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Abstracts presentados en congresos internacionales 2018

DEPARTAMENTO DE MEDICINA

31 ANNUAL CONGRESS ESICM LIVES 2018 – PARÍS, FRANCIA

PENTOXYPHYLLINE INHIBITS M1 POLARIZATION AND FAVORS M2 OF MURINE MACROPHAGES TREATED WITH TLR4 AGONIST

M.C. Montero, J. Guerrero

INTRODUCTION. Pentoxifylline (PTX) is a phosphodiesterase inhibitor that increases intracellular cAMP. Recently, PTX has been recognized as a pharmacological modulator of inflammation that may improve outcomes in septic patients (1). In neonatal sepsis, the use of PTX as an adjunct to antibiotics therapy decreased all-cause mortality and the length of hospital stays, without significant adverse effects (2). Authors had proposed its effect may be mediated by adenosine-dependent pathways for polymorphonuclear leukocytes and T cells (3). Results of studies in whole new born umbilical blood showed that PTX inhibited the inflammatory cytokine response induced by Toll-like receptors (TLR) agonists, TLR4, TLR7 and TLR8 (4). Considering that peripheral blood macrophages can reprogram their phenotype and orchestrate the inflammatory response, we tested if PTX modifies inflammatory cytokines profile in response to a TLR-4 agonist in a macrophage cell line. **OBJECTIVE.** To assess if PTX modulates macrophage TLR4-dependent polarization in vitro. **METHODS.** Murine macrophages (Raw 264.7 cells) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) (control), or in the presence of lipopolysaccharide (LPS, Sigma -Aldrich Chemie®, Germany[LM1]) 25ng/mL, LPS + PTX (dose-response curve; SigmaAldrich Chemie®, Germany) or PTX alone. We analyzed cell viability by trypan blue exclusion assay and the time-course of changes in TNF-alpha and IL-10 mRNA content (as surrogate markers of M1 or M2 polarization, respectively) in the presence or absence of LPS, PTX or LPS plus PTX by real-time qPCR. **RESULTS.** PTX (100-250-500 and 1000mg/ml by 1-1.5 or 2h) had no effect on cell viability or TNF-alpha mRNA abundance. LPS induced TNF-alpha mRNA (3 times of control level; n= 4, p< 0,05) and PTX inhibited TNF-alpha mRNA induced by LPS (p< 0,05). The inhibitory effect of PTX on LPS-dependent TNF-alpha mRNA induction was greater with 250 mg /ml and over 1h of exposition. Interestingly, after 1.5 h of exposure, PTX+ LPS significantly increased the cellular content of IL-10 mRNA. **CONCLUSIONS.** PTX modulates macrophage inflammatory cytokines response induced by a TLR-4 agonist. We postulate that PTX modifies the polarization profile of macrophages (M1 to M2). In the context of TLR4 activation, the increase of cAMP induced by PTX may activates PKA, stabilize the IκB inhibitor and suppress NF-κB nuclear translocation. Besides, cAMP-PKA-dependent CREB phosphorylation may explain the induction of IL-10 mRNA at a transcriptional level.

ENDOCRINOLOGÍA

ENDOCRINE SOCIETY'S ANNUAL MEETING – CHICAGO, USA

COMBINATION OF HIGH PREVALENCE SIGN/SYMPATOM PAIRS: AN APPROACH TO THE DIAGNOSIS OF CUSHING'S SYNDROME

Aida Veronica Araya, Claudio Liberman, Pedro Miguel Pineda, Mmarcela Barberan, Francisco Cordero, Alejandra Lanan, Claudia Munizaga, Luis Toro.

Most of the clinical features of Cushing's syndrome (CS) are nonspecific and could be present in obesity particularly when this condition is associated with the metabolic syndrome. Frequently, diagnosis is overlooked in these patients and treatment delayed. Combinations of signs, symptoms and laboratory could be useful tools to clinician when there is suspicion of a CS. **Objective:** To evaluate the frequency of clinical signs, symptoms and biochemical alterations in patients with confirmed endogenous CS, treated in our Center and identify diagnostic dyads. **Methods:** Retrospective descriptive study of clinical files, laboratory tests, radiological exams and biopsies of patients studied in our center in the period 1980-2017. We excluded patients whose physical exam was not performed by an endocrinologist and incomplete records. At least two of the following tests confirmed diagnosis of CS: free urinary cortisol, Nugent test and nocturnal salivary cortisol. The etiology was confirmed by the following exams: plasma ACTH, functional tests and radiological exams. Patients operated on had confirmatory biopsy. The rate of coexistence of 2 specific symptoms and/or clinical or laboratory signs in each patient was determined by matching data using STATA v 12.0 software. For a pair of sign and/or symptom, a prevalence $\geq 30\%$ it was considered clinically relevant. **Results:** 102 patients, 89 women (87.2%), 36.9 ± 13 years were included. The etiology of CS was pituitary (69%), adrenal (23%) and ectopic ACTH (8%). The most frequent reasons of consultation were: rapid weight gain (56%), menstrual disorders in reproductive age women (58%), muscle weakness or decreased strength (22%), hirsutism (19%). At

physical examination the most frequent signs were moon face (90%), centripetal fat depot (78%), buffalo hump (66%); in women hirsutism and/or acne (65%), hypertension (60%), muscular atrophy (52%), red striae (42%). At the general laboratory we found hyperglycemia (60.5%), eosinophil count <1% (44%), hypokalemia (29%), lymphocytes count <1000 (18%). Between 520 matching signs and symptoms, we identified 47 dyads with both features present over 30%. We selected 10 in which both features were over 49% or, in the opinion of experts were more relevant: Cushing facies/supraclavicular fat; Cushing facies/muscular atrophy; muscular atrophy/aneosinophilia; muscular atrophy/centripetal fat depot; systolic or diastolic hypertension/aneosinophilia; Cushing facies/rapid weight gain; hirsutism and or acne/muscular atrophy and skin striae/aneosinophilia. Conclusions: Several dyads of clinical and laboratory characteristics could allow an early diagnosis and treatment of CS. Recognition of these sign/symptom pairs permits an earlier biochemical confirmation and treatment reducing the risks associated to this condition.

GASTROENTEROLOGÍA

MEETING OF THE FEDERATION OF NEUROGASTROENTEROLOGY - AMSTERDAN, HOLANDA

THE ROLE OF BCL-3 POLYMORPHISM RS2927488 (G/A) IN CHILEAN PATIENTS WITH IRRITABLE BOWEL SYNDROME: A PILOT STUDY

Caroll Beltrán Munoz, Claudio Pérez, Edith Pérez de Arce, Daniela Vera, Hugo Portillo, Veronica Torres, Ana María Madrid

Objective. We aim to assess the role of Bcl-3 SNP-rs2927488 in IBS and its relationship with the expression of Bcl-3 in this disorder. **Methods.** In 79 IBS patients (IBS-D n=19; IBS-C n=13; IBS-M n=46; IBS-U n=1) and 44 HC was genotyped the SNP-rs2927488(G/A) by PCR-RFLP method. In a subgroup of IBS(n=27) patients and HC(n=16) was evaluated the level of Bcl-3 mRNA expression at ileal and colonic mucosa by qPCR, and its association degree with rs2927488(G/A). **Results/Discussion.** There was no difference of genotype distribution of these SNPs between HC (AA: 2.27%; GA: 34.09%; GG: 63.64%) and IBS patients (AA:0%; GA: 44.87%; GG: 55.13%). No association was found between gene polymorphism and clinical characteristics in IBS patients, however a trend of increased GA frequency was observed for IBS-C subtype (GA: 69,23%; GG: 30,77%). Increased Bcl-3 mRNA levels at colonic mucosa was observed for GA haplotype in full universe ($p=0.474$), trending higher for IBS patients group.

NOCTURNAL ESOPHAGEAL BASELINE IMPEDANCE A DIAGNOSTIC TOOL TO DIFFERENTIATE SUBGROUPS OF PATIENTS WITH GERD SYMPTOMS

Claudia Defilippi, Macarena Hevia

Objective. Mean nocturnal esophageal baseline impedance (MNBI) is a new parameter useful in patients with gastro esophageal reflux symptoms (GERD). Recent publications demonstrate that this parameter reflects the mucosal integrity of the esophagus and is an in vivo measurement of esophageal mucosa trans-epithelial resistance. GERD patients have lower MNBI values than healthy subjects. There are limited data available regarding MNBI measurements in different subgroups of patients with GERD symptoms. **AIMS:** To evaluate and compare MNBI in a group of patients with acid reflux (AR) and a group of patients with functional heartburn (FH) and reflux hypersensitivity (RH). **Methods.** 19 patients with AR were studied, 9 women, mean age 47 years (range 22-70 years) and 19 patients with FH and RH, 14 women, mean 45 years (range 17-71 years). Patients were evaluated with a symptoms scale, upper digestive endoscopy, high resolution esophageal manometry and multichannel intraluminal pH-impedance without using proton pump inhibitors. MNBI was recorded in sensors located 3 and 17 cm above the esophagogastric junction, in a manual form, selecting three different periods of 10 minutes during the night, avoiding reflux episodes, swallows and pH drops. Statistical analysis was performed with Mann Whitney and Spearman correlation coefficient. **Results / Discussion.** Distal esophageal MNBI was significantly lower in patients with AR ($1146 \pm 617 \Omega$) versus the FH and RH group ($3327 \pm 1422 \Omega$) ($p < 0.0001$). There were no differences in proximal esophageal MNBI. We found a negative correlation between MNBI levels and the acid exposure time ($r = -0.8$, $p < 0.0001$), both in the group with AR and in the global group.

PSYCHOSOCIAL RISK FACTORS IN IRRITABLE BOWEL SYNDROME (IBS) PATIENTS

Ana María Madrid, Macarena Hevia, Daniela Vera, Caterina Chesta

Objective. Irritable Bowel Syndrome (IBS) is presented as a biopsychosocial model according to Rome criteria. In Chile, there are no reports on psychosocial risk factors (PRF) in patients with IBS. **Aim:** To evaluate PRF in IBS patients and the association with clinical severity, phenotypes and related pathologies and to determine whether there were any differences compared to Healthy Control (HC). **Methods.** 98 IBS patients and 37 HC were evaluated according to Rome IV criteria (paired by sex, 82% women), 50 ± 14 years. In accordance with clinical criteria: 36% severe, 46% moderate and 18% mild. The patients were consulted during the clinical interview about PRF: sexual abuse, rape, abandonment, loss or death of a parent, traumatic events in childhood and adulthood, happy or unhappy childhood appraisal, previous infectious events and/or posterior symptoms appearance and associated pathologies. The severity of the PRF was assessed by scoring 3 points for each PRF (0-27). Statistical analysis with Kruskal-Wallis test. **Results / Discussion.** 94 patients presented PRF (96%) and 4 patients reported an infectious episode prior to the appearance of symptoms. PRF score in patients with severe, moderate and mild IBS were 13 ± 4 , 8.5 ± 3.7 and 6.4 ± 3.9 ($p < 0.0001$), without differences between phenotypes. The most important factors reported were traumatic events in childhood (83%), familiar abuse during adulthood (60%), sexual abuse (24%) and rape (12%). 67% of patients qualified their childhood as unhappy vs 2.7% of HC ($p < 0.0001$). Prevalence of other pathologies: 47% depression and 27% fibromyalgia. HC did not present other pathologies.

ALTERATION OF ENTEROENDOCRINE CELLS NUMBER IN INTESTINAL MUCOSA OF IRRITABLE BOWEL SYNDROME (IBS) PATIENTS

Caroll Beltrán Munoz

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by a gut-brain-microbiome axis imbalance leading to neuroinunoendocrine disturbances. Changes in the enteroendocrine cells (EC) population in intestinal mucosa have been associated with motility disorders in diverse digestive diseases, although for IBS this association is still controversial. Chromogranin A (CgA) is a glycoprotein co-released with serotonin, commonly used as an EC marker, mainly enterochromaffin cells. **AIMS:** To measure the density of EC cells in ileal and colonic mucosa of patients

with IBS, compare them with healthy subjects (HS) and evaluate their association with IBS phenotype. Methods. Ileal and colonic mucosa samples of IBS patients (n=18; IBS-D, n=8; IBS-C, n=5; IBS-M, n=3, IBS-U, n=2), recruited under Rome III criteria; and HS (n=13), obtained by colonoscopy. We determined EC density (cell number/intestinal area/HPF) with indirect immunofluorescence for CgA. Results / Discussion. EC CgA positive density in ileal samples tends to be higher in IBS than in HS (IBS: 2.532 ± 1.130 ; HS: 1.718 ± 0.602 cells/mm²), but not in colonic samples (IBS: 1.908 ± 1.567 ; HS: 1.635 ± 1.148 cells/mm²), without statistically significant differences for both segments. We did not find differences between IBS phenotypes.

ARE THERE SMALL INTESTINAL MOTILITY DISORDERS IN IRRITABLE BOWEL SYNDROME (IBS) PATIENTS?

Ana María Madrid, Macarena Hevia, Daniela Vera

Objective. Irritable Bowel Syndrome (IBS) affects communication of the brain-gut axis, associated with small intestinal motility disorders. It is a frequent cause of gastroenterology consultation. Motility studies have shown diverse results. Aims: To study small intestinal motility disturbances in IBS patients with and without Small Intestine Bacterial Overgrowth (SIBO) and to determine whether there were any differences compared to Healthy Control (HC). Methods. 46 IBS patients were recruited, 37 ± 14 years, 33 IBS-Constipation (IBS-C) and 37 HC without SIBO. Duodenal motor activity was studied by means of a multilumen, perfused catheter (internal diameter, 0.9 mm). The manometric catheters were attached to external TP-400t pressure transducers and connected to a Nihon Kohden polygraph. Studies were performed in a fasting state. The different phases of the migrating motor complex and clustered contractions (CC) were identified by visual inspection using the following criteria: phase I absence of contractions; phase II irregular phasic contractions and phase III characterized by rhythmic phasic contractions at a frequency of 12 cpm. The frequency and amplitude were calculated by means of the computer program. CC were defined as a sequence of three to ten rhythmic contractions, preceded and followed by a quiescent period of 1–5 min. Motility Index (MI) corresponds frequency by the amplitude in phase II. SIBO was diagnosed with lactulose breath standardized. Statistical analysis Mann-Whitney test. Results / Discussion. 61% of IBS presented SIBO. We found differences between IBS and HC in frequency and amplitude phase II 0.68 ± 0.3 vs 1.2 ± 0.6 cpm and 22 ± 5.7 vs 31 ± 6.7 mmHg, amplitude phase III 23 ± 6.2 vs 38 ± 12 mmHg; MI 15.8 ± 9.5 vs 36 ± 15 and CC 2.8 ± 2.7 vs 0.26 ± 0.54 /hr ($p < 0.0001$). There were no differences in motility study comparing IBS-C vs non IBS-C and SIBO vs without SIBO. The SIBO vs without SIBO had more frequent clustered contractions, 3.9 ± 2.9 vs 1.2 ± 1.8 /hr ($p = 0.0017$). The intestinal motor compromise was classified 74% as unspecified disorder, 13% neuromyopathic and 13% normal.

DEMOGRAPHIC, CLINICAL AND MANOMETRIC FEATURES OF A COHORT OF CHILEAN PATIENTS WITH ACHALASIA DIAGNOSED IN THE HIGH RESOLUTION ERA

Claudia Defilippi, Macarena Hevia

Objective. High resolution esophageal manometry (HREM) has improved achalasia diagnosis allowing the recognition of different subtypes. In Chile we don't have a characterization of achalasia patients diagnosed with high resolution. Aims: To study the demographic, clinical and manometric characteristics of a group of patients newly diagnosed with achalasia, using HREM and analyze the performed treatment. Methods. We reviewed 1292 HREM performed in our hospital and select patients newly diagnosed with achalasia. We analyzed in each patient a symptom scale, endoscopic, radiologic and manometric findings, in addition to the treatments they received. Statistical analysis was performed with Kruskal-Wallis and Mann-Whitney tests. Results / Discussion. We found 103 patients, 58 men, mean age 53 years (range 17-84). Chagas serology was positive only in 1.9%. The most frequent symptoms were dysphagia (97%), regurgitation (71.8%), heartburn (69.9%) and chest pain (53%). The upper digestive endoscopy and esophagogram were suggestive of achalasia diagnosis in 70 and 80% respectively. In relation to the different manometric subtypes, 88% was type II (with pan pressurization), 8.7% type III (spastic) and 3% type I (without pressurization). The mean esophagogastric junction pressure was 38 mmHg, mean IIRP 36 mmHg without any significant differences between manometric subtypes. Type I achalasia displayed a higher global symptom score* and higher chest pain score* compared to the other groups (* $p = 0.0482$). Regarding treatment, we could have information only from 58 patients due to the fact that many patients live in rural areas and was difficult to contact them. 28 patients underwent surgery, endoscopic dilatation was performed in 6, POEM in 2 and 22 patients did not receive any kind of treatment even though they were diagnosed.

GENÉTICA

INTERNATIONAL CONGRESS OF GENETICS 2018 - FOZ DE UGUAZU, BRASIL

CONGENITAL ANOMALIES AND ABORTION IN CHILE: A NEW LAW

Pardo R

Objective: To describe the development of a law that change the public health policy and impact the rate of newborns with congenital anomalies in Chile. Methods: This is a report on the process concerning the conception, approval and execution of the law of interruption of pregnancy. Results: In January 2015, it was applied a law proposal of voluntary interruption of pregnancy (VIP) for three reasons: vital risk of the mother, fetal anomalies incompatible with life (FAIL) and rape. This text was evaluated by the Chamber of Deputies and the Senate, its discussion following two steps by chamber: a) in their Health Commission and b) as a plenary session. When each Health Commission was analysing the text, representatives of human rights, civil and medical societies were invited to give their position in front of the law proposal and give information to the legislators. The law was approved by the Congress in August 2017, including some modifications: emphasizing the accompaniment of the woman throughout the process. Minister of Health published the technical norms in order to regulate the practice of VIP in December 2017, and data in the public health system until April 2018, report 49 VIP by congenital anomalies, and 12 women who despite having had fetus with fail chose to continue with their pregnancy. Conclusion: To modify laws is a longer process that need the active participation of authorities, legislators, community and experts. After modifications in a health public policy it is important to supervise and include modifications when it is necessary.

UNIDAD DEL DOLOR

20TH ANNUAL CONFERENCE OF THE INTERNATIONAL SOCIETY FOR BIPOLAR DISORDERS - MEXICO DF, MÉXICO

CHANGE IN CORPORALITY FUNCTIONS AND GLOBAL FUNCTIONALITY IN WOMEN WITH FIBROMYALGIA AND BIPOLAR DISORDER THAT RECEIVED DRAMATICS INTERVENTIONS THERAPY

D. Diez de Medina, M.J. Pacheco, C. Arteaga, A. Vivero

Background and Aims: The 12% of patients have bipolar disorder (BD). Dramatics techniques are unusual in the management of these. Measure the change in the corporality functions and global functionality in women with fibromyalgia and BD that received dramatics interventions during 1 year. **Method:** Prospective Cohort research. Operationalization of corporality functions and structure level using the OPD2 model. OPD2 semi-structural Interview and fill out corporal and structure form, at the beginning, 6 and 12 month of treatment and use of scales self-applied. **Results:** Damaged functions of corporal module: Self-regulation of corporal-self: Tolerance to relative affections of the body, self-esteem regulation in relation to one's own body. Communication with the inner body, empathy with another's corporal state. Body in the framework of internal and external objects attachment, establish affectionate corporal contact, receive and provide corporal support. Damaged functions in structural module: Self-destructive and self-devaluative tendencies. Over-regulation and loss of regulation of self-esteem. Difficulties in regulation of affections and the body; to express one's own affections; to be touched by other people's affections; to take distance and regulate them from one's own affections; to separate from others. All patients show improvement in global functionality, alexithmia, anxiety-depression symptoms, anhedonia and decrease of pain score at the 6 and 12 m. Improvements are ss ($P < 0.05$). OPD2 corporal functions are improving since 6 m of treatment at 12 m the improvements remain. **Conclusion:** These techniques improvement statistical significant between beginning treatment at 12 m, alexitimia and corporality functions, global functionality. These could to modify the psiquical structure across the corporality function improvement.

EPIDEMIOLOGICAL PROFILE OF PATIENTS WITH FIBROMYALGIA AND BIPOLAR DISORDER THAT ARE BEEN TREATED IN CHRONIC PAIN UNIT. DESCRIPTIVE RESEARCH

J.P. Cornejo Diez de Medina, A. Viveros, M.J. Pacheco, C. Arteaga, D. Diez De Medina

Background and Aims: Fibromyalgia is chronic pain disorder with important medical comorbidity. Mood disorders are frequently related with fibromyalgia. The 12% aprox of patients with fibromyalgia are suffering bipolar disorder. The epidemiological characterization of this patients is unknow. **Aim:** Epidemiological Characterization the patients with fibromyalgia and bipolar disorder that are in treatment in chronic pain unit. **Method:** Analysis of medical records and clinical interviews of those patients. Descriptive statistical analysis. **Results:** 15/130 (11,5%) patients has fibromyalgia and bipolar disorder. All patients are women. 13/15 has bipolar disorder type 2 criteries diagnosis (87%), 2/15 (13%) has bipolar type 1 criteries diagnosis. 12/15 (80%) has stress post traumatic disorder criteries diagnosis. obsessive, anxious, somatization, inestable affectivity and dependence are the most frequent personality traits, 5/15 (33%) has personality disorder criteries diagnosis. High Alexitimia level is caraterizing in all patients. Autonomy/care-need and submission/control are most prevalent OPD 2 conflicts. Medium and Medium-high level are most frequent Structural functionality in analysis of OPD 2. Corporal OPD2 analysis showed that the most importants disfunctions are connectivity mind-body, hypercontrol and hyper repression of emotions to inner the body, expression emotions problems, problems for use the body for regulation the relationships with others, problems for recognizing positive emotions about own corporality. Principal attachment style is anxious-ambivalent. Analysis of coping skills demonstrated that affective isolated and over emotional expression are the most frequent mechanisms. Risk commit suicide is not severe, only three patients tried commit suicide with mechanisms of low lethality. **Conclusion:** Those patients are multi-complex and need multi-integrative initial evaluation.

BIPOLAR DISORDER SCREENING DIAGNOSIS PROTOCOL IN WOMEN WITH FIBROMYALGIA IN TREATMENT IN CHRONIC PAIN UNIT

J.P. Cornejo Diez de Medina

Background and Aims: Fibromyalgia is relation to with important medical comorbidity. 12% suffer bipolar disorder (BD). No researches of screening protocol of BD exist. Describe BD screening diagnosis protocol in women with fibromyalgia. **Method:** Elaborate protocol. Protocol has four steps; First step: self-applicable evaluation. Fill MODQ, PHq9, TAS20, IPDE, CAMIR, Sheehan anhedony and functionality scale. Second: psychiatry interview searching hipomania-mania and mixed episodes, and soft indicator of BD. If important doubts of diagnosis exists continue to step three. Third: A close relative is interviewed searching elements of BD in the index case. Fourth: Build a biographical life-line and analysis. **Results:** 22/130 had MODQ(+), 15/130(11,5%) had BD. 7/22 were false positives. 13/15 have BD2(87%), 2/15(13%) have BD1. 84/130(65%), 12/15 (80%) have post traumatic disorder stress(PTSD). The most frequent diagnoses with false positive MODQ were Personality disorder, PTSD. 20/130(18%), 5/15(33%) has PD. most frequent are Dependent, somatoform, obsessive and affectively unstable. Three patients were diagnosed BD during treatment due to switch on to mix symptoms or Secondary hypomania caused by use of dual AD in high doses without mood stabilizers in optimum doses. **Conclusion:** These patients are multi-complex and require a multi-integrative initial evaluation, screening for BD is extremely necessary before using dual Anti-depressive drugs in combination with mood stabilizers in high doses for chronic pain relief, being lamotrigine 300-600 mg/d, and coadyuvants mood stabilizers with effect in the pain management kind pregabalin 150-300 mg/d, topiramate 300-600 mg/d, ziprazidone 5-20 mg/d. Without use of mood stabilizers in optimum doses with AD, the switch on risk in those patients is evident.

ONCOLOGÍA

ASCO ANNUAL MEETING – CHICAGO, EEUU

ANALYSIS OF PROGNOSTIC FACTORS FOR GALLBLADDER CANCER (GBC) OF PATIENTS ASSISTED IN AN ACADEMIC HOSPITAL IN CHILE.

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Background: Chile is the country with highest incidence and mortality rates of the GBC in the world. The GBC is an aggressive cancer with poor survival. Many studies include GBC in the group of biliary tract cancers, but the study as its own entity has been limited. The aim of this study is to evaluate

the prognostic factors associated with overall survival (OS) in patients (pts) with the diagnosis of GBC. Methods: Retrospective study that includes pts with diagnosis of GBC confirmed by biopsy, classified according to images or surgical procedures. They were treated in Hospital Clínico Universidad de Chile between January 2010 to December 2015. The analysis was according to demographic, clinical and pathological variables and related to chemotherapeutic treatment (CT). Results: There were 130 pts, 82 women and 48 men. The mean age was 63 (35-96) years. Histopathological diagnosis was adenocarcinoma NOS in 67% of the cases. Seventy-one pts (56%) debuted with IV stage disease. Twenty-one pts (27,6%) received first line of CT. 90% of this pts received gemcitabine with cisplatin, mean cycles was 5.5 (1-19) cycles. OS of stage IV group that received first line CT was 13.6 months (ms) vs 4,2 ms in pts not treated with CT (HR: 0,58, 95% CI 0,35-0,95, p = 0,04). There were 18 pts with stage IIIA and 13 pts with stage IIIB. They did not present statistical significant (ns) in OS (10,9 vs 8,1 ms, respectively, p = ns). Only 5 pts received adjuvant treatment. Our analysis showed factors that determined a better OS were ECOG 0-1 vs ≥ 2 with OS 10 vs 2,2 ms (HR 0.38, 95% CI 0,18-0,79; p = 0,0001). Albumin $\geq 3,5$ showed better OS than albumin $< 3,5$ g/dl (OS 9,1 vs 5,6 ms; p = ns). The women treated with CT had a superior OS than men (17,2 versus 13,5 ms; p = ns). There were not statistically differences in the OS according to gender, BMI, hemoglobin nor age in all group. Conclusions: In our analysis, pts with ECOG 0-1 and levels of albumin $\geq 3,5$ g/dl demonstrated a better OS due to good functional and nutritional status. Women who received chemotherapy had a better prognosis. Perhaps, this finding is due to early consultation. The absence of adjuvant therapy could explain the poor results obtained in stage III pts.

COMPLETE PREOPERATIVE CHEMOTHERAPY REGIMEN FLOT: EVALUATING THE SAFETY AND HISTOPATHOLOGIC RESULTS IN GASTRIC CANCER (GC).

Luis Villanueva, Jaime Anabalón, Olga Barajas, Carlos Gallardo, Jose Luis Leal, Mauricio Mahave, Luis Matamala, Angelica Molina, Felipe Reyes, Pamela Salman, Jean M Butte, Roberto Charles, Nicolas Devaud, Sebastian Hoefler, Sergio Enrique Panay, Elizabeth Milla, Maria Alejandra Muñoz, Christian Caglevic

Background: The perioperative regimen FLOT has been associated with a better outcome in GC and a higher chance of having pathological complete response (pCR). Thus, giving all cycles of chemotherapy before surgery might improve pCR and having a positive impact on survival. The aim of this study is to evaluate the histological and safety results of FLOT regimen administered before the surgery in patients (pts) of our institution. Methods: Retrospective study that evaluates pts with diagnosis of GC (T1-4, N+, M0) confirmed by biopsy, categorized according to preoperative images and post operative surgical procedures. They were presented to oncological committee joint of Instituto Oncológico FALP between november 2016 and september 2017 and received complete preoperative regimen FLOT. They were analyzed by demographic, clinical, safety and histopathologic variables. Results: There were 19 pts. 11 men (57,9%) and 8 women (42,1%) with median age of 65 years (32-80 years). Most of pts presented ECOG 0 (73,7%). Principal histopathologic diagnosis were adenocarcinoma NOS (33%) and tubular adenocarcinoma (33%). Nine pts (47,4%) had a clinical IIB stage before the treatment. The mean of cycles was 7,4 (3-8 cycles). Ten pts required diminishing or suspending doses. Adverse events G3 or G4 occurred in 47,3%. Neutropenia G3-4 was the most frequent complication. Fifteen pts had been operated on. Three pts are pending surgery and 1 patient was not operated because presented progressive disease. All resected pts were undergone gastrectomy and D2 dissection. Three pts (20%) achieved pCR and 4 (26,6%) cases had metastatic disease (peritoneal carcinomatosis). No 30-day mortality occurred. Conclusions: Our data suggests that intensive and complete preoperative FLOT chemotherapy is feasible, safety and effective in GC. Most of pts received all the cycles of FLOT before surgery. The achievement of pCR was similar to other docetaxel-based chemotherapy trials, although our sample size is small. We had a high rate of metastatic patients perhaps an optimal staging is necessary before starting treatment.

REUMATOLOGÍA

EULAR 2018 - AMSTERDAN, HOLANDA

INTERSTITIAL LUNG DISEASE AND MICROSCOPIC POLYANGIITIS IN CHILEAN PATIENTS

P. Wurmman, F. Elgueta, D.E. Vargas, M.L. Molina, K. Vergara, M. Mac-Namara, A. Goecke, H. Gatica, F. Sabugo, S. Saavedra, F. Bozán, J.C. Diaz

Background: Microscopic Polyangiitis (MPA) is an ANCA associated vasculitis (AAV), associated with p-ANCA (perinuclear) fluorescence pattern and anti-myeloperoxidase (MPO) specificity. Most frequently involved organs are kidney (80%–100%), peripheral nervous system and skin (30%). There is Pulmonary involvement in 25%–35% of patients, being alveolar haemorrhage frequently described. Interstitial lung disease (ILD) has also been recognised. Objectives: The aim of our study is to report the characteristics of MPA Chilean patients with ILD and to compare it with other series. Methods: Retrospective study. Patient diagnosed between 2007 and 2016 at the Hospital Clínico Universidad de Chile, with ILD, defined as interstitial lung disease on CT scan with Usual Interstitial Pneumonia (UIP) or Non Specific Interstitial Pneumonia (NSIP) pattern, and MPA were included. Demographic, clinical, laboratory and mortality data were plotted. Data from other series were compared with our results. Other causes that could explain the pulmonary involvement were excluded. Results: From 94 patients with AAV, 36,1% were MPA, being 16 patients with ILD. All were Hispanic, median age 65.3 years, 32–84 female 62,5% (table 1). Common manifestations were constitutional symptoms (100%), weight loss (68,7%) and fever (68,7%). All patients had anaemia, high ESR (mean 84 mm/hr. range 33–120) and CRP (8–22 times above upper normal limit). All patients were ANCA-p and MPO positive. In 10 cases ILD was diagnosed concomitantly with MPA and in 6 was 0.5 to 15 years before. 4 patients developed pulmonary haemorrhage. Images patterns were 10 UIP and 5 NSIP. All patients received corticosteroid as induction therapy, 15 also received cyclophosphamide. One patient plasmapheresis, and one received Rituximab after a relapsed. Azathioprine was used as Maintenance therapy. Four patients died during follow-up. table 2 shows data from other worldwide region compared with our data. Conclusions: Among Chilean patients there are more females, have a more NSIP pattern, and less mortality that other worldwide series.

AMERICAN COLLEGE OF RHEUMATOLOGY'S ANNUAL MEETING – CHICAGO, USA

IGG4-RELATED DISEASE, CLINICAL SERIES ON CHILEAN PATIENTS

Carolina Cuéllar, Oscar Neira, Alejandra Herrera, Miguel Gutiérrez, Fabián Elgueta, Pamela Wurmman, Bellanides Mansilla, Javier Basualdo, Jorge Vega, Daniel Erlij, Cristián Labarca, Cristián Vergara, Verónica Mezzano, Paula Pastenes, Lilith Stange, Susana Michalland, Francisco Silva, Aquiles Jara, I. Annelise Goecke et al. IgG4-related disease (IgG4-RD) is a chronic fibroinflammatory condition that can affect almost

any organ. Gold standard for diagnosis, biopsy, can show lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and IgG4+ plasma cell infiltrate. High serum IgG4 levels is observed only in 50% of patients. Disease is more frequent in males, around 60 years old, affecting one or multiple organs with subacute development of tumors or organomegaly. Lymphadenopathies are common, and 40% of patients have a history of allergies. Umehara's diagnostic criteria (2012), based on clinical features, serum IgG4 levels and histopathology are the most accepted. Disease was described in 2003, and Chilean reports are scarce. We describe clinical, laboratory, histopathology findings, and treatment on Chilean IgG4-RD patients. Methods: We analyzed retrospectively clinical records of 48 patients with IgG4-RD from nine medical centers. Patients with possible, probable and definitive diagnosis, according to Umehara criteria, were included. Results: Our cohort was 56% male, with a mean age of 52 (18-76) years. Histological confirmation of IgG4-RD was obtained in 44 of 45 patients who underwent a biopsy. Twenty-three percent of patients had allergic background, 27% had eosinophilia and 43% had elevated plasma levels of IgG4 (≥ 135 mg/dl). The clinical involvement was: pleural and lung disease 38%, kidney 27%, orbital pseudotumor 25%, lymphadenopathy 21%, retroperitoneal fibrosis 19%, aortitis 19%, sialoadenitis 17%, pancreas 17%, pericardium 15% and meninges in 8%. There were three patients with hypophysitis and two with mediastinal fibrosis. Multiple organ involvement (≥ 2 organs), observed in 69%, was significantly more frequently in males ($p < 0.05$). There was a statistically significant association between renal disease and low complement levels ($p < 0.01$). All patients who had renal or pulmonary disease had multiple organ involvement. Multiple organ involvement was not related with immunosuppressive treatment requirement. Pathology confirmation, in 44 patients, showed: lymphoplasmacytic infiltrate in 43 (98%), storiform fibrosis in 29 (66%) and none had obliterative phlebitis. All tissues had diagnostic IgG4 (+) immunohistochemical staining. Storiform fibrosis was present in all lung and kidney biopsy, but only half of salivary gland, orbital and retroperitoneal tissue. Regarding treatment, all patients received glucocorticoids. In 30 patients (63%) was required immunosuppressive treatment: azathioprine, followed by methotrexate and mycophenolate mofetil were drugs most used. Rituximab was used in 8 patients. Clinical response was good, but one patient dies because extensive mediastinal disease. Conclusion: IgG4-RD in Chilean patients is similar that described elsewhere. In most of patients serum levels of IgG4 were normal, then biopsy was essential to diagnosis. Multiple organ involvement was frequent, being pleuropulmonary, kidney, orbital and lymph node most usual localizations. Renal and pulmonary localization occurred always in context of multiorganic disease.

DEPARTAMENTO DE OTORRINOLARINGOLOGÍA

ENDOSCOPIC SURGERY OF THE PARANASAL SINUSES, SKULL BASE, BRAIN AND SPINE – BARCELONA, ESPAÑA

ANTERIOR SKULL BASE CEREBROSPINAL FLUID LEAKS: ENDOSCOPIC REPAIR. EXPERIENCE CLINICAL HOSPITAL UNIVERSIDAD DE CHILE.
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Introduction. Anterior skull base cerebrospinal fluid leaks (CSF) must be included in differential diagnosis of unilateral rhinorrhea. Clinical suspicion and an appropriate preoperative anatomic evaluation is essential to plan the surgery. Endoscopic approach is the first choice. New techniques with flap use have allowed an appropriate repair, with variable success rates, near of 90%. Objectives. Describe and analyze clinical, epidemiologic features, and results of endoscopic surgical treatment done in clinical hospital Universidad de Chile, in patients with anterior skull base CSF leak. Results. Retrospective study, descriptive in base to clinical record. Patients with anterior skull base CSF leaks undergo endoscopic surgical treatment between the years 2012 to 2017 are included. Epidemiological, clinical, surgical and recurrence variables were analyzed. The series is constituted by 12 patients, with an average age of 40 years; 10 women and 2 men. The clinic was characterized entirely by unilateral rhinorrhea/rhinoliquorrhea, in 2 cases it was associated with meningitis. The etiology was mostly idiopathic, followed by a history of surgery or previous trauma. The most frequent location was the sphenoid and ethmoidal sinus. The closure was multi-layered in all cases. The follow-up period of the series varies from 3 to 34 months. Recurrence is observed in 1 patient. Conclusions. The management of the cerebrospinal fluid fistula of the anterior skull base through endoscopic approach, has been shown to be effective in our center, with a low rate of complications, and with recurrence in only 1 patient. Team work between neurosurgeons and otolaryngologists can be beneficial in the management of these patients.

DEPARTAMENTO DE NEUROLOGÍA Y NEUROCIRUGÍA

2018 AAN ANNUAL MEETING – LOS ANGELES, EEUU

EARLY DISEASE STAGE OF MULTIPLE SCLEROSIS IN CHILEAN PATIENTS: COGNITIVE IMPAIRMENT IS A KEY DOMAIN AND DOES NOT RELATE TO MRI MEASURES

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Objective: To describe clinical and quantitative magnetic resonance imaging (qMRI) parameters in Chilean patients with Multiple Sclerosis (MS) in the early stages. Background: Chile is a long, narrow country ranging from latitude 17 to 56, "isolated" between the Andes Mountain chain and the Pacific Ocean. Chilean MS patients may have specific clinical and MRI profiles. Design/Methods: This prospective study recruited 45 patients with MS at the University of Chile (relapsing-remitting MS 74%, clinically isolated syndrome 26%). Structural Imaging Evaluation with Normalization of Atrophy analysis was performed to assess global brain volume, and its partitions of grey and white matters and ventricular volumes. Brief International Cognitive Assessment (BICAMS) was used for cognitive impairment. Results: The mean age was 34 years (range 18-59), 67.3% female, disease duration 2.06 years (0.4 -7.1), Kurtzke EDSS 1.37 (0-4). First line DMT: 39.2% interferon, 10.9% glatiramer acetate, 17.4% fingolimod, 6.5% teriflunomide and 26% DMT-naïve. According to normative data in Hispanic population for BICAMS, 50% of patients performed badly on the Symbol Digit Modalities Test (mean \pm SD: 43.2 \pm 12), 41% on the California Verbal Learning Test 2 (53.9 \pm 10.7), and 17% performed badly on the Brief Visual Spatial Memory Test-Revised (23.7 \pm 7). qMRI volumes were between normal limits: mean whole brain 1561 ml (range 1344-1680), grey matter 745 ml (642-814), white matter 816 ml (702-899) and ventricular volume 435 ml (246-774). BICAMS correlates

negatively well with the EDSS score ($r: -0.37$; $p=0.01$) and age ($r: -0.50$; $p<0.001$). QMRI variables did not show correlations with clinical variables. Conclusions: In the early stages of MS, cognitive impairment is already present in at least 50% of Chilean MS patients and correlates with clinical disability and age, but not with qMRI measures. Thus, cognitive impairment is a key domain to consider when choosing the first line therapy.

OHBM 2018 ANNUAL MEETING - SINGAPUR

COCHLEAR AGING IS ASSOCIATED WITH COGNITIVE DECLINE AND BRAIN ATROPHY IN ELDERLY

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Introduction: Hearing loss has emerged as one of the most important modifiable risk factors for preventing dementia (1-2). Increasing epidemiological evidence has shown a relationship between age-related hearing loss, cognitive decline and structural brain changes in elderly people. However the mechanisms that link these associations remain elusive. Aging affects the auditory system at the receptor level (cochlear hair cell loss) and at the central auditory pathways, and both processes could contribute to cognitive decline. We hypothesize that cochlear dysfunction is associated with greater volume atrophy in brain regions important for auditory and language processing (temporal regions), reflecting an interaction of sensory and cognitive functions. We measured distortion product otoacoustic emissions (DPOAE), a common non-invasive clinical tool used to assess inner ear function (3). In addition, neuropsychological evaluations and structural magnetic resonance imaging (MRI) were performed and correlated with DPOAEs. **Methods:** 29 patients from the Auditory and Dementia Study (ANDES) cohort (subjects aged > 65 years, without dementia with a Mini Mental State Examination score ≥ 24) participated in this study. DPOAEs (2f₁ – f₂) measurements (Etymotic Research, ER10C) were performed using eight pairs of primary tones (f₁ and f₂, at 65 and 55 dB SPL, f₂/f₁ ratio of 1.22) in each ear covering a frequency range from 1105 to 5572 Hz. The numbers of detectable DPOAE were counted in each ear (going from zero when the subject had none DPOAE to eight when the subject had all the DPOAE). A complete Neuropsychological assessment was done and MRI data were acquired with a 3-Tesla whole-body system, equipped with a head volume coil (Siemens Skyra, Germany). T1-weighted images (TR 2300 ms, TE 232 ms). Voxel-based morphometry analyses were statistically explored by FreeSurfer (www.surfer.nmr.mgh.harvard.edu). Automated regions segmentations were generated using recon-all command. It executes regional segmentation and measures gross regional volume in a conformed space (256x256x256 matrix, with coronal re-slicing to 1 mm³ voxels). All procedures were approved by the Ethics Committee of the Clinical Hospital of the University of Chile. **Results:** Mean age and education were 74.5 (± 5.05) and 9.75 (± 4.32) years. Association between DPAOEs and age showed significant negative correlation ($r = -0.66$ $P < .001$). Correlation analysis of DPAOEs with cognitive scores demonstrated that scores from cognitive tests declined linearly with increasing levels of hearing loss (Figure 1). Associations between greater temporal, hippocampal, parahippocampal and orbitofrontal volume loss and lower scores on DPAOEs were significant (Table 1). Stronger associations were observed between hippocampus and temporal volume loss and measures of processing speed ($P < .05$). **Conclusions:** Several potential mechanisms have been postulated for the association between hearing loss and cognitive decline. Our principal findings were the strong relations between cochlear aging and left temporal lobe and right hippocampal volume loss, specifically a significant relation with hippocampus independent of age. These results suggest a common cause of neurodegeneration causing cochlear hair cell loss and right hippocampal atrophy, and secondly that peripheral hearing impairment induce left temporal atrophy through neural deprivation of the auditory system by loss of sensory input (4). The impairment in non-auditory cognitive test could be related with an increase in cognitive load due to effortful listening diminishing the cognitive reserve or by the brain dysfunction secondary to neurodegeneration. These exploratory results may contribute to a further understanding of the link between peripheral hearing impairment and structural brain changes by assessing DPAOEs absence as a marker of neurodegeneration. More data are needed to confirm these statements.

AAIC SATELLITE SYMPOSIUM: BUENOS AIRES, ARGENTINA

RARE VARIANTS IN PLCG2, ABI3, AND TREM2 GENES ARE ASSOCIATED WITH ALZHEIMER'S DISEASE IN AN ARGENTINIAN SAMPLE: IS IT A EUROPEAN HERITAGE?

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Background, Rare coding variants in TREM2, PLCG2, and ABI3 were recently associated with the susceptibility to Alzheimer's disease (AD) in Caucasians. Interestingly, although TREM2 p.R47H (rs75932628) increases AD risk in Caucasians and African Americans, its association with AD could not be observed in East Asian population, because its frequency is extremely low. Hence, frequencies and effects of some genetic variants associated with AD may vary across ethnicities. Latin American populations are admixture of Native, Caucasian, and African ancestors, which present a huge gap in AD genetic studies. Consequently, we explored the effect of these rare coding variants on AD susceptibility in a population sample from Argentina and Chile. The admixed nature of this population would help us elucidate the ancestry of these rare variants. **Methods.** Four rare coding variants, in TREM2 (rs143332484 and rs75932628), PLCG2 (rs72824905), and ABI3 (rs616338) genes, were genotyped in 419 AD cases and 488 healthy controls from Argentina. Statistical power was increased by including in the analysis 266 Chilean controls. In addition, Argentinian samples underwent Genome Wide Association Study (GWAS), genotyping 696,375 variant. First, ancestry of rare variant carriers will be determined. Then, all variants neighboring the rare variants will be extracted and analyzed in order to evaluate the existence of a common haplotype with a suggestive founder effect. These haplotypes will be compared with results obtained by the European Alzheimer's Disease DNA bank, and data in 1000 Genomes. **Results.** The four variants were detected in the sample with minor allele frequencies similar to those reported in Caucasians. TREM2 rs75932628 and ABI3 rs616338 were validated as risk factors for AD (OR=7.17 [$p=0.04$] and OR=2.77 [$p=0.04$], respectively) in this Latin American sample. The PLCG2 rs72824905 showed a suggestive protective effect (OR=0.61 [$p=0.39$]). Currently we are running the analysis to determine ancestry and the haplotype associated to these rare variants. **Conclusions.** Rare coding variants in TREM2, PLCG2, and ABI3 also modulate susceptibility to AD in populations from South America, and they might originate from Europe. GWAS results analysis would shed light on this regard, and they will be presented at the AAIC2018.

INTERNATIONAL ANNUAL CONGRESS OF THE WORLD MUSCLE SOCIETY - MENDOZA, ARGENTINA

REDEFINING THE MORPHOLOGICAL SPECTRUM OF RYR1 RECESSIVE MYOPATHIES

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The RYR1 gene encodes the ryanodine receptor1, a Ca²⁺ channel expressed on sarcoplasmic reticulum membranes at the triad junction of skeletal muscle fibres. Dominant mutations lead to CCD and MHS phenotypes whereas recessives manifest with a wide range of clinical and morphological presentation. We present a monocentric revision of muscle biopsies from more than 50 genetically confirmed RYR1 recessive patients. We performed histological, immunohistochemical and ultrastructural analysis of 58 muscle biopsies from 53 patients. Moreover, levels of RYR1 expression in muscle biopsies have been assessed by Western Blot (WB) and its pertinence with genetics background, clinical severity and morphological findings has been investigated. By optic microscopy, 10 muscle biopsies showed typical cores (single or multiple, central or eccentric) and 6 core and rods association in the same biopsy. Five biopsies showed isolated type1 uniformity/predominance with or without mild myofibrillar disorganization. Most of muscle biopsies presented a unique histological feature characterized by association of irregular myofibrillar disorganization, granular cytoplasmic material deposition, type1 fiber predominance and nuclear internalization and centralization. In rare cases these findings were observed just in few muscle fibers. One third of these cases the myofibrillar pathway presented a targetoid appearance by oxidative stains in variable number of fibers. In one case both the latter histological presentation and cores were simultaneously present. By electron microscopy, typical cores, core and rods and the biopsies showing the peculiar features, presented areas of myofibrillar disorganization ranging from few sarcomeres to more than 50 sarcomeres of variable width sometimes occupying almost the entire muscle fiber. Areas of disorganization contained variable degree of osmophilic dense filamentous material deposition (possibly corresponding to granular material by optic microscopy) and disorganized thickened z-line fragments. WB analysis on muscle biopsies revealed a constant reduction of RYR1. The percentage of reduction seems to be more pronounced in more severe clinical cases and in patients showing the peculiar morphological phenotype compared to isolated type1 prevalence/uniformity.

THE LATIN AMERICA EXPERIENCE WITH A NEXT GENERATION SEQUENCING GENETIC PANEL FOR RECESSIVE LIMB-GIRDLE MUSCULAR WEAKNESS

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Limb-girdle muscular dystrophy (LGMD) is a group of neuromuscular disorders of heterogeneous genetic etiology with more than 30 directly related genes. LGMD is characterized by progressive muscle weakness involving the shoulder and pelvic girdles. An important differential diagnosis among patients presenting with proximal muscle weakness (PMW) is late-onset Pompe disease (LOPD), a rare neuromuscular glycogen storage disorder, which typically presents with respiratory insufficiency in addition to PMW. Patients with PMW, with or without respiratory symptoms, were included in this study to evaluate the profile of variants for the included genes related to LGMD and LOPD and the frequency of variants in each gene among the patient population. Over 20 institutions across Latin America (Brazil, Argentina, Peru, Ecuador, Mexico, Chile) enrolled 2103 individuals during 2016 and 2017. Dried blood spots were collected from patients and sent to the laboratory. Nine autosomal recessive LGMDs and Pompe disease were investigated in a 10-gene panel (ANO5, CAPN3, DYSF, FKRP, GAA, SGCA, SGCB, SGCD, SGCG, TCAP), based on reported disease frequency in Latin America. Sequencing was performed with Illumina's NextSeq500 and variants were classified according to ACMG guidelines; pathogenic and likely pathogenic treated as one category (P) and variants of unknown significance (VUS) will be described. This panel yielded a total of 1304 variants (246 homozygous, 234 two heterozygous variants in the same gene, and 56 one heterozygous). The gene with the highest number of variants was DYSF, with 496 variants (213 P, 283 VUS), followed by CAPN3 (254; 162 P, 92 VUS), GAA (126; 52 P, 74 VUS), ANO5 (119; 46 P, 73 VUS), SGCA (110; 67 P, 43 VUS), FKRP (80; 45 P, 35 VUS), SGCG (34; 14 P, 20 VUS), SGCB (31; 15 P, 16 VUS), TCAP (30; 15 P, 15 VUS) and SGCD (24; 5 P, 19 VUS). These results show the importance of the inclusion of GAA for the investigation of patients with PMW.

IMAGING PHENOTYPE IN DYSFERLINOPATHY AND ITS RELATIONSHIP WITH DISEASE DURATION AND DISABILITY ARE UNRAVELLED BY HEATMAPS AND RANDOM FORESTS.

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Imaging phenotype of dysferlinopathies has been described, but how muscle imaging pattern changes along the disease evolution and the increasing disability is still to be understood. In a previous report we showed the utility of using MRI to correlate degree and distribution of muscle involvement with functional assessment scores. In this work we analysed the imaging phenotype in dysferlinopathy and its relationship with disease duration and disability, by using heat maps and random forests. Whole-body MRI was performed 33 patients with dysferlinopathy and fibroadipose infiltration of 61 muscles were scored according to Kornblum scale. Scores were represented in a heat map. We trained regressive random forests to predict disease duration, dimension 1 of MFM and modified Rankin scale based on muscle scoring and applied a variable selection algorithm to select the most important muscle scoring for the prediction. Heatmaps helps to delineate a positive and negative fingerprint of dysferlinopathy imaging phenotype. Disease duration is related with fibroadipose infiltration of infraspinatus, teres minor, supraspinatus and flexor digitorum longus. Dimension 1 of MFM increases with higher infiltration of teres minor, triceps, sartorius and adductor magnus and brevis. Modified Rankin scale is related with infiltration of vastus medialis, gracilis, infraspinatus and sartorius. Our work demonstrates the positive and negative fingerprints in dysferlinopathy. Thigh muscle and specially, upper limb muscle infiltration may be important markers of disease progression in dysferlinopathy and should be considered in planning future studies with quantitative MRI in the affected patients.

SPONTANEOUS RECOVERY IN A CHILD WITH ANTI-HMGCR AUTOIMMUNE NECROTIZING MYOPATHY

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Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have recently been associated with immune-mediated necrotizing myopathy (IMNM), a subgroup of idiopathic inflammatory myopathies (IIMs). Most patients require long term immunomodulatory therapy for

remission and only a few cases of spontaneous improvement in adults have been reported. We present a six-year-old Chilean girl, with an anti-HMGCR IMNM initially diagnosed with muscular dystrophy. At the age of 4, she had a subacute onset of progressive proximal weakness with high CK level (7.842 U/L), muscle biopsy with a dystrophic pattern, normal immunohistochemical labeling for membrane sarcolemmal proteins and no inflammatory infiltrates. NGS panel for muscular dystrophy and Pompe disease was negative. Ten months after symptom's onset, she developed spontaneous improvement of strength, reaching near-full capacity for daily activities and climbing stairs without support objectified by the Expanded Hammersmith Functional Motor Scale (HFMS) and CK decline levels. High levels of anti-HMGCR (> 200) drove us to establish an anti-HMGCR IMNM as her definitive diagnosis. Clinical observation was done at first, but after a six months follow-up, she reached a clinical plateau, remaining with slight residual proximal limb weakness and mild cervical weakness. She received one pulse of IV-Ig treatment (2 gr/kg IV) reaching maximal strength (HFMS 66/66), which has maintained after ten months follow-up. This clinical report shows that spontaneous remission can occur in pediatric IMNM patients and that the phenotypic spectrum remains to be fully described. The lack of information about the natural evolution of the disease precludes the elaboration of a treatment algorithm. It is crucial to define groups of better prognosis like this case, in whom less aggressive treatment can be done at the beginning, avoiding long-term adverse effects of steroidal and immunomodulatory therapies.

DISTAL UPPER LIMB ONSET MYOPATHY IN THE FIRST CHILEAN CASE REPORTED WITH TITINOPATHY

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The titin gene (TTN, OMIM188840) in 2q31.2, comprises 364 exons and codifies for the giant muscle protein titin. Mutations in TTN cause of at least eleven different phenotypes including LGMD2J, CMD1G cardiomyopathy, dilated 1G (AD), EOMFL congenital myopathy with fatal cardiomyopathy (AR), HMERF (AD), TMD tibial muscular dystrophy (AD), CMH9 cardiomyopathy, familial, hypertrophic 9 (AD), centronuclear myopathy related to TTN (AR). Up to date no patients with titinopathy have been identified in Chile. We describe the case of a 30-year-old man presenting with asymmetric extensor finger weakness in the upper limbs at onset, followed by selective deltoid involvement, with relative sparing of leg muscles. MR imaging revealed selective finger extensors and deltoid involvement in upper limbs, in addition to semitendinosus and peroneal muscles in the thighs and legs respectively. No respiratory or cardiac involvement was observed. Deltoid muscle biopsy showed severe dystrophic changes, rimmed vacuoles and protein aggregates with desmin, titin and myotilin labelling on immunohistochemistry. CK levels were slightly increased. There were no other affected relatives. A NGS panel for 115 genes related to congenital and progressive muscle dystrophies, and congenital myasthenic syndromes performed with MiSeq (Illumina) revealed two missense mutations on TTN: c.54710T>C, (p.Leu18237Pro) on exon 282; and c.95372G>A, (p.Gly31791Asp) on exon 343, both mutations and their in trans segregation in the family were confirmed by Sanger sequencing. The patient's onset phenotype does not correspond entirely with none of the described forms of titinopathy. The mutation c.95372G>A was reported associated to AD-HMERF in a family of European origin; but the mutation c.54710T>C, also affecting the A-band of titin, has uncertain pathogenic significance (VUS). Our case adds yet another presenting phenotype titinopathy: adult onset, recessive upper limb, distal titinopathy.

DEPARTAMENTO DE UROLOGÍA

10TH CONGRESS OF THE EUROPEAN ACADEMY OF ANDROLOGY – BUDAPEST, HUNGRIA

PENILE LOW INTENSITY SHOCK WAVE TREATMENT FOR PDE5 REFRACTORY ERECTILE DYSFUNCTION: A RANDOMIZED SHAM-CONTROLLED TRIAL

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Background: Erectile dysfunction (ED) is a prevalent condition in males, affecting around 30% of men over 40 years. Lately, the use of penile low intensity shock wave treatment (LIST) has been studied on vascular ED patients, because of its potential role in modifying several pathways of ED pathophysiology. The theoretical effect of LIST is based on its ability to increase the blood supply of treated areas. Objective: To investigate the effect of electromagnetic LIST on the erectile function of patients suffering PDE5 refractory vascular ED. Methods: Randomized, simple-blind, sham-controlled study. 76 patients completed the study. 40 men were treated with linear electromagnetic penile LIST (1 session/week for 4 weeks, 5000 shocks/session, using 0.09 mJ/mm² of energy density) and 36 were treated with a sham probe. Baseline and post-treatment (1, 3 and 6 months) evaluations were done using validated erectile function questionnaires (IIEF-EF, EHS, SEP2, SEP3 and GAQ1). Results: Active and sham groups were similar regarding age and comorbidity load. Both groups had moderate ED, with IIEF-EF medians of 12 (IQR 8–17) in the treated group and 13 (IQR 8–17) in the sham group ($p=0.352$). 3 months after treatment, median changes in IIEF-EF scores for active and sham groups were 3.5 (IQR 0–10) and 0.5 (IQR 8–17), respectively ($p<0.05$). 6 months after treatment, 21 patients (52.5%) in the active group and 10 patients (27.8%) in the sham group presented EHS > 2 ($p<0.05$). At the same evaluation, 16 (40.0%) and 5 patients (13.9%) had positive answers to the GAQ-1 question ($p<0.05$), in the treated and sham groups, respectively. Conclusion: In vitro and in vivo studies have hypothesized 4 pathways in which shock waves could improve cavernous tissue blood supply: neo-angiogenesis, recruitment of pro-genitor cells, modulation of vasodilation and nerve regeneration. Only one previous group carried out a randomized clinical trial with patients presenting refractory ED, obtaining similar results to this current study, with shorter follow up and smaller sample size. In this study, linear electromagnetic LIST improved different erectile function parameters at 3 and 6 months of follow-up, when used on refractory ED patients vs. sham treated patients. No adverse events were observed during treatment or follow-up. Currently, there is no good quality evidence, with low risk of biases, that could really assess the role of LIST as a treatment option for vascular ED. It is mandatory to carry on a multicentric clinical trial, using different energy sources, several shock wave protocols and considering different causes of ED, with a follow up of more than 1 year.