INVESTIGACIÓN ARGENTINA A LA DDW 2008

En esta nueva sección de la revista se publicarán anualmente los trabajos seleccionados para su presentación en la DDW (Digestive Disease Week-USA)

THE PANCREATITIS-INDUCED MEMBRANE PROTEIN VMP1 THAT TRIGGERS AUTOPHAGY INTERACTS WITH S100A10

PARDO ROMINA,1 IOVANNA JUAN L,2 ROPOLO ALEJANDRO,1 BOGGIO VERONICA,1 IOVANNA JUAN L,1 VACCARO MARIA L1

1. School of Medicine, University of Buenos Aires, Buenos Aires, Argentina. 2. Unite 624, INSERM, Marseille, France.

ABSTRACT BODY:
The VMP1 gene was characterized by its early and strong expression during the acute phase of pancreatitis. VMP1 is necessary in autophagy and its expression induces the formation of autophagosomes. In order to analyze the function of VMP1 at a molecular level, the purpose of this work was to select the most significant protein targets by the Two-Hybrid assay. VMP1 expression is directly involved in Caes-induced autophagy, VMP1 expression was silenced using two different specific VMP1-siRNAs. As a result we found out that VMP1 is a novel autophagy related membrane protein that triggers autophagosome formation in mammalian cells. Our aim was to study the role of VMP1-mediated autophagy in pancreatic acinar cells. AR42J cells were cultured in nutrient and grown factor-replete conditions and treated with increasing doses of caerulein (Ca) in a time course scheme. We found that Ca treatment induces VMP1 expression in AR42J cells by RT-PCR and Western Blot analysis. We also found that Ca treatment induces autophagy, it was demonstrated by pRFP-LC3 recruitment and by Western Blot of endogenous LC3. Apart from that, using trypan blue and acridine orange strategies, it was shown that Ca treatment eventually leads to cell death. Finally, in order to know whether VMP1 expression is directly involved in Ca-induced autophagy, VMP1 expression was silenced using two different specific VMP1-siRNAs. As a result we found out that Ca treatment failed to induce autophagy in VMP1-silenced cells and the effect was rescued after transfecting cells with a VMP1-expression plasmid. Moreover, silencing VMP1 expression decreased significantly AR42J cells survival under Ca treatment. Our results indicate that VMP1 is involved in caerulein-induced autophagy and suggest that VMP1-mediated autophagy is a survival mechanism in AR42J pancreas cells.

GASTRIC ACID SUPPRESSION OF ORAL POWDER 20 mg OMEPRAZOLE. PILOT STUDY IN HEALTHY SUBJECTS

SOFIER LUIS,1 PERALTA DANIEL ANGEL,1 CARUSO NORBERTO1

1. Unidad de Nutrición y Fisiología Funcional Digestiva – Cátedra Autónoma de Buenos Aires, Argentina. 2. Laboratorio Bagó S.A. - Medical Department - Cátedra Autónoma de Buenos Aires, Argentina.

Background: once Omeprazol is acid labile, it is rapidly degraded by gastric acid secretion. The combination of Omeprazole plus sodium bicarbonate and algic acid could protect Omeprazol from acid degradation and enhance the speediness of action of the proton pump inhibitor. The rapid neutralization of gastric acid produced by sodium bicarbonate activates the proton pumps, rendering them more susceptible to Omeprazole action. Aim: To assess, in healthy subjects, the acid suppression capacity and the speediness of action of an oral powder formulation (Omeprazol 20 mg plus sodium bicarbonate 668 mg and algic acid 250.08 mg) using 24 h pHmetry. Methods: twenty healthy subjects (10 men and 10 women, aged 25-45 years) were studied. Each subject was divided into two periods of 6 days each. Period 1: during the first 6 days subjects received no medication, and then the powder association took the medication for the six previous days, including the study day. Period 2: the second period of 6 days was performed with the subjects taking the medication for the six previous days, including the study day. Four 24-h pHmetry were performed on two different occasions in the same group of healthy subjects (day 0 and day 6). During the first pHmetry 6 subjects received no medication, and 7 took the powder association 2 h before the end of the procedure. The second study was performed with the subjects taking the medication for the six previous days, including the study day. Data comparison non-paramet- ric Wilcoxon test was performed. Measurements: % time with pH < 4, time to reach the maximum pH value, and % peak pH after first drug administration. Results: the comparison between first and second study shows a significant reduction in gastric acidity.
LOW DOSE ASPIRIN AFFECTS THE SMALL BOWEL MUCOSA. RESULTS OF A PILOT STUDY USING A MULTIDIMENSIONAL ASSESSMENT


Gastroenterology Hospital, Buenos Aires, Argentina;*University Hospital, Zaragoza, Spain;**University of Alberta, Edmonton, Canada.

Background/Aim: Data indicating that low-dose aspirin could determine intestinal damage are controversial. Our aim in this prospective study was to determine if the small bowel may be damaged by low-dose aspirin (ASA: 100 mg) on a long-term basis.

Material and Methods: Twenty healthy volunteers (13 female; mean age: 39 yr; range: 19-64) underwent a baseline videocapapule endoscopy (VCE) (Given M2Apuls video capa-sule system; Given Imaging Ltd, Yodpeam, Israel), fcal calpsectin determination (Calprest, Eurospital, Italy) and permeability tests (sucrose and lactulose/mannitol [lac/man] ratio, in order to evaluate gastric and small bowel permeability, respectively).

After the baseline determinations, subjects ingested 100 mg of enteric-coated aspirin once a day (with esomeprazole 20 mg twice a day for gastroprotection) for a total of 14 days. At the end of the drug period, all investigational procedures were repeated. Video capsule im- ages were blindly assessed by an expert endoscopist who reported the results using an endoscopic scale. Results: Pre- and post-ASA VCE were assessed in 19 subjects detecting 10 cases (52.6%) with alterations not evidenced in baseline studies (6 cases had pretest- chism; 3 had erosions and one had a bleeding ulcer and erosions in jejunum). Post-ASA lac/man ratio was above the upper end of normality (>0.025) in 10/20 controls. The median baseline lac/man ratio (0.02; range: 0.011–0.045) increased after ASA adminis- tration (0.036; range: 0.007–0.258) but this difference was not significant (p=0.097). The median baseline lac/mann ratio (1.9; range: 0.5–7.9) increased significantly following ASA administration (2.15; range: 1.0–15.1; p=0.0001). Four of 9 subjects with abnormal findings at VCE had lac/man ratios above the cutoff. Median baseline sucrose urinary excretion (70.0 mg; range: 11.8-151.3) incre- ased significantly following ASA administration (22.5 _g/g; range 3.1–75.3 _g/g; p=0.0001). Median baseline lac/man ratio (0.021; range: 0.011-0.045) increased after ASA adminis- tration (0.036; range: 0.007–0.258) but this difference was not significant (p=0.097).

Conclusions: The short-term administration of ASA at a low dose regimen is associated with the presence of macroscopic abnormalities in the small bowel mucosa seen by VCE, a high prevalence of abnormal intestinal permeability and evidence of inflammation as shown by calprotectin (ASA-induced enteropathy). Our study also shows that the daily 100 mg ASA administration produces modifications in gastric permeability that seems not to be completely protected by the use of enteric-coated aspirin and esomeprazole.

TIME-COURSE ASSESSMENT OF THE CELIAC DISEASE-SPECIFIC SEROLOGY AFTER INITIATION OF A GLUTEN-FREE DIET

EMILIA SUGAI, FABIO NACHMAN, HORACIO VAZQUEZ, ANDREA GONZALEZ, PAOLA ANDREAANDAC, ANDREA CZECH, SONIA NIVELONI, ROBERTO MAZURE, EDGARDO SMECULLO, EDUARDO MAUROI, JULIO C. BAI

Servicio de Laboratorio; Departamento de Medicina y Departamento de Alimentación; Hospital de Gastroenterología “Dr. C. Bonorino Udaondo” Buenos Aires, Argentina.

Background: The celiac disease (CD)-related antibodies are the most specific and sensitive tools for suspicion and diagnosis of a clinical disorder. However, despite its systematic use, the utility of the celiac disease serology after the initiation of the gluten-free diet (GFD) has not been fully assessed adequately. Aim: To prospectively determine the time-course of the CD antibodies loading for the best assay(s) in order to monitor the response to the GFD. Patients: We enrolled 84 adult patients consecutively diagnosed with CD who had completed a one-year follow-up.

Methods: Serum samples obtained at diagnosis and every three months after initiation of a GFD were assayed for a battery of tests: 1- IgA antigliadin (Aga); 2- IgA anti-tissue transglutaminase (a-TTG); 3- IgA endomysial (EmA); 4- IgA and 5- IgG-diamidated gliadin peptide antigens (a-DGP); 6- dual detection of IgA+IgG isotypes of a-DGP (IgA+IgG a-DGP); 7- dual detection of IgA+IgG isotypes of both a-DGP and a-tTG (DGP/tTG); and 8- IgA antiactin antibodies (AAA). Results:

Celiac disease serology with very high accuracy may obviate diagnostic intestinal biopsy in different clinical scenarios


Background: Current diagnostic criteria for celiac disease (CD) are based on specific serology and man- datory intestinal biopsy. However, no critical analysis has been performed considering their comparat- ive value and whether one can replace the other in the context of the heterogeneity of the disorder. Aim: to establish the diagnostic performance of a series of serologic tests and combinations there of in order to determine an accurate non-invasive diagnosis of CD in the context of the populations with various pretest probability.

Methods: We prospectively enrolled 592 individuals grouped according to the pretest probability of CD in high risk (n=141) and low risk (n=451) for the disorder. All subjects underwent endoscopic biopsy from the duodenum and cecum in a complete panel of CD-related serologic tests. Diagnosis of CD was based on histological grounds (Marsh’s III or greater).

Results: Based on histology, 60 and 14 patients were diagnosed with CD in the high (prevalence 44.5%) and low risk groups (prevalence 3.1%), respectively. In the high pretest probability group, the combination of dual conjugate IgA+IgG a-DGP with IgA a-tTG had 99% sensitivity, 100% spe- cificity and 100% positive predictive value (PPV) when both tests were positive. No subjects with con- cordantly negative results for both assays were found to have CD. In the low pretest probability group, two assay combinations provided the best approach: IgA+DGP plus IgA a-tTG and the dual IgA+DGP plus IgA a-DGP, reaching 76.8% sensitivity, 100% specificity. 100% PPV if both tests are positive and 99.5% and 99.3% of NPV if both are concordantly negative for each option, respectively.

Conclusions: Our study suggests that appropriate use of CD serology may accurately identify the vast majority of CD patients and controls in different clinical scenarios. The serologic approach described may impact the diagnostic algorithm of CD, obtaining the need of duodenal biopsy in more than 90% of individuals. Appropriate choice of serologic assays can result in considerable cost saving and better acceptance by patients.
INTRODUCTION:
Celiac disease (CD) is a gluten-sensitive enteropathy characterized by a chronic inflammatory injury in the small bowel, caused by gluten intolerance in genetically predisposed individuals. CD's different forms of presentation resemble a multisystem disorder than a primary gastrointestinal disease, frequently remaining undiagnosed by primary care physicians.

OBJECTIVE: To determine the prevalence of CD diagnosis within an health maintenance organization (HMO) population composed, predominantly, of middle-class individuals who live in an urban area.

MATERIAL AND METHODOLOGY: A cross sectional analysis of the electronic medical record system (EMR) of our HMO population between 1999 and 2006 was carried out. All patients in our adult population with clinical problems related to CD were identified by primary care physicians or specialists. People tested for Iga anti-transglutaminase antibodies (TG-Ab) during the period were analyzed as well. The criteria used to define the case was based on a diagnosis of CD in the EMR and/or a TG-Ab value >15U.

RESULTS: According to these criteria, out of a total enrollment of 128,626 individuals in the HMO, 276 patients with CD diagnosis were identified. The prevalence of CD was 0.21%. The mean age of this group of people was of 40.8 years, of which 76.8% were females.

The age distribution of the CD population was as follows: 26% under 18 years old, 30% between 18 to 49 years, 22% 50-59 and 5% 60 years old. The age distribution of the HMO population was as follows: 50-59 17.2, 40-49 23.6, 5.55, 25.0.

The prevalence of CD was significantly higher among women (32.8%) than men (13.3%) (OR: 2.53; 95% CI 1.68-3.79; P<0.0001). The prevalence of CD was very high among young adults and females (3.0% and 2.5%, respectively). In the population aged 50-59, the prevalence of CD was 1.3% (95% CI 0.7-2.4).

The mean age of the CD population was 40.8 years, of which 76.8% were females (95% CI 74.8-78.8). We found a global prevalence of 24.1% for PML and 1.1% for CRC. Average risk group (n=476; females 46; mean age 61 years SD= ±11.2). We found a prevalence of 22.8% for PML (CI 95% 19.3-25.8), in which 19.2% had low-grade and 2.5% high-grade dysplasia. The prevalence of CRC was 0.10%. Four-degree relatives group (n=757); female <45; mean 54.9 years SD= ±11.3) showed a prevalence of 29.2% (CI 95% 22.1-38.3), in which 20% had a low-grade and 4.8% high-grade dysplasia. The prevalence of CRC in this group was 1.2%. The evaluation set a logistic regression model showed that family history of CRC was independently associated with increased risk of PML (OR=1.56 CI 95% 1.15-2.43; P=0.04). This difference was greater in younger subjects (table I). Male sex was also independently associated with an increased risk of PML (OR=4.95; CI 95% 1.15-20.7; P=0.04).

CONCLUSION: Approximately a quarter of the population presented at least one PML and a significantly increased risk in four-degree relatives with CRC and was not observed. These results may contribute to issue local guidelines for CRC prevention.

Table I. Prevalence in different age groups

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Average risk</th>
<th>Five degree relatives with CRC (%)</th>
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</thead>
<tbody>
<tr>
<td>40-49</td>
<td>5.55</td>
<td>22.8</td>
</tr>
<tr>
<td>50-59</td>
<td>17.2</td>
<td>23.6</td>
</tr>
<tr>
<td>60-69</td>
<td>27.7</td>
<td>35.3</td>
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<tr>
<td>70-80</td>
<td>25.0</td>
<td>35.2</td>
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ARGON PLASMA COMBINATION FOR THE TREATMENT OF RADIATION INDUCED PROCTITIS

GONZALEZ MARÍA LAURA,1 CARIELLO MARINA,1 MACÍAS GÓMEZ CARLOS ALBERTO,1 VAN DOMSELAAR FERNANDO,1 DÁVOLOS JORGE R1
Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

INTRODUCTION: Radiation-induced proctitis (RIP) is a relative common complication of pelvic radiation therapy. Medical treatment generally fails in control bleeding. Argon Plasma Coagulation (APC) is established as an alternative effective therapeutic method. However, APC usefulness and safety have not been studied in our Country. AIMS: To assess the usefulness and safety of APC in the management of patients with (RIP). PATIENTS AND METHODS: We analized the clinical records of fourteen patients with radiation proctitis derived to our Endoscopic Unit for APC treatment from July 2004 through March 2007. Indication for radiation therapy, onset of symptoms after the procedure, APC related complications and post treatment clinical evolution were analyzed retrospectively. Diagnosis of radiation proctitis was made based on endoscopic findings in rectal or sigmoidal mucosa. Such as single or multiple telangiectasias and/or friability or contact bleeding in patients with previous pelvic radiotherapy without any other bleeding source. Clinical outcome was classified as completely response: no recurrence of bleeding, partial response: intermittent slight bleeding or no response: without improvement or worsen of bleeding. We used ERBE (Tübigen, Germany) APC 300 system with a 3,2 mm probe in all patients. The gas flow was 2 l/min. and the power setting used was 10 W in 2 seconds pulses.

RESULTS: Fourteen consecutive patients, (M/F: 12/2, mean age 74 (61-84 years) were retrospectively included. Male patients received RT due to prostate cancer and female for uterine cancer. Onset of symptoms after RT was 23 months (0-108). The follow up was 15 months (2-34). All patients had overt bleeding, 6 of them had anemia (3 were transfused). Only one patient received previous medical treatment and no response: without improvement or worsen of bleeding. Eleven patients (79%) responded to APC treatment. Six in the first session and four required second session. Patient had no response and refused a second session. Three patients had no response. One underwent only one session, other received palliative management and the last one died from no related procedure causes. Anemia improved in all patients, no transfusions were required and no complications occurred. CONCLUSION: APC was useful and safe in our patients for RIP treatment and should be recommended as an available therapeutic tool in our country.

PREDICTIVE VALUE OF ALARM SYMPTOMS IN COLORECTAL CANCER DIAGNOSIS

TOBAL FEDERICO,1 POGORELSKY VALERIA,1 TOBAL DANIEL,1 GENBA, Junin, Buenos Aires, Argentina

BACKGROUND: The existence of alarm symptoms states the need of performing endoscopic studies so as to discard colorectal cancer. However, the diagnostic value of alarm symptoms is uncertain.

AIM: To assess the predictive value of alarm symptoms for colorectal cancer diagnosis in patients without family history.

PATIENTS AND METHODS: Cross sectional survey of 294 (male 147, female 147; mean age 57.4 yrs) consecutive adults with alarm symptoms referred to our endoscopic center for colonoscopy in a one year period. Patients with hematocritia, anemia, positive fecal occult blood test and weight loss were considered as patients having alarm symptoms.

RESULTS: Colorectal cancer was found in 33 (male 24, female 9; mean age 66.8 yrs (range 22-87) patients. The global positive predictive value of alarm symptoms was 11.2%. Colorectal cancer was detected in 19 (male 14, female 5; mean age 66.9 yrs (range 32-87) patients out of 164 with hematocritia (VPP 11%, VPN 89%, S 57%, E 44%); in 8 (male 4, female 4; mean age 69.6 yrs (range 53-76) patients out of 60 with anemia (VPP 13.5%, VPN 83.3%, S 24%, E 80%); in 1 (male, age 80 yrs) patient out of 53 with positive FOBT (VPP 1.8%, VPN 86.7%, S 3%, E 80 %) and 5 (all males; mean age 53.4 yrs (range 22-67) patients out of 17 with weight loss (VPP 29.4%, VPN 89.9%, S 15%, E 95%).

CONCLUSIONS: Only one out of ten patients with alarm symptoms had colorectal cancer. According to international studies, hematocritia is the commonest alarm symptom associated with colorectal cancer.