1

Tensegrity: The Importance of Mechanical Forces in Scleroderma Fibrosis

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Objective:
The main cause of lethality in the autoimmune connective tissue disease scleroderma is organ fibrosis. Cellular behavior is altered by their local microenvironment, which includes enhanced local stimulation of mechanical signaling pathways. Fibrotic lesions are, by their nature, characterized by significantly enhanced mechanical forces relative to healthy tissue. Previous evidence from our laboratory has identifed the myofibroblast (a highly adhesive and contractile fibroblast that exerts mechanical tension on surrounding tissue) as the critical effector cell in the fibrosis observed in scleroderma. This observation led us to test the hypothesis that enhanced mechanosignaling was required for fibrogenesis. The signaling receptors required for mechanotransduction are the integrins, and we have previously shown that a neutralizing antibody to integrin beta 1 reverses the fibrotic phenotype of lesional scleroderma fibroblasts and that integrin beta 1 knockout mice are resistant to bleomycin-induced skin fibrosis.

Methods:
We use fibroblast-specific integrin beta1 knockout mice as well as primary dermal fibroblasts to assess the effect of loss of integrin b1 on skin homeostasis and connective tissue sythesis and depoistion. Specific chemical inhibitors were used to identify the mechanism underlying the basis for integrin beta activity in fibroblasts.

Results:
We show that integrin beta 1 is an essential mechanosignaling receptor required for connective tissue production and deposition. We also show that integrin beta 1 promotes this activity through a focal adhesion kinase/rac1/NADPH oxidase/reactive oxygen species-dependent mechanism.

Conclusion:
Inhibitors of the integrin beta 1/focal adhesion kinase/rac1/NADPH oxidase/reactive oxygen species pathway, which are currently being considered as anti-cancer regimens. may be useful to prevent excessive connective tissue deposition and remodeling seen in scleroderma. Our data further suggest that altering how fibrotic cells perceive their microenvironment via mechanosignaling receptors may be prove to be a crucial, novel paradigm in treating chronic connective tissue disease.

2

Imbalance of Prevalence and Specialty Care for First Nations with Osteoarthritis in Alberta

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Objective:
To compare osteoarthritis (OA) prevalence and healthcare use in Alberta First Nations (FN) and non-First Nations (non-FN) populations.

Methods:
Using population-based healthcare administrative data (years 1993 to 2010), a prevalent OA cohort was determined based on diagnosis codes (2 physician claims within 2 years or 1 hospitalization with ICD9 code 715x, or ICD10 codes M15-19). FN patients were identified based on premium payer status and represent 3.8% of the Alberta population. OA prevalence (fiscal year 2007/2008) and visits to primary care physicians, orthopedic surgeons, and rheumatologists, and hospitalizations (joint replacement and all-cause) were calculated.

Results:
Age and sex standardized prevalence of OA in FN persons was 160.0 cases/1,000 population, compared to 78.2 cases in non-FN persons (standardized rate ratio 2.06; 95%CI 2.00-2.12). Age and sex standardized prevalence was highest for rural residents (186.7/1,000 FN, 88.5/1,000 non-FN) and females (184.9/1,000 FN, 93.1/1,000 non-FN). Primary care physician contact for FN persons was more frequent than for non-FN (16.7 vs 10.8 visits/1,000 person-years (py), respectively), with 15% of these visits being coded for OA. FN persons with OA were less likely to see an orthopedic surgeon (290.4 FN vs 460.3 non-FN visits/1,000py; rate difference -0.170, 95%CI -0.175 to -0.165). Rheumatology visits were also less frequent for FN persons (39.0 FN vs 51.4 non-FN visits/1,000py; rate difference -0.012, 95%CI -0.014 to -0.010). FN with OA were less likely to have hip or knee replacements (6.2 FN vs 20.0 non-FN surgeries/1,000py; rate difference -0.014, 95%CI -0.015 to -0.013). All-cause hospitalization rates were highest in FN females with OA (355.8 admissions/1,000py) followed by FN males, non-FN males and non-FN females, and for rural compared to urban residents.

Conclusion:
Our work suggests disparities in OA care in FN persons given an estimated 2-fold higher disease prevalence. This finding may be driven in part by an increased probability of diagnosis through frequent primary care contact. Use of rheumatology and orthopedic services is lower in FN compared to non-FN persons. This may be due to access barriers for FN patients.

3

TNF-Inhibitors Slow Radiographic Progression of Ankylosing Spondylitis

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Objective:
Tumor Necrosis Factor-Alpha (TNF)-inhibitors are excellent in giving symptomatic releif for patients with spondyloarthritis. Yet to date, there is no evidence that it has a disease modifying effect. The use of non-steroidal anti-inflammatory drugs (NSAID) has recently been proposed to have a disease modifying effect. Our objective was to determine whether TNF-inhibitors slow spine damage in AS patients.

Methods:
All patients satisfied the modified New York criteria for AS and were enrolled in prospective observational cohorts in five tertiary care centers across North America. All 334 patients who had at least two sets of spinal radiographs available at a minimum gap of 1.5 years were included. Disease activity at baseline was assessed by a validated patient reported index, Bath AS Disease Activity Index (BASDAI) as well as by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Baseline predictors including HLA-B27, gender and smoking (pack-years) were studied. Radiographic disease severity in AS was assessed by the validated scoring method, modified Stokes Ankylosing Spondylitis Spine Score (mSASSS). Patients with a rate of mSASSS progression more than 1 mSASSS unit per year were considered progressors. Univariate regression analysis followed by multivariate analysis was done to identify predictors of progression. Propensity score matching (PSM) was performed.

Results:
There was a 50% reduction in the odds of progression of radiographic damage (OR:0.50;CI:0.27-0.91;p=0.02) in AS patients treated with TNF-inhibitors. Patients who started TNF-inhibitors within 10 years of disease onset had the greatest reduction in odds of progression (OR:0.36; CI:0.15-0.91;p=0.03). Males had higher rate of progression than females but after correcting for baseline mSASSS, none of the baseline demographic factors independently predicted radiographic progression. Baseline CRP, ESR, smoking and mSASSS were significant independent predictors of progression. There was no effect of NSAID use on radiographic progression even after correcting for baseline ESR or CRP values.

Conclusion:
This is the first study to show the disease modifying potential of TNF-inhibitor therapy in AS patients. Early initiation of TNF-inhibitors was associated with a greater likelihood of slowing progression arguing for earlier diagnosis. Smoking and baseline inflammation are important baseline predictors of radiographic progression in AS.

4

Long-Term Outcomes of Children Born to Women with Systemic Lupus Erythematosus

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Objective:
SLE can cause considerable morbidity during pregnancy. Although several studies have evaluated foetal outcome in lupus pregnancy, few have examined the long-term outcome of children born to mothers with SLE. We aimed to < /span>< span lang="EN-CA" style="font-family:Arial">determine if children born to women with SLE have an increased risk of major congenital anomalies, serious infections, and cardiac conduction disturbances compared to children born to women without SLE.

Methods:
We identified all women who had ≥1 hospitalization for delivery after SLE diagnosis using Quebec"s administrative databases (1989-2009). Women were defined as SLE cases if they had: 1) ≥1 hospitalization with a diagnosis of SLE prior to the delivery, 2) a diagnosis of SLE recorded at the time of their hospitalization for delivery, or 3) ≥2 physician visits with a diagnosis of SLE, occurring 2-24 months apart, prior to the delivery. We randomly selected a general population control group, composed of women matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE cases and their matched controls and obtained information on all physician visits and hospitalizations incurred by these children. We ascertained major congenital anomalies (i.e. ≥1 hospitalization or physician visit for a major congenital anomaly < 12 months of life), serious infections (i.e. ≥1 hospitalization with a primary diagnosis of infection), and cardiac conduction disturbances hospitalization or 2 physician visits within 2-24 months) through to end of database follow-up. We performed multivariate analyses to adjust for maternal demographics, sex and birth order of child, major maternal co-morbidities and/or obstetrical complications, and relevant maternal medication.

Results:
509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Compared to controls, children born to women with SLE experienced slightly more major congenital anomalies [13.5% (95%CI 11.1,16.2) vs 10.4% (95%CI 9.8,11.1)], serious infections [23.9% (95%CI 17.6,31.5) vs 16.3% (95% CI 14.6,18.1)], and cardiac conduction disturbances [3.1% (95%CI 2.0,4.7) vs 1.2% (95%CI 1.0,1.4)]. In multivariate analyses, children born to women with SLE had substantially increased risks of major congenital anomalies (OR 1.35, 95%CI 1.07,1.70). serious infections (HR 1.88, 95%CI 1.17,3.03) and cardiac conduction disturbances (HR 4.52, 95%CI 1.23,16.59) compared to controls.

Conclusion:
Compared to children from the general population, children born to women with SLE have an increased risk of major congenital anomalies, serious infections, and cardiac conduction disturbances.

5

The ACR/EULAR Classification Criteria for Systemic Sclerosis (SSc).

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Objective:
A joint EULAR and ACR committee was established to develop new classification criteria for SSc.

Methods:
A nominal group technique were used to create potential items for SSc classificaiton. The validity was tested in databases of SSc cases and controls. Next, twenty cases were prospectively collected to represent the spectrum of SSc (low probability to high probability) which were ranked by SSc experts. Conjoint analysis (1000 Minds®) was used to assign weights to the items resulting in 17 items in 13 domains. Experts agreed that all patients with sclerodactyly and scleroderma skin involvement proximal to the MCPs were considered SSc; patients with skin involvement due another scleroderma-like disorder (e.g. scleromyxedema) were excluded. A threshold was established to classify definite SSc based on the sum of weights of 17 items. To test the algorithm, data on the items were prospectively collected in cases and controls. To refine the threshold, a subset of cases (n=25) within the range of borderline probability of SSc was selected from the collected data. Experts were then asked to determine whether each case had 'definite SSc' or not, leading to a new threshold. During a face-to-face meeting of the Steering Committee, the 17 items were reduced to 9 while maintaining adequate sensitivity and specificity, tested in a random sample of cases and controls of 100 from North America and 100 from Europe (derivation sample). Cases of SSc and mimickers were collected at several sites in NA and Europe where approximately half of SSc had early disease. Weights were simplified by dividing each weight by 5 and rounding to the nearest whole number. The data were then re-analyzed in the remaining cases and controls (validation set; n=405).

Results:
Mimickers of SSc need to be excluded. If sclerodactyly with involvement proximal to MCPs then SSc is classified. Otherwise, only the maximum score in each domain is counted (skin: puffy fingers=2 or sclerodactyly entire fingers=4, finger tip ulcers=2 or digital pits=3, telangiectasia=2, nailbed abnormal capillaries=2, PAH or ILD=2, RP=3, SSc antibody (centromere, topo1, RNApol3)=3. Nine or more (out of 19) had a sensitivity of 91% and specificity of 92% in the validation cohort (n=405). The sensitivity and specificity of the former 1980 ARA criteria in this database were 75% and 72%, respectively.

Conclusion:
The ACR/EULAR classification criteria for SSc performed better than 1980 Preliminary ARA Criteria for SSc. These criteria can be endorsed for epidemiological studies and clinical trials.

6

2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria Predicts Radiogical, but Not Clinical Outcomes at 18 Months into Disease in a Canadian Early Arthritis Cohort

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Objective:
Analyze the potential of the 2010 ACR/EULAR rheumatoid arthritis (RA) classification criteria to discriminate early arthritis patients according to their clinical and radiological outcomes at 18 months

Methods:
Consecutive patients with at least 3 swollen joints (SJC≥ 3) were recruited; duration of disease was more than 1 and less than 12 months; microcrystalline arthritides and connective tissue diseases were actively excluded. All patients were treated with the target of SJC= 0, using whatever DMARDs was required. According to the 2010 RA criteria, our cohort was classified in two groups: RA and non-specific inflammatory arthritis (NSIA). Both groups were compared at baseline and at 18 months into disease according to radiological and clinical outcomes: Sharp erosion score (classified erosive if ≥ 3), Health Assessment Questionnaire (HAQ), Disease Activity Score in 28 joints (DAS28-CRP), and pain (0-100 mm VAS). Remission rates at 18 months were calculated based on DAS 28 and ACR 2011 remission criteria.

Results:
A total of 422 patients were available at baseline. Of these, 319 (75.6%) were classified as RA. Based on clinical outcome measures, RA patients had more severe disease than NSA patients at baseline (higher DAS 28, HAQ and pain scores measures – $p< 0.001$). At 18 months, this initial clinical discrepancy had now disappeared, but more RA patients had progressed to erosive status than NSIA patients (54% vs 33%; $p< 0.001$). Using two different definitions of remission, there was no difference in remission rates.

Conclusion:
In this early arthritis cohort actively treated to SJC= 0, there was no difference in the 18-month clinical outcomes (HAQ, DAS 28, Pain, Remission rates) between 2010 ACR/EULAR criteria-defined RA and NSIA patients. Patients with RA had a worse radiological outcome, but significant joint damage occurred in one third of NSIA patients. Early intensive treatment of NSIA patients, and not only of early RA patients, thus appears warranted.

7

Microparticle-Associated Immune Complexes Derived from Platelets are Elevated in the Plasma of Patients with Systemic Lupus Erythematosus and Discriminate between Levels of Disease Activity

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Objective:
Immune complexes (IC) are implicated in the pathogenesis of several autoimmune diseases including systemic lupus erythematosus (SLE). In SLE, submicron extracellular vesicles, called microparticles (MP), are thought to serve as an antigenic surface promoting the deposition of immunoglobulins and the formation of MP-associated immune complexes (mpIC). However, the cellular origin of these mpICs and whether they correlate with disease activity and particular clinical features remains to establish.

Methods:
The concentrations of mpICs in platelet-poor plasma from 193 women with SLE were determined using high sensitivity flow cytometry. Considering the recently revealed role of platelets in SLE, we further scrutinized the contribution of platelets to mpICs formation. The platelet and non-platelet MPs and mpICs were tested for association with lupus disease activity, damage, history of previous arterial disease, and the carotid intima-media thickness and plaque area on ultrasound. To assess if disease activity and damage are associated with levels of MPs and mpICs, univariate and multivariate negative binomial models were built using the SLE disease activity index 2000 (SLEDAI-2K) and the SLICC/ACR damage index (SDI) as outcome variables. In all models, the predictor variable was the level of MPs or mpICs. When necessary, models were adjusted for covariables such as age, disease duration, menopausal status, hypertension, diabetes, anticoagulant or anti-platelet medication, antimalarial medication, prednisone use, smoking status, and ethnicity.

Results:
The clinical characteristics of the 193 women studied were: age of [mean (sd)] 46.3 (14.7) years; disease duration 18.5 (12.0) years; ethnicity (% Caucasian) 57%; ever-smoker 34%; menopausal in 55%; hypertentive 30%; diabetic 5%; prescribed anticoagulant or anti-platelet medication 25%; prescribed antimalarial medication 74%; prescribed prednisone 44%. Univariate analyses for activity revealed that platelet-derived mpICs, but not mpICs from other cells, were associated with SLEDAI-2K. In the multivariate model, this association remained significant ($p=0.02$ for annexin V+ platelet mpICs and $p=0.0006$ for annexin V-platelet mpICs) after adjusting for

disease duration, hypertension and currently on prednisone. There was no association between platelet mpICs and SDI.

Conclusion:
Platelets are a major source of MPs serving to mpIC formation in SLE. Platelet-derived mpICs are associated with lupus disease activity level on the SLEDAI-2K but not with damage. This is the first report of an association between platelet mpICs and clinical marker of activity in SLE and in any autoimmune disease. Platelet mpICs as a possible biomarker of lupus disease activity needs to be further considered.

8

Survival in Rheumatoid Arthritis Associated Pulmonary Arterial Hypertension is Comparable to Idiopathic Pulmonary Arterial Hypertension

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Objective:
To evaluate survival in rheumatoid arthritis associated pulmonary arterial hypertension (RA-PAH) compared to idiopathic PAH (IPAH) population. Secondary outcomes included differences in sex predisposition, age of diagnosis, disease severity, co-morbid diseases and pulmonary hypertension treatment.

Methods:
Data were collected by a single abstractor from charts, standardized protocols, and hospital electronic records using a standardized abstraction form from the University Health Network Pulmonary Hypertension Programme, Toronto, Canada. PAH based on a mean pulmonary artery pressure ≥25 mmHg and a pulmonary capillary wedge pressure < 15 mmHg on cardiac catheterization. Mortality data was obtained from electronic records and obituaries. Student's t-test and Pearson's Chi-squared test were used to evaluate baseline differences between groups. Unadjusted survival was evaluated using Kaplan-Meier survival curves. Differences in survival distributions were evaluated using the log rank test. Propensity score models were used to adjust for differences in baseline covariates. Propensity score adjusted Cox proportional hazards models were used to estimate survival.

Results:
Eighteen RA-PAH and 155 IPAH patients were identified. RA-PAH patients had a lower proportion of males (17% versus 30%), and had an older median age of onset (64.0 years versus 53.7 years). RA-PAH patients more frequently had coronary artery disease (33% versus 16%), lower baseline mPAP (43 mmHg versus 51 mmHg), lower proportion of WHO functional class III or IV (39% versus 52%), lower median baseline BNP (58.4 pg/mL versus 95.0 pg/mL) and longer 6-minute walk distance (478 m versus 381 m), less use of calcium channel blocker (22% versus 29%), phophodiesterase-5 inhibitors (11% versus 19%) and prostaglandin analogues (6% versus 15%). There were 35 deaths, 2/18 (11%) RA-PAH patients and 33/155 (21%) IPAH patients. The unadjusted 1-year survival for RA-PAH patients was 93% and for IPAH was 94%. RA-PAH patients had improved survival compared to IPAH patients, with increasing separation of the survival curves over time. The unadjusted hazard ratio comparing RA-PAH to IPAH survival was 1.52. A propensity score matched cohort matching 18 RA-PAH patients to 18 IPAH patients resulted in significant reductions in the standardized differences of baseline

characteristics. In the matched cohort there were 7 deaths, 2/18 (11%) RA-PAH patients and 5/18 (28%) IPAH patients. The propensity score adjusted hazard ratio was 1.53.

Conclusion:
PAH is a life-threatening manifestation of RA. Despite milder disease at presentation, survival is comparable to IPAH.

9

Association of Clinical Findings with MRI-Based Cartilage Damage in an Asymptomatic Population

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Objective:
Cartilage damage is an important feature of osteoarthritis but has not been extensively explored in asymptomatic populations. This cross-sectional study will determine the prevalence of MRI-defined cartilage damage of the knee in an asymptomatic population-based cohort, and evaluate clinical correlates of cartilage damage.

Methods:
Subjects aged 40-79 years without knee pain (n=73) were recruited as a random population sample from the Greater Vancouver area. Recruitment and cross-sectional assessments were performed identically to a previous study of symptomatic knee subjects and included comprehensive evaluation with questionnaires, standardized knee examination, x-ray and MRI. Six knee joint surfaces were assessed on MRI, including the medial and lateral tibial plateaux and femoral condyles, patella, and trochlear groove. Using magnetic resonance cartilage (MRC) scores (range 0-4), subjects were classified into 2 groups: those with normal cartilage (< 2) and those with cartilage damage (≥ 2) on at least one surface. Univariate logistic regression analysis was used to evaluate the association of each clinical variable with cartilage damage, followed by backward stepwise multivariable logistic regression, with adjustment for age and gender. Assessment of OA risk factors included age, gender, body mass index (BMI) currently and at age 25, history of mild and severe knee injury, duration of regular sports activity after age 20, and family history of OA or of knee/hip arthroplasty. Other predictor variables included physical examinations for gait, quadriceps weakness, quadriceps atrophy, knee effusion, flexion contracture by goniometer, and smoking pack years.

Results:
Of 73 subjects, 48 (66%) had cartilage damage on MRI, while 25 (34%) had normal cartilage. The frequency distribution of MRC scores in ascending order from 0-4 were as follows: 34%, 1%, 37%, 21%, 7%. On univariate analysis, cartilage damage was associated with current BMI (OR 2.60, 95% CI 1.22-5.54, per 5 unit increase), while change in BMI since age 25 was of borderline significance (OR 2.33, 95% CI 0.99-5.49, per 5 unit increase). In the multivariable model, only current BMI was significantly associated with cartilage damage (OR 2.63, 95% CI 1.17-5.89, per 5 unit increase). There was no significant association with other clinical variables.

Conclusion:
MRI-based cartilage damage was highly prevalent (66%) in this asymptomatic population-based cohort. Prevalent cartilage damage was significantly associated with self-reported current BMI but not with BMI at age 25 or change in BMI. Based on our findings and the literature, BMI is a risk factor for early asymptomatic cartilage damage.

10

The Impact of Reaching Low Disease Activity in the First Year on Future Disability and Damage in Patients with Early Rheumatoid Arthritis

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Objective:
The objective of this study was to assess the impact of acieving low disease activity (LDA) at one year on patient function and x-ray progression.

Methods:
We used data from The Study Of New Onset Rheumatoid Arthritis (SONORA), a North American prospective cohort of patients with early RA. Our analysis is based on 3 years of follow-up. The Simplified Disease Activity Index (SDAI) and patients' function (HAQ-DI) were measured at baseline, years 1, 2 and 3. Hand x-ray was performed yearly up to year 2; a modified sharp score of ≥3.5 indicated important x-ray progression1. Multivariate linear regression analysis was performed to assess the impact of reaching LDA (yes/no) at year 1 on future HAQ. Logistic regression was used to assess the impact of reaching LDA at year 1 on x-ray progression (yes/no) at year 2. Both analyses were adjusted for potential clinical confounders. Missing data were imputed using Multiple Imputation.

Results:
Baseline characteristics of 984 eligible patients included: mean (sd) age 53 (14.8), disease duration 5.3 (3.1) months, swollen joint count (SJC) 9.4(7.1), tender joint count (TJC) 10.1 (8.0), CRP 1.4 (1.5), SDAI 30.5 (16.6) and median (IQR) HAQ 1.0 (0.37-1.63) and modified Sharp score 3.0 (0.0-7.0). Year 1 LDA was achieved in 37% of patients and x-ray progressed in 17%.Year 1 LDA was strongly associated with lower HAQ at 3 years (p=0.0003). Other predictors included higher baseline HAQ (p< .0001), older age (p=0.002), higher Joint space narrowing (JSN) score (p=0.03) and gender (female) (p=0.007) which were associated with higher HAQ. Complete case and imputed analyses showed similar results. Year 1 LDA was significantly associated with less X-Ray progression at year 2 (OR 0.68, 95% CI 0.47-0.98; p=0.04) in the imputed case analysis (was not significant in complete case analysis). Baseline Sharp score (1.06, 1.01-1.12; 0.03), positive rheumatoid factor (1.98, 1.2-3.2; 0.01), positive anti-CCP (1.95, 1.1-3.4; 0.03), higher CRP 1.15 (1.01-1.30; 0.03) were also predictors of x-ray progression.

Conclusion:
Reaching low disease activity is associated with improved long term outcomes in early RA. This provides strong supports for the current treat to target recommendations. An assessment of prognostic factors at baseline is essential and can help clinicians stratify patients and individualize RA treatment Reference: 1-K Bruynesteyn, M Boers, et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. Ann Rhuem Dis.2005 Feb;64(2):179-82

11

Epidemiology of Rheumatoid Arthritis (RA) in a Universal Public Health Care System: Results from the Ontario RA Administrative Database (ORAD)

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Objective:
To describe trends in incidence and prevalence of Rheumatoid Arthritis (RA) in a universal public health care system over the past 15 years.

Methods:
We used the Ontario Rheumatoid Arthritis administrative Database (ORAD), a validated population-based research database that includes all individuals with RA living in Ontario. Patients are included in ORAD if they are admitted to a hospital with a RA diagnosis or have at least 3 Ontario Health Insurance Plan (OHIP) physician service claims over two years on which RA is the recorded diagnosis, with at least 1 of these claims made by a musculoskeletal specialist (rheumatologist, orthopedic surgeon or internist). ORAD has a high sensitivity (80%), specificity (100%) and positive predictive value (78%) for identifying RA patients according to medical record reviews of both primary care and rheumatology charts. We used ORAD to calculate crude and age/sex-standardized incidence and prevalence rates among men and women aged 15 years or older over the period of 1995-2010. Age/sex-standardized rates by area of patient residence also were determined. A 5-year run-in period was used to distinguish between incident and prevalent cases.

Results:
As of 2011, there were 99,130 patients (72% female) with RA living in Ontario, corresponding to a cumulative prevalence of 0.9% (females 1.3%, males 0.5%). Age/sex-standardized RA prevalence per 100,000 population increased steadily over time from 469 in 1996 to 782 in 2010 (0.5% to 0.9%). Prevalence increased with age: 15-24y (0.1%), 25-34y (0.2%), 35-44y (0.5%), 45-54y (0.9%), 55-64y (1.5%), 65-74y (2.1%), 75-84 (2.6%) to ≥85y (2.7%) as of 2010. Prevalence was higher in northern rural communities (835-1035/100,000) than southern urban areas (e.g., Toronto: 687-748/100,000). Age/sex-standardized incidence per 100,000 decreased gradually over time from 63 in 1996 to 55 in 2010. Despite increasing prevalence observed among seniors (>65y) over time, after adjusting for sex, incidence was stable among adults < 65y, but decreasing among seniors.

Conclusion:
RA prevalence rates have increased significantly over time and may be partially attributable to an increase in the aging background population. Incidence appears to be slowly declining over time (with a shift toward fewer patients with elderly age at onset); however, this may be partly due to prevalent cases being misclassified as incident cases during the early years of study. Regional prevalence rates illustrate the high burden of RA in all locales, especially in northern communities, highlighting the importance of regional differences for planning for health care provisions for RA.

12

Recognizing Childhood Inflammatory Brain Diseases in Canada

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Objective:
Childhood inflammatory brain diseases are life-threatening diseases causing devastating brain damage in previously healthy children, if left untreated. In 2000, the diagnosis was only made on autopsy. Over the past decade recognition has increased. Since 2007, the BrainWorks network prospectively captures children with inflammatory brain diseases around the world. The aim of the study was to determine the spectrum of inflammatory brain diseases in Canadian children and identify presenting features of distinct subtypes.

Methods:
Consecutive pediatric patients enrolled into the BrainWorks study at Canadian centers from January 2007 until September 2012 were identified. Children with inflammatory brain disease were included, if predetermined information at the baseline visit were complete. Demographic characteristics, diagnosis at enrollment, baseline clinical, laboratory and neuroimaging features and brain biopsy characteristics were reviewed.

Results:
In total 247 Canadian children were included; these were 132 boys and 115 girls; mean age at diagnosis was 9.33 years. The most common inflammatory brain diseases were primary CNS vasculitis with 90 children having non-progressive large vessel vasculitis (63 boys, 27 girls, mean age 8.15 years), 57 having small vessel vasculitis (19 boys, 38 girls, mean age 11 years) and 25 progressive large vessel vasculitis (21 boys, 4 girls, mean age 10.3 years). Anti-NMDAR-encephalitis was diagnosed in 25 children (7 males, 18 females, mean age 9.9 years), and other neuronal antibody mediated diseases in 6 children. Secondary CNS vasculitis was present in 29 children (12%); of whom 13 were associated with infection, 10 had an underlying rheumatic disease and 6 a systemic vasculitis. Rare inflammatory brain diseases were found in 15 children. At presentation focal deficits were most commonly seen in large vessel CNS vasculitis (79% non-progressive, 84% progressive), while diffuse deficits were reported in small vessel CNS vasculitis and NMDAR encephalitis (61% and 72%). Seizures were seen in all inflammatory brain diseases, more frequently in NMDAR encephalitis and small vessel CNS vasculitis (80% and 61%) compared to large vessel CNS vasculitis subtypes (non-progressive 18%, progressive 18%).

Conclusion:
Inflammatory brain diseases are increasingly diagnosed in Canadian children of all ages. In this study the majority presented with primary inflammatory CNS diseases. Vasculitis is the most common childhood inflammatory brain disease, however NMDAR encephalitis is increasingly recognized and has to be considered given the widely overlapping clinical presentation.

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Interferon-Associated Cytokine and Chemokine Expression in Patients with Serologically Active Clinically Quiescent (SACQ) Systemic Lupus Eryhematosus (SLE)

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Objective:
Interferon-α (IFN-α) plays a prominent pro-inflammatory role in SLE. Studies suggest clinical/serologic discordance may illuminate SLE pathophysiology: peripheral IFN-α production is blunted in autoantibody-producing, clinically quiescent SLE mice despite abundant IFN-α-producing plasmacytoid dendritic cells (pDCs); continuous pDC stimulation yields reversible blunting of the IFN-α response in vitro. Thus SACQ patients, who exhibit persistent autoantibody production despite durable clinical quiescence, may provide unique insights. We thus measured IFN-associated cyto/chemokines in SACQ patients, compared to serologically and clinically active (SACA) and serologically and clinically quiescent (SQCQ) patients.

Methods:
We defined SACQ and SQCQ as ≥2-year periods without clinical activity, with/without persistent serologic activity, respectively, by SLE Disease Activity Index 2000 (SLEDAI-2K), over which antimalarials were permissible; corticosteroids/immunosuppressives were not. SACA was defined as disease activity, by SLEDAI-2K, which compelled immunosuppression. Clinical and lab data were collected at each visit. Plasma cyto/chemokines were measured by 65-plex Luminex panel, with the 16 most relevant selected a priori for analysis. Bonferroni correction was applied. Non-parametric univariate and logistic regression analyses were conducted.

Results:
We identified 25, 28 and 48 SACQ, SQCQ and SACA patients, respectively. IFN-α, IL-6, IL-10, IP-10 and MCP-1 levels were lower in SACQ vs SACA patients ($p = 0.006$, 0.0018, and < 0.0001 (last three), respectively). There were no differences in cyto/chemokine levels between SACQ and SQCQ patients. IFN-α and IP-10 moderately correlated ($r=0.79$). Disease duration at study start differed between SACQ and SACA patients (18.5±12.1 vs 7.4±7.3 yrs, $p=0.0002$) as did proportion with anti-Ro, -La, and –RNP positivity (84.0 vs 53.6%; 48 vs 32.1%; 40 vs 28.6%, $p=0.005$, 0.004 and 0.023, respectively). There were no clinical differences between SACQ and SACA patients. Logistic regression revealed increased levels of IL-10 (OR 7.35 [1.04,51.93]) and MCP-1 (OR 2.33 [1.23,4.41]) were associated with SACA status. Increased disease duration (OR 1.12 [1.03, 1.23] and anti-Ro positivity (OR 20 [2.38,166.67]) were associated with SACQ status. When SACA patients with disease duration < 6 years were excluded, MCP-1 elevation remained associated with SACA (OR 1.95 [1.28,2.97] and anti-Ro positivity with SACQ (OR 7.14[1.47,33.33]. Regression analysis applied to SACQ vs SQCQ patients similarly revealed anti-Ro positivity was associated with SACQ status (OR 4.55[1.23,16.67]).

Conclusion:
IFN-associated cyto/chemokine profiles differed between SACQ and SACA, but not SACQ and SQCQ, patients. Elevations in MCP-1 and IL-10 were associated with SACA status; there were no cyto/chemokines associated with SACQ status. These findings warrant further pursuit as they may facilitate clinical prediction.

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Involvement in Leisure Activities among Children and Youth with Arthritis

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Objective:
Objectives: To describe leisure activities in terms of diversity, intensity and enjoyment, as well as to identify potential socio-demographic and disease-related determinants.

Methods:
Methods: Fifty children and youth aged 8 to 18 years diagnosed with juvenile idiopathic arthritis (JIA) and their families participated in this cross-sectional study. Children and youth were administered the Children's Assessment of Participation and Enjoyment (CAPE), which measures involvement in leisure activities (recreation, physical, social, skill-based, self-improvement). The disease characteristics were abstracted from the child's medical file (JIA sub-type, active joint count, age of diagnosis) and pain perception was obtained through self-report (visual analog scale). Parents completed questionnaires on socio-demographic data and family structure.

Results:
Results: The most popular activities (>90%) were playing board games, playing computer/video games, watching television, hanging out with friends, doing chores and doing homework. Least popular activities were (<10%) martial arts and horseback riding. The level of enjoyment was highest for social activities (mean: 4.2 ±0.5). Involvement in informal leisure activities showed a significant negative association with age (β= -0.421, 95% CI= -0.148, -0.032), p=0.003), and with disease activity (β= -0.401, 95% CI= -0.732, -0.133), p=0.006).

Conclusion:
Conclusion: Greater disease activity may dissuade children and youth from participating in more active pursuits, which places them at greater risk for adopting sedentary lifestyles. The identification of determinants of leisure activities in children and youth with arthritis may allow healthcare professionals to assess children's health needs with more precision and promote a healthier lifestyle.