we have tried to be as objective as possible in the selection of these articles some subjectivity may have involuntarily permeated. Perhaps we have failed to select the papers which are closer to the authors' hearts; if that is the case we ask them for their forgiveness.

A very short introductory comment precedes each of the selected articles (only one representative abstract from the selected articles is being reproduced for each of these authors).
EDUARDO ACEVEDO-VÁSQUEZ

Dr. Acevedo's group was the first one to bring attention to the fact that the tuberculin skin test (PPD) is not appropriate for the screening of latent tuberculosis infection in patients with rheumatoid arthritis. This information is of great relevance in view of the fact that this test is being increasingly used for this purpose prior to initiation of biologic therapy in these patients.


Division of Rheumatology, Hospital Nacional Guillermo Almenara Irigoyen, EsSalud, Lima; Universidad Mayor Nacional de San Marcos, Lima, Peru.

BACKGROUND: The purified protein derivative (PPD) skin test is the only widely used method which detects latent tuberculosis infection (LTBI) and is dependent on a normal T cell function. In rheumatoid arthritis (RA) the T cell function is altered, which may result in an inability to develop an adequate PPD reaction. OBJECTIVES: To evaluate the response to PPD in patients with RA and to compare it with that of control subjects. METHODS: 112 patients with RA and 96 healthy controls were studied. PPD 5 U was applied using the Mantoux method, and skin reaction was measured at 72 hours. The reaction was considered negative for PPD <5 mm. RESULTS: There were no significant differences in age, sex, history of bacille Calmette-Guerin vaccination, or tuberculosis contact between the two groups. The median size of the PPD induration in the patients with RA was significantly less than that in the control group (4.5 vs 11.5 mm, p<0.01). 79 (70.6%) patients with RA compared with 25 (26%) of the control group had a negative reaction to PPD (p<0.01), a response not influenced by disease activity or duration of disease in the patients with RA. CONCLUSION: A PPD skin test is not an appropriate test for recognising LTBI in patients with RA in our population.

PMID: 16100342 [PubMed - indexed for MEDLINE]
GRACIELA S. ALARCÓN

This study is one of the most recent publications from the LUMINA cohort, a long-term study of lupus outcome sponsored by the National Institute of Health (USA) in Hispanic, African-American, and Caucasian populations afflicted with this disease. It clearly shows that socioeconomic-demographic (age, ethnicity, health insurance) and behavioral/psychological (abnormal illness-related behaviors among others) variables are important mediators of high levels of disease activity in SLE over its course, in contrast with what occurs early in the disease in which genetic factors are important. This cohort has contributed to our understanding of the role played by non-genetic factors in the course and outcome of SLE among minority population groups in the US.


The University of Alabama at Birmingham, United States.

Purpose: To ascertain the predictive factors of high levels of disease activity in systemic lupus erythematosus (SLE). Patients and METHODS: SLE patients (ACR criteria), inverted exclamation mark*16 years of age, inverted exclamation mark*5 years of disease, of Hispanic (Texas and Puerto Rico), African American and Caucasian ethnicity were included. The outcome was high disease activity at any one time [SLAM-R > 10]. A basic multivariable model (age, gender, ethnicity, health insurance, social support, abnormal illness-related behaviors, helplessness and prior disease activity) was first examined. Additional models were built by including other variables. RESULTS: Five hundred and forty four patients (100 Hispanics - Texas, 94 Hispanics - Puerto Rico, 199 African Americans, 161 Caucasians) and 2366 visits were analyzed; 47% of the patients and 29% of the visits met the high disease activity definition [more common among African Americans (72.0 %) and Hispanics - Texas (71.3 %) than Caucasians (43.9 %) and Hispanics - Puerto Rico (31.9 %)]. Variables found to predict high levels of disease activity were Hispanic - Texas and African American ethnicities, lack of health insurance, helplessness, abnormal illness-related behaviors and poor social support; age was negatively associated with it. African admixture and anti-dsDNA antibodies also predicted high levels of disease activity as did prior disease activity. None of the HLA variables were retained in the models. CONCLUSIONS: Socioeconomic-demographic (age, ethnicity, health insurance), behavioral/psychological variables are important mediators of high levels of disease activity in SLE over its course. Interventions aimed at modifiable factors may substantially improve SLE outcomes.

PMID: 16439440 [PubMed - as supplied by publisher]


JUAN ANGULO-SOLIMANO
This collaborative work between Peruvian and Swedish investigators in which Dr. Angulo played a leadership role, is the first one demonstrating that a polymorphism of tumor necrosis factor is associated with rheumatoid arthritis in a non-white population.


OBJECTIVE: To study the association between rheumatoid arthritis (RA) and HLA and tumour necrosis factor (TNF) polymorphism in Peruvian mestizo patients in comparison with ethnically similar controls. METHODS: Seventy nine patients with RA and 65 ethnically matched healthy controls were genotyped for HLA-DRB1, HLA-DQA1, HLA-DQB1, and TNFalpha and TNFbeta alleles using PCR amplification. Clinical severity was assessed as mild, moderate, or severe in 35 of the patients. RESULTS: TNFalpha6 showed the strongest association with disease susceptibility. The TNFalpha6 allele was more common in patients than in controls (p<0.0076) and the proportion of patients with at least one copy of this allele was greater (p<0.015, relative risk 2.35). Among the HLA-DRB1* alleles with the shared epitope sequence, only the DRB1*1402 allele was significantly increased in patients compared with controls (p<0.0311), as was the proportion of patients with at least one copy of this allele (p<0.0232, relative risk 2.74). In contrast, the overall frequency of alleles with the shared epitope was not different in patients and controls. The haplotype HLA-DRB1*1402-DQB1*0301-DQA1*0401 was significantly more common in patients. TNFalpha6 was more common in patients whether or not they had this haplotype. None of the 11 patients lacking the TNFalpha6 allele had severe disease. CONCLUSIONS: This study shows for the first time that TNF gene polymorphism is associated with susceptibility to RA in a non-white population. TNFalpha6 and HLA-DRB1*1402 independently conferred significantly increased risk in Peruvian mestizo patients.

PMID: 11454644 [PubMed - indexed for MEDLINE]

TOMÁS BOCANEGRA
In this paper which was published when Dr. Bocanegra was a trainee of Dr. Luis Espinoza at the University of South Florida in Tampa, the mechanism by which reactive arthritis may ensue in the context of infestation with Taenia saginata and Strongyloides stercoralis is reported.

**Bocanegra TS, Espinoza LR, Bridgeford PH, Vasey FB, Germain BF.**
Arthritis developed in two patients during the course of parasite infestation with Strongyloides stercoralis and Taenia saginata, respectively. The joint involvement was polyarticular and symmetrical but seronegative and nonerosive radiologically. We found evidence of abnormal humoral immunity to the parasites, immune complexes in serum and synovial fluid, and immunoglobulin deposits in the synovia. Nonsteroidal anti-inflammatory agents proved ineffective but specific antiparasitic treatment resulted in resolution of the symptoms and immunologic abnormalities. Our findings provide further documentation of the interaction between the body's immune system and parasites and suggest that arthritis induced by parasitic infestation may be mediated by immune complex formation in susceptible hosts.

PMID: 7469214 [PubMed - indexed for MEDLINE]


OSWALDO CASTAÑEDA-JIMENEZ
This is one of the first studies to critically evaluate the American College of Rheumatology preliminary criteria for remission in rheumatoid arthritis. The criteria were found to be highly specific in both patient groups but the sensitivity of the criteria was lower in the American than in the Peruvian patients. This is an important study in view of the high remission rates encountered nowadays with the use of biologic compounds.


Department of Medicine, University of Alabama, Birmingham 35294.

OBJECTIVE. To determine the long-term safety and efficacy of 10-deazaaminopterin (10-DAM) in the treatment of rheumatoid arthritis (RA). METHODS. A 1-year continuation of an initial 15-week randomized, double-blind clinical trial of 10-DAM and methotrexate (MTX). RESULTS. 10-DAM (n = 10) and MTX (n = 8) had comparable safety and efficacy profiles. One 10-DAM-treated and 2 MTX-treated patients experienced transient side effects; 1 MTX-treated patient experienced recurrent nausea and discontinued MTX. CONCLUSION. 10-DAM appears to be as beneficial and This is one of the first studies to critically evaluate the American College of Rheumatology preliminary criteria for remission in rheumatoid arthritis. The criteria were found to be highly specific in both patient groups but the sensitivity of the criteria was lower in the American than in the Peruvian patients. This is an important study in view of the high remission rates encountered nowadays with the use of biologic compounds as safe as MTX for the treatment of RA.

PMID: 1445448 [PubMed - indexed for MEDLINE]


CECILIA P. CHUNG-NAKANDAKARI
Since joining Vanderbilt University, Dr. Chung has studied the risk factors associated with the development of accelerated atherosclerosis in patients with lupus and rheumatoid arthritis (RA). In this article, Dr. Chung and her collaborators studied 141 patients with RA (70 with early disease and 71 with established disease) and 86 normal subjects for the presence of coronary calcifications as a measure of atherosclerosis (more frequent and severe in patients than in controls). Risk factors for this outcome included smoking, disease duration and elevated sedimentation rate suggesting that in patients with RA (and probably other chronic inflammatory disorders) traditional and disease-related risk factors need to be taken into consideration to improve the outcome of patients with RA.

Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, Pincus T, Avalos I, Stein CM. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6602, USA.

OBJECTIVE: To compare the prevalence and severity of coronary-artery atherosclerosis in patients with early and established rheumatoid arthritis (RA) and controls. METHODS: Electron-beam computed tomography was used to measure the extent of coronary-artery calcification in 227 subjects, of whom 70 had early RA, 71 had established RA, and 86 were controls. Coronary-artery calcification calculated according to the Agatston calcium score was compared in patients and controls, and its relationship to clinical characteristics was examined. Adjusted odds ratios (ORs) were obtained with the use of proportional odds logistic regression models to determine independent associations of early and established RA and coronary-artery calcification. RESULTS: Calcium scores were higher in patients with established RA (median 40.2, interquartile range [IQR] 0-358.8) compared with those with early disease (median 0, IQR 0-42.6) and controls (median 0, IQR 0-19.2) (P = 0.001). Coronary-artery calcification occurred more frequently in patients with established RA (60.6%) than in patients with early RA (42.9%) and control subjects (38.4%) (P = 0.016) The OR for the likelihood of having more severe coronary-artery calcification (defined as an Agatston score >109) in patients with established disease was 3.42 (P = 0.002) after adjusting for cardiovascular risk factors. Among patients with RA, smoking (OR 1.02, P = 0.04) and an elevated erythrocyte sedimentation rate (OR 1.02, P = 0.05) were associated with more severe coronary-artery calcification after adjustment for age and sex. CONCLUSION: The prevalence and severity of coronary calcification is increased in patients with established RA and is related, in part, to smoking and an increased erythrocyte sedimentation rate.

PMID: 16200609 [PubMed - indexed for MEDLINE]
LUIS R. ESPINOZA
Dr. Espinoza's group was one of the first to call attention to the rheumatic manifestations occurring in the context of infections with the Human Immunodeficiency Virus (HIV). In this landmark article, his group studied 100 consecutive patients infected with HIV; in addition to report the high frequency of musculoskeletal and rheumatic manifestations in these patients, his group was the first one to report the syndrome of severe intermittent oligoarthritis, usually requiring more than NSAIDs to control them.


Department of Internal Medicine, University of South Florida College of Medicine, Tampa 33612.

PURPOSE: The prevalence and characteristics of the rheumatic and extra-rheumatic manifestations of human immunodeficiency virus (HIV) infection were determined in a prospective manner.

PATIENTS AND METHODS: One hundred one patients with HIV infection were consecutively interviewed and examined. The prevalence of autoantibodies and their association with rheumatologic symptoms were also determined. RESULTS: The musculoskeletal system was involved in 72 patients. Thirty-five patients had arthralgias, 10 had Reiter's syndrome, two had psoriatic arthritis, two had myositis, and one had vasculitis. Also found were two previously unreported syndromes. The first, occurring in 10 patients, consisted of severe intermittent pain involving less than four joints, without evidence of synovitis, of short duration (two to 24 hours), and requiring therapy (ranging from nonsteroidal anti-inflammatory drugs to narcotics). The second, occurring in 12 patients, consisted of arthritis (oligoarticular in six patients, monoarticular in three patients, and polyarticular in three patients) involving the lower extremities and lasting from one week to six months. The synovial fluid of five patients (three with arthritis, one with Reiter's syndrome, and one with psoriatic arthritis) was sterile and inflammatory.

CONCLUSION: Musculoskeletal complications are common in advanced stages of HIV infection. Persons in a high-risk group for HIV infection who manifest oligoarthritis with or without any other extra-articular manifestation suggestive of Reiter's syndrome or other form of spondyloarthropathy should be tested for HIV.

PMID: 3260453 [PubMed - indexed for MEDLINE]


46. Bocanegra TS, Germain BF, Saba HI, Bridgeford PH, Saba SR, Lowenstein MB, Vasey FB, Espinoza LR. In vitro cytotoxicity of human endothelial cells in polyarthritis rheumatica and giant cell arteritis. Rheumatol Int.
RAFAEL GRAU
In this important article, Dr. Grau delivers a critical review of the clinical characteristics, diagnostic basis, differential diagnosis and pathogenic pathways of the pseudovasculitic syndromes. This article is “a must reading” for all those interested in the study of vasculitis


Division of Rheumatology, Indiana University School of Medicine, 1110 W. Michigan Street, Room 545, Indianapolis, IN 46202-5100, USA. rgrau@iupui.edu

Pseudovasculitis, vasculitis-like syndromes, or mimics of vasculitis represent a heterogeneous collection of disorders that are capable of simulating a vasculitic disorder. Some conditions such as cardiac myxomas, choleslerol embolization, and fibromuscular dysplasia are more apt to cause confusion, but numerous other conditions can do so also. Inappropriate diagnosis leads to delay or absence of proper management and exposure to potentially deleterious treatment modalities such as corticosteroids and cytotoxic agents. The diagnosis of a pseudovasculitic disorder requires a high index of suspicion and should always be part of the differential diagnosis of vasculitis. The endothelium is thought to be pivotal in vascular injury; much has been learned using in vitro human umbilical vein endothelial cell cultures. Application of this knowledge to human disease and to vasculitic disorders and their imitators is still premature.

PMID: 11798987 [PubMed - indexed for MEDLINE]

RAQUEL M. HICKS

Dr. Hicks had the privilege of being member of the team who reported the first community-wide outbreak of Kawasaki syndrome in the USA (Hawaii). Herein, this group reported that patients with Kawasaki syndrome, compared to the general population of the island, were more likely to be of Japanese ancestry, to have a high-income, and possibly a history of respiratory infection in the preceding month (44%).


A community-wide outbreaks of Kawasaki syndrome, apparently the first in the United States, occurred in Hawaii in the first half of 1978. Twenty-seven of the 33 cases were subjected to intensive epidemiologic and microbiologic study. Patients with Kawasaki syndrome, compared to the general population, more often had Japanese ancestry, high-income status, and possibly a history of respiratory infection in the preceding month (44%). Staphylococcus aureus was not found in high frequency in the patients (15%), and viral cultures and serologic studies, immune electron microscopy, and guinea pig and primate inoculation did not reveal a causative microorganism. Febrile illnesses in guinea pigs inoculated with a skin biopsy specimen should not be further passed.

PMID: 7062202 [PubMed - indexed for MEDLINE]

LUIS JAVIER JARA
This recently published article by Dr. Jara’s group emphasizes the seriousness of the primary antiphospholipid syndrome as recruitment of additional organ systems over the course of relatively few years occurs in the majority of these patients despite standard treatment (oral anticoagulation).


Research Division, Hospital de Especialidades Centro Medico La Raza, Seris y Zaachila S/N Col. La Raza, Mexico, CP 02990. luis_jara_quezada@hotmail.com.

The prevalence of mono-organic and multi-organic involvement during long-term follow-up in patients with primary antiphospholipid syndrome (pAPS) was investigated. We studied 60 pAPS patients followed up at least 5 years. Patients with associated systemic lupus erythematosus were excluded. All patients received oral anticoagulant therapy. A diagnosis of mono-organic involvement was considered when one organ was affected exclusively, and multi-organic involvement was considered when two or more organs became affected during follow-up. Average age at diagnosis was 32.9 +/- 12.4 years. 40 subjects were female and 20 male, and mean disease evolution totaled 11.5 +/- 4.5 years. The mean number of clinical events was 3.75 +/- 1.87. Among patients, immunoglobulin G anticardiolipin (IgM aCL) titers totaled 50 +/- 40.3 IgG phospholipid units, and IgM aCL titers totaled 47.3 +/- 35.4 IgM phospholipid units. The most frequent clinical manifestations at study onset were deep venous thrombosis, stroke, pulmonary thromboembolism, fetal loss, and pre-eclampsia. At the beginning of follow-up, 46 patients had mono-organic involvement and 14 had multi-organic involvement (P = 0.0001). In contrast, at the end of the study, only 8 patients still had mono-organic involvement, leading to deep venous thrombosis (n = 3), stroke (n = 3), and retinal thrombosis (n = 2) (P = 0.0001). Kaplan-Meier analysis showed that the probability of remaining with mono-organic involvement decreased throughout the cumulative years, especially during the first 3. The hazard risk ratio for developing multi-organic involvement was 1.47 patients per year. In conclusion, PAPS is a chronic disorder with unpredictable clinical course and multi-organic involvement, especially during the first years. The conversion to multi-organic involvement supports the concept that pAPS is a systemic autoimmune disease.

PMID: 16126972 [PubMed - in process]
SERGIO JIMENEZ

This is a comprehensive clinical and laboratory analyses of a fairly large number of patients (n=9) afflicted with a recently recognized disorder: nephrogenic fibrosing dermopathy. Findings from this study suggest that the fibrotic process affects not only the dermis, but also the subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs. The authors go on to conclude that this is a systemic fibrosing process, and suggest that “dialysis-associated systemic fibrosis” is a better name for this disorder.

Division of Rheumatology, Thomas Jefferson University, Philadelphia, Pennsylvania 19107-5541, USA.

OBJECTIVE: Nephrogenic fibrosing dermopathy (NFD) is a newly recognized cutaneous fibrotic disorder occurring in individuals with end-stage renal disease (ESRD). The aim of the present study was to describe the clinical and histopathologic features of 9 new cases and to characterize the inflammatory cells and expression of transforming growth factor beta1 (TGFbeta1) in affected skin. METHODS: Clinical and laboratory assessments, including serology and pulmonary function studies, were performed in 9 patients undergoing long-term dialysis (8 hemodialysis; 1 peritoneal dialysis) for ESRD of diverse etiologies. Skin, fascia, striated muscles, lungs, and heart were examined by histopathology. Inflammatory cells were characterized by immunophenotyping using specific monoclonal antibodies. TGFbeta1 expression was determined by in situ hybridization. RESULTS: All patients displayed cutaneous features resembling both systemic sclerosis and diffuse fasciitis, with severe loss of motion and flexion contractures in multiple joints. Six patients displayed woody induration of the muscles of the legs, thighs, and forearms. Five of the 6 patients with lung involvement had a reduced diffusion capacity for carbon monoxide on pulmonary function testing. Marked elevations of the erythrocyte sedimentation rate and/or C-reactive protein level were found in 6 patients. Antinuclear antibodies were present at low titers in 4 patients. Histopathologic studies indicated that in addition to the dermis, the fibrotic process affected the subcutaneous tissue, fascia, striated muscles, lungs, and myocardium. Large numbers of CD68+/factor XIIIa+ dendritic cells and increased expression of TGFbeta1 were found in affected skin and muscle. CONCLUSION: Our findings indicate that the fibrotic process of NFD affects not only the dermis, but also the subcutaneous tissues, fascia, and other organs, including striated muscles, heart, and lungs. We therefore believe this is a systemic fibrosing process, and we suggest that dialysis-associated systemic fibrosis would be a better term for the condition.

PMID: 15334482 [PubMed - indexed for MEDLINE]


27. Philip N, Bashay RI, Jimenez SA. Increased alpha 1(I) procollagen gene expression in tight skin (Tsk) mice is a myocardial fibrosis is due to a reduced interaction of a negative regulatory sequence with AP-1 transcription factor. J Biol Chem. 1995 Apr 21;270(16):9313-21. PMID: 7721853 [PubMed - indexed for MEDLINE]


44. Reginato AM, Jimenez SA. Biochemical characterization of the native tissue form of type X collagen from
MEDLINE


ISAIAS SPILBERG
Our prematurely departed compatriot was involved in the study of the pathogenesis of
gout. In this classic paper Spilberg and collaborators from Washington University
demonstrated the occurrence of an acute inflammatory response in the joint cavities of
rabbits administered monosodium urate-derived chemotactic factor suggesting that this
is the mechanism by which acute gout occurs in humans

Spilberg I, Rosenberg D, Mandell B. Induction of arthritis by
purified cell-derived chemotactic factor: role of chemotaxis and

The injection of monosodium urate-induced chemotactic factor
into the joint cavities of rabbits induces an acute inflammatory
response that resembles the one produced by monosodium urate
crystals. The leukocyte accumulation induced by the factor was
not accompanied by a measurable increase in vascular permeability as measured by appearance of 125I-albumin in the
joint cavity. When histamine was injected into the joints, a marked
increase in vascular permeability but no leukocytosis above
control levels was observed. The above results suggest that the
cell-derived factor is primarily responsible for the accumulation
of cells seen in the acute inflammation induced by monosodium urate crystals.

PMID: 838864 [PubMed - indexed for MEDLINE]
PETER STASTNY

This landmark article describes the association between HLA-Dw4 (*HLA-DRB1*04 per current nomenclature) with rheumatoid arthritis; numerous studies around the world have been conducted since to determine if this association, which he described in white patients with seropositive disease held true in patients with seronegative disease and/or from other ethnic groups. It also marks the beginning of our understanding of the genetic basis for the occurrence (and severity) of this disease.


Previous testing of patients with rheumatoid arthritis showed that one HLA-D type, Dw4, occurred more frequently than in normal controls. B-cell alloantigens closely related to HLA-D can now be identified by a simple serologic procedure. Using this test, I studied 80 white patients with erosive, rheumatoid-factor-positive rheumatoid arthritis. The B-cell alloantigen HLA-DRw4 occurred in 70 per cent of 54 patients, as compared to 28 per cent of the 68 normal controls (P less than 10(-5)). Both groups were also tested for the HLA-A, B and C antigens and for HLA-D. HLA-Dw4 occurred in 54 per cent of the patients and 16 per cent of the controls (P less than 10(-5)). Small differences observed in several of the HLA-A and B antigens were not statistically significant. The results indicate that rheumatoid arthritis in whites is associated with genes of the HLA-D region and that immunogenetic factors linked to HLA have a role in its pathogenesis.

PMID: 147420 [PubMed - indexed for MEDLINE]


162


