

Cuban Research in Current International Journals

The following selection—alphabetical by title—reflects Cuban medical publishing in international journals over the last quarter on an array of topics. Links to these journal articles may be found at www.medicc.org/mediccreview.

An alternative for improving the diagnosis of smear-negative tuberculosis and other bronchopulmonary disorders in Cuba. Sevy Court J, Machado Molina D, Armas Pérez L, Peralta Pérez M, Carreras Corzo L, Sánchez de la Osa R, et al. Arch Bronconeumol. 2008 Nov;44(11):604-10.

Objective The diagnosis of tuberculosis in patients with negative acid-fast bacillus smears poses a challenge to both clinicians and public health authorities. In an attempt to aid diagnosis in such cases, an expert committee was established in Ciudad de La Habana, Cuba in 1995. The aim of this study was to describe the progress of the committee's work and the corresponding results for the period 1996 through 2003. **Patients and Methods** For each patient studied by the commission, we analyzed the following data: patient's residence and referring center, tentative diagnosis proposed by the attending physician, history of antibiotic treatment, and final diagnosis made by the commission. **Results** Of the 1,703 patients studied, 84.8% were from La Habana, 48.4% were 55 years or older and 63.8% were men. Between 2001 and 2003, 11.3% of patients were already on antituberculosis treatment when their case was studied by the commission. The corresponding percentage for 1996 through 2000 was 16.9% ($P = .001$). Active tuberculosis was confirmed in 43.1% of a total of 918 patients with full test results during the period 1996–2000 and in 52.2% of a total of 619 patients during the period 2001–2003 ($P < 0.001$). Of 344 patients with suspected pulmonary tuberculosis and negative acid-fast bacillus smears between 2001 and 2003, 128 (37.2%) were diagnosed with active tuberculosis. **Conclusions** These findings indicate that the work of the commission is viable, sustainable, and useful for preventing overdiagnosis and inappropriate treatment, and that it also serves an educational purpose.

An epidemiological study of neuromyelitis optica in Cuba. Cabrera-Gómez JA, Kurtzke JF, González-Quevedo A, Lara-Rodríguez R. J Neurol. 2009 Feb 9. Epub ahead of print.

Introduction Two population-based studies of neuromyelitis optica (NMO) in nonwhite populations provided prevalence rates of 0.32 and 3.1 per 100,000 population. **Objective** To estimate NMO prevalence in the multiethnic Cuban population by nation-wide case ascertainment. **Methods** The study was conducted from October 1, 2003 to November 30, 2004. Ninety percent of general practitioners and all neurologists responded positively to the request for information

on cases suspected of optic neuritis (ON), transverse myelitis (TM), multiple sclerosis (MS), or NMO. Among the population of 11,177,743 there were 798 suspected cases, including 89 with possible NMO, relapsing ON (RON) and TM. Of the 89, 87 were examined by two of us (Cabrera JA, Lara R) who selected the NMO cases according to the 1999 Mayo Clinic criteria as well as those with relapsing TM and RON. **Results** 58 cases provided a prevalence rate of 0.52 per 100,000 (95% CI: 0.39–0.67). Rates for the 7 males and 51 females were 0.13 (CI: 0.05–0.26) and 0.91 (CI: 0.68–1.20). The estimated average annual incidence rate was 0.053 per 100,000 (CI 0.040–0.068). Prevalence rates did not differ significantly among the three ethnic groups. Black NMO cases were significantly older, with more relapses and motor deficit, as well as more abnormalities in brainstem evoked potentials and in brain MRI (not meeting MS criteria). The predominant clinical form was relapsing over monophasic. **Conclusions** This Cuban multiethnic population had a prevalence of NMO of 0.52 per 100,000 and an estimated average annual incidence rate of 0.053 per 100,000 with no differences by ethnicity. Black patients were older, with more relapses and motor impairment.

BET differences among simultaneous evoked frequency band responses during early-stage visual processing distinguish schizophrenia from healthy subjects. González-Hernández JA, Pita-Alcorta C, Castañeda H, Trujillo-Barreto N, Scherbaum WA. Neuroscience Letters. 2009 Jan 23;450(1):7-11.

In this work, we attempt to extend to the schizophrenia's research the evidence that different frequency bands may emerge from different sources during early-stage visual processing, in a mental state-specific manner, while subjects are passively viewing a visual stimulus. We applied standard pattern reversal stimulation (checkerboard), a task with low cognitive demands, coupled to a dense EEG recording system to estimate the neural correlates of the evoked θ , α , β , β_1 , and γ frequency band responses by means of brain electrical tomography (BET). After filtering the evoked activity using different bandpasses, a very different picture about the current sources during P100 will emerge. The results showed notable differences between the two groups. In healthy subjects we localized the significances in the anterior cingulate, caudate nucleus, thalamus, precuneus region, and superior parietal that were more active for γ band. In patients with schizophrenia, differences occupy the hippocampus, parahippocampus, thalamus, midbrain, precuneus,

and superior parietal regions. Most areas were more active for γ band except precuneus and superior parietal region more active for θ and α frequency band. These sets of regions, in both groups, reflect events that are parallel to, and partly independent of the P100 component, while in the schizophrenia, these regions have been previously linked to the major symptoms of the disease. We concluded that this result provides important evidence indicating that the proposed method is able to differentiate electrophysiological patterns in healthy subjects from those in patients with schizophrenia.

Immunoglobulin E-dependent regulation of the CCR3 chemokine receptor by Interferon-Gamma in atopic asthmatics. García-Vega Y, Rodríguez-Pérez J, Bermúdez-Badell C, Blanco-Garcés E, Valenzuela-Silva C, López-Saura P, et al. Int Arch Allergy Immunol. 2009;148:219-27.

Background The chemokine receptor CCR3 mediates the migration of cells that play an important role in the pathogenesis of asthma to inflammatory foci. Interferon (IFN)- γ is known to downregulate the expression of some chemokine receptors. Therefore, we decided to analyze the regulation of CCR3 by IFN- γ in asthmatics and to characterize the dependence of this process on immunoglobulin E (IgE) levels. **Methods** Atopic asthmatics were treated with IFN- γ or placebo, and the IgE concentration in the blood was measured using an ultra-micro-ELISA for total IgE. Mononuclear cells from patients and controls were isolated by Ficol-Hypaque gradient and incubated in the absence or presence of IFN- γ for different periods of time. After incubation, the cells were washed and lysed for RT-PCR analysis, which was performed using a Perkin-Elmer kit. **Results** IFN- γ treatment apparently improved the evaluated clinical variables; however, the differences were not significant compared to the placebo group. We found that IFN- γ downregulated CCR3 mRNA expression *ex vivo* and *in vivo* in those patients with IgE levels higher than 500 IU/ml, whereas IFN- γ upregulated CCR3 mRNA expression in patients with IgE levels lower than 500 IU/ml. Correspondence between *ex vivo* and *in vivo* results was observed using this approach. There was found to be a direct correlation between total serum IgE and CCR3 mRNA expression. **Conclusions** In those asthmatic patients with high levels of IgE, who are thus susceptible to downregulation of CCR3 by IFN- γ , a significant therapeutic effect with systemic IFN- γ might be expected.

Intrathecal synthesis of IgE in children with eosinophilic meningoencephalitis caused by *Angiostrongylus cantonensis*. Padilla-Docal B, Dorta-Contreras AJ, Bu-Coifu-Fanego R, Fundora Hernández H, Callol Barroso J, Sánchez-Martínez C. *Cerebrospinal Fluid Res.* 2008 Nov 25;5:18.

Background Eosinophilic meningoencephalitis caused by the helminth *Angiostrongylus cantonensis*, is an emerging infectious disease in America. The objective of this paper was to determine if the intrathecal synthesis of immunoglobulin E is produced during the acute phase of the disease. **Methods** Thirteen patients, mean age 4.5 years were studied; a diagnostic lumbar puncture was performed and serum samples taken. Immunoglobulin E (IgE) in serum and in cerebrospinal fluid (CSF) was quantified by nephelometry. Control patients had other infections or other neurological diseases. **Results** The mean cell count in the CSF was 500×10^{-6} cells/L and of these 23% were eosinophils. In blood the eosinophils were 13%. The chief symptoms of the patients were migraine, vomiting and fever and 50% presented some meningeal signs. IgE intrathecal synthesis analyzed by the corresponding quotient diagram (Reibergram) was observed in all patients. No intrathecal IgE synthesis was seen in control patients. **Conclusion** Intrathecal synthesis of IgE demonstrates the participation of this immunoglobulin in the destruction of the third stage larvae of the parasite in the CSF. The test should be considered in our environment as a tool to aid diagnosis.

Left ventricular dysfunction secondary to ischemia in women with angina and normal coronary angiograms. Peix A, González A, García EJ, Valiente J, Cabrera LO, Sixto S, et al. *J Womens Health (Larchmt).* 2009 Feb;18(2):155-61.

Background Microvascular disease is proposed as a cause of segmental myocardial blood flow abnormalities and heterogeneous myocardial perfusion in cardiac syndrome X. **Objective** To assess if myocardial ischemia can be evidenced through both perfusion abnormalities and post-stress left ventricular ejection fraction (LVEF) reduction by gated single photon emission tomography (SPECT) myocardial scintigraphy in women with syndrome X in a similar way to those with epicardial coronary lesions. **Methods** Three groups of postmenopausal women were studied: group I, 20 women with angina, perfusion defects, and normal coronary angiography; group II, 20 women with epicardial coronary lesions ($\geq 50\%$ of coronary lumen reduction); group III, 15 volunteers without signs or symptoms of ischemia (control group). Each underwent technetium-99m (^{99m}Tc) methoxyisobutylisonitrile gated SPECT myocardial scintigraphy (protocol: exercise-stress-rest), brachial artery endothelial function measured by ultrasonography, and lipi-dogram. **Results** Groups I and III patients had a higher body mass index (BMI). There were more

smokers in groups I and II. Very low density lipoprotein cholesterol (VLDL-C) and triglycerides were higher in group II patients. The brachial artery vasodilator responsiveness after 5 minutes of ischemia was similarly lower in patients of groups I and II compared with those of group III (3% vs. 6.5%, respectively; $p = 0.03$ group III vs. group I and group II). Mean ΔLVEF (LVEF poststress minus LVEF at rest) was -3.86% , -2.90% , and 4.18% in groups I, II, and III, respectively ($p = \text{NS}$ between I and II, $p = 0.005$ between II and III, and $p = 0.003$ between I and III). In 43% of group I patients and in 10 of 18 group III patients with perfusion defects, there was a poststress LVEF reduction of $>5\%$. **Conclusions** Stress-induced ischemia is associated with poststress LVEF reduction as a probable manifestation of myocardial stunning in postmenopausal women with typical angina and normal coronary angiography.

N-glycosylation pattern of E2 glycoprotein from classical swine fever virus. Montesino R, Toledo JR, Sánchez O, Zamora Y, Barrera M, Royle R, et al. *J Proteome Res.* 2008 Dec 18. Epub ahead of print.

The extracellular domain of E2 glycoprotein outer surface of the classical swine fever virus was expressed in epithelial kidney pig cells. The N-glycosylation determined by combination of Normal Phase-HPLC, Weak Anion Exchange-HPLC, exoglycosidase digestions and Mass Spectrometry revealed a complex mixture of neutral and monosialylated multiantennary N-glycans with variable number of alpha1-3-Gal-Gal antennae terminals. The most abundant neutral N-glycan has a composition of Hex(7)HexNAc(4)dHex(1). Negative ion ESI-MS/MS confirmed the presence of the alpha1-3-Gal-Gal motif on each arm of the fucosylated biantennary N-glycan. The most abundant monosialylated glycan was Hex(6)HexNAc(4)dHex(1)Neu5Ac(1), with the sialic acid linked to the terminal beta1-4-Gal-GlcNAc. Sialic acid on the antenna capping position was predominantly of the N-acetyl form.

Oral manifestations of HIV infection in adult patients from the province of Sancti Spiritus, Cuba. Carpio E, López V, Fardales V, Benítez I. *J Oral Pathol Med.* 2009 Jan;38(1):126-31.

Background Studies on the prevalence of HIV-related oral lesions (HIV-OL) have shown great variations among different countries. The aim of this study was to describe the prevalence of HIV-OL in adults infected with HIV in the province of Sancti Spiritus, Cuba, and to determine the factors associated with the presence of HIV-OL. **Methods** A cross-sectional observational study was performed between November 2006 and August 2007 at the Hospital General Universitario 'Camilo Cienfuegos', Sancti Spiritus. One hundred and fifty-four HIV-infected patients were included. Patients were examined and interviewed by a periodontal specialist. Diagnosis

of HIV-OL was based on clinical criteria. Demographical, clinical and laboratory data were obtained. Independent association of each factor with HIV-OL was assessed by logistic regression modeling. **Results** The prevalence of HIV-OL was 40.9%. The most common manifestation was oral hairy leucoplakia ($n = 19$; 12.3%); oral candidiasis ($n = 17$; 11%); herpes simplex virus infection ($n = 11$; 7.4%); and aphthous ulcer ($n = 9$; 5.8%). Principal factors associated with the presence of HIV-OL were CD4+ lymphocytes <500 cells/ mm^3 (OR: 2.06; 95% CI: 1.019–4.195) and smoking (OR: 2.03 CI: 1.037–3.982). **Conclusion** This study described the prevalence of HIV-OL in 154 HIV-infected patients which represent about 80% of those known to be infected in the province of Sancti Spiritus. The prevalence of HIV-OL was lower than those reported from developing countries. Oral hairy leucoplakia and oral candidiasis were the most prevalent HIV-OL. Smoking and CD4+ cells count <500 cells/ mm^3 were the two factors independently associated with the presence of HIV-OL.

Predicting functional residues in *Plasmodium falciparum* plasmepsins by combining sequence and structural analysis with molecular dynamics simulations. Valiente PA, Batista PR, Pupo A, Pons T, Valencia A, Pascutti PG. *Proteins.* 2008 Nov 1;73(2):440-57.

Plasmepsins are aspartic proteases involved in the initial steps of the hemoglobin degradation pathway, a critical stage in the *Plasmodium falciparum* life cycle during human infection. Thus, they are attractive targets for novel therapeutic compounds to treat malaria, which remains one of the world's biggest health problems. The three-dimensional structures available for *P. falciparum* plasmepsins II and IV make structure-based drug design of antimalarial compounds that focus on inhibiting plasmepsins possible. However, the structural flexibility of the plasmepsin active site cavity combined with insufficient knowledge of the functional residues and of those determining the specificity of parasitic enzymes is a drawback when designing specific inhibitors. In this study, we have combined a sequence and structural analysis with molecular dynamics simulations to predict the functional residues in *P. falciparum* plasmepsins. The careful analysis of X-ray structures and 3D models carried out here suggests that residues Y17, V105, T108, L191, L242, Q275, and T298 are important for plasmepsin function. These seven amino acids are conserved across the malarial strains but not in human aspartic proteases. Residues V105 and T108 are localized in a flap of an interior pocket and they only establish contacts with a specific non-peptide achiral inhibitor. We also observed a rapid conformational change in the L3 region of plasmepsins that closes the active site of the enzyme, which explains earlier experimental findings. These results shed light on the role of V105 and T108 residues in plasmep-

sin specificities, and they should be useful in structure-based design of novel, selective inhibitors that may serve as antimalarial drugs.

Saccade velocity is reduced in presymptomatic spinocerebellar ataxia type 2. Velázquez-Pérez L, Seifried C, Abele M, Wirjatijasa F, Rodríguez-Labrada R, Santos-Falcón N, et al. Clin Neurophysiol. 2009 Feb 6. Epub ahead of print.


Objective A characteristic feature of spinocerebellar ataxia type 2 (SCA2) is saccadic slowing at early disease stages. We sought to determine whether this sign is detectable before clinical manifestation and quantifies the disease progression throughout life in linear fashion. **Methods** In a specialized ataxia clinic, 54 presymptomatic carriers of SCA2 polyglutamine expansions and 56 relatives without mutation were documented with regard to their maximal saccade velocity (MSV). **Results** Among the control individuals, a significant effect of aging on MSV was observed. After elimination of this age influence through a matched-pair approach, a presymptomatic decrease of MSV could be shown. The MSV reduction was stronger in carriers of large expansions. In the years before calculated disease manifestation, the MSV impairment advanced insidiously. **Conclusion** Saccade velocity is a sensitive SCA2 endophenotype that reflects early pontine degeneration and may be a useful diagnostic parameter before the onset of ataxia. **Significance** Future neuroprotective therapies of polyglutamine neurodegeneration may be assessed by MSV from earliest to preclinical disease stages.


Seasonal variation in mortality for five main death causes. Cuba, 1996–2006. Cou-

tin Marie G, Torres González RM, Morales Palanco I. The Internet Journal of Epidemiology. 2009;6(2). **Background and purpose** Mortality's seasonal variation has long been described all over the world for many death causes. Periodic changes in the weather conditions of temperate countries have been well recognized as risk factors for seasonal mortality but there is no sufficient evidence of this in tropical countries where seasons are not so well defined and there are no great differences in temperature. There are no recent studies about this matter in Cuba. The aim of this paper is to describe the seasonality of 5 different death causes (heart diseases, cerebrovascular diseases, accidents, suicides and homicides) based on monthly data collected during the period 1996–2006 using a simple and replicable method for undeveloped countries. **Methods** The presence of seasonal variation in several causes of death was explored with box and whiskers plots. Monthly total numbers of deaths were adjusted to a standard 30 days month in all time series. Death causes were selected according to their relevance and data obtained from National Bureau of Statistics of the Cuban Ministry of Health for the period January 1996–December 2006. **Results** A total of 868,982 deaths occurred during the 11 year period of the study in Cuba: heart diseases (232,829), cerebrovascular diseases (89,263), accidents (53,341), suicides (19,007) and homicides (7,316). Monthly deaths due to heart diseases showed high median values in January, February and December. Deaths by cerebrovascular diseases showed their highest median values during the months of January, February, March and December. The median number of monthly deaths by accidents was highest during July and August. Deaths due to suicides were higher in May, June and July. Seasonality of

monthly deaths by homicides was not so evident. **Conclusions** Seasonal variation of mortality for several death causes was highlighted using a simple, easy and replicable method to quickly ascertain the presence of seasonality of death causes which can be very attractive for undeveloped countries.

Validation of an immunologic diagnostic kit for infectious vaginitis by *Trichomonas vaginalis*, *Candida* spp., and *Gardnerella vaginalis*. Betancourt Bravo A, Sánchez Miranda, Fernández Lima O, Villoch Cambas A, Lorenzo Henández M, Álvarez JM. Diagn Microbiol Infect Dis. 2009 Mar;63(3):257-60

FemPure is a kit for the rapid diagnosis of vaginitis by *Trichomonas vaginalis*, *Candida* spp., and *Gardnerella vaginalis*, based on aggregation of latex particles joined to specific antibodies. The validation of the method involved the parameters specificity, detection limit, robustness, clinical sensitivity, and clinical specificity. Also, samples analyzed in parallel by the validated test and other recognized tests conducted by external laboratory were included. The method was specific for the 3 infectious agents, and no cross-reaction with other microorganisms usually present in vaginal exudates. The detection limit $\geq 1 \times 10^6$ CFU/mL for *Candida albicans* and *G. vaginalis* avoids the detection of concentrations considered normal flora, whereas *T. vaginalis* was detected until 1×10^5 cells/mL. Values of clinical sensitivity $\geq 80\%$, clinical specificity $\geq 90\%$ and concordance $\geq 90\%$ were found between samples evaluated in parallel by different methods. Robustness showed that the test can be used in laboratories with different management systems; its simple implementation without equipment allows the use in primary health care areas. 



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