1er Congreso Mexicano Canadiense de Reumatología

XXXIV Congreso Mexicano de Reumatología

26a Reunión Anual de la Sociedad Canadiense de Reumatología

Plenarias

P01

ANÁLISIS DE ASOCIACIÓN DEL GEN PTPN22 CON LUPUS ERITEMATOSO SISTÉMICO DE INICIO EN EDAD PEDIÁTRICA Y ARTRITIS REUMATOIDE JUVENIL EN POBLACIÓN MEXICANA

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Introducción: Recientemente se ha identificado un polimorfismo (1858 C/T) en el gen PTPN22 como un alelo de riesgo para desarrollar diversas enfermedades autoinmunes como diabetes Tipo I, artritis reumatoide, lupus eritematoso sistémico (LES), enfermedad de Graves y artritis idiopática juvenil (AIJ). Estos hallazgos y la agregación familiar de enfermedades autoinmunes diferentes sugieren que estas enfermedades comparten ciertos genes de susceptibilidad. El gen PTPN22 también conocido como LYP (fosfatasa de linfocito) codifica para una proteína tirosin fosfatasa específica de tejido hematopoyético la cual inhibe la activación de células T a través de su asociación con la tirosin cinasa Csk. Esta variante polimórfica (SNP) en el gen PTPN22 resulta en la sustitución de arginina por triptofano en el codón 620 (R620W) afectando la unión de Csk con el dominio de unión-SH3 de la proteína, provocando una hiperactividad de las células T, fenómeno característico de muchas enfermedades autoinmunes.

Objetivo. El objetivo de este estudio es determinar el posible papel del polimorfismo 1858 C/T del gen PTPN22 en LES y artritis reumatoide juvenil (ARJ), en pacientes pediátricos mexicanos.

Pacientes y métodos: Se incluyeron en el estudio 200 pacientes con diagnóstico de LES antes de los 16 años de edad (^{3} 4 criterios del ACR) y 116 pacientes con ARJ (criterios del ACR) y 320 controles sanos. La genotipificación del SNP 1858C>T se realizó mediante el método fluorescente de 5'exonucleasa (Taqman). La asociación del SNP con LES y ARJ se investigó mediante un análisis de casos y controles utilizando la prueba de chi-cuadrada o exacta de fisher y se tomó como significativa cuando la P fue <0.05.

Resultados: El SNP 1858 C/T del gen PTPN22 mostró diferencias significativas en los pacientes con LES cuando se comparó con el grupo control (P=0.013; OR=3.03, 95% CI: 1.20-7.66), sin embargo, dicho polimorfismo no mostró diferencias significativas en la frecuencia alélica de los pacientes con ARJ cuando se compararon con el grupo control (P=0.06; OR=3.55, 95% CI: 0.88-14.32).

Conclusiones: Nuestros resultados muestran que el polimorfismo T en la posición 1858 del gen PTPN22 también es un alelo de riesgo en pacientes pediátricos mexicanos con LES, aunque en ARJ no parece tener ningún efecto.

P02

ASOCIACIÓN DE LOS POLIMORFISMOS G721A (ICAM-1), G1238C (VCAM-1, LA EXPRESIÓN DE sICAM-1 Y sVCAM-1 CON LA ACTIVIDAD CLINICA DE PACIENTES CON ARTRITIS REUMATOIDE

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Objetivo: La artritis reumatoide (AR) es una enfermedad poligenica, inflamatoria y crónico-degenerativa. Los procesos inmuno-patológicos se presentan principalmente en la sinovia articular. Las moléculas de adhesión ICAM-1 (intercelular adhesión molecule 1) y VCAM-1 (vascular adhesión molecule 1), expresadas en las células del endotelio vascular sinovial están involucradas en el desarrollo y progresión de la enfermedad. El objetivo fue investigar la asociacion entre los polimorfismos G721A de ICAM-1, G1238C de VCAM-1, los niveles de sICAM y sVCAM en la actividad clinica de pacientes con AR.

Metodos: Se incluyeron 60 pacientes con AR clasificados de acuerdo los criterios del ACR (1987) y 60 controles clínicamente sanos (CCS), no relacionados entre sí, definidos como población de mestizos mexicanos. Los niveles de sICAM-1 y sVCAM-1 se determinaron con la técnica de ELISA y el factor reumatoide (FR), velocidad de sedimentación globular (VSG) y proteína C reactiva (pCr) por métodos convencionales. Los genotipos se caracterizaron por PCR-RFLP´s. La actividad de la enfermedad se evaluó con los índices Spanish HAQ-DI y DAS28. El análisis estadístico se realizo con SPSS v 10.0.

Resultados: En AR, el alelo A721 (ICAM-1) (OR=1.9 [(95%)CI 1.02-3.65]) y el fenotipo A (G/A+A/A) OR=2.3 [(95%)IC 1.11-5.04], (p<0.05), se asociaron con AR.

El grupo de AR mostró niveles incrementados de sICAM-1 y sVCAM-1 (´x=284 y 481 ng/mL respectivamente *p*=0.002) *vs* CCS. Encontramos correlaciones significativas entre: i) sICAM-1 y sVCAM-1 con FR (0.404 y 0.442, respectivamente); ii) sVCAM-1 con VSG (0.426), y con los índices Spanish HAQ-DI (0.276) y DAS28 (0.342) p<0.05.

Conclusiones: El polimorfismo de *ICAM-1* se asocia con AR en pacientes del Occidente de México. Los niveles séricos de sVCAM-1 pueden ser usados como marcadores clínicos de actividad en AR.

P03

VARIANTE C677T DEL GEN DE LA METILENO-TETRAHIDROFOLATO REDUCTASA EN PACIENTES CON ARTRITIS REUMATOIDE TRATADOS CON METOTREXATE. IMPLICACIÓN CON AUMENTO EN EL NIVEL DE TRANSAMINASAS.

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Introducción: La variante C677T del gen de la enzima metileno-tetrahidrofolato- reductasa (MTHFR), involucrada en el metabolismo de la homocisteína, ha sido considerada como factor de riesgo genético para la elevación del nivel de las transaminasas en pacientes con artritis reumatoide (AR) tratados con metotrexate (MTX).

Objetivo: Determinar el genotipo de los pacientes con AR tratados con MTX y su posible asociación con el incremento en los niveles séricos de transaminasas.

Pacientes y métodos: Estudio transversal analítico que incluyó 71 pacientes con AR (ACR 1987) tratados con MTX. Datos demográficos, clínicos, de laboratorio y tratamiento fueron obtenidos mediante cuestionario. Análisis molecular: la región de interés se amplificó y sometió a digestión mediante PCR/RFLP *Hinf1*. Análisis estadístico, la distribución alélica para las poblaciones fue comparada usando X^2.

Resultados: El 18% (13/71) de los pacientes tuvieron elevación de transaminasas. Las frecuencias génicas –FG- (n, %) del grupo total de pacientes fueron: CC (20, 28%), CT (38, 54%), TT (13, 18%); las frecuencias alélicas –FA- C (78, 55%) y T (64, 45%). Las FG del subgrupo de AR-MTX sin aumento de transaminasas fueron CC (18, 31%) CT (30, 52%) TT (10, 17%). Con FA para C (66, 57%) y T(50, 43%). Las FG entre el subgrupo AR-MTX con incremento de transaminasas: CC (3, 23%) CT (8, 62%) TT (2, 15%) con FA, C (14, 54%) y T (12, 46%). La FA de T fue mayor en los AR-MTX con elevación de transaminasas (46 vs 43). El 77 % de los pacientes que presentaron transaminasemia tuvieron al menos un alelo mutado, comparado con el 69% que no desarrollaron este evento.

Conclusión: En individuos con AR que reciben MTX la identificación del genotipo MTHFR CT o TT, podría ser útil como un predictor de riesgo de elevación de transaminasas en estos pacientes, lo que implicaría establecer tratamiento más individualizado.

P04

PROSTAGLANDINS AS AUTACOIDS IN HUMAN OSTEOCLASTS.

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Introduction: Osteoclasts are central elements in the pathophysiology of rheumatoid arthritis and osteoporosis. Prostaglandins, which are produced by bone and present in high levels in inflammatory exsudates have complex actions on bone metabolism through multiple influences on both osteoblasts and osteoclasts., but little is known about PG production and receptors in osteoclasts. Our objective was to determine if human osteoclasts present the enzymes needed for prostaglandin synthesis, phospholipase A2 (PLA2) and cyclooxygenase (COX), if they actually produce prostaglandins and to determine the eventual impact of these eicosanoids on cell functions.

Methods: Experiments were performed on human osteoclast-like (hOCL) cells differentiated from peripheral blood mononuclear cells in the presence of M-CSF and RANKL. COX and PLA2 activities were evaluated at the single cell level using fluorescent probes and immunohistochemistry. hOCL were partially purified, allowing the recovery of a fraction enriched in multinucleated cells used to investigate bone resorption and total prostaglandin production.

Results Obtained and Conclusion: Human osteoclasts present strong cytosolic PLA2 as well as COX-1 and COX-2 activities, results confirmed by immunohistochemistry in human bone. An enriched population of hOCL (82.5  2.2% of the cells were TRAP-positive and had more than 3 nuclei) produced prostaglandins in basal conditions and this production was inhibited by cyclooxygenase inhibitors. Specific inhibition of COX-1 increased bone resorption but COX-2 inhibition had no effect on this parameter.

Brief Conclusion: This is the first study to show that human osteoclasts present phospholipase A2 and cyclooxygenase activity and actively produce prostaglandins. They support the hypothesis that prostaglandins could be autacoids implicated in the autoregulation of osteoclast activity. More interestingly, although both COX-1 and COX-2 were present and active in these cells, only the COX-1 pathway seems to be implicated in the inhibition of bone resorption by osteoclasts. Further studies are being performed to identify the specific prostaglandins produced by these cells and to characterize the receptors implicated in their effects.

P05

BIOMARKERS DIFFERENTIATE PRE-RADIOGRAPHIC AND RADIOGRAPHIC SYMPTOMATIC KNEE OSTEOARTHRITIS FROM SYMPTOMATIC CONTROLS: RESULTS OF A POPULATION-BASED STUDY USING MRI

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Objective: To determine the association of cartilage biomarkers with pre-radiographic and radiographic symptomatic knee OA compared to symptomatic normal controls.

Methods: Subjects, 40-79 years, with knee pain were assembled, stratified by age decade and gender, in a cross-sectional population-based study and evaluated clinically, with MRI, xray, serum and urine biomarkers (Ibex). MR cartilage (MRC) defects (score 0-4) and xrays (Kellgren-Lawrence [KL] grade 0-4) were read blinded. Subjects were classified as No OA (NOA) (KL<2, MRC=0), pre-radiographic OA (PROA) (KL<2, MRC>0) or radiographic OA (ROA) (KL>1, MRC>0). Serum was analyzed for type II collagen degradation (C2C), type I and II collagen degradation (C1,2C), type II procollagen synthesis (CPII), aggrecan epitope 846 (846) and ratios of C1,2C/C2C, C1,2C*CPII/C2C, C2C/CPII and C2C/846. Urine was analyzed for C2C and C1,2C. Multicategory logistic regression (adjusted for age, sex, BMI) was used to evaluate the association of OA category (using NOA as the

reference group) with each log transformed biomarker, incorporating stratum sampling weights.

Results Obtained and Conclusion: Of 201 Caucasians, 9% had NOA, 54% PROA and 37% ROA. None of the biomarkers distinguished PROA from ROA. However, the risk of ROA compared to NOA was significantly reduced for CPII (per 0.35 unit increase) (OR 0.72, 95%CI 0.54-0.96), and increased for C2C/CPII (per 0.29 unit increase) (OR 1.42, 95%CI 1.03-1.96). For both ROA and PROA compared to NOA, urine C2C (per 0.35 unit increase) (OR 1.63, 95%CI 1.05-2.53; and OR 1.60, 95%CI 1.06-2.42, respectively) and urine C1,2C (per 0.64 unit increase) (OR 1.63, 95%CI 1.06-2.50 and OR 1.62, 95%CI 1.09-2.40, respectively) were increased significantly.

Brief Conclusion: In this population-based study, biomarkers did not differentiate between MRI-defined PROA and ROA. However, serum and urine type II collagen synthesis and degradation markers were significantly associated with ROA and urine degradation markers were associated with PROA.

Po6

RECOGNIZING OSTEOPOROSIS AND ITS CONSEQUENCES IN QUEBEC (ROCQ): THE CARE GAP FOLLOWING A FRAGILITY FRACTURE

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Objective: The objective of this analysis is to evaluate the diagnostic and treatment rates of osteoporosis six months following a fragility fracture in women 50 years and over participating in a patient health-management programme (ROCQ).

Methods: Seventeen centers in three socio-sanitary regions in the Province of Quebec (Canada) are participating in the ROCQ programme. At phase 1, women with fractures are recruited during their visit to a cast or outpatient clinic and later contacted by phone to answer a short questionnaire to identify the specific circumstances of their fracture. During the first phone contact, there is no reference about the possible association between their fracture and osteoporosis, and no investigation or intervention is proposed. Six months after the fracture event, women are contacted for a second time by phone (phase 2) to determine the diagnostic (informed of osteoporosis and/or BMD measurement with diagnosis of osteoporosis) and treatment (bisphosphonates, raloxifene, nasal calcitonin or teriparatide) rates of osteoporosis.

Results Obtained and Conclusion: After 22 months, 1,774 women (mean age: 65.8 years) completed phase 1. A total of 1,456 (82%) sustained a fragility fracture and 318 (18%) sustained a traumatic fracture. The ratio of fragility: traumatic fractures increased with age. Eighty-one out of 468 women (17%) with fragility fracture who completed the questionnaire at phase 2 were already on treatment for osteoporosis at the time of their fracture. Of those who were not prescribed an osteoporosis treatment at phase 1, 18% initiated pharmacological therapy within the six-month period following their fracture. At phase 2, 27% of participants either received a diagnosis of osteoporosis or were on treatment despite that 73% of these women consulted a physician (other that an orthopaedic surgeon) during the six to eight months between phases 1 and 2.

Brief Conclusion: In ROCQ, 82% of fractures were considered related to osteoporosis, higher than previously reported (70% over age 45). Despite the availability of adequate diagnostic modalitie and effective treatments for osteoporosis, there is a substantial care gap in the management of this disease. The proportion of fragility fractures is higher than expected and the management of osteoporosis is not optimal.

Po7

RASGOS Y ESTILOS DE ENFRENTAMIENTO EN ENFERMEDADES REUMÁTICAS

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La forma en que el enfermo reumático se enfrenta a su enfermedad se relaciona con su apego al tratamiento, calidad de vida y discapacidad laboral. El término enfrentamiento se refiere al conjunto de pensamientos, sentimientos y acciones con los que el enfermo responde a los problemas con el fin de conservar un estado de bienestar. La identificación de enfrentamiento incluye las dimensiones "estabilidad" (rasgo) y varias más que obedecen a situaciones específicas (estados). El enfrentamiento se relaciona directamente con el contexto cultural en el que vive el individuo.

Objetivo: Describir las características del enfrentamiento utilizado por enfermos reumáticos.

Material y métodos: Estudiamos una cohorte de 694 pacientes con artritis reumatoide de reciente inicio [ARRI; 37%], espondilitis anquilosante [EA; 32.6%] y gota [29.7%] asistentes a 11 centros de atención médica de la SS, IMSS; PEMEX y consulta privada en 5 ciudades del país. En la visita inicial, se aplicó un cuestionario con 6 dimensiones: 1. vida (rasgo) y 2. salud, familia, amigos, pareja y escuela/trabajo (estados). Cada dimensión incluye 4 categorías de enfrentamiento: directo, emocional, evasivo y re-valorativo. El punto de corte para las categorías se estableció en 4; en cada dimensión, la categoría de mayor puntaje fue considerada como predominante.

Resultados: Todos los participantes respondieron las dimensiones de vida y salud; 40.1% no respondió el apartado de escuela/trabajo por no asistir a la escuela o estar desempleado; 20.9 % no respondió el apartado acerca de la pareja y 15.1% el de los amigos por no contar con uno y otros. El patrón re-valorativo predominó en el rasgo de vida: ARRI 14.6, EA 15.7 y gota 14.8. El patrón evasivo predominó en la situación salud (ARRI 20.2 y ; EA 21.3 y gota 26.3; $p < 0.001$), en la familia (ARRI 17.2, EA 18.5 y gota 17.5; $p = 0.03$), en los amigos (ARRI 19.5, EA 17 y gota 19.7; $p=0.03$), en la pareja (ARRI 16.3, EA 18.2 y gota 16.4; $p<0.001$) y en la escuela/trabajo (ARRI 16.5, EA 17.9 y gota 17.9, $p=0.14$).

Conclusiones: El estado evasivo predominó en todas las dimensiones; el puntaje mayor se encontró en la dimensión salud. Esta observación tiene implicaciones clínicas importantes ya que el estado evasivo se ha asociado a un menor apego terapéutico y menor calidad de vida.

Po8

DEVELOPMENT AND VALIDATION OF THE EDMONTON ANKYLOSING SPONDYLITIS METROLOGY INDEX (EDASMI)

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Objective: Assessment of spinal and hip mobility has been recommended by the Assessments in AS Working Group (ASAS)though 2 of the

3 recommended measures, occiput-to-wall and the modified Schober's, primarily reflect structural damage. One composite measure has also been developed, the Bath AS Metrology Index (BASMI), though 2 of the 5 measures primarily reflect structural damage. Our objective was to validate a simple, 4-item composite measure of spinal and hip mobility, the Edmonton AS Metrology Index (EDASMI), which measures cervical rotation, chest expansion, lateral lumbar flexion, and internal rotation of the hip, but only requires the use of a tape measure.

Methods: We assessed the EDASMI and the BASMI in a total of 263 patients from 3 countries, Canada (n = 205), Australia (n = 29), and Colombia (n = 29), that included patients from community and tertiary-based practice. Intra- and inter-observer reliability was assessed in 44 patients by ANOVA. The Bath AS Disease Activity (BASDAI), and Function (BASFI) Indices, and the modified Stoke AS Spinal Score (mSASSS), were recorded to assess construct validity. Responsiveness was assessed in a subset of 33 patients that were either randomized to anti-TNF therapy:placebo (n = 22) or received open label infliximab (n = 4) or pamidronate (n = 7) over 24 weeks.

Results Obtained and Conclusion: The measures comprising the EDASMI, as well as the composite itself, were normally distributed whilst 3 of the BASMI measures, tragus-to-wall, modified Schober's, intermalleolar distance, and the BASMI itself, demonstrated substantial floor effects. Both the EDASMI and the BASMI were highly reliable (ICC >0.90 for both intra- and inter-observer reproducibility) and demonstrated similar construct validity (correlations for EDASMI with age (0.44), disease duration (0.52), BASDAI (0.24), BASFI (0.61), BASRI (0.79), mSASSS (0.75); $p < 0.001$ for all). The change in EDASMI was significant after 24 weeks of therapy (standardized response mean = 0.40; $p = 0.03$) but not for the BASMI.

Brief Conclusion: The EDASMI is a simple, rapid, and reliable tool for the routine assessment of hip and spinal mobility in AS that is responsive to therapeutic intervention.

P09

DIFFERENCES IN THE MINIMALLY CLINICALLY IMPORTANT DIFFERENCE (MCID) IN THE HEALTH ASSESSMENT QUESTIONNAIRE DISABILITY INDEX (HAQ-DI) BETWEEN IMPROVEMENT AND WORSENING IN RA PATIENTS

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Objective: We wanted to determine the relationship between patients changing on a 5 point likert overall scale (from much worse, worse, same, better, much better) and the change in HAQ-DI.

Methods: The MCID for the HAQ-DI in RA (rheumatoid arthritis) from RCTs has been described as 0.2 to 0.22 on a 0 to 3 scale. 245 patients with RA serially seen by one rheumatologist and followed for a subsequent visit completed the HAQ-DI and global likert scale. Statistical analyses were done to determine those who were the same, worse or much worse and what the mean HAQ-DI change (most recent subtract baseline) and range was in each group, and likewise comparisons were made between same, better and much better.

Results Obtained and Conclusion: The mean age was 60.5 years; 82% were women and mean HAQ was 1.0 ± 0.05. The mean HAQ-DI change to move one point on the likert scale from same to worse was 0.15 and from same to better was -0.09. There was a dose response where the change for much worse or much better was large (0.50 for much worse, 0.15 for worse, 0.028 for same, −0.09 for better, and −0.57 for much better, $p<0.0001$).

Brief Conclusion: In RA clinical practice, the MCID is similar or better than that in clinical trials. There may also be directional asymmetry. This has been described by others in global assessments where patients are more apt to be optimistic, requiring more change to rate themselves as worse (vs. same or better). The MCID results are bidirectionally different and this should be considered when interpreting RA studies that use the HAQ-DI.

P10

CYTOKINE PROFILES OF SERUM PROTEOMIC PATTERNS IN THE SERA OF PEDIATRIC PATIENTS WITH MACROPHAGE ACTIVATION SYNDROME (MAS): IMPLICATIONS FOR RAPID DIAGNOSIS

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Objective: Macrophage activation syndrome (MAS) is a life threatening clinical entity caused by pathological activation and proliferation of mature macrophages. It can be primary (familial hemophagocytic lymphohistiocytosis) or secondary to rheumatic diseases, infections or malignancies. Currently the diagnostic gold standard for MAS is biopsy documented hemophagocytosis in the bone marrow, liver, spleen, or lymph nodes. Limitations to biopsy include patchy disease with a high false negative rate, risk of anesthesia and post-procedural bleeding. Delay in diagnosis often contributes to delayed treatment and subsequently high morbidity and mortality.

We postulated that diverse immunological pathways that ultimately lead to the common end result of activated macrophages would involve distinct set of cytokines. Our objective was to test known MAS patients' sera with a high-throughput multiplexed antibody array technique to identify possible "MAS cytokine signature" to aid in rapid diagnosis.

Methods: Sera were collected from three patients at time of MAS diagnosis (biopsy confirmed) before treatment was initiated. Sera from age and sex matched normal children was used as controls.

Sera (50 microliters) diluted in blocking buffer were incubated with arrays containing antibodies to an extensive set of inflammatory cytokines and peptides. Proteins bound to respective antibodies were detected by pooled secondary antibodies labeled with biotin and avidin linked HRPO and developed with luminescent reagents. Resulting images were captured with a digital camera and quantified using Image J visual analysis software.

Results Obtained and Conclusion: All patients had elevated IL-6. Compared to controls, patients had distinct patterns of increased cytokines and related proteins, including enhanced expression of IL-8, IL-10, MCP-1, RANTES, MIG and GRO. These findings were validated by conventional ELISA. The test provided rapid results in 3 hours.

Brief Conclusion: 1) Common inflammatory cytokine IL-6 was consistently elevated in all MAS patients' sera tested.2) Each patient had a specific cytokine profile but a small group of cytokines were common to all patients. 3)If these "signatures" are consistently found in an expanded sample size, these findings can be used as a tool for rapid and non-invasive diagnosis of MAS. Such signatures would also facilitate accurate classification of MAS and related conditions.

P11

POLIMORFISMOS DE UN SOLO NUCLEÓTIDO (SNPS) EN EL GEN DE LA ENZIMA CATECOL-O-METILTRANSFERASA (COMT) COMO MARCADORES DE SUSCEPTIBILIDAD AL DOLOR EN PACIENTES CON FIBROMIALGIA.

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Se ha propuesto que la fibromialgia (FM) es un síndrome doloroso mantenido por hiperactividad simpática (Curr Pain Headache Rep 2004;8:385). La catecol-O-metil-transferasa (COMT) es la vía catabólica primordial de los neurotransmisores simpáticos. Recién se ha publicado que existen varios SNPs en el gen de la COMT que están fuertemente ligados a una enzima COMT defectuosa y que se asocian a una hipersensibilidad al dolor en personas sanas (Hum Mol Genet 2005;14:135).

El objetivo de nuestra investigación fue el explorar la presencia de los SNPs de susceptibilidad al dolor del gen de la COMT en pacientes con FM.

Se estudiaron 25 mujeres con FM y 25 mujeres sanas de edades similares. Se aisló el DNA genómico de sangre. Se exploraron los SNPs de gen de la COMT asociados a sensibilidad al dolor en personas sanas: rs4633, rs4818, rs6269 y rs165599. Se utilizó la técnica PCR en tiempo real con las sondas Taq Man 5' Exonucleasa.

Resultados: Un genotipo asociado a la susceptibilidad al dolor en personas sanas, el C/C del SNP rs4818 fue mas frecuente en las pacientes (33% vs 17.5% que en las controles). Otro genotipo asociado a la resistencia al dolor en personas sanas, G/G del SNP rs165599, se encontró significativamente mas escaso en las pacientes vs controles (16% vs 43%) p=0.036, OR=0.25.

Conclusiones: Estos datos sugieren que la disfunción autonómica de muchas pacientes con FM está genéticamente determinada por una enzima COMT defectuosa y por otro lado dan sustento genómico a la propuesta de la FM como síndrome doloroso mantenido por hiperactividad simpática.Estudio patrocinado por la American Fibromyalgia Syndrome Association.

P12

INDUCCIÓN DE AUTOANTICUERPOS Y VIRAJE DEL FENOTIPO LINFOCITARIO DE T_H1 A T_H2 POSTERIOR A BLOQUEO DE LA COESTIMULACIÓN EN PACIENTES CON ARTRITIS REUMATOIDE

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Resumen: Mas del 50% de pacientes con AR tratados con infliximab desarrollan autoanticuerpos (ANA y anti-dsDNA). CTLA-4Ig es una molécula diseñada para bloquear la coestimulación de LT que ha demostrado ser eficaz en AR; no se ha reportado desarrollo de ANA a los 6 meses de uso.

Estudiamos 14 pacientes con AR incluidos en un ensayo clínico con CTLA-4Ig. Se buscó la presencia de ANA (^{3}1:80) y anti-dsDNA (>99 U/mL) a las 0, 24, 48, 72 y 96 semanas. Se detectaron ANA en el 7.1, 14.2, 30.7, 35.7 y 54.5% de pacientes (p=0.045 [0 vs 96]), respectivamente. Los anti-dsDNA fueron negativos excepto a las 78 semanas (28.5% [p=0.015]).

CTLA-4 une de manera preferencial a CD80, por lo que CTLA-4Ig podría mantener la coestimulación mediada por CD86, la cual induce diferenciación hacia T_H2. Se midió IFNg e IL4 séricos antes y a los 6 meses en 2 pacientes con CTLA-4Ig, 1 con infliximab y 1 sin tratamiento biológico. La relación IFNg/IL4 en la medición basal fue de 1.3, 0.17, 0.27 y 0.28, respectivamente; a los 6 meses fue de 0.28, 0.16, 0.19 y 0.30. El índice IFNg/IL4 disminuyó de manera considerable (-78.5%) en el paciente con CTLA-4Ig cuya relación estuvo elevada inicialmente, mientras que se mantuvo en los demás pacientes (-5.9, -29.6 y +7.1%).

CTLA-4Ig sí induce autoanticuerpos a largo plazo y puede desviar el perfil de citocinas de T_H1 a T_H2 en pacientes con una relación IFNg/IL4 inicial elevada, mientras que no la modifica en aquellos con una relación baja. Este viraje a T_H2 podría facilitar la producción de autoanticuerpos y ser un mecanismo de acción adicional de CTLA-4Ig no descrito previamente.

P13

REACTIVIDAD DE LOS ANTICUERPOS ANTI-β_2GP-I DE PACIENTES MEXICANOS CON SAF CONTRA LA β_2GP-I HUMANA DE LOS FENOTIPOS VALINA/VALINA (VV), VALINA/LEUCINA (VL) Y LEUCINA/LEUCINA (LL) EN LA POSICIÓN 247.

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Resumen: El genotipo V^{247} de la β_2GP-I está asociado a títulos altos de aβ_2GP-I-IgG y a trombosis arteriales en pacientes mexicanos con SaFP.

Objetivo: Estudiar la reactividad de los aβ_2GP-I de los pacientes con SaF contra la β_2GP-I de fenotipos VV, VL y LL^{247}.

Métodos: Estudiamos 55 pacientes con SaF secundario a LEG, 38 con SaFP y 44 sujetos sanos. Determinamos el polimorfismo de la β_2GP-I^{247} por PCR-RLFP. Purificamos β_2GP-I de los 3 fenotipos (cromatografía de afinidad) y detectamos aβ_2GP-I-IgG contra cada uno (ELISA) en placas no irradiadas. Determinamos los valores normales de aβ_2GP-I para cada fenotipo (90 percentila). Estadística: U-Mann Whitney y exacta de Fisher.

Resultados: Los títulos de aβ_2GP-I contra los 3 fenotipos fue mayor en los pacientes con SaFS y SaFP que los controles (p<0.001). El 80% (44/55) de los pacientes con SaFS reconocieron el fenotipo LL y sólo el 13% de los SaFP (p<0.001). Los pacientes con SaFP tuvieron reactividades similares contra los 3 fenotipos de la β_2GP-I. El 93% de los sueros de los pacientes con SaFS con genotipo LL reconocieron primordialmente a la β_2GP-I del fenotipo correspondiente (p<0.05). El 94 y 30% de los pacientes con SaFS y SaFP tuvieron aβ_2GP-I contra dos fenotipos (p<0.001). Mientras que ningún paciente con SaFP tuvo anticuerpos contra los 3 fenotipos, el 54% de los SaFS sí los tuvieron (p<0.001)

Conclusiones: Confirmamos la importancia del polimorfismo de la β_2GP-I^{247} en la generación de aβ_2GP-I. La heterogeneidad de los aβ_2GP-I entre pacientes con SaFP y SaFS es una diferencia más entre ambas variantes.

P14

DEFLAZACORT INDUCED STRONGER IMMUNOSUPPRESSION THAN EXPECTED

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Resumen: Prednisone (PDN) impairs cognitive functioning and brain structures in humans and animals. Deflazacort (DFZ) is a synthetic glucocorticoid claimed to have less side effects than prednisone.

Objective: To assess whether chronic administration (90 days) of DFZ produces less neuronal degeneration and glial reactivity than PDN.

Methods: Male Swiss-Wistar rats were studied. Controls received 0.1 ml distilled water orally. The PDN group received prednisone 5 mg/kg/day orally, and the DFZ group received deflazacort 6 mg/kg/day orally. This model had to be assembled in three different occasions due to excess mortality in the DFZ group. A four model was assembled using only the DFZ group and slides of water- and PDN-exposed rats from a previous study were used as comparators. The index of degenerated neurons and the number and cytoplasmic transformation of astrocytes and microglia cells were evaluated in the prefrontal cortex, CA1 and CA3 hippocampus.

Results: The overall mortality was 49% in the DFZ group, 4.5% in the PDN group and none of the controls died. Routine necropsy

showed infection in multiple organs. PDN had two times higher neuronal degeneration in the prefrontal cortex, almost eleven times in CA1 and four times in CA3 hippocampus when compared with controls and DFZ group. Astrocytes reactivity was increased in the PDN- and DFZ-exposed rats compared with controls. The DFZ group showed an average of four times less microgial cells in the three studied regions when compared with controls and the PDN group.

Conclusions: It seems that DFZ at the equivalent licensed dose produced a stronger immunosuppressive effect –systemic and in brain tissue-- than PDN, but induced less neuronal damage. The immunesuppressant magnitude of DFZ should be further studied in clinical settings.

P15

EN RELACIÓN A LA VALIDEZ APARENTE Y DE CONTENIDO DEL INSTRUMENTO: "SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS / AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX" (SLICC) EN LAS FORMAS JUVENILES DE LUPUS ERITEMATOSO SISTÉMICO (LES)

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Introducción: Diferentes estudios cuestionan la sensibilidad (validez aparente y de contenido) del SLICC como instrumento para evaluar daño acumulativo en las formas juveniles de LES.

Objetivo: Determinar el índice total de daño (SLICC / ACR-DI), así como la frecuencia de los diferentes órganos o sistemas afectados que toma en cuenta el instrumento en pacientes con formas juveniles de LES en conjunto con otras variables clínicas.

Métodos: Estudio transversal analítico en donde se incluyeron los datos de la última visita, de pacientes con diagnóstico de LES (4 criterios de clasificación según el ACR), de al menos 6 meses de evolución, con edad de inicio <18 años y con evaluación clínica completa (peso, talla, Tanner, características en su caso de menarca e SLICC-DI). Falla en el crecimiento fue definida como talla debajo del percentil 5 para la edad. Retraso puberal fue definido como cambios puberales tardios (>2.5 DE) de la media para la edad. Amenorrea primaria fue definida con la ausencia de menarca a los 16 años de edad.

Resultados: Un total de 1015 pacientes (edad media al diagnóstico: 11.9 ± 3.1; duración media de la enfermedad (años): 4.0 ± 3.6; edad media de la última evaluación del SLICC (años): 15.9 ± 4.1). Un total de 610 niños (60.1%) tuvo un SLICC / ACR-DI=0; 213 (21%) de 1; 79 (7.8%) de 2; 50 (4.9%) de 3; 25 (2.5%) de 4; 19 (1.9%) de 5 y el otro 1% con calificaciones entre 6 hasta 12. El daño ocurrió primariamente a nivel renal (132 [13.0%]), neuro-psiquiátrico (109 [10.7%]), músculo-esquelético (109 [10.7%]), ocular (83 [8.2%]) y cutáneo (77 [7.6%]). Proteinuria en rango nefrótico, diagnosticada en 103 (10.1%), fué el daño renal más frecuente y la complicación más frecuente vista en estos pacientes. Mielitis transversa, claudicación, diabetes y los dominios cardiopulmonar y gastrointestinal con excepción de enfermedad valvular, pericarditis e infarto / resección gastrointestinal tuvieron una frecuencia menor al 0.5%. No se encontraron complicaciones como: angina o infarto al miocardio, ruptura tendinosa, o malignidad. Por el contrario: 115 (11%) pacientes cumplieron la definición de falla en el crecimiento, retraso puberal en 53 (5.3%) pacientes y amenorrea primaria en 46 niñas (4.6%).

Conclusión: La validez aparente y de contenido del SLICC indica que es un instrumento con poca sensibilidad (validez cualitativa) para su uso en Pediatría. Deberán de desarrollarse instrumentos que detecten daño en los pacientes pediátricos principalmente en su crecimiento y desarrollo.

P16

MEASUREMENT OF DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) USING MICROARRAY GENE EXPRESSION ANALYSIS

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Objective: Assessment of disease activity in SLE incorporates measurement of multiple clinical and laboratory variables. As a-dsDNA antibodies (Ab) are present in only 70% of patients at diagnosis and up to 25% of patients are serologically discordant, there is a need for better biomarkers of SLE disease activity. We sought to determine whether the gene expression profile of SLE patients, measured using microarray technology correlates with disease activity measured using SLEDAI.

Methods: RNA isolated from peripheral blood of 253 SLE patients was profiled on a custom SLE focus microarray comprised of 423 probes (329 genes) selected from a pilot study comparing profiles generated on Affymetrix Genechips from 72 SLE and 81 comparison samples. A heat map was generated and hierarchical clustering yielded two major clusters: 'high' and 'low' interferon (IFN)-regulated gene expression profiles. Clustering was refined to 146 probes (100 genes). Factors associated with IFN-regulated gene expression were determined using statistical methods. Categorical and continuous variables were analyzed using Fishers exact (or Chi-square) and Mann-Whitney test respectively. Stepwise logistic regression was performed.

Results Obtained and Conclusion: 152 patients had high and 101 patients had low IFN-regulated gene signature. SLEDAI was higher in those with high IFN-regulated gene expression (SLEDAI 4.5 vs. 2.9, $p<0.001$). Patients with high IFN signatures were younger (42.2 vs. 49.6 years, $p<0.001$). In logistic regression analysis, age, arthritis, positive a-dsDNA Ab and low complement ($p<0.007$) were significantly associated with high IFN-regulated gene expression. Only 72 (47%) of 152 patients with high IFN-regulated gene signature and 18 (18%) of 101 patients with low IFN-regulated gene signature had a-dsDNA Ab.

Brief Conclusion: Disease activity was higher in SLE patients with high IFN-regulated gene expression. Anti-dsDNA Ab was a significant but not the sole correlate of IFN-regulated gene expression. The role of microarray gene expression analysis in assessment of SLE disease activity, especially in the subset of patients with serologically discordant disease merits further investigation in a longitudinal study.

P17

EVIDENCE FOR ABNORMAL B AND T CELL ACTIVATION IN LUPUS PATIENTS BUT NOT THEIR PARENTS

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Objective: SLE is a complex genetic disease, with multiple genetic and environmental factors contributing to its pathogenesis. In animal models of lupus, mice with a single or small cluster of lupus susceptibility genes demonstrate abnormal lymphocyte activation in the absence of full-blown symptoms of lupus, suggesting that abnormal lymphocyte activation may be a useful marker of genetic susceptibility to lupus. To examine this possibility in humans, we characterized the lymphocyte activation phenotype in SLE patients and investigated whether their family members have a similar activation profile.

Methods: Peripheral blood was obtained from 99 patients with SLE and their parents, and 25 healthy controls. Peripheral blood mononuclear cells were isolated over a Ficoll gradient, stained with various combinations of differentiation and activation markers, and subjected to flow cytometry with 20,000 to 200,000 events being acquired, depending on the stain. Information on age, gender, ethnicity, drug treatment, and disease activity was obtained using a standardized protocol as part of the Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus (CaNIOS). Non-parametric statistical methods were used to compare measures of differentiation and activation in cases and controls. A regression analysis, accounting for family clustering, gender, and age, was performed to compare parental results to cases and controls.

Results Obtained and Conclusion: Several peripheral blood lymphoid subsets were altered in lupus patients as compared to controls. There was a significantly increased proportion of naïve B cells and significantly decreased proportions of memory B cells, CD4+ T cells, and NKT cells. Lupus patients also had evidence of increased lymphocyte activation, with increased proportions of recently activated CD69+ B and T cells, and increased expression of B7.2 on both naïve and memory B cells. Our preliminary analysis of the parents of lupus patients revealed no evidence of abnormal lymphocyte activation, however we are continuing to recruit siblings and additional age-matched controls.

Brief Conclusion: Lupus patients have increased B cell and T cell activation. At present we do not have strong evidence for abnormal lymphocyte activation in the parents of these patients.

P18

IMMUNIZATION WITH BACTERIAL HSP65 INDUCES A BREAK IN TOLERANCE TO SELF-HSP60

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Objective: Anti-heat shock protein (hsp) 60 autoantibodies from SLE patients induce endothelial cell apoptosis in vitro, and are associated with an increased frequency of thrombosis in patients with lupus anticoagulant antibodies (Dieudé et al. Arthritis Rheum., 2004). However, little is known about the trigger that leads to the break in tolerance against this self-protein. We propose two hypotheses to explain the appearance of these autoantibodies. The first is that endothelial activation induces overexpression and secretion of hsp60, thereby presenting high amounts of a normally intracellular protein self-protein to the immune system. The alternative hypothesis is that the immune system encounters bacterial hsp65, which induces a crossreactive response to hsp60 due to the highly conserved nature of this protein across different species.

Methods: In order to test our hypotheses, we have immunized C57BL/6 mice biweekly with 10 micrograms of either mouse hsp60 or bacterial hsp65 with or without incomplete Freund's adjuvant (IFA). We have then monitored the development of anti-hsp60 and anti-hsp65 in the sera of the immunized mice by enzyme-linked immunoassay following each immunization.

Results Obtained and Conclusion: High titers of anti-hsp65 were detected in mice immunized with hsp65 and IFA after the first immunization, and in mice immunized with hsp65 alone after two immunizations. In contrast, no antibody response to either hsp60 or hsp65 was observed in mice immunized with hsp60 even following the fourth immunization. However, high titers of anti-hsp60 antibodies were observed in some of the mice immunized with hsp65 and IFA after only two immunizations. These data suggest that autologous hsp are not immunogenic even when introduced at high concentration, but that bacterial hsp is able to induce a response to self-hsp in mice immunized with hsp65. We propose that bacterial infection, through molecular mimicry, could trigger a break in tolerance to self-hsp, leading to the production of anti-hsp60 autoantibodies and the eventual endothelial injury and thrombosis in SLE patients.

P19

ANORMALIDADES EN EL FLUJO SANGUÍNEO CEREBRAL DE PACIENTES CON SÍNDROME DE ANTICUERPOS ANTIFOSFOLÍPIDO PRIMARIO DEMOSTRADAS POR DOPPLER TRANSCRANEAL. UN ESTUDIO CONTROLADO

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Introducción: El Doppler Transcraneal (DTC) permite estudiar la circulación cerebral y puede ser útil en la evaluación de pacientes con Síndrome de Anticuerpos Antifosfolípido Primario (SAAFP).

Objetivo: Evaluar los patrones de DTC en pacientes con SAAFP.

Pacientes y métodos: Se incluyeron pacientes con SAAFP y controles sanos pareados por edad y género. Se les efectuó DTC a través de ventana temporal, orbitaria y occipital con medición de la velocidad media (VM) de flujo de las arterias craneales. Se consideró DTC anormal si las velocidades medias salían del rango normal de acuerdo a la edad o presencia de asimetría de flujo (diferencia de > 20% entre el flujo derecha-izquierda). Al momento del estudio ninguno de los pacientes presentaba manifestaciones neurológicas. Se utilizaron medidas de tendencia central y dispersión, chi cuadrada y prueba de T de Student para la comparación de medias.

Resultados: Se estudiaron 24 pacientes con SAAFP, 15 mujeres y 9 hombres con edad de 41.4 ± 11.2 años (rango: 20-60), tiempo de evolución de 11 ± 2.7 años (rango: 6-16) y 18 controles sanos. Solamente 5 pacientes tuvieron antecedente de evento vascular cerebral. Al comparar la VM (cm/seg) en ambos grupos ésta fue significativamente superior en el grupo de pacientes con SAAFP en comparación con los controles ($p< 0.05$) en arterias cerebrales medias (70.4 ± 19.15 vs 58.3 ± 10.3), anteriores (64.8 ± 23.3 vs 48.9 ± 9.7), posteriores (50.3 ± 17.4 vs 38.6 ± 7.9), vertebrales (45.1 ± 13.1 vs 35.6 ± 5.3) y basilar (47 ± 16.9 vs 37 ±5.6). No se encontró variabilidad en cuanto a asimetría de flujo en ambos grupos.

Conclusiones: Este estudio demuestra que los pacientes con SAAFP presentan alteraciones importantes en la velocidad de flujo cerebral en la mayoría de las arterias en comparación con los controles. Estas anormalidades pueden estar en relación a aterosclerosis acelerada subclínica y/o vasculopatía por SAAFP.

P20

RECENT CORTICOSTEROID USE AND RECENT DISEASE ACTIVITY: ARE THEY INDEPENDENT DETERMINANTS OF CORONARY HEART DISEASE RISK FACTORS IN SYSTEMIC LUPUS ERYTHEMATOSUS?

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Objective: Systemic lupus erythematosus (SLE) is characterized by a markedly elevated risk for coronary heart disease (CHD), the exact pathogenesis of which is unknown. In particular, the causal roles of corticosteroid therapy and SLE disease activity and whether their pu-

tative effects are mediated through conventional risk factors remain unclear.

Methods: Data abstracted retrospectively from the charts at 11,359 available clinic visits for 310 SLE patients were used to investigate the associations of (i) recent corticosteroid dose and (ii) recent Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, with each of eight CHD risk factors (total serum cholesterol, HDL-cholesterol, LDL-cholesterol, Apolipoprotein B, triglycerides, systolic blood pressure (SBP), body mass index (BMI), and blood glucose), as well as the aggregate estimate of two-year CHD risk. Separate multivariable hierarchical linear regression models estimated the mutually adjusted effects of average daily corticosteroid dose and average SLEDAI score within past year on the current level of each risk factor while adjusting for age, sex, cumulative damage score, disease duration, and, where appropriate, use of relevant medications.

Results Obtained and Conclusion: Higher past-year corticosteroid dose was independently associated with significantly higher overall two-year CHD risk and higher levels of all eight individual risk factors. Higher past-year lupus disease activity level was independently associated with higher overall two-year CHD risk and lower HDL-cholesterol and higher values of SBP, Apolipoprotein B, triglycerides, and blood glucose.

Brief Conclusion: In SLE, both recent use of corticosteroids and recent lupus activity are independently associated with higher values of several well-recognized CHD risk factors and overall two-year CHD risk.

P21

DIFFERENTIAL AGE OF ONSET BETWEEN MEXICAN AND CANADIAN RHEUMATOID ARTHRITIS (RA) PATIENTS

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Resumen: The mean age of RA onset is 49 yrs as reported in several clinical trials involving Caucasian patients. Yet our clinical observations suggest that Mexican RA patients' disease is initiated at a younger age.

Objective: To explore the age of onset in Mexican and Canadian RA patients.

Methods: Certified Rheumatologist from Canada and Mexico directly interviewed consecutive rheumatoid arthritis patients attending their clinics regarding the date patient first noticed a swollen joint. None of the participant rheumatologists were aware of the primary aim of this exploratory study at the time of the interviews. Differences between two continuous variables were determined using t-test; differences between three continuous variables were determined using one way ANOVA, and Scheffé for multiple comparisons. Differences in proportions were determined using chi-squared. Significance was set at p £ 0.05.

Results: At the time of submission of this abstract, data is available from 89 Mexican (91% women) and 64 Canadian patients (72% women) collected by 3 rheumatologists in each country. Disease onset was not different within countries. However, there were significant differences in the age of onset between Mexican patients and Canadian patients (36 ± 11 yrs in Mexicans. Vs. 48 ± 15 in Canadians, p< 0.001; mean difference 11.3 years). Frequency distribution by age groups showed that almost 50% of Mexicans but only 23% of Canadians had their first swollen joint before the age of 35 yrs. In contrast, almost one third of Canadians but only 4% of Mexicans had onset of disease after the age of 56 yrs. (all p<0.001).

Conclusions: It appears that RA begins at a much younger age in Mexican than Canadian patients. If this is confirmed after controlling for different confounders and biases, it would have important societal, economic and therapeutic implications.

P22

RHEUMATIC DISEASE IN ABORIGINAL MANITOBANS

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Objective: To describe the prevalence and spectrum of rheumatic disease in Manitoba's Aboriginal (First Nations/ Métis) people.

Methods: The prevalence of rheumatic disease was ascertained using three separate data sources: Physician visits for 3 common ICD-9 musculoskeletal diagnoses were abstracted from the Manitoba Health (MH) database for Registered First Nations (RFN) Manitobans compared to all other Manitobans. Self-reported arthritis rates were obtained from the Manitoba First Nations Regional Longitudinal Health Survey (MFNRLHS), which surveyed Manitoba First Nations on-reserve. Data on ethnicity and diagnoses was abstracted from the Arthritis Centre (AC) research database, which contains records of all patients seen at the AC.

Results Obtained and Conclusion: MH data demonstrated twice the rate of rheumatoid arthritis (RA), degenerative arthritis, and undifferentiated arthropathy in RFN Manitobans compared to all other Manitobans. MFNRLHS data identified rates of self-reported arthritis of 20%, with rates of RA of 3.0%. Thirty percent of RFN Manitobans reported stiff and painful joints in the last year; only 51% consulted a physician for these symptoms. Data for 687 Aboriginal patients, and 4135 Caucasian patients was abstracted from the AC database. The number of Aboriginal patients was proportional to the provincial representation at 13.4%, in spite of the higher rates of arthritis identified above. Prevalence rates of inflammatory rheumatologic diseases, including RA, lupus, juvenile RA, vasculitis and reactive arthritis, were two to four times higher than that seen for Caucasians, while referrals for osteoarthritis and other non-inflammatory conditions were significantly less frequent in Aboriginal patients compared to Caucasians. Aboriginal patients had an earlier disease onset of arthritis (34 vs. 43 years) using both MH and AC data, adding to the burden of disease.

Brief Conclusion: The data highlights increased prevalence of a wide spectrum of rheumatic disease in Aboriginal Manitobans. However, many Aboriginal people not accessing care for their symptoms, and for those that do, there is a relative under-referral to specialists. There are large gaps in our knowledge of how, why and when Aboriginal Manitobans access medical care, and how they experience interaction with the medical system. Further research into these areas is urgently needed.

P23

¿CAMBIARÁ LA PERCEPCIÓN DE CALIDAD DE VIDA RELACIONADA A LA SALUD (CVRS) EN NIÑOS CON ARTRITIS IDIOPÁTICA JUVENIL (AIJ), DE TRES REGIONES GEOGRÁFICAS DIFERENTES?

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Objetivos: 1) Identificar diferencias en CVRS en niños con AIJ de tres diversas zonas geográficas. 2) Investigar si las diferencias son secundarias al estado clínico de los pacientes.

Métodos: Evaluación de las variables de mejoría en AIJ (ACR-Ped-30) y de CVRS con el "Child Health Questionnaire Parent Form 50®" (CHQ) en 3167 niños con AIJ de 30 países, en un diseño transversal analítico. Los países fueron divididos en tres regiones: 1) Europa Occidental (EOc): Austria, Bélgica, Dinamarca, Finlandia, Francia, Alemania, Grecia, Italia, Holanda, Noruega, Portugal, España, Suecia, Suiza, Reino Unido, e Israel. 2) Europa Oriental (EOr): Bulgaria, Croacia, Checoslovaquia, Georgia, Hungría, Latvia, Polonia, Rusia, Eslovaquia y Serbia-Montenegro. 3) Latino-América (LA): Brasil, México, Argentina y Chile. Las diferencias entre las tres regiones para el ACR-Ped-30 y el CHQ, fueron identificadas mediante análisis de la varianza y la prueba "post-hoc" de Scheffé. Los predictores clínicos para obtener una calificación física (CHQ-CF) y psicológica (CHQ-CP) <30 (<2 DE) del CHQ fueron obtenidos por medio de análisis de regresión logística.

Resultados: La evaluación clínica y de CVRS fue completada por 2749 niños con AIJ (EOc: n=1783; EOr: n=593; LA: n=373). No se encontraron diferencias significativas entre las tres regiones con el CHQ-CF y el CHQ-CP. Sin embargo, la salud en general, el dolor corporal, la autoestima, la percepción general de salud, el cambio en el estado de salud y la cohesión familiar, fueron los conceptos de salud del CHQ estadísticamente diferentes en las tres regiones (p<0.001). El índice de discapacidad del "Child Health Assessment Questionnaire" (CHAQ) y la EVA de dolor incluida en el mismo, fueron, entre otros, los predictores clínicos más importante para un CHQ-CF (<30) [OR: 4.9; IC95%: 3.4-6.9; (p<0.0001)]; y un CHQ-CP (<30) [OR: 4.1; IC95%: 2.2-1.7; (p<0.0001)]; respectivamente, en las tres regiones estudiadas.

Conclusión: Los cambios en el estado clínico de los pacientes con AIJ de las tres estudiadas predicen cambios en CHQ-CF y el CHQ-CP; por lo que el CHQ es un instrumento de medición de CVRS útil relacionado al estado clínico del paciente. No se pueden descartar otros factores socioculturales o etno-raciales en los conceptos de salud del CHQ que fueron diferentes en las tres regiones.

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LONG-TERM OUTCOME IN A KAWASAKI DISEASE COHORT TREATED WITH INTRAVENOUS IMMUNOGLOBULIN AND LOW DOSE ASPIRIN: EVALUATION WITH ECHOCARDIOGRAPHY AND EXERCISE CHALLENGE

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Objective: Patients with Kawasaki disease (KD) may be at risk for late cardiac complications. We have followed a cohort of KD patients since 1985. Here we report on their long-term outcome, including the results of a sub-group evaluated by combined exercise stress single photon emission computed tomography using 99mTc-Sestamibi (stress-MIBI testing).

Methods: We reviewed the records of 221 patients admitted with a diagnosis of KD between 1985 and 1999 and treated in the acute phase with IVIG and low dose aspirin. This cohort was contacted to conduct late follow-up echocardiograms (echo). KD patients identified as having echo abnormalities on early (within 8 weeks of diagnosis) or late follow-up were matched 1:1 with KD patients (controls) who showed no echo abnormalities, and both groups were recruited to undergo stress-MIBI testing with continuous ECG monitoring.

Results Obtained and Conclusion: Of the 221 patients, 159 underwent late follow-up echos a mean of 8.2 years (2.2 - 17.1) after diagnosis. Retrospective evaluation of early follow-up data revealed that 38/159 (23.9%) had echo abnormalities, of whom 12/38 had coronary artery lesions (CAL) for an incidence of 7.5% (12/159); 121/159 had no echo abnormalities. All 38 had complete resolution of original abnormalities, while 8 of the 38 (21.1%) developed new pathology on long-term follow-up; 1/8 had new CALs. Seven of the 121 patients (5.8%) without cardiac abnormalities on early follow-up had echo abnormalities on late follow-up (including 1/7 with a new CAL). Thirty-five patients underwent stress-MIBI testing on late follow-up, 18 with echo abnormalities either at early or late follow-up, and 17 without abnormalities. Of the 18 with abnormalities, 1 had an abnormal stress ECG. Of the 17 controls, 1 had an abnormal stress ECG and 1 had an abnormal stress-MIBI.

Brief Conclusion: Late cardiac abnormalities are uncommon. However, our study shows that cardiac abnormalities may appear late, even in patients with no previous evidence of cardiac involvement. Long-term cardiology follow-up is warranted in all patients with a history of KD.