El material que se presenta a continuación proviene de los datos proporcionados por la OAIC (Oficina de Apoyo a la Investigación Clínica) de nuestro Hospital, así como de los recolectados por nuestra Revista.

Abstracts de publicaciones internacionales ISI

ANATOMÍA PATOLÓGICA

RESPIROLOGY (2015) 20, 873–883

HISTOPATHOLOGY OF THE IDIOPATHIC INTERSTITIAL PNEUMONIAS (IIP): A REVIEW

Gabriela C. Tabaj, Cristina F. Fernandez, Eduardo Sabbagh, Kevin O. Leslie

The 2013 American Thoracic Society/European Respiratory Society consensus classification update of the idiopathic interstitial pneumonias (IIP) included several important Modifications to the organization and spectrum of the diseases that were proposed in an earlier multidisciplinary consensus document in 2002. The histopathology of the now 'major' and 'rare' IIP is presented here with exposition of the newly included entity of a distinctive upper lobe fibrotic lung disease referred to as idiopathic pleuroparenchymal fibroelastosis. The 'rare histological patterns' of acute fibrinous and organizing pneumonia and bronchiolocentric patterns of interstitial pneumonia are illustrated and discussed.

DIS MARKERS. 2015;2015:503762.

NONCODING GENOMICS IN GASTRIC CANCER AND THE GASTRIC PRECANCEROUS CASCADE: PATHOGENESIS AND BIOMARKERS.

Sandoval-Bórquez A, Saavedra K, Carrasco-Avino G, Garcia-Bloj B, Fry J, Wichmann I, Corvalán AH.

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death, whose patterns vary among geographical regions and ethnicities. It is a multifactorial disease, and its development depends on infection by Helicobacter pylori (H. pylori) and Epstein-Barr virus (EBV), host genetic factors, and environmental factors. The heterogeneity of the disease has begun to be unraveled by a comprehensive mutational evaluation of primary tumors. The low-abundance of mutations suggests that other mechanisms participate in the evolution of the disease, such as those found through analyses of noncoding genomics. Noncoding genomics includes single nucleotide polymorphisms (SNPs), regulation of gene expression through DNA methylation of promoter sites, miRNAs, other noncoding RNAs in regulatory regions, and other topics. These processes and molecules ultimately control gene expression. Potential biomarkers are appearing from analyses of noncoding genomics. This review focuses on noncoding genomics and potential biomarkers in the context of gastric cancer and the gastric precancerous cascade.

ONCOL REP. 2015 APR;33(4):1599-608.

PROAPOPTOTIC EFFECT OF ENDOCANNABINOIDS IN PROSTATE CANCER CELLS.

Orellana-Serradell O, Poblete CE, Sanchez C, Castellón EA, Gallegos I, Huidobro C, Llanos MN, Contreras HR.

In the early stages, prostate cancer is androgen- dependent; therefore, medical castration has shown significant results during the initial stages of this pathology. Despite this early effect, advanced prostate cancer is resilient to such treatment. Recent evidence shows that derivatives of Cannabis sativa and its analogs may exert a protective effect against different types of oncologic pathologies. The purpose of the present study was to detect the presence of cannabinoid receptors (CB1 and CB2) on cancer cells with a prostatic origin and to evaluate the effect of the in vitro use of synthetic analogs. In order to do this, we used a commercial cell line and primary cultures derived from prostate cancer and benign prostatic hyperplasia. The presence of the CB1 and CB2 receptors was determined by immunohistochemistry where we showed a higher expression of these receptors in later stages of

the disease (samples with a high Gleason score). Later, treatments were conducted using anandamide, 2-arachidonoyl glycerol and a synthetic analog of anandamide, methanandamide. Using the MTT assay, we proved that the treatments produced a cell growth inhibitory effect on all the different prostate cancer cultures. This effect was demonstrated to be dose-dependent. The use of a specific CB1 receptor blocker (SR141716) confirmed that this effect was produced primarily from the activation of the CB1 receptor. In order to understand the MTT assay results, we determined cell cycle distribution by flow cytometry, which showed no variation at the different cell cycle stages in all the cultures after treatment. Treatment with endocannabinoids resulted in an increase in the percentage of apoptotic cells as determined by Annexin V assays and caused an increase in the levels of activated caspase-3 and a reduction in the levels of Bcl-2 confirming that the reduction in cell viability noted in the MTT assay was caused by the activation of the apoptotic pathway. Finally, we observed that endocannabinoid treatment activated the Erk pathway and at the same time, produced a decrease in the activation levels of the Akt pathway. Based on these results, we suggest that endocannabinoids may be a beneficial option for the treatment of prostate cancer that has become nonresponsive to common therapies.

CARDIOLOGÍA

PHARMACOL REP. 2015 APR;67(2):399-403.

INVOLVEMENT OF NITRIDERGIC AND OPIOIDERGIC PATHWAYS IN THE ANTINOCICEPTION OF GABAPENTIN IN THE OROFACIAL FORMALIN TEST IN MICE.

Miranda HF, Sierralta F, Lux S, Troncoso R, Ciudad N, Zepeda R, Zanetta P, Noriega V, Prieto JC.

BACKGROUND: Pain is one of the most common problems in clinical medicine. There is considerable evidence that pharmacologic approaches are the most widely used therapeutic options to ameliorate persistent or chronic pain. In this study it was evaluated the effect of l-NAME and naltrexone in the antinociception induced by administration of gabapentin in the orofacial formalin test of mice. METHODS: The algesiometer assay was performed by the administration of 20 µl of 2% formalin solution injected into the upper right lip of each mouse. RESULTS: The dose of gabapentin that produces the 50% of the maximum possible effect (ED50) was significantly increased by the pretreatment with l-NAME or naltrexone. CONCLUSIONS: These results suggest that gabapentin produce antinociception partly via the activation nitridergic pathways and opioid system.

PHARMACOLOGY. 2015;95(1-2):59-64.

ANTINOCICEPTIVE SYNERGISM OF GABAPENTIN AND NORTRIPTYLINE IN MICE WITH PARTIAL SCIATIC NERVE LIGATION.

Miranda HF, Noriega V, Zepeda R, Zanetta P, Prieto-Rayo J, Prieto JC, Sierralta F.

BACKGROUND AND METHODS: Neuropathic pain results from nerve injury, and gabapentin, an antiepileptic drug, has been approved for the treatment of several types of neuropathic pain. On the other hand, nortriptyline, an antidepressant drug, has been suggested as an alternative treatment. In partial sciatic nerve ligation (PSNL) mice, the interaction of gabapentin with nortriptyline was evaluated by the hot plate assay using isobolographic analysis. RESULTS: Gabapentin (3-100 mg/kg, i.p.) or nortriptyline (1-30 mg/kg, i.p.) induced dose-dependent antinociception, with an ED50 of 11.60 ± 0.54 mg/kg for gabapentin and of 5.16 ± 0.21 mg/kg for nortriptyline. The potency of gabapentin and nortriptyline in PSNL mice at 7 and 14 days after ligation was significantly increased ($p < 0.05$). Coadministration of gabapentin with nortriptyline, at a 1:1 ratio of their ED50, had a synergistic effect, with an interaction index of 0.311 and 0.348 for these mice at 7 and 14 days, respectively. CONCLUSION: The data showed a synergy in antinociception at a gabapentin-to-nortriptyline ratio of 1:1 in PSNL mice. This finding suggests that this combination could provide a therapeutic alternative that can be used for neuropathic pain management.

CIRUGÍA

OBES SURG (2015) 25:2430–2435

GASTROESOPHAGEAL REFLUX DISEASE AND SLEEVE GASTRECTOMY

John Melissas, Italo Braghetto, Juan Carlos Molina,, Gianfranco Silecchia, Angelo Iossa, Antonio Iannelli, Mirto Foletto

Gastroesophageal reflux disease (GERD) and/or hiatus hernia (HH) are one of the most common disorders of the upper gastrointestinal tract. Despite the positive effect of sleeve gastrectomy (SG) regarding weight loss and improvement in obesity co-morbidities, there are concerns about the development of de novo gastroesophageal reflux disease or worsening the existing GERD after this bariatric operation. Furthermore, controversy exists on the consequences of SG in lower esophageal sphincter function and about the ideal procedure when a hiatus hernia is preoperatively diagnosed or discovered during the laparoscopic SG. This review systematically

investigates the incidence, the pathophysiology of GERD and/or HH in morbidly obese individuals before and after SG, and the treatment options for concomitant.

DERMATOLOGÍA

PEDIATRIC DERMATOLOGY 2015, VOL. 32 NO. 4 468–475

COLOR DOPPLER ULTRASOUND FOLLOW-UP OF INFANTILE HEMANGIOMAS AND PERIPHERAL VASCULARITY IN PATIENTS TREATED WITH PROPRANOLOL

Ana M. Kutz, Ligia Aranibar, Nelson Lobos, Ximena Wortsman

Background: Infantile hemangiomas (IHs) are the most common vascular tumors in childhood. Diagnosis of IHs is usually clinical, however, to determine the actual dimensions of the lesion or the anatomic changes that occur during its evolution and treatment, a color Doppler ultrasound (CDU) examination can be performed. To date, there are few publications that assess the sonographic response to propranolol in IHs, and to our knowledge, none that consider simultaneous evaluation of both intralesional and normal peripheral blood vessels in these cases. Objective: Evaluation of the anatomic effect of propranolol in IHs and peripheral blood vessels using CDU. Methods: A cohort study was performed in 10 pediatric patients with a diagnosis of IH in whom systemic therapy with propranolol was indicated. The patients underwent a baseline and 3-month follow-up CDUs of the tumor and the main peripheral vessels of the right upper extremity. Results: The group was composed of 7 (70%) girls and 3 (30%) boys. The average CDU decrease in size of the longitudinal axis was 11%; of the transverse axis, 24%; tumor thickness, 30%; and intralesional vessel thickness, 46%. Hemangioma volume measured by CDU decreased an average of 51%. The thickness of the peripheral vessels did not change significantly between the baseline and 3-month follow-up CDUs. Conclusion: CDU permits noninvasive quantification of the changes in IHs and peripheral vessels in patients receiving propranolol therapy. In our cohort of cases there was a significant reduction in tumor volume; however, peripheral vascularity was not significantly affected.

BMC DERMATOL. 2015 MAY 8;15:8.

EFFECTS OF TOFACITINIB ON LYMPHOCYTE SUB-POPULATIONS, CMV AND EBV VIRAL LOAD IN PATIENTS WITH PLAQUE PSORIASIS.

Valenzuela F, Papp KA, Pariser D, Tyring SK, Wolk R, Buonanno M, Wang J, Tan H, Valdez H

BACKGROUND: Plaque psoriasis is a debilitating skin condition that affects approximately 2% of the adult population and for which there is currently no cure. Tofacitinib is an oral Janus kinase inhibitor that is being investigated for psoriasis. METHODS: The design of this study has been reported previously (NCT00678210). Patients with moderate to severe chronic plaque psoriasis received tofacitinib (2 mg, 5 mg, or 15 mg) or placebo, twice daily, for 12 weeks. Lymphocyte sub-populations, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) DNA were measured at baseline and up to Week 12. RESULTS: Tofacitinib was associated with modest, dose-dependent percentage increases from baseline in median B cell count at Week 4 (24-68%) and Week 12 (18-43%) and percentage reductions from baseline in median natural killer cell count at Week 4 (11-40%). The proportion of patients with detectable CMV and EBV DNA (defined as >0 copies/500 ng total DNA) increased post-baseline in tofacitinib-treated patients. However, multivariate analyses found no relationship between changes in CMV or EBV viral load and changes in lymphocyte sub-populations or tofacitinib treatment. CONCLUSIONS: Twelve weeks of treatment with tofacitinib had no clinically significant effects on CMV or EBV viral load, suggesting that lymphocyte sub-populations critical to the response to chronic viral infections and viral reactivation were not significantly affected. Replication of these findings during long-term use of tofacitinib will allow confirmation of this observation.

LANCET 2015; 386: 552–61

TOFACITINIB VERSUS ETANERCEPT OR PLACEBO IN MODERATE-TOSEVERE CHRONIC PLAQUE PSORIASIS: A PHASE 3 RANDOMISED NON-INFERIORITY TRIAL

Hervé Bachelez, Peter C M van de Kerkhof, Robert Strohal, Alexey Kubanov, Fernando Valenzuela, Joo-Heung Lee, Vladimir Yakusevich, Sergio Chimenti, Jocelyne Papacharalambous, James Proulx, Pankaj Gupta, Huaming Tan, Margaret Tawadrous, Hernan Valdez, Robert Wolk, for the OPT Compare Investigators

Background New therapeutic options are needed for patients with psoriasis. Tofacitinib, an oral Janus kinase inhibitor, is being investigated as a treatment for moderate-to-severe chronic plaque psoriasis. In this study, we aimed to compare two tofacitinib doses with high-dose etanercept or placebo in this patient population. Methods In this phase 3, randomised, multicentre, double-dummy, placebo-controlled, 12-week, non-inferiority trial, adult patients with chronic stable plaque psoriasis (for ≥12

months) who were candidates for systemic or phototherapy and had a Psoriasis Area and Severity Index (PASI) score of 12 or higher and a Physician's Global Assessment (PGA) of moderate or severe, and had failed to respond to, had a contraindication to, or were intolerant to at least one conventional systemic therapy, were enrolled from 122 investigational dermatology centres worldwide. Eligible patients were randomly assigned in a 3:3:3:1 ratio to receive tofacitinib 5 mg or 10 mg twice daily at about 12 h intervals, etanercept 50 mg subcutaneously twice weekly at about 3–4 day intervals, or placebo. Randomisation was done by a computer-generated randomisation schedule, and all patients and study personnel were masked to treatment assignment. The co-primary endpoints were the proportion of patients at week 12 with at least a 75% reduction in the PASI score from baseline (PASI75 response) and the proportion of patients achieving a PGA score of "clear" or "almost clear" (PGA response), analysed in the full analysis set (all patients who were randomised and received at least one dose of study drug). This study is registered with ClinicalTrials.gov, number NCT01241591. Findings Between Nov 29, 2010, and Sept 13, 2012, we enrolled 1106 eligible adult patients with chronic plaque psoriasis and randomly assigned them to the four treatment groups (330 to tofacitinib 5 mg twice daily, 332 to tofacitinib 10 mg twice daily, 336 to etanercept 50 mg twice weekly, and 108 to placebo). Of these patients, 1101 actually received their assigned study medication (329 in the tofactinib 5 mg group, 330 in the tofacitinib 10 mg group, 335 in the etanercept group, and 107 in the placebo group). At week 12, PASI75 responses were recorded in 130 (39·5%) of 329 patients in the tofacitinib 5 mg group, 210 (63·6%) of 330 in the tofacitinib 10 mg group, 197 (58·8%) of 335 in the etanercept group, and six (5·6%) of 107 in the placebo group. A PGA response was achieved by 155 (47·1%) of 329 patients in the tofacitinib 5 mg group, 225 (68·2%) of 330 in the tofacitinib 10 mg group, 222 (66·3%) of 335 in the etanercept group, and 16 (15·0%) of 107 in the placebo group. The rate of adverse events was similar across the four groups, with serious adverse events occurring in seven (2%) of 329 patients in the tofacitinib 5 mg group, fi ve (2%) of 330 in the tofacitinib 10 mg group, seven (2%) of 335 in the etanercept group, and two (2%) of 107 in the placebo group. Three (1%) of 329 patients in the tofacitinib 5 mg group, ten (3%) of 330 in the tofacitinib 10 mg group, 11 (3%) of 335 in the etanercept group, and four (4%) of 107 patients in the placebo group discontinued their assigned treatment because of adverse events. Interpretation In patients with moderate-to-severe plaque psoriasis, the 10 mg twice daily dose of tofacitinib was non-inferior to etanercept 50 mg twice weekly and was superior to placebo, but the 5 mg twice daily dose did not show non-inferiority to etanercept 50 mg twice weekly. The adverse event rates over 12 weeks were similar for tofacitinib and etanercept. This study indicates that in the future tofacitinib could provide a convenient and well-tolerated therapeutic option for patients with moderate-to-severe plaque psoriasis.

J EUR ACAD DERMATOL VENEREOL. 2015 APR;29(4):702-7.

ULTRASOUND AS PREDICTOR OF HISTOLOGIC SUBTYPES LINKED TO RECURRENCE IN BASAL CELL CARCINOMA OF THE SKIN.

Wortsman X, Vergara P, Castro A, Saavedra D, Bobadilla F, Sazunic I, Zemelman V, Wortsman J.

BACKGROUND: Basal cell carcinoma (BCC) recurrences, especially in the facial region, represent a complex cosmetic problem. To date the possibility of predicting recurrence is supported solely by the histologic subtype. OBJECTIVE: To evaluate the relationship between BCC histologic subtypes linked to high and low risk of recurrence and the presence of hyperechoic spots on sonography. METHODS: Retrospective analysis of the pre-surgical ultrasound examinations of primary BCC tumours with visualization and counting of intra-tumoural hyperechoic spots. The data were then correlated with the corresponding histologic subtype. RESULTS: Thirty one patients with histologically proven BCC were included in the study. Hyperechoic spots were detected in all cases and there was a positive, statistically significant association between hyperechoic spots count and high recurrence risk histologic subtypes. Higher hyperechoic spots count was found in the recurrence-prone micronodular, sclerosing variant and morpheiform BCC subtypes. Low risk and high risk of recurrence showed a significant difference on the mean hyperechoic spots count of 5.5 (range: 3-25) and 8 (4-81). A cut-off point ≥7 hyperechoic spots presented a sensitivity of 79% and specificity of 53% for predicting the high risk of recurrence subtypes. CONCLUSION: The presence and count of hyperechoic spots within BCC lesions may help predicting the high risk of recurrence histologic subtypes.

INTERNATIONAL JOURNAL OF DERMATOLOGY. DOI: 10.1111/IJD.13147

CUTANEOUS GRANULOMAS IN GRISCELLI TYPE 2 SYNDROME

Carmen L. Navarrete, Ligia Araníbar, Felipe Mardones, Ricardo Avila, Luis Velozo.

Griscelli syndrome (GS) is a rare autosomal recessive disease that may compromise the skin, nervous, immune, and lymphoreticular systems as well as solid internal organs. Mutations in genes responsible for cellular membrane trafficking control have been identified. This may explain the dysfunction of melanocytes, neurons, and immune cells.[1] Correlation between genetic defects

and clinical manifestations have been reported: neurologic defects are frequent and severe in type 1 GS, milder in type 2, and absent in type 3. Immunological abnormalities such as hypogammaglobulinemia, natural killer cell dysfunction, and infiltration of lymphoid organs are observed only in types 2 and 3.[2] Type 2 GS has a poor prognosis, with rapid development of hemophagocytic syndrome and death in the absence of bone marrow transplantation. Dermatological signs are usually limited to characteristic silvery scalp hair and eyebrows and skin hypopigmentation.[3] Few reports of other cutaneous manifestations in GS have been published. In this case, we describe a child with type 2 GS associated with granulomatous lesions.

INDIAN J DERMATOL. 2015 JUL-AUG;60(4):421.

MULTIDIMENSIONAL ULTRASOUND AND COMPUTED TOMOGRAPHY IMAGING SUPPORT IN BLEEDING PLEXIFORM NEUROFIBROMATOSIS OF THE SCALP: A CASE REPORT AND LITERATURE REVIEW.

Wortsman X, Lobos N, De la Parra R, Carreno L.

Active bleeding in plexiform neurofibromatosis can be a life-threatening complication in neurofibromatosis type 1 (NF1). The prompt imaging support of 2D-3D ultrasound (US) and computed tomography (CT) during the active hemorrhage phase of cutaneous neurofibromas has not been previously reported. We report a case with NF1 who experienced a sudden swelling in the parieto-temporal region that corresponded to a massive and active hemorrhage within a plexiform neurofibroma. The US and CT imaging characteristics of this bleeding tumor are shown. Active hemorrhage in a plexiform neurofibroma of the scalp appeared in US as a heterogeneous hypodermal mass. CT demonstrated a fully hyperdense soft tissue mass. These characteristics differ from the non-complicated or old hemorrhagic imaging appearances of scalp plexiform neurofibromas and encourage prompt surgical treatment. This case report demonstrates the usefulness of imaging support in the early diagnosis of this hemorrhagic complication of NF1 in the scalp and also stimulates multispecialty management.

IMAGENOLOGÍA

ANAT REC (HOBOKEN). 2015 JUL;298(7):1261-70.

THE PREDICTABILITY FROM SKULL MORPHOLOGY OF TEMPORALIS AND MASSETER MUSCLE CROSS-SECTIONAL AREAS IN HUMANS.

Toro-Ibacache V, Zapata MuÑoz V, O'higgins P.

To carry out functional simulations of the masticatory system that aim to predict strain magnitudes it is important to apply appropriate jaw-elevator muscle forces. Force magnitude estimation from directly measured muscle physiological cross-sectional area or anatomical cross-sectional area (CSA) is not possible for fossils and skeletal material from museum collections. In these cases, muscle CSAs are often estimated from bony features. This approach has been shown to be inaccurate in a prior study based on direct measurements from cadavers. Postmortem alterations as well as age changes in muscle form might explain this discrepancy. As such, the present study uses CT images from 20 living individuals to directly measure temporalis and masseter muscle CSAs and estimated cross-sectional areas (ECSAs) from bony features. The relationships between CSAs and ECSAs were assessed by comparing mean values and by examining correlations. ECSAs are up to 100% greater than CSA and the means of these variables for each muscle differ significantly. Further, ECSA is significantly correlated with CSA for temporalis but not masseter. Cranial centroid size is only significantly associated with CSA for temporalis. These findings indicate that ECSAs should be employed with caution in simulations of human masticatory system functioning; they do not reflect CSAs and it is plausible that this also applies to studies of closely related living and fossil taxa. When ECSAs are used, sensitivity analyses are required to determine the impact of potential errors.

RESPIR MED. 2015 JUL;109(7):882-9

EMPHYSEMA AND DLCO PREDICT A CLINICALLY IMPORTANT DIFFERENCE FOR 6MWD DECLINE IN COPD.

Díaz AA, Pinto-Plata V, Hernández C, Peña J, Ramos C, Díaz JC, Klaassen J, Patino CM, Saldías F, Díaz O.

BACKGROUND: Exercise impairment is a central feature of chronic obstructive pulmonary disease (COPD), and a minimal clinically important difference (MCID) for 6-min walk distance (6MWD) decline (>30 m) has been associated with increased mortality. The predictors of the MCID are not fully known. We hypothesize that physiological factors and radiographic measures predict the MCID. METHODS: We assessed 121 COPD subjects during 2 years using clinical variables, computed tomographic (CT) measures of emphysema, and functional measures including diffusion lung capacity for carbon monoxide (DLCO). The association between an MCID for 6MWD and clinical, CT, and physiologic predictors was assessed using logistic analysis. The C-statistic was used to assess the predictive ability of the models. RESULTS: Forty seven (39%) subjects had an MCID. In an imaging-based model, log emphysema

and age were the best predictors of MCID (emphysema Odds Ratio [OR] 2.47 95%CI [1.28-4.76]). In a physiologic model, DLCO, age, and male gender were selected the best predictors (DLCO OR 1.19 [1.08-1.31]). The C-statistic for the ability of these models to predict an MCID was 0.71 and 0.75, respectively. CONCLUSION: In COPD patients the burden of emphysema on CT scan and DLCO predict a clinically meaningful decline in exercise capacity.

DEPARTAMENTO DE MEDICINA

GASTROENTEROLOGÍA

ANTIVIR THER. 2015;20(4):453-6. DOI: 10.3851/IMP2886.

GENOTYPE F OF HEPATITIS B: RESPONSE TO INTERFERON.

Venegas M, Poniachik J, Fuster F, Hurtado C, Villanueva RA, Brahm J.

BACKGROUND: The relevance of HBV genotype diversity on interferon (IFN) therapy outcome in chronic hepatitis B patients has recently been highlighted. Data available for genotype F is poor. The aim of this work was to analyse the response of HBV genotype F to treatment with IFN. Additionally, response was analysed according to the role of single nucleotide polymorphisms (SNPs) near to the IL28B gene. METHODS: A total of 29 HBeAg-positive patients with chronic infection were included with a median age 47 (18-68) years. Of them, 27 were male. One patient was treated with standard IFN-α for 16 weeks, 6 patients received PEG-IFN-α2a 180 µg weekly for 24 weeks and 22 patients for 48 weeks. Response to treatment was defined as loss of HBeAg, anti-HBe seroconversion and decline of HBV DNA level to below 3 log of baseline (IU/ml) at the 6-month of follow-up. The SNPs rs12979860, rs12980275 and rs8099917 were studied by PCR-RFLP. RESULTS: The overall response was obtained in 18 (62%) patients, including one patient who was treated with standard IFN. Additionally, a total of 9 (31%) patients cleared HBsAg, with appearance of anti-HBs. The viral load was undetectable in all of these patients. The same IL28B variants associated with IFN response in HCV infections were also more frequently found in HBV patients compared with non-responders. CONCLUSIONS: Our study indicates that treatment with IFN is effective in patients with HBV genotype F.

DIS MARKERS. 2015;2015:128653

ALPHA-2-MACROGLOBULIN IN SALIVA IS ASSOCIATED WITH GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Aitken Saavedra, Juan; Ortiz, Carolina; Morales Bozo, Irene; Rojas Alcayaga, Gonzalo; Baeza Paredes, Mauricio; Beltrán Muñoz, Caroll; Escobar Álvarez, Alejandro

Background. Subjects with type 2 diabetes mellitus (DM2) require an adequate glycemic control to avoid diabetic complications. Currently, saliva biomarkers are used as a diagnostic tool and can be indicative of the degree of progression and control of various diseases. Several studies indicate that α-2-macroglobulin levels are elevated in diabetic patients. Methods. 120 subjects with DM2 were enrolled and classified into two groups according to their glycemic control (percentage of glycated hemoglobin-A1c (HbA1c), <7% adequate glycemic control group; >7% inadequate glycemic control group). The relationship between α-2-macroglobulin levels from saliva samples and HbA1c was subsequently evaluated. Results. We found a positive correlation between α-2-macroglobulin and HbA1c (and). Area under the receivers operating characteristic (ROC) curve of α-2-macroglobulin indicated a positive discrimination threshold of α-2-macroglobulin (AUC = 0.903, CI 95%: 0.847–0.959,) to diagnose glycemic control. Conclusions. Our data strongly suggest that the level of saliva α-2-macroglobulin is an indicator for the degree of glycemic control in diabetic patients and represents a promising alternative method to evaluate this parameter.

GENÉTICA

HORM RES PAEDIATR 2015;84:254–257

A DELETION OF MORE THAN 800 KB IS THE MOST RECURRENT MUTATION IN CHILEAN PATIENTS WITH SHOX GENE DEFECTS

Poggi, Helena; Vera, Alejandra; Avalos, Carolina; Lagos, Marcela; Mellado, Cecilia; Aracena, Mariana; Aravena Cerda, Teresa; García, Hernán; Godoy, Claudio; Cattani, Andreina; Reyes, Loreto; Lacourt, Patricia; Rumie, Hana; Mericq, Verónica; Arriaza, Marta; Martinez Aguayo, Alejandro

Background: Deletions in the SHOX gene are the most frequent genetic cause of Leri-Weill syndrome and Langer mesomelic dysplasia, which are also present in idiopathic short stature. Aim: To describe the molecular and clinical findings observed in 23 of 45 non-consanguineous

Chilean patients with different phenotypes related to SHOX deficiency. Methods: Multiplex ligation-dependent probe amplification was used to detect the deletions; the SHOX coding region and deletion-flanking areas were sequenced to identify point mutations and single-nucleotide polymorphisms (SNPs). Results: The main genetic defects identified in 21 patients consisted of deletions; one of them, a large deletion of >800 kb, was found in 8 patients. Also, a smaller deletion of >350 kb was observed in 4 patients. Although we could not precisely determine the deletion breakpoint, we were able to identify a common haplotype in 7 of the 8 patients with the larger deletion based on 22 informative SNPs. Conclusion: These results suggest that the large deletion-bearing allele has a common ancestor and was either introduced by European immigrants or had originated in our Amerindian population. This study allowed us to identify one recurrent deletion in Chilean patients; also, it contributed to expanding our knowledge about the genetic background of our population.

SCI REP. 2015 NOV 24;5:17154

MUTATIONS IN THE HEAT-SHOCK PROTEIN A9 (HSPA9) GENE CAUSE THE EVEN-PLUS SYNDROME OF CONGENITAL MALFORMATIONS AND SKELETAL DYSPLASIA

Royer Bertrand, Beryl; Castillo Taucher, Silvia; Moreno Salinas, Rodrigo; Cho, Tae-Joon; Chae, Jong-Hee; Choi, Murim; Kim, Ok-Hwa; Dikoglu, Esra; Campos Xavier, Belinda; Girardi, Enrico; Superti Furga, Giulio; Bonafe, Luis; Rivolta, Carlo; Unger, Sheila; Superti Furga, Andrea

We and others have reported mutations in LONP1, a gene coding for a mitochondrial chaperone and protease, as the cause of the human CODAS (cerebral, ocular, dental, auricular and skeletal) syndrome (MIM 600373). Here, we delineate a similar but distinct condition that shares the epiphyseal, vertebral and ocular changes of CODAS but also included severe microtia, nasal hypoplasia, and other malformations, and for which we propose the name of EVEN-PLUS syndrome for epiphyseal, vertebral, ear, nose, plus associated findings. In three individuals from two families, no mutation in LONP1 was found; instead, we found biallelic mutations in HSPA9, the gene that codes for mHSP70/mortalin, another highly conserved mitochondrial chaperone protein essential in mitochondrial protein import, folding, and degradation. The functional relationship between LONP1 and HSPA9 in mitochondrial protein chaperoning and the overlapping phenotypes of CODAS and EVEN-PLUS delineate a family of "mitochondrial chaperonopathies" and point to an unexplored role of mitochondrial chaperones in human embryonic morphogenesis.

INMUNOLOGÍA

FRONT IMMUNOL. 2015 SEP 29;6:496.

SYSTEMIC SCLEROSIS PATIENTS PRESENT ALTERATIONS IN THE EXPRESSION OF MOLECULES INVOLVED IN B-CELL REGULATION.

Soto L, Ferrier A, Aravena O, Fonseca E, Berendsen J, Biere A, Bueno D, Ramos V, Aguillón JC, Catalán D.

The activation threshold of B cells is tightly regulated by an array of inhibitory and activator receptors in such a way that disturbances in their expression can lead to the appearance of autoimmunity. The aim of this study was to evaluate the expression of activating and inhibitory molecules involved in the modulation of B cell functions in transitional, naive, and memory B-cell subpopulations from systemic sclerosis patients. To achieve this, blood samples were drawn from 31 systemic sclerosis patients and 53 healthy individuals. Surface expression of CD86, MHC II, CD19, CD21, CD40, CD22, Siglec 10, CD35, and FcγRIIB was determined by flow cytometry. IL-10 production was evaluated by intracellular flow cytometry from isolated B cells. Soluble IL-6 and IL-10 levels were measured by ELISA from supernatants of stimulated B cells. Systemic sclerosis patients exhibit an increased frequency of transitional and naive B cells related to memory B cells compared with healthy controls. Transitional and naive B cells from patients express higher levels of CD86 and FcγRIIB than healthy donors. Also, B cells from patients show high expression of CD19 and CD40, whereas memory cells from systemic sclerosis patients show reduced expression of CD35. CD19 and CD35 expression levels associate with different autoantibody profiles. IL-10(+) B cells and secreted levels of IL-10 were markedly reduced in patients. In conclusion, systemic sclerosis patients show alterations in the expression of molecules involved in B-cell regulation. These abnormalities may be determinant in the B-cell hyperactivation observed in systemic sclerosis.

APPL NEUROPSYCHOL CHILD. 2015;4(1):72-8.

AN 11-YEAR-OLD GIRL WITH UP TO 19,200 COUGHS PER DAY: BROADENING THERAPEUTIC STRATEGIES.

Cortes AA, Landaeta M, Silva C.

An 11-year-old girl was transferred to the Universidad de Chile Clinical Hospital after 2.5 months of persistent and unresponsive treatment for coughlike spasms. On arrival, the frequency of symptoms was 1 cough every 4 s, which disappeared during sleep. A

multidisciplinary examination excluded allergic, viral, respiratory, epileptic, and other more usual causes of similar conditions. Two diagnoses (psychogenic cough and transient vocal tic disorder) and a mixed intervention were proposed leading to resolution in 12 days of treatment. No recurrence of symptoms was observed during several evaluations within 12 months of medical follow-up. An association between the 2 diagnoses is proposed and discussed.

ALLERGY. 2015 NOV;70(11):1372-92. DOI: 10.1111/ALL.12686.

MACVIA-ARIA SENTINEL NETWORK FOR ALLERGIC RHINITIS (MASK-RHINITIS): THE NEW GENERATION GUIDELINE IMPLEMENTATION.

Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, Casale T, Guzmán MA, J et al.

Several unmet needs have been identified in allergic rhinitis: identification of the time of onset of the pollen season, optimal control of rhinitis and comorbidities, patient stratification, multidisciplinary team for integrated care pathways, innovation in clinical trials and, above all, patient empowerment. MASK-rhinitis (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) is a simple system centred around the patient which was devised to fill many of these gaps using Information and Communications Technology (ICT) tools and a clinical decision support system (CDSS) based on the most widely used guideline in allergic rhinitis and its asthma comorbidity (ARIA 2015 revision). It is one of the implementation systems of Action Plan B3 of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). Three tools are used for the electronic monitoring of allergic diseases: a cell phone-based daily visual analogue scale (VAS) assessment of disease control, CARAT (Control of Allergic Rhinitis and Asthma Test) and e-Allergy screening (premedical system of early diagnosis of allergy and asthma based on online tools). These tools are combined with a clinical decision support system (CDSS) and are available in many languages. An e-CRF and an e-learning tool complete MASK. MASK is flexible and other tools can be added. It appears to be an advanced, global and integrated ICT answer for many unmet needs in allergic diseases which will improve policies and standards.

AUTOIMMUN REV. 2015 JUN;14(6):517-27.

SKEWING DENDRITIC CELL DIFFERENTIATION TOWARDS A TOLEROGENIC STATE FOR RECOVERY OF TOLERANCE IN RHEUMATOID ARTHRITIS.

Schinnerling K, Soto L, García-González P, Catalán D, Aguillón JC.

To date, the available options to treat autoimmune diseases such as rheumatoid arthritis (RA) include traditional corticoids and biological drugs, which are not exempt of adverse effects. The development of cellular therapies based on dendritic cells with tolerogenic functions (TolDCs) has opened a new possibility to efficiently eradicate symptoms and control the immune response in the field of autoimmunity. TolDCs are an attractive tool for antigen-specific immunotherapy to restore self-tolerance in RA and other autoimmune disorders. A promising strategy is to inject autologous self-antigen-loaded TolDCs, which are able to delete or reprogram autoreactive T cells. Different protocols for the generation of stable human TolDCs have been established and the therapeutic effect of TolDCs has been investigated in multiple rodent models of arthritis. Pilot studies in humans confirmed that TolDC application is safe, encouraging clinical trials using self-antigen-loaded TolDCs in RA patients. Although an abundance of molecular regulators of DC functions has been discovered in the last decade, no master regulator of tolerogenicity has been identified yet. Further research is required to define biomarkers or key regulators of tolerogenicity that might facilitate the induction and monitoring of TolDCs.

MEDICINA NUCLEAR

J ADDICT MED. 2015 MAR-APR;9(2):139-46.

CHANGES IN REGIONAL CEREBRAL BLOOD FLOW ARE ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION MARKERS IN COCAINE-DEPENDENT PATIENTS UNDER RECENT ABSTINENCE.

Massardo T, Quintana JC, Jaimovich R, Sáez CG, Cabreras MJ, Pereira-Flores K, Ibáñez C, Pallavicini J, Véliz J, Mezzano D, Pereira J.

OBJECTIVES: Cocaine is a known risk factor for several vascular ischemic events. The underlying mechanisms leading to the complications are not fully understood, although thrombus formation and accelerated atherosclerosis are prominent findings. Evidence of endothelial dysfunction (ED), a key phenomenon in the pathogenesis of atherogenesis, has been demonstrated in cocaine-dependent individuals. Abnormal regional cerebral blood flow (rCBF) is a common finding among chronic cocaine users. The aim of this study was to evaluate whether brain perfusion changes were associated with ED markers in cocaine-dependent

individuals. METHODS: Circulating endothelial cells (CECs), soluble intercellular cell adhesion molecule, and the chemokine regulated on activation normal T cells expressed and secreted were measured in 27 DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition) cocaine-dependents patients. Regional cerebral blood flow was assessed using single-photon emission computed tomography at baseline (after recent cocaine consumption) and after 4 weeks of strict abstinence under standard benzodiazepine or antipsychotic therapy. We used statistical parametric mapping analysis to evaluate the covariates. RESULTS: Endothelial cell damage/activation markers were significantly higher in cocaine-dependent individuals after recent consumption and were reduced after 1-month abstinence ($P < 0.05$). Global rCBF exhibited no significant difference between baseline and after abstinence. When regional perfusion was analyzed in association with ED covariates, significant differences were observed in bilateral cortical areas, including the limbic lobes. CONCLUSIONS: We demonstrated an association between systemic ED markers and rCBF in cocaine-dependent patients. These findings suggest that vascular injury may play a role in the pathogenesis of abnormal rCBF.

RESPIRATORIO

EUR RESPIR J 2015; 45: 347–354

PEDOMETERS TO ENHANCE PHYSICAL ACTIVITY IN COPD: A RANDOMISED CONTROLLED TRIAL

Mendoza Inzunza, Laura; Horta, Paula; Espinoza, José; Aguilera, Miguel; Balmaceda, Nicolás; Castro Lara, Ariel; Ruiz Carmona, Mauricio; Díaz, Orlando; Hopkinson, Nicholas

Physical inactivity is a cardinal feature of chronic obstructive pulmonary disease (COPD), and is associated with increased morbidity and mortality. Pedometers, which have been used in healthy populations, might also increase physical activity in patients with COPD. COPD patients taking part in a 3-month individualised programme to promote an increase in their daily physical activity were randomised to either a standard programme of physical activity encouragement alone, or a pedometer-based programme. Assessments were performed by investigators blinded to treatment allocation. Change in average 1-week daily step count, 6-min walking distance (6MWD), modified Medical Research Council scale, St George's respiratory questionnaire (SGRQ) and COPD assessment test (CAT) were compared between groups. 102 patients were recruited, of whom 97 completed the programme (pedometer group: n=50; control group: n=47); 60.8% were male with a mean±SD age of 68.7±8.5 years, and forced expiratory volume in 1 s (FEV1) 66.1±19.4% and FEV1/forced vital capacity 55.2±9.5%. Both groups had comparable characteristics at baseline. The pedometer group had significantly greater improvements in: physical activity 3080±3254 steps·day–1 versus 138.3±1950 steps·day–1 ($p<0.001$); SGRQ –8.8±12.2 versus –3.8±10.9 ($p=0.01$); CAT score –3.5±5.5 versus –0.6±6.6 ($p=0.001$); and 6MWD 12.4±34.6 versus –0.7±24.4m ($p=0.02$) than patients receiving activity encouragement only. A simple physical activity enhancement programme using pedometers can effectively improve physical activity level and quaLity of life in COPD patients.

REUMATOLOGÍA

ACTA OPHTHALMOL. 2015 SEP;93(6):E475-80.

EARLIER IMMUNOMODULATORY TREATMENT IS ASSOCIATED WITH BETTER VISUAL OUTCOMES IN A SUBSET OF PATIENTS WITH VOGT-KOYANAGI-HARADA DISEASE.

Urzua CA, Velasquez V, Sabat P, Berger O, Ramirez S, Goecke A, Vásquez DH, Gatica H, Guerrero J.

PURPOSE: To evaluate clinical outcomes of first-line immunomodulatory therapy (IMT) and prednisone alone or late IMT in Vogt-Koyanagi-Harada disease. METHODS: Retrospective cohort study of 152 patients with Vogt-Koyanagi-Harada disease evaluated in a referral uveitis clinic in Chile from 1985 to 2011. Medical records of these patients were reviewed. Demographic data, clinical evaluation, type of treatment, functional outcomes, glucocorticoid (GC) dose and complications were recorded. Multivariate logistic regression was used to identify prognostic factors of poor response to GC. RESULTS: There were no significant differences between first-line IMT group and prednisone alone/late IMT group in terms of visual acuity (VA) improvement, complications and GC sparing effect. There was a trend for a higher frequency of systemic adverse effects leading to discontinuation of treatment in patients receiving IMT than in those receiving prednisone (14.6% and 6.5%, respectively). The subgroup of patients with poor response to GC who showed functional improvement had a significantly earlier time to IMT initiation than the patients who had no improvement. We identified following prognostic factors of poor response to GC: VA ≤ 20/200, fundus depigmentation, chronic disease and tinnitus at diagnosis. Patients with a prognostic factor (excluding tinnitus) and VA improvement had an earlier IMT initiation than those who had

worse functional outcome. CONCLUSION: There were no differences in outcomes between first-line IMT and prednisone alone/late IMT in the entire VKH group. However, in a subset of patients, there was a significant better functional outcome with earlier IMT initiation.

NEUROIMMUNOL. 2015 OCT 15;287:1-8

CATALYTIC AUTOANTIBODIES AGAINST MYELIN BASIC PROTEIN (MBP) ISOLATED FROM SERUM OF AUTISTIC CHILDREN IMPAIR IN VITRO MODELS OF SYNAPTIC PLASTICITY IN RAT HIPPOCAMPUS.

Gonzalez-Gronow M, Cuchacovich M, Francos R, Cuchacovich S, Blanco A, Sandoval R, Gomez CF, Valenzuela JA, Ray R, Pizzo SV.

Autoantibodies from autistic spectrum disorder (ASD) patients react with multiple proteins expressed in the brain. One such autoantibody targets myelin basic protein (MBP). ASD patients have autoantibodies to MBP of both the IgG and IgA classes in high titers, but no autoantibodies of the IgM class. IgA autoantibodies act as serine proteinases and degrade MBP in vitro. They also induce a decrease in long-term potentiation in the hippocampi of rats either perfused with or previously inoculated with this IgA. Because this class of autoantibody causes myelin sheath destruction in multiple sclerosis (MS), we hypothesized a similar pathological role for them in ASD.

UNIDAD DEL DOLOR

ANN RHEUM DIS. 2015 JUN;74(6):1150-5

DISCONTINUATION OF TUMOUR NECROSIS FACTOR INHIBITORS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN LOW-DISEASE ACTIVITY: PERSISTENT BENEFITS. DATA FROM THE CORRONA REGISTRY.

Kavanaugh A, Lee SJ, Curtis JR, Greenberg JD, Kremer JM, Soto L, Etzel CJ, Cox V, Yoshida K, Reed GW, Solomon DH.

BACKGROUND: There is increasing interest in discontinuing biological therapies for patients with rheumatoid arthritis (RA) achieving good clinical responses, provided patients maintain clinical benefit. METHODS: We assessed patients with RA from the Corrona registry who discontinued treatment with their first tumour necrosis factor inhibitor (TNFi) while in low-disease activity (LDA) or lower levels of disease activity. Patients were followed until they lost clinical benefit, defined as increased disease activity or change in RA medications. Duration of maintenance of clinical benefit was estimated using the Kaplan-Meier method. Cox proportional hazard models were assessed to identify factors related to maintenance of benefit. RESULTS: We identified 717 eligible patients with RA from 35,656 in the Corrona registry. At discontinuation, patients had a median RA duration of 8 years, mean clinical disease activity score of 4.3±0.11; 41.8% were using TNFi as monotherapy. 73.4% of patients maintained benefit for >12 months after discontinuing therapy and 42.2% did so through 24 months. Factors predictive of maintaining clinical benefit in multivariate analysis included lower disease activity, less pain and better functional status at the time of TNFi discontinuation. Among 301 patients initiating their first TNFi within the registry, faster responders (ie, those who achieved LDA in 4 months or less) did better than slower responders (HR 1.54 (95% CI 1.17 to 2.04)). RA disease duration did not affect maintenance of clinical benefit. CONCLUSIONS: Discontinuation of a first course of TNFi may be associated with persistent clinical benefit. Half of patients maintained response through 20 months. Several patient characteristics may help predict persistent benefit.

NEUROLOGÍA Y NEUROCIRUGÍA

CLIN AUTON RES (2015) 25:193–197

CARDIOVAGAL AND SOMATIC SENSORY NERVE FUNCTIONS IN HEALTHY SUBJECTS

Idiaquez, J.; Guiloff Davis, Roberto

Heart rate response to deep breathing (HRDB), which depends on the integrity of cardiac vagal preganglionic neurons and efferent fibers, and the function of sural nerve fibers are both associated with an age-related decline process. The aim of this study was to determine whether the effects attributed to aging on cardiovagal and sural nerve function decline are associated. HRDB and sural sensory nerve action potential (SNAP) amplitude, latency, and conduction velocity (SCV) were measured in one hundred healthy asymptomatic subjects (aged 14-92 years, 41 women). Multiple and simple linear regressions were used to analyze the relationships between the variables. There were significant linear relationships between sural SNAP amplitude and HRDB with age. There was also a significant linear relationship between sural SNAP amplitude and HRDB (correlation coefficient 0.46, $p < 0.0001$), but the model explained only 21.5 % of the variability in HRDB. Cardiovagal function assessed by HRDB is associated with sural SNAP amplitude in healthy subjects. Age-related decline only partially explained the variability seen in the association. Other genetic and environmental factors may also play a role.

MUSCLE NERVE. 2016 JAN;53(1):49-57.

TOWARD AN OBJECTIVE MEASURE OF FUNCTIONAL DISABILITY IN DYSFERLINOPATHY.

Woudt L, Di Capua GA, Krahn M, Castiglioni C, Hughes R, Campero M, Trangulao A, González-Hormazábal P, Godoy-Herrera R, Lévy N, Urtizberea JA, Jara L, Bevilacqua JA.

INTRODUCTION: Understanding the natural history of dysferlinopathy is essential to design and quantify novel therapeutic protocols. Our aim in this study was to assess, clinically and functionally, a cohort of patients with dysferlinopathy, using validated scales. METHODS: Thirty-one patients with genetically confirmed dysferlinopathy were assessed using the motor function measure (MFM), Modified Rankin Scale (MRS), Muscle Research Council (MRC) scale, serum creatine kinase (CK) assessment, baseline spirometry data, and echocardiographic and electrophysiologic studies. RESULTS: MFM and MRC scores showed a significant negative correlation with disease duration and inverse correlation with MRS, but not with onset age, clinical phenotype, or CK levels. Percent forced vital capacity (%FVC) correlated negatively with disease duration and onset age. Eight known pathogenic mutations were identified recurrently, 4 of which accounted for 79% of the total. CONCLUSIONS: The results suggest that MFM is a reliable outcome measure that may be useful for longitudinal follow-up in dysferlinopathy. Recurrent mutations suggest a founder effect in the Chilean population.

OBSTETRICIA Y GINECOLOGÍA

ULTRASOUND OBSTET GYNECOL 2015; 46: 363–366

ANAL SPHINCTER TRAUMA AND ANAL INCONTINENCE IN UROGYNECOLOGICAL PATIENTS

R. A. Guzman Rojas, I. Kamisan Atan, K. L. Shek, H. P. Dietz

Objectives To determine the prevalence of evidence of residual obstetric anal sphincter injury, to evaluate its association with anal incontinence (AI) and to establish minimal diagnostic criteria for significant (residual) external anal sphincter (EAS) trauma. Methods This was a retrospective analysis of ultrasound volume datasets of 501 patients attending a tertiary urogynecological unit. All patients underwent a standardized interview including determination of St Mark's score for those presenting with AI. Tomographic ultrasound imaging (TUI) was used to evaluate the EAS and the internal anal sphincter (IAS). Results Among a total of 501 women, significant EAS and IAS defects were found in 88 and 59, respectively, and AI was reported by 69 (14%). Optimal prediction of AI was achieved using a model that included four abnormal slices of the EAS on TUI. IAS defects were found to be less likely to be associated with AI. In a multivariable model controlling for age and IAS trauma, the presence of at least four abnormal slices gave an 18-fold (95% CI, 9–36; P < 0.0001) increase in the likelihood of AI, compared with those with fewer than four abnormal slices. Using receiver–operating characteristics curve statistics, this model yielded an area under the curve of 0.86 (95% CI, 0.80–0.92). Conclusions Both AI and significant EAS trauma are common in patients attending urogynecological units, and are strongly associated with each other. Abnormalities of the IAS seem to be less important in predicting AI. Our data support the practice of using, as a minimal criterion, defects present in four of the six slices on TUI for the diagnosis of significant EAS trauma.

AUSTRALIAN & NEW ZEALAND JOURNAL OF OBSTETRICS & GYNAECOLOGY 2015. VOLUMEN: 55 NÚMERO: 5 PÁGINAS: 487-492

DEFECT-SPECIFIC RECTOCELE REPAIR: MEDIUM-TERM ANATOMICAL, FUNCTIONAL AND SUBJECTIVE OUTCOMES

Guzmán Rojas, Rodrigo; Atan, Ixora; Shek, Ka Lai; Dietz, Hans

Background: Rectocele is a herniation of the anterior wall of the rectal ampulla through a defect in the rectovaginal septum causing protrusion of the posterior vaginal wall. Common symptoms include symptoms of prolapse and obstructed defecation. AimsTo describe subjective, anatomical and functional results of defect-specific rectocele repair. Materials and Methods: This is an internal audit of 137 women who underwent defect-specific rectocele repair. Pre- and post-operative assessment included a standardised interview, clinical examination and 3D/4D transperineal ultrasound. Outcome measures were symptoms of obstructed defecation, recurrent prolapse symptoms, clinical posterior compartment recurrence and rectocele recurrence on ultrasound. Results: At a mean follow-up of 1.4years, 117 (85%) of women considered themselves cured or improved. Thirty-four (25%) complained of recurrent prolapse symptoms and 47 (34%) symptoms of obstructed defecation, a significant reduction (P<0.0001). Clinical recurrence (Bp-1) was seen in 19 women (14%) and recurrence on ultrasound in 27 (20%). The mean depth of recurrence was 16.6mm (10.3-25.1). We tested multiple potential predictors of recurrence, including age, BMI, vaginal parity, previous hysterectomy and/or prolapse surgery, follow-up time, pre-operative clinical and ultrasound findings. Only hiatal area on Valsalva (OR 0.95 for

sonographic recurrence, P=0.01) and enterocele (for clinical and sonographic recurrence, OR 4.03, P=0.01 and OR 2.72, P=0.02, respectively) reached significance. Conclusion: Defect-specific rectocele repair is effective both in restitution of normal anatomy and in resolving prolapse and obstructed defecation symptoms at a mean follow-up of 1.4years.

MED HYPOTHESES. 2015 JAN;84(1):72-7.

A PUTATIVE ROLE FOR TELOCYTES IN PLACENTAL BARRIER IMPAIRMENT DURING PREECLAMPSIA.

Bosco C, Díaz E, Gutiérrez R, González J, Parra-Cordero M, Rodrigo R, Barja P.

Preeclampsia (PE) is a major health problem occurring in pregnant women and the principal cause of maternal morbidity and perinatal mortality. It is characterized by alteration of the extravilli trophoblast cell migration toward the endometrial spiral arteries with a concomitant reduction in maternal blood flow in the placenta. This result in a state of ischemia-hypoxia which triggers an oxidative stress stage with production of reactive oxygen species. A cascade of cellular and molecular events leads then to endothelial dysfunction, transduction pathway signal disruption and induction of apoptosis and necrosis mechanisms and therefore a significant reduction in the amount of nutrients required for normal fetal development. Placental anchoring chorionic and stem villi present a skeleton of myofibroblasts arranged in parallel disposition to its longitudinal axis. The intraplacental blood volume is controlled by the contraction/relaxation of these myofibroblasts, promoting the delivery of nutrients and metabolites to the fetus. Recently, a new mesodermal originated cell type has been described in the villous stroma, the so named “telocytes”. These cells are strategically located between the smooth muscle cells of the blood vessel wall and the myofibroblasts, and it is reasonable to hypothesize that they may play a pacemaker role, as in the intestine. This study provide new information supporting the notion that the occurrence of oxidative stress in PE is not only related to endothelial dysfunction and apoptosis of the trophoblast cells, but also involves telocytes and its putative role in the regulation of fetal blood flow and the intra-placental blood volume. Some ideas aimed at dilucidating the relationship between placental failure and the behavior of telocytes in pathological organs in adulthood, are also discussed.

STEROIDS. 2015 DEC;104:189-95.

EXPRESSION OF STEROID SULFATED TRANSPORTERS AND 3B-HSD ACTIVITY IN ENDOMETRIUM OF WOMEN HAVING POLYCYSTIC OVARY SYNDROME.

Plaza-Parrochia F, Poblete C, Gabler F, Carvajal R, Romero C, Valladares L, Vega M.

Intracrinology mechanism involves the metabolism of steroids in peripheral tissues, such as DHEA, to molecules with estrogenic or androgenic activity. Proliferation rate of endometria from Polycystic Ovary Syndrome women (PCOS) is increased, favoring hyperplasia development. Besides, in endometria from PCOS-women the synthesis of androst-5-ene-3β,17β-diol (androstenediol), an estrogenic molecule, is enhanced concomitantly to increased cellular proliferation. DHEA, the major intracrinological precursor, circulates mainly in its sulfated form and requires transporters for cell intake, that belong to the families of organic anion transporting polypeptides (OATP) and organic anion transporters (OAT). The aim of this study was to determine protein levels and activity of sulfated steroid transporters OATP2B1, OATP3A1, OATP4A1 and OAT4 in endometria from control and PCOS-women and to evaluate the activity of the enzyme 3β-HSD. Levels of transporters were done by RT-PCR (OAT4 only) and Western-blot (WB). Additionally, in primary culture cells stimulated with steroids, protein levels by WB and uptake of tritiated DHEAS, were evaluated; 3β-HSD activity was assessed using radiolabel substrate. PCOS-endometrium had higher levels of OATP2B1 and OATP4A1 than CE ($p<0.05$); decreased OATP4A1 levels were found in androstenediol or testosterone-stimulated cells. Accordingly, the entry of DHEAS to cells was lower in cells stimulated with testosterone ($p<0.05$); 3β-HSD-activity was similar in control and PCOS-endometria. Therefore, this study describes that steroids can modulate the expression and activity of transporters of OATPs-family in human endometria and that some transporter levels are increased in PCOS-endometria, suggesting a potential role in the pathogenesis of endometrial hyperplasia of these patients.

HORM METAB RES. 2015 NOV;47(12):901-9.

ENDOMETRIA FROM OBESE PCOS WOMEN WITH HYPERINSULINEMIA EXHIBIT ALTERED ADIPONECTIN SIGNALING.

García V, Oróstica L, Poblete C, Rosas C, Astorga I, Romero C, Vega M.

Hyperandrogenemia, hyperinsulinemia, and obesity affect 60-70% of patients with Polycystic Ovarian Syndrome (PCOS), who exhibit an altered endometrial insulin signaling. The aim of the study was to evaluate whether hyperandrogenism, hyperinsulinism, and obesity present in PCOS patients impair the endometrial adiponectin signaling pathway. The ex vivo study was conducted on 27

samples from lean (n=9), obese (n=9), and obese-PCOS (n=9) patients. The in vitro assays were performed in immortalized human endometrial stromal cells stimulated with testosterone, insulin, or testosterone plus insulin. Serum steroid-hormones, adiponectin, glucose, and insulin; body mass index, free androgen index, ISI-Composite, and HOMA were evaluated in the 3 groups. Ex vivo and in vitro gene expression and protein content of adiponectin, AdipoR1, AdipoR2, and APPL1 were determined. Adiponectin serum levels were decreased in obese-PCOS patients compared to lean (78%) and obese (54%) controls ($p<0.05$). AdipoR1 protein and gene expression were increased in obese group vs. obese-PCOS and lean groups (2-fold, $p<0.05$). In turn, AdipoR2 protein and mRNA content was similar between the 3 groups. APPL1 protein levels were reduced in endometria from both obese groups, compared to lean group (6-fold, $p<0.05$). Testosterone plus insulin stimulation of T-HESC and St-T1b leads to a reduction of adiponectin, AdipoR1, AdipoR2, and APPL1 protein content in both endometrial cell lines ($p<0.05$), whereas, in the presence of testosterone or insulin alone, protein levels were similar to basal. Therefore, endometrial adiponectin-signaling pathway is impaired in hyperandrogenemic and hyperinsulinemic obese-PCOS patients, corroborated in the in vitro model, which could affect endometrial function and potentially the implantation process.

BMC CANCER. 2015 JUN 10;15:463.

ENHANCED CAVEOLIN-1 EXPRESSION INCREASES MIGRATION, ANCHORAGE-INDEPENDENT GROWTH AND INVASION OF ENDOMETRIAL ADENOCARCINOMA CELLS.

Diaz-Valdivia N, Bravo D, Huerta H, Henriquez S, Gabler F, Vega M, Romero C, Calderon C, Owen Gl, Leyton L, Quest AF.

BACKGROUND: Caveolin-1 (CAV1) has been implicated both in tumor suppression and progression, whereby the specific role appears to be context dependent. Endometrial cancer is one of the most common malignancies of the female genital tract; however, little is known about the role of CAV1 in this disease. METHODS: Here, we first determined by immunohistochemistry CAV1 protein levels in normal proliferative human endometrium and endometrial tumor samples. Then using two endometrial cancer cell lines (ECC: Ishikawa and Hec-1A) we evaluated mRNA and protein levels of CAV1 by real time qPCR and Western blot analysis, respectively. The role of CAV1 expression in ECC malignancy was further studied by either inducing its expression in endometrial cancer cells with the tumor promotor 12-O-tetradecanoyl-phorbol-13-acetate (4β-TPA) or decreasing expression using short-hairpin RNA constructs, and then evaluating the effects of these changes on ECC proliferation, transmigration, matrigel invasion, and colony formation in soft agar. RESULTS: Immunohistochemical analysis of endometrial epithelia revealed that substantially higher levels of CAV1 were present in endometrial tumors than the normal proliferative epithelium. Also, in Ishikawa and Hec-1A endometrial cancer cells CAV1 expression was readily detectable. Upon treatment with 4β-TPA CAV1 levels increased and coincided with augmented cell transmigration, matrigel invasion, as well as colony formation in soft agar. Reduction of CAV1 expression using short-hairpin RNA constructs ablated these effects in both cell types whether treated or not with 4β-TPA. Alternatively, CAV1 expression appeared not to modulate significantly proliferation of these cells. CONCLUSION: Our study shows that elevated CAV1, observed in patients with endometrial cancer, is linked to enhanced malignancy of endometrial cancer cells, as evidenced by increased migration, invasion and anchorage-independent growth.

INT UROGYNECOL J. 2015 DEC 15. [EPUB AHEAD OF PRINT]

THE PREVALENCE OF ABNORMAL POSTERIOR COMPARTMENT ANATOMY AND ITS ASSOCIATION WITH OBSTRUCTED DEFECATION SYMPTOMS IN UROGYNECOLOGICAL PATIENTS.

Guzman Rojas R, Kamisan Atan I, Shek KL, Dietz HP.

INTRODUCTION AND HYPOTHESIS: Symptoms of obstructive defecation (OD) are common in women. Transperineal ultrasound (TPUS) has been used for the evaluation of defecatory disorders. The aim of our study was to determine the overall prevalence of anatomical abnormalities of the posterior compartment and their correlations with OD in women seen in a tertiary urogynecology clinic. METHODS: This is a retrospective study on 750 women seen at a tertiary urogynecological unit who had undergone a standardized interview, clinical examination, and 4D TPUS. Univariate and multivariate logistic regression analyses were undertaken to study the association between examination findings and symptoms of OD. This study was approved by the local human research ethics committee (Nepean Blue Mountains Local Health District Human Research Ethics Committee, IRB approval no. 13-16). RESULTS: The datasets of 719 women were analyzed. Mean age was 56.1 (18.4-87.6) years. Ninety-seven patients (13 %) reported fecal incontinence, 190 (26 %) constipation, and 461 (64 %) symptoms of OD. On examination, 405 women (56 %) were diagnosed with significant posterior compartment prolapse (POP-Q $\geq$ stage 2), which was associated with symptoms of OD ($p < 0.0001$). On ultrasound, 103 (14 %) patients had an enterocele, 382 (53 %) a true rectocele and 31 (4.3 %) had rectal intussusception. On multivariate analysis true rectocele ($p = 0.003$) and rectal intussusception ($p = 0.004$) remained significantly associated with

symptoms of OD. CONCLUSION: Both symptoms of OD and anatomical abnormalities of the posterior compartment are highly prevalent in urogynecological patients. Ultrasound findings of a true rectocele and rectal intussusception are significantly associated with obstructed defecation.

INT UROGYNECOL J. 2015 MAY;26(5):737-41

DOES CHILDBIRTH PLAY A ROLE IN THE ETIOLOGY OF RECTOCELE?

Guzmán Rojas R, Quintero C, Shek KL, Dietz HP.

INTRODUCTION AND HYPOTHESIS: Rectoceles are common among parous women and they are believed to be due to disruption or distension of the rectovaginal septum as a result of childbirth. However, the etiology of rectocele is likely to be more complex since posterior compartment prolapse does occur in nulliparous women. This study was designed to determine the role of childbearing as an etiological factor in true radiological rectocele. METHODS: This was a secondary analysis of the data from 657 primiparous women recruited as part of a previously reported study and another ongoing prospective study. Women were invited for antenatal and postnatal appointments comprising an interview, clinical examination and translabial ultrasonography. The presence and depth of any rectocele were determined on maximum Valsalva maneuver, as was descent of the rectal ampulla. Potential demographic and obstetric factors as predictors of rectocele development were evaluated using either multiple regression or logistic regression analysis as appropriate. RESULTS: A true rectocele was identified in 4% of women antenatally and in 16% after childbirth ($P < 0.001$). Mean rectocele depth was 13.5 mm (10 - 23.2 mm). The mean antepartum position of the rectal ampulla on Valsalva maneuver was 4.39 mm above and it was 1.64 mm below the symphysis pubis postpartum ($P < 0.0001$). De novo appearance of true rectocele was significantly associated with a history of previous <20 weeks pregnancy and fetal birth weight. Body mass index and length of the second stage were associated with rectocele depth increase. CONCLUSIONS: Childbirth seems to play a distinct role in the pathogenesis of rectocele. Both maternal and fetal factors seem to contribute.

NUTRIENTS. 2015 AUG 4;7(8):6405-24

MODIFICATION OF DOCOSAHEXAENOIC ACID COMPOSITION OF MILK FROM NURSING WOMEN WHO RECEIVED ALPHA LINOLENIC ACID FROM CHIA OIL DURING GESTATION AND NURSING.

Valenzuela R, Bascuñán K, Chamorro R, Barrera C, Sandoval J, Puigrredon C, Parraguez G, Orellana P, Gonzalez V, Valenzuela A.

α-Linolenic acid (ALA) is the precursor of docosahexaenoic acid (DHA) in humans, which is fundamental for brain and visual function. Western diet provides low ALA and DHA, which is reflected in low DHA in maternal milk. Chia oil extracted from chia (Salvia hispanica L.), a plant native to some Latin American countries, is high in ALA (up to 60%) and thereby is an alternative to provide ALA with the aim to reduce DHA deficits. We evaluated the modification of the fatty acid profile of milk obtained from Chilean mothers who received chia oil during gestation and nursing. Forty healthy pregnant women (22-35 years old) tabulated for food consumption, were randomly separated into two groups: a control group with normal feeding ($n = 21$) and a chia group ($n = 19$), which received 16 mL chia oil daily from the third trimester of pregnancy until the first six months of nursing. The fatty acid profile of erythrocyte phospholipids, measured at six months of pregnancy, at time of delivery and at six months of nursing, and the fatty acid profile of the milk collected during the first six months of nursing were assessed by gas-chromatography. The chia group, compared to the control group, showed (i) a significant increase in ALA ingestion and a significant reduction of linoleic acid (LA) ingestion, no showing modification of arachidonic acid (AA), eicosapentaenoic acid (EPA) and DHA; (ii) a significant increase of erythrocyte ALA and EPA and a reduction of LA. AA and DHA were not modified; (iii) a increased milk content of ALA during the six months of nursing, whereas LA showed a decrease. AA and EPA were not modified, however DHA increased only during the first three months of nursing. Consumption of chia oil during the last trimester of pregnancy and the first three months of nursing transiently increases the milk content of DHA.

INT UROGYNECOL J. 2015 NOV;26(11):1667-72.

THE REPEATABILITY OF SONOGRAPHIC MEASURES OF FUNCTIONAL PELVIC FLOOR ANATOMY.

Tan L, Shek KL, Atan IK, Rojas RG, Dietz HP.

INTRODUCTION AND HYPOTHESIS: Translabial 3D/4D ultrasound is increasingly being used in the diagnostic evaluation of pelvic floor dysfunction. The result of the assessment is influenced by a number of confounders that are generally unrecognised. The aim of this study was to determine the short- to medium-term repeatability of translabial ultrasound measures of female pelvic organ support and pelvic floor anatomy. METHODS: This is a retrospective study analyzing archived ultrasound volume datasets of 106 patients with pelvic floor dysfunction. Every subject was assessed twice at an average interval of 73 days. Outcome measures

including hiatal area on Valsalva, descent of the bladder neck, bladder, uterus and rectal ampulla, rectocele depth, diagnosis of true rectocele, and levator integrity (avulsion) were compared at the first and second appointments. RESULTS: All parameters of organ descent demonstrated good to excellent reliability (ICC 0.73-0.93) except for rectocele descent, which showed moderate reliability (ICC 0.44, CI 0.26-0.58). The most highly repeatable measure was hiatal area on Valsalva or "ballooning" (ICC 0.93, CI 0.90-0.95). For the diagnosis of levator avulsion and true rectocele, agreement was very high (kappa 0.91 for avulsion (CI 0.77-0.94) and kappa 0.73 (CI 0.56-0.84) for true rectocele). CONCLUSIONS: The short- to medium-term repeatability of translabial ultrasound measures of functional pelvic floor anatomy seems to be high. Hiatal area on Valsalva (ballooning) and diagnosis of levator avulsion were the most repeatable measures. The least repeatable measures related to the posterior compartment.

OTORRINOLARINGOLOGÍA

JOURNAL OF VOICE, VOL. 29, NO. 1, 2015

LARYNGOSCOPIC AND SPECTRAL ANALYSIS OF LARYNGEAL AND PHARYNGEAL CONFIGURATION IN NON-CLASSICAL SINGING STYLES

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Purpose. The present study aimed to assess three different singing styles (pop, rock, and jazz) with laryngoscopic, acoustic, and perceptual analysis in healthy singers at different loudness levels. Special emphasis was given to the degree of anterior-posterior (A-P) laryngeal compression, medial laryngeal compression, vertical laryngeal position (VLP), and pharyngeal compression. Study Design. Prospective study. Methods. Twelve female trained singers with at least 5 years of voice training and absence of any voice pathology were included. Flexible and rigid laryngeal endoscopic examinations were performed. Voice recording was also carried out. Four blinded judges were asked to assess laryngoscopic and auditory perceptual variables using a visual analog scale. Results. All laryngoscopic parameters showed significant differences for all singing styles. Rock showed the greatest degree for all of them. Overall A-P laryngeal compression scores demonstrated significantly higher values than overall medial compression and VLP. High loudness level produced the highest degree of A-P compression, medial compression, pharyngeal compression, and the lowest VLP for all singing styles. Additionally, rock demonstrated the highest values for alpha ratio (less steep spectral slope), L1-L0 ratio (more glottal adduction), and Leq (more vocal intensity). Statistically significant differences between the three loudness levels were also found for these acoustic parameters. Conclusions. Rock singing seems to be the style with the highest degree of both laryngeal and pharyngeal activity in healthy singers. Although, supraglottic activity during singing could be labeled as hyperfunctional vocal behavior, it may not necessarily be harmful, but a strategy to avoid vocal fold damage.

FRONT CELL NEUROSCI. 2015 MAR 31;9:110.

CHANGES IN THE REGULATION OF THE NOTCH SIGNALING PATHWAY ARE TEMPORALLY CORRELATED WITH REGENERATIVE FAILURE IN THE MOUSE COCHLEA.

Maass JC, Gu R, Basch ML, Waldhaus J, Lopez EM, Xia A, Oghalai JS, Heller S, Groves AK.

Sensorineural hearing loss is most commonly caused by the death of hair cells in the organ of Corti, and once lost, mammalian hair cells do not regenerate. In contrast, other vertebrates such as birds can regenerate hair cells by stimulating division and differentiation of neighboring supporting cells. We currently know little of the genetic networks which become active in supporting cells when hair cells die and that are activated in experimental models of hair cell regeneration. Several studies have shown that neonatal mammalian cochlear supporting cells are able to trans-differentiate into hair cells when cultured in conditions in which the Notch signaling pathway is blocked. We now show that the ability of cochlear supporting cells to trans-differentiate declines precipitously after birth, such that supporting cells from six-day-old mouse cochlea are entirely unresponsive to a blockade of the Notch pathway. We show that this trend is seen regardless of whether the Notch pathway is blocked with gamma secretase inhibitors, or by antibodies against the Notch1 receptor, suggesting that the action of gamma secretase inhibitors on neonatal supporting cells is likely to be by inhibiting Notch receptor cleavage. The loss of responsiveness to inhibition of the Notch pathway in the first postnatal week is due in part to a down-regulation of Notch receptors and ligands, and we show that this down-regulation persists in the adult animal, even under conditions of noise damage. Our data suggest that the Notch pathway is used to establish the repeating pattern of hair cells and supporting cells in the organ of Corti, but is not required to maintain this cellular mosaic once the production of hair cells and supporting cells is completed. Our results have implications for the proposed used of Notch pathway inhibitors in hearing restoration therapies.

J ASSOC RES OTOLARYNGOL. 2015 APR;16(2):223-40.

THE OLIVOCOCHLEAR REFLEX STRENGTH AND COCHLEAR SENSITIVITY ARE INDEPENDENTLY MODULATED BY AUDITORY CORTEX MICROSTIMULATION.

Dragicevic CD, Aedo C, León A, Bowen M, Jara N, Terreros G, Robles L, Delano PH.

In mammals, efferent projections to the cochlear receptor are constituted by olivocochlear (OC) fibers that originate in the superior olivary complex. Medial and lateral OC neurons make synapses with outer hair cells and with auditory nerve fibers, respectively. In addition to the OC system, there are also descending projections from the auditory cortex that are directed towards the thalamus, inferior colliculus, cochlear nucleus, and superior olivary complex. Olivocochlear function can be assessed by measuring a brainstem reflex mediated by auditory nerve fibers, cochlear nucleus neurons, and OC fibers. Although it is known that the OC reflex is activated by contralateral acoustic stimulation and produces a suppression of cochlear responses, the influence of cortical descending pathways in the OC reflex is largely unknown. Here, we used auditory cortex electrical microstimulation in chinchillas to study a possible cortical modulation of cochlear and auditory nerve responses to tones in the absence and presence of contralateral noise. We found that cortical microstimulation produces two different peripheral modulations: (i) changes in cochlear sensitivity evidenced by amplitude modulation of cochlear microphonics and auditory nerve compound action potentials and (ii) enhancement or suppression of the OC reflex strength as measured by auditory nerve responses, which depended on the intersubject variability of the OC reflex. Moreover, both corticofugal effects were not correlated, suggesting the presence of two functionally different efferent pathways. These results demonstrate that auditory cortex electrical microstimulation independently modulates the OC reflex strength and cochlear sensitivity.

FOLIA PHONIATR LOGOP. 2015;67(2):68-75. DOI: 10.1159/000437353.

DO DIFFERENT SEMI-OCCLUDED VOICE EXERCISES AFFECT VOCAL FOLD ADDUCTION DIFFERENTLY IN SUBJECTS DIAGNOSED WITH HYPERFUNCTIONAL DYSPHONIA?

Guzman M, Calvache C, Romero L, Muñoz D, Olavarria C, Madrid S, Leiva M, Bortnem C.

OBJECTIVE: To observe the possible differential effects of 8 different semi-occluded vocal tract exercises on glottal contact quotient (CQ) as a measure of vocal fold impact stress. PATIENTS AND METHODS: Eighty participants were divided into two groups: an experimental group with hyperfunctional dysphonia and a control group of vocally healthy subjects. The participants were recorded before, during and after the exercises. Electroglottographic samples were analyzed to obtain CQ. RESULTS: For the experimental group, all exercises, except lip trills and tongue trills, had an overall significant effect when conditions before, during and after the exercises were compared. The CQ presented differently across the 8 semi-occluded postures during exercise for both groups. For the experimental group, most exercises increased the CQ during practice. Only lip and tongue trills demonstrated lower CQ during exercise. CONCLUSIONS: Different semi-occluded exercises differentially affect vocal fold adduction. Lip and tongue trills produced the lowest CQ. Therefore, they may be recommended for decreasing glottal adduction. A straw submerged 10 cm below the water surface presented the greatest CQ. A shallower depth led to a lower CQ, while deeper submersion produced a higher.

FRONT SYST NEUROSCI. 2015 SEP 30;9:134.

CORTICOFUGAL MODULATION OF PERIPHERAL AUDITORY RESPONSES.

Terreros G, Delano PH.

The auditory efferent system originates in the auditory cortex and projects to the medial geniculate body (MGB), inferior colliculus (IC), cochlear nucleus (CN) and superior olivary complex (SOC) reaching the cochlea through olivocochlear (OC) fibers. This unique neuronal network is organized in several afferent-efferent feedback loops including: the (i) colliculo-thalamic-cortico-collicular; (ii) cortico-(collicular)-OC; and (iii) cortico-(collicular)-CN pathways. Recent experiments demonstrate that blocking ongoing auditory-cortex activity with pharmacological and physical methods modulates the amplitude of cochlear potentials. In addition, auditory-cortex microstimulation independently modulates cochlear sensitivity and the strength of the OC reflex. In this mini-review, anatomical and physiological evidence supporting the presence of a functional efferent network from the auditory cortex to the cochlear receptor is presented. Special emphasis is given to the corticofugal effects on initial auditory processing, that is, on CN, auditory nerve and cochlear responses. A working model of three parallel pathways from the auditory cortex to the cochlea and auditory nerve is proposed.

J NEUROSCI. 2015 MAY 13;35(19):7552-64.

THE SPECIFICATION OF CORTICAL SUBCEREBRAL PROJECTION NEURONS DEPENDS ON THE DIRECT REPRESSION OF TBR1 BY CTIP1/BCL11A.

Cánovas J, Berndt FA, Sepúlveda H, Aguilar R, Veloso FA, Montecino M, Oliva C, Maass JC, Sierralta J, Kukuljan M.

The acquisition of distinct neuronal fates is fundamental for the function of the cerebral cortex. We find that the development of subcerebral projections from layer 5 neurons in the mouse neocortex depends on the high levels of expression of the transcription factor CTIP1; CTIP1 is coexpressed with CTIP2 in neurons that project to subcerebral targets and with SATB2 in those that project to the contralateral cortex. CTIP1 directly represses Tbr1 in layer 5, which appears as a critical step for the acquisition of the subcerebral fate. In contrast, lower levels of CTIP1 in layer 6 are required for TBR1 expression, which directs the corticothalamic fate. CTIP1 does not appear to play a critical role in the acquisition of the callosal projection fate in layer 5. These findings unravel a key step in the acquisition of cell fate for closely related corticofugal neurons and indicate that differential dosages of transcriptions factors are critical to specify different neuronal identities.

PEDIATRÍA

ARCH ARGENT PEDIATR 2015;113(4):303-309

STRESS IN PARENTS OF VERY LOW BIRTH WEIGHT PRETERM INFANTS HOSPITALIZED IN NEONATAL INTENSIVE CARE UNITS. A MULTICENTER STUDY

Francisca Wormald, José L. Tapia, Gabriela Torres, Paula Cánepa, María Aurelia González, Diana Rodríguez, Marisol Escobar, Bernardita Reyes, Carola Capelli, Laura Menéndez, Patricia Delgado, Sergio Treuer, Rodrigo Ramírez, Norma Borja, Angélica Domínguez, and the Neocosur Neonatal Network

Introduction. The birth of a premature baby is a stressful event for parents. The objective of this study was to determine early stress in parents of very low birth weight infants (VLBWIs) hospitalized in 12 neonatal intensive care units from a South American Neonatal Network, to identify associated factors, and to compare the level of parental stress in public versus private healthcare facilities. Population and Methods. Cross-sectional study in mothers/fathers of VLBWIs (500 to 1500 g). Early parental stress was measured using the Parental Stressor Scale, with a score from 1 (low stress) to 5 (high stress). The sociodemographic characteristics of parents and newborn infants were collected and associated with levels of parental stress. Results. The study included273 fathers/mothers of a total of218 VLBW preterm infants. The survey was administered at 5.9 Â± 2.0 days of life. The average total parental stress was 3.1 Â± 0.8, and the highest score was obtained for the parental role subscale (3.6). A lower education level, unemployment, not having held the newborn infant, and respiratory support requirement were associated with higher parental stress levels. Stress was higher among mothers than fathers, and at public facilities versus private ones. Conclusions. Among parents of VLBWIs, a moderate early parental stress was observed. Parental role alteration was the most relevant factor. Parental stress was higher among mothers and at public healthcare facilities. A greater sensitization, further research and interventions in this area are required.

PSIQUIATRÍA Y SALUD MENTAL

J CLIN PSYCHOPHARMACOL 2015; 35 (3): 319-323

13-WEEK, RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER TRIAL OF ZIPRASIDONE IN BIPOLAR SPECTRUM DISORDER

Patkar, Ashwin; Pae, Chi Un; Vohringer Cárdenas, Paul; Mauer, Sivan; Narasimhan, Meera; Dalley, Shannon; Loebel, Antony; Masand, Prakash; Ghaemi, S. Nassir

Objective: Features of bipolarity in a major depressive disorder sample were used to define a “bipolar spectrum disorder” population for treatment with a neuroleptic agent, ziprasidone. Methods: Forty-nine acutely depressed patients were randomized to ziprasidone-washout-placebo or placebo-washout-ziprasidone in this double-blind, prospective, 13-week crossover trial. All patients met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for a major depressive episode and were positive for at least 3 predictors of bipolarity: family history of bipolar disorder, antidepressant-induced mania, highly recurrent depressive episodes (>5), atypical depression, early onset of depression (<age 20), failure to respond to antidepressants or antidepressant tolerance. The most common bipolarity inclusion criteria were antidepressant tolerance and nonresponse, and atypical depression. Approximately 52% received ziprasidone in monotherapy, 48% as

adjunct to antidepressants. Results: There was a small statistically nonsignificant benefit with ziprasidone compared with placebo on Montgomery Asberg Depression Rating Scale change [-1.5 (p = 0.48)]. Statistical carryover effects were observed. Conclusions: Ziprasidone, alone or added to antidepressants, was not more effective than placebo in this population. A false-negative finding due to the crossover design is suggested by statistical carryover effects. Alternatively, this definition of bipolar spectrum illness may have been too nonspecific to show neuroleptic benefit, unlike other definitions, like "mixed depression." Also, this study did not test potential neuroleptic efficacy without the potentially mood-destabilizing effects of antidepressants.

JOURNAL OF AFFECTIVE DISORDERS184 (2015) 318–321

ANTIDEPRESSANTS WORSEN RAPID-CYCLING COURSE IN BIPOLAR DEPRESSION: A STEP-BD RANDOMIZED CLINICAL TRIAL

El-Mallakh, Rif S.; Vöhringer Cárdenas, Paul; Ostacher, Michael M.; Baldassano, Claudia F.; Holtzman, Niki S.; Whitham, Elizabeth A.; Thommi, Sairah B.; Goodwin, Frederick K.; Ghaemi, S. Nassir

Background: The use of antidepressants in rapid-cycling bipolar disorder has been controversial. We report the first randomized clinical trial with modern antidepressants on this topic. Methods: As part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, we analyzed, as an a priori secondary outcome, rapid cycling as a predictor of response in 68 patients randomized to continue vs. discontinue antidepressant treatment, after initial response for an acute major depressive episode. Outcomes assessed were percent time well and total number of episodes. All patients received standard mood stabilizers. Results: In those continued on antidepressants (AD), rapid cycling (RC) subjects experienced 268% (3.14/1.17) more total mood episodes/year, and 293% (1.29/0.44) more depressive episodes/year, compared with non-rapid cycling (NRC) subjects (mean difference in depressive episodes per year RC vs. NRC was 0.85 +/- 0.37 (SE), df=28, p=0.03). In the AD continuation group, RC patients also had 28.8% less time in remission than NRC patients (95% confidence intervals (9.9%, 46.5%), p=0.004). No such differences between RC and NRC subjects were seen in the AD discontinuation group (Table 1). Analyses within the rapid-cycling subgroup alone were consistent with the above comparisons between RC and NRC subjects, stratified by maintenance antidepressant treatment, though limited by sample size. Conclusions: In an a priori analysis, despite preselection for good antidepressant response and concurrent mood stabilizer treatment, antidepressant continuation in rapid-cycling was associated with worsened maintenance outcomes, especially for depressive morbidity, vs. antidepressant discontinuation.

JAMA PSYCHIATRY. 2015;72(2):112-118

PSYCHIATRIC HOSPITAL BEDS AND PRISON POPULATIONS IN SOUTH AMERICA SINCE 1990 DOES THE PENROSE HYPOTHESIS APPLY?

Mundt, Adrian P.; Chow, Winnie; Arduino, Margarita; Barrionuevo Chebel, Hugo; Fritsch, Rosemarie; Girala, Nestor; Minoletti, Alberto; Mitkiewicz, Flávia; Rivera, Guillermo; Tavares, María; Priebe, Stefan

IMPORTANCE In 1939, English mathematician, geneticist, and psychiatrist Lionel Sharples Penrose hypothesized that the numbers of psychiatric hospital beds and the sizes of prison populations were inversely related; 75 years later, the question arises as to whether the hypothesis applies to recent developments in South America. OBJECTIVE To explore the possible association of changes in the numbers of psychiatric hospital beds with changes in the sizes of prison populations in South America since 1990. DESIGN, SETTING, AND PARTICIPANTS We searched primary sources for the numbers of psychiatric hospital beds in South American countries since 1990 (the year that the Latin American countries signed the Caracas Declaration) and compared these changes against the sizes of prison populations. The associations between the numbers of psychiatric beds and the sizes of prison populations were tested using fixed-effects regression of panel data. Economic variables were considered as covariates. Sufficiently reliable and complete data were obtained from 6 countries: Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay. MAIN OUTCOMES AND MEASURES The numbers of psychiatric beds and the sizes of prison populations. RESULTS Since 1990, the numbers of psychiatric beds decreased in all 6 countries (ranging from -2.0% to -71.9%), while the sizes of prison populations increased substantially (ranging from 16.1% to 273.0%). Panel data regression analysis across the 6 countries showed a significant inverse relationship between numbers of psychiatric beds and sizes of prison populations. On average, the removal of 1 bed was associated with 5.18 more prisoners (95% CI, 3.10-7.26; P = .001), which was reduced to 2.78 prisoners (95% CI, 2.59-2.97; P < .001) when economic growth was considered as a covariate. The association between the numbers of psychiatric beds and the sizes of prison populations remained practically unchanged when income inequality was considered as a covariate (-4.28 [95% CI, -5.21 to -3.36]; P < .001). CONCLUSIONS AND RELEVANCE Since 1990, the numbers of psychiatric beds have substantially decreased in South America, while the sizes of the prison populations have increased against a background of strong economic

growth. The changes appear to be associated because the numbers of beds decreased more extensively when and where the sizes of prison populations increased. These findings are consistent with and specify the assumption of an association between the numbers of psychiatric beds and the sizes of prison populations. More research is needed to understand the drivers of the capacities of psychiatric hospitals and prisons and to explore reasons for their association.

CIRCULATION VOLUMEN: 132 NÚMERO: 19 PÁGINAS: 1825-1833

STATIN USE AND ADRENAL ALDOSTERONE PRODUCTION IN HYPERTENSIVE AND DIABETIC SUBJECTS

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Background—Statins substantially reduce cardiovascular mortality and appear to have beneficial effects independent of their lipid lowering properties. We evaluated the hypothesis that statin use may modulate the secretion of aldosterone, a well-known contributor to cardiovascular disease Methods and Results—We measured adrenal hormones in two intervention studies. In study 1 in hypertensive subjects, aldosterone was analyzed at baseline and after angiotensin-II stimulation (AngII) on both high (HS) and low sodium (LS) diets (1122 observations, 15% on statins > 3 months). Statin users had 33% lower aldosterone levels in adjusted models ($p < 0.001$). Cortisol was not modified by statins. In secondary analyses, the lowest aldosterone levels were seen with lipophilic statins and with higher doses. Statin users had lower blood pressure (BP) and reduced salt sensitivity of BP ($p=0.001$). In study 2, aldosterone was measured in diabetic patients on a HS diet, before and after AngII stimulation (143 observations, 79% statin users). Again, statin users had 26% lower aldosterone levels ($p =0.006$), particularly those using lipophilic statins. Ex vivo studies in rat adrenal glomerulosa cells confirmed that lipophilic statins acutely inhibited aldosterone, but not corticosterone, in response to different secretagogues Conclusions—Statin use among hypertensive and diabetic subjects was associated with lower aldosterone secretion in response to AngII and LS diet in two human intervention studies. This effect appeared to be most pronounced with lipophilic statins and higher doses. Future studies to evaluate whether aldosterone inhibition may partially explain the robust cardioprotective effects of statins are warranted.

J AFFECT DISORD. 2016 JAN 1;189:207-13.

THE COURSE OF MAJOR DEPRESSION DURING IMPRISONMENT - A ONE YEAR COHORT STUDY.

Baier A, Fritsch R, Ignatyev Y, Priebe S, Mundt AP.

BACKGROUND: First longitudinal studies in prisoners point to improvements of depressive symptoms during imprisonment. The aim of the present study was to assess the course of major depressive disorder during imprisonment and to identify factors influencing remission. METHODS: Prisoners with major depressive disorder in a sample of consecutive admissions to the penal justice system in Santiago de Chile were reassessed after one year of imprisonment. Psychiatric diagnoses were established using the Mini-International Neuropsychiatric Interview; psychological symptoms were assessed with the Symptom-Check-List 90 Revised (SCL-90-R). Mean symptom scores were compared at baseline and follow-up using Student's t-test. Odds ratios (OR) of comorbid disorders and socio-demographic factors at baseline to predict depression at follow-up were calculated. RESULTS: N=79 out of 80 inmates (99%) with major depression at baseline were included. Thirty-five prisoners (44%) had major depression at follow-up. The mean global severity score and all mean subscale scores of the SCL-90-R improved. High suicide risk was present in 37 prisoners (47%) at admission and in 11 (14%) at follow-up. The comorbid diagnosis of PTSD (OR 6.3; $p<0.001$) at admission and having been previously imprisoned (OR 2.5; $p=0.05$) predicted major depressive disorder at follow-up. LIMITATIONS: The study could not account for temporary improvements between the assessments. CONCLUSION: In spite of important symptom improvements, only about half of the prisoners with major depression at admission remit after one year of imprisonment. New interventions should target people with major depression and comorbid PTSD at admission.

CAD SAUDE PUBLICA. 2015 JUN;31(6):1305-12.

[DOES THE GHQ-12 SCORING SYSTEM AFFECT ITS FACTOR STRUCTURE? AN EXPLORATORY STUDY OF IBERO AMERICAN STUDENTS].

Urzúa A, Caqueo-Urízar A, Bargsted M, Irarrázaval M.

This study aimed to evaluate whether the scoring system of the General Health Questionnaire (GHQ-12) alters the instrument's factor structure. The method considered 1,972 university students from nine Ibero American countries. Modeling was performed with structural equations for 1, 2, and 3 latent factors. The mechanism for scoring the questions was analyzed within each type

of structure. The results indicate that models with 2 and 3 factors show better goodness-of-fit. In relation to scoring mechanisms, procedure 0-1-1-1 for models with 2 and 3 factors showed the best fit. In conclusion, there appears to be a relationship between the response format and the number of factors identified in the instrument's structure. The model with the best fit was 3-factor 0-1-1-1-formatted, but 0-1-2-3 has acceptable and more stable indicators and provides a better format for two- and three-dimensional models.

J CLIN PSYCHOPHARMACOL. 2015 OCT;35(5):605-8

ANTIDEPRESSANTS IN TYPE II VERSUS TYPE I BIPOLAR DEPRESSION: A RANDOMIZED DISCONTINUATION TRIAL.

Vöhringer PA, Ostacher MJ, El-Mallakh RS, Holtzman NS, Thommi SB, Whitham EA, Sullivan MC, Baldassano CF, Goodwin FK, Baldessarini RJ, Ghaemi SN.

BACKGROUND: We sought to test the hypothesis that antidepressants (ADs) may show preferential efficacy and safety among patients with type II bipolar disorder (BD, BD-II) more than patients with type I BD (BD-I). METHODS: Patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, BD-I (n = 21) and BD-II (n = 49) in acute major depressive episodes were treated with ADs plus mood stabilizers to euthymia sustained for 2 months and then randomized openly to continue or discontinue ADs for up to 3 years. Outcomes were episode recurrences and changes in standardized symptom ratings. RESULTS: In follow-up averaging 1.64 years, both subgroups showed improvement in depressive episode frequency with AD continuation, but contrary to the hypothesis, more improvement was seen in BD-I than in BD-II (for type II, mean [standard deviation] decrease in depressive episodes per year, 0.21 [0.26]; for type I, mean (SD) decrease, 0.35 [0.15]). Subjects with BD-II who continued on ADs had slightly more depressive, but fewer manic/hypomanic, episodes than subjects with BD-I. No notable differences were seen in either group in time to a recurrence of mood episodes or total time-in-remission. CONCLUSIONS: The findings do not confirm the hypothesis that long-term AD treatment in patients with BP-II has better outcomes than in patients with BD-I, except somewhat lower risk of manic/hypomanic episodes.

TRIALS. 2015 JUL 24;16:311

COMPREHENSIVE TECHNOLOGY-ASSISTED TRAINING AND SUPERVISION PROGRAM TO ENHANCE DEPRESSION MANAGEMENT IN PRIMARY CARE IN SANTIAGO, CHILE: STUDY PROTOCOL FOR A CLUSTER RANDOMIZED CONTROLLED TRIAL.

Rojas G, Martínez P, Vöhringer PA, Martínez V, Castro-Lara A, Fritsch R.

BACKGROUND: Depression is a common and disabling condition. Since 2001, Chile has had a national program for depression in primary care and universal access to treatment for depressed people over the age of 15. There are National Guidelines to treat depression but no training program exists. The aim of the present study protocol is to measure the effectiveness of a comprehensive technology-assisted training and supervision program to enhance depression management in primary care. METHODS AND DESIGN: This is a two-arm, single-blind, cluster randomized controlled trial to compare the efficacy of the program versus usual care to treat depression in primary care clinics. In total, 434 depressed persons 18 to 65 years of age, recruited from four primary care clinics located in Santiago, will participate in the study. DISCUSSION: In order to ensure the quality of interventions supported by the national program for depression in Chile, it is desirable to have training programs of proven effectiveness.

ARCH WOMENS MENT HEALTH. 2015 AUG;18(4):607-12

FIRST VALIDATION OF A SPANISH-TRANSLATED VERSION OF THE EDINBURGH POSTNATAL DEPRESSION SCALE (EPDS) FOR USE IN PREGNANT WOMEN. A CHILEAN STUDY.

ALVARADO R, JADRESIC E, GUAJARDO V, ROJAS G.

The objective of the study was to evaluate the psychometric properties of the Edinburg Postnatal Depression Scale (EPDS) to detect depression during pregnancy in Chile. The EPDS was applied to a sample of 111 pregnant women, who were attending an antenatal appointment in primary care centers. The Beck Depression Inventory (BDI-I) was used to assess the convergent validity, and the Depressive Episode module of the MINI was used to identify cases. The factor analysis showed that there was a good fit, with a factor model that explains 57.6 % of the total variance. There was a high degree of internal consistency (Cronbach's $\alpha = 0.914$) and good convergent validity with the BDI-I (rho = 0.850, $p < 0.001$). The EPDS was capable of differentiating cases of depression from non-cases. The best cutoff point was between 12 and 13, corresponding to an overall accuracy of 87.4 %. The questionnaire has good psychometric properties and can be useful for detecting cases of depression during pregnancy.

PHARMACOL RES. 2015 NOV;101:74-85.

METABOLIC SYNDROME AND OBESITY AMONG USERS OF SECOND GENERATION ANTIPSYCHOTICS: A GLOBAL CHALLENGE FOR MODERN PSYCHOPHARMACOLOGY.

Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K, Jara B.

Second generation antipsychotics (SGAs), such as clozapine, olanzapine, risperidone and quetiapine, are among the most effective therapies to stabilize symptoms schizophrenia (SZ) spectrum disorders. In fact, clozapine, olanzapine and risperidone have improved the quality of life of billions SZ patients worldwide. Based on the broad spectrum of efficacy and low risk of extrapyramidal symptoms displayed by SGAs, some regulatory agencies approved the use of SGAs in non-schizophrenic adults, children and adolescents suffering from a range of neuropsychiatric disorders. However, increasing number of reports have shown that SGAs are strongly associated with accelerated weight gain, insulin resistance, diabetes, dyslipidemia, and increased cardiovascular risk. These metabolic alterations can develop in as short as six months after the initiation of pharmacotherapy, which is now a controversial fact in public disclosure. Although the percentage of schizophrenic patients, the main target group of SGAs, is estimated in only 1% of the population, during the past ten years there was an exponential increase in the number of SGAs users, including millions of non-SZ patients. The scientific bases of SGAs metabolic side effects are not yet elucidated, but the evidence shows that the activation of transcriptional factor SRBP1c, the D1/D2 dopamine, GABA2 and 5HT neurotransmitions are implicated in the SGAs cardiovascular toxicity. Polypharmacological interventions are either non- or modestly effective in maintaining low cardiovascular risk in SGAs users. In this review we critically discuss the clinical and molecular evidence on metabolic alterations induced by SGAs, the evidence on the efficacy of classical antidiabetic drugs and the emerging concept of antidiabetic polyphenols as potential coadjutants in SGA-induced metabolic disorders.

TRAUMATOLOGÍA

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CONVERSION OF TIBIOTALAR ARTHRODESIS TO TOTAL ANKLE ARTHROPLASTY

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Background: Conversion of ankle arthrodesis to total ankle arthroplasty remains controversial. Although satisfactory outcomes have been published, not all foot and ankle surgeons performing total ankle arthroplasty have embraced this modality. Methods: Twenty-three total ankle arthroplasties were performed in patients who had undergone a prior or an attempted ankle arthrodesis. The mean age at surgery was fifty-nine years (range, forty-one to eighty years), and the mean duration of follow-up was 33.1 months (minimum, twelve months). Indications for the procedure were symptomatic adjacent hindfoot arthritis (twelve patients) or symptomatic tibiotalar or subtalar nonunion (eleven) after tibiotalocalcaneal arthrodesis. We performed concomitant surgical procedures in eighteen ankles (78%), with the most common procedure being prophylactic malleolar fixation (70%). We prospectively evaluated clinical outcomes using the Short Form-36 (SF-36), Short Musculoskeletal Function Assessment (SMFA), and visual analog scale (VAS) for pain and assessed initial weight-bearing radiographs and those made at the most recent follow-up evaluation. Results: The mean VAS pain score (and standard deviation) improved from 65.7 +/- 21.8 preoperatively to 18.3 +/- 17.6 at the most recent follow-up evaluation ($p < 0.001$), with five patients being pain-free (VAS score = 0). The mean SMFA bother and function indexes improved from 55 +/- 22.9 and 46.7 +/- 12.6 preoperatively to 30.6 +/- 22.7 and 25.4 +/- 17.4 at the most recent follow-up visit ($p = 0.001$ and $p < 0.001$, respectively). The mean SF-36 total score improved from 37.7 +/- 19.3 to 56.4 +/- 23.1 ($p = 0.002$). The implant survival rate was 87%. Four (20%) of the tibial components and fourteen (70%) of the talar components that were not revised exhibited initial settling and then were seen to be stabilized radiographically without further change in implant position. Three total ankle replacements (13%) showed progressive talar subsidence, prompting revision. Ten patients (43%) had minor complications not requiring repeat surgery. Conclusions: Short-term follow-up after conversion of ankle arthrodesis to total ankle arthroplasty demonstrated pain relief and improved function in a majority of patients. Patients who undergo this surgery frequently require concomitant procedures; we recommend prophylactic malleolar fixation when performing conversion total ankle arthroplasty. The rate of complications, particularly talar component settling and migration, is cause for concern. We do not recommend the procedure for ankle arthrodeses that included distal fibulectomy.

UPC

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IMPAIRMENT OF EXOGENOUS LACTATE CLEARANCE IN EXPERIMENTAL HYPERDYNAMIC SEPTIC SHOCK IS NOT RELATED TO TOTAL LIVER HYPOPERFUSION.

Tapia P, Soto D, Bruhn A, Alegría L, Jarufe N, Luengo C, Kattan E, Regueira T, Meissner A, Menchaca R, Vives MI, Echeverría N, Ospina-Tascón G, Bakker J, Hernández G.

INTRODUCTION: Although the prognostic value of persistent hyperlactatemia in septic shock is unequivocal, its physiological determinants are controversial. Particularly, the role of impaired hepatic clearance has been underestimated and is only considered relevant in patients with liver ischemia or cirrhosis. Our objectives were to establish whether endotoxemia impairs whole body net lactate clearance, and to explore a potential role for total liver hypoperfusion during the early phase of septic shock. METHODS: After anesthesia, 12 sheep were subjected to hemodynamic/perfusion monitoring including hepatic and portal catheterization, and a hepatic ultrasound flow probe. After stabilization (point A), sheep were alternatively assigned to lipopolysaccharide (LPS) (5 mcg/kg bolus followed by 4 mcg/kg/h) or sham for a three-hour study period. After 60 minutes of shock, animals were fluid resuscitated to normalize mean arterial pressure. Repeated series of measurements were performed immediately after fluid resuscitation (point B), and one (point C) and two hours later (point D). Monitoring included systemic and regional hemodynamics, blood gases and lactate measurements, and ex-vivo hepatic mitochondrial respiration at point D. Parallel exogenous lactate and sorbitol clearances were performed at points B and D. Both groups included an intravenous bolus followed by serial blood sampling to draw a curve using the least squares method. RESULTS: Significant hyperlactatemia was already present in LPS as compared to sham animals at point B (4.7 (3.1 to 6.7) versus 1.8 (1.5 to 3.7) mmol/L), increasing to 10.2 (7.8 to 12.3) mmol/L at point D. A significant increase in portal and hepatic lactate levels in LPS animals was also observed. No within-group difference in hepatic DO2, VO2 or O2 extraction, total hepatic blood flow (point D: 915 (773 to 1,046) versus 655 (593 to 1,175) ml/min), mitochondrial respiration, liver enzymes or sorbitol clearance was found. However, there was a highly significant decrease in lactate clearance in LPS animals (point B: 46 (30 to 180) versus 1,212 (743 to 2,116) ml/min, $P < 0.01$; point D: 113 (65 to 322) versus 944 (363 to 1,235) ml/min, $P < 0.01$). CONCLUSIONS: Endotoxemia induces an early and severe impairment in lactate clearance that is not related to total liver hypoperfusion.

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NEURAL OSCILLATORY DEFICITS IN SCHIZOPHRENIA PREDICT BEHAVIORAL AND NEUROCOGNITIVE IMPAIRMENTS.

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Paying attention to visual stimuli is typically accompanied by event-related desynchronizations (ERD) of ongoing alpha (7-14 Hz) activity in visual cortex. The present study used time-frequency based analyses to investigate the role of impaired alpha ERD in visual processing deficits in schizophrenia (Sz). Subjects viewed sinusoidal gratings of high (HSF) and low (LSF) spatial frequency (SF) designed to test functioning of the parvo- vs. magnocellular pathways, respectively. Patients with Sz and healthy controls paid attention selectively to either the LSF or HSF gratings which were presented in random order. Event-related brain potentials (ERPs) were recorded to all stimuli. As in our previous study, it was found that Sz patients were selectively impaired at detecting LSF target stimuli and that ERP amplitudes to LSF stimuli were diminished, both for the early sensory-evoked components and for the attend minus unattend difference component (the Selection Negativity), which is generally regarded as a specific index of feature-selective attention. In the time-frequency domain, the differential ERP deficits to LSF stimuli were echoed in a virtually absent theta-band phase locked response to both unattended and attended LSF stimuli (along with relatively intact theta-band activity for HSF stimuli). In contrast to the theta-band evoked responses which were tightly stimulus locked, stimulus-induced desynchronizations of ongoing alpha activity were not tightly stimulus locked and were apparent only in induced power analyses. Sz patients were significantly impaired in the attention-related modulation of ongoing alpha activity for both HSF and LSF stimuli. These deficits correlated with patients' behavioral deficits in visual information processing as well as with visually based neurocognitive deficits. These findings suggest an additional, pathway-independent, mechanism by which deficits in early visual processing contribute to overall cognitive impairment in Sz.

UROLOGÍA

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ESTUDIO URODINÁMICO EN MUJERES CON SÍNTOMAS DE INCONTINENCIA URINARIA DE ESFUERZO PURA

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Objective: To describe the results of urodynamic study in women with pure stress urinary incontinence symptoms, including the characteristics of the overactive detrusor. No other clinical assessments were taken into account. Material and methods: A retrospective study in women with urinary incontinence consecutively evaluated by urodynamic study. From a total of 710 women, only 108 (15%) with pure stress urinary incontinence symptoms were selected. Women with prior urinary incontinence surgery, pelvic organ prolapse (stage ≥ iii), pelvic radiotherapy, using medication active on the lower urinary tract a nd neurological diseases were excluded. Infusion rate was 70 ml/min. Detrusor overactivity was induced only by cough. A standardized cough stress test with progressive cough intensity was carried out. Results: Reference urodynamic values for stress incontinent women are described. Urodynamic stress incontinence was observed in 79 women (73.1%), detrusor overactivity in 4 (3.7%) and mixed urodynamic diagnosis in 15 (13.8%). Test was inconclusive in 10 patients (9.2%). Two women had detrusor overactivity incontinence (1.9%). One patient had detrusor overactivity induced by cough without urodynamic stress incontinence (0.9%). There was an association between detrusor overactivity and nocturia ≥ 2 (P = .002; odds ratio: 3.74; 95% confidence interval: 1.22-11.39). One woman had a bladder outlet obstruction (0.9%). Conclusions: In women with pure stress urinary incontinence, without knowing the outcome of other clinical assessments, urodynamic study can provide useful information to define the proper therapy.

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MICROSURGICAL SPERMATIC CORD DENERVATION AS A TREATMENT FOR CHRONIC SCROTAL CONTENT PAIN: A MULTICENTER OPEN LABEL TRIAL.

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PURPOSE: We prospectively evaluated the results of microsurgical spermatic cord denervation in a series of patients with chronic scrotal content pain in a multicenter study, including 1 center in Germany and 3 centers in Chile. MATERIALS AND METHODS: A total of 50 patients with chronic scrotal content pain more than 3 months in duration were prospectively selected for standardized operative microsurgical spermatic cord denervation as pain treatment. In all patients preoperative management included a positive response to a spermatic cord block test with local anesthesia. Pain severity was assessed using an analog visual pain scale (range 0 to 10) for 30 consecutive days. A total of 52 testicular units were operated on using a subinguinal approach. In all cases a surgical microscope was used to identify the arteria testicularis. RESULTS: No intraoperative complications were observed and no testicular units were lost. Two reoperations were performed, including 1 for hematocele and 1 for hydrocele. Six months after surgery 40 patients (80%) were completely pain-free. In 6 patients (12%) intermittent testicular discomfort persisted, which could be managed by acetaminophen on demand. Four patients (8%) had no change in pain severity after surgery. CONCLUSIONS: After proper selection of patients microsurgical spermatic cord denervation seems to be a safe and efficient procedure to treat chronic scrotal content pain. Considering the limitations of the study, a randomized, controlled trial with longer followup is highly warranted.

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COMPARISON BETWEEN RETROGRADE INTRARENAL SURGERY AND EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY IN THE TREATMENT OF LOWER POLE KIDNEY STONES UP TO 15 MM. PROSPECTIVE, RANDOMIZED STUDY.

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INTRODUCTION: Extracorporeal Shock Wave Lithotripsy (ESWL) is currently the recommended treatment for intra-renal calculi smaller than 2 cm. However the low Stone Free Rate (SFR) in lower pole calculi gives rise to new techniques, such us retrograde intrarenal surgery (RIRS), for improve the surgery outcomes. OBJECTIVE: To compare the efficacy of a treatment with ESWL with RIRS, in terms of SFR after surgery, in patients with kidney stones up to 15 mm in the lower pole. MATERIAL AND METHODS: A prospective study was carried out in order to assess the results of ESWL and RIRS in patients with lower pole stones less than 15 mm. Among a total of 55 patients, 31 were underwent to ESWL (Group 1) and the remaining 24 to RIRS (Group 2). Clinical data recorded, including general characteristics of each patient, were: calculi size, side, operative time, complications according to Clavien scale, SFR and the presence of residual fragments at 2 months post-treatment assessed by a CT scan. STATA 11 was used to perform the statistical analysis. RESULTS: There were no differences for general descriptors among groups with the exception

of a significantly longer operative time for RIRS. The rates of SFR and residual fragments lesser than 3 mm. were lower in the RIRS group than in ESWL ones. RIRS also showed a lower rate of clinically significant fragments (0% vs 42.3%. P < .05). In the subgroup of patients with stones between 10/15 mm RIRS showed higher SFR (75% vs. 41.2%) and a lower rate of stones>3 mm (0% vs. 58.8%), being statistically significant (P < .05). Clavien III or higher complications were not reported in any of the groups. CONCLUSIONS: In the treatment of lower pole stone RIRS has the same results than ESWL in terms of SFR. Regarding absence of a clinically significant residual fragment, RIRS was superior to ESWL. A bigger sample size is required in order to confirm these results.

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FIRST EVIDENCE OF NEOSAXITOXIN AS A LONG-ACTING PAIN BLOCKER IN BLADDER PAIN SYNDROME.

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INTRODUCTION AND HYPOTHESIS: Neosaxitoxin is a phycotoxin whose molecular mechanism of action shows a reversible inhibition of voltage-gated sodium channels at the axonal level, impeding nerve impulse propagation. This study was designed to evaluate the clinical efficacy of neosaxitoxin as a long-acting pain blocker in the treatment of bladder pain syndrome (BPS). METHODS: Five patients with a diagnosis of BPS received a total dose of 80 μg of neosaxitoxin in an isoosmotic solution of 0.9 % NaCl, pH 6.5. Infiltration was performed via cystoscopy under spinal anesthesia. Questionnaires were administered immediately before and 7, 30 and 90 days after the procedure to measure the patients' reported pain severity and quality of life. RESULTS: This study, for the first time, showed the effect of blocking the neuronal transmission of pain by local infiltration of neosaxitoxin into the bladder submucosa. All five patients successfully responded to the treatment. Furthermore, the analgesic effect lasted for the entire 90 days of follow-up without the need for a second infiltration, and no adverse reactions to neosaxitoxin were detected. CONCLUSIONS: Neosaxitoxin infiltration was shown to be a safe and effective intervention to control pain related to BPS. It was well tolerated by patients, who experienced extended pain relief and associated beneficial effects over a follow-up of 90 days. These results confirm the effectiveness of neosaxitoxin as a long-acting local pain blocker.

OAIC

FRONT IMMUNOL. 2015 OCT 20;6:535.

ROLE OF DENDRITIC CELLS INTHE INDUCTION OF LYMPHOCYTE TOLERANCE.

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The ability of dendritic cells (DCs) to trigger tolerance or immunity is dictated by the context in which an antigen is encountered. A large body of evidence indicates that antigen presentation by steady-state DCs induces peripheral tolerance through mechanisms such as the secretion of soluble factors, the clonal deletion of autoreactive T cells, and feedback control of regulatory T cells. Moreover, recent understandings on the function of DC lineages and the advent of murine models of DC depletion have highlighted the contribution of DCs to lymphocyte tolerance. Importantly, these findings are now being applied to human research in the contexts of autoimmune diseases, allergies, and transplant rejection. Indeed, DC-based immunotherapy research has made important progress in the area of human health, particularly in regards to cancer. A better understanding of several DC-related aspects including the features of DC lineages, milieu composition, specific expression of surface molecules, the control of signaling responses, and the identification of competent stimuli able to trigger and sustain a tolerogenic outcome will contribute to the success of DC-based immunotherapy in the area of lymphocyte tolerance. This review will discuss the latest advances in the biology of DC subtypes related to the induction of regulatory T cells, in addition to presenting current ex vivo protocols for tolerogenic DC production. Particular attention will be given to the molecules and signals relevant for achieving an adequate tolerogenic response for the treatment of human pathologies.

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OVEREXPRESSION OF CONNEXIN 43 REDUCES MELANOMA PROLIFERATIVE AND METASTATIC CAPACITY.

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BACKGROUND: Alterations in connexin 43 (Cx43) expression and/or gap junction (GJ)-mediated intercellular communication are implicated in cancer pathogenesis. Herein, we have investigated the role of Cx43 in melanoma cell proliferation and apoptosis sensitivity in vitro, as well as metastatic capability and tumour growth in vivo. METHODS: Connexin 43 expression levels, GJ

coupling and proliferation rates were analysed in four different human melanoma cell lines. Furthermore, tumour growth and lung metastasis of high compared with low Cx43-expressing FMS cells were evaluated in vivo using a melanoma xenograft model. RESULTS: Specific inhibition of Cx43 channel activity accelerated melanoma cell proliferation, whereas overexpression of Cx43 increased GJ coupling and reduced cell growth. Moreover, Cx43 overexpression in FMS cells increased basal and tumour necrosis factor-α-induced apoptosis and resulted in decreased melanoma tumour growth and lower number and size of metastatic foci in vivo. CONCLUSIONS: Our findings reveal an important role for Cx43 in intrinsically controlling melanoma growth, death and metastasis, and emphasise the potential use of compounds that selectively enhance Cx43 expression on melanoma in the future chemotherapy and/or immunotherapy protocols.

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ROLE OF DENDRITIC CELLS IN THE INITIATION, PROGRESS AND MODULATION OF SYSTEMIC AUTOIMMUNE DISEASES.

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Dendritic cells (DCs) play a key role in the activation of the immune response against pathogens, as well as in the modulation of peripheral tolerance to self-antigens (Ags). Furthermore, an imbalance in the activating/inhibitory receptors expressed on the surface of DCs has been linked to increased susceptibility to develop autoimmune diseases underscoring their immunogenicity potential. It has been described that modulation of activating or inhibitory molecules expressed by DCs, such as CD86, TLRs, PDL-1 and FcγRs, can define the immunogenic phenotype. On the other hand, T cell tolerance can be achieved by tolerogenic DCs, which have the capacity of blocking undesired autoimmune responses in several experimental models, mainly by inducing T cell anergy, expansion of regulatory T cells and limiting B cell responses. Due to the lack of specific therapies to treat autoimmune disorders and the tolerogenic capacity of DCs shown in experimental autoimmune disease models, autologous tolDCs are a potential therapeutic strategy for fine-tuning the immune system and reestablishing tolerance in human autoimmune diseases. New advances in the role of DCs in systemic lupus erythematosus (SLE) pathogenesis and the identification of pathogenic self-Ags may favor the development of novel tolDC based therapies with a major clinical impact. In this review, we discuss recent data relative to the role of DCs in systemic autoimmune pathogenesis and their use as a therapy to restore tolerance.