

CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Boháček

ibohacek@hiim.hr



Adamec I, Bošković M, Skvorc A, Posavec V, Radmilović M, Gabelić T, Habek M. Do we need broad immunological work-up in all patients with CIS? J Neurol Sci. 2012 Apr 15;315(1-2):86-8.

University Hospital Center Zagreb, Department of Neurology, Referral Center for Demyelinating Diseases of the Central Nervous System, Zagreb, Croatia.

BACKGROUND: The aim of this study was to determine the prevalence of altered immunological tests and their clinical significance in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS).

PATIENTS AND METHODS: The information was gathered from medical records of patients hospitalized in the Referral Center for Demyelinating Diseases in the 2008-2010 period. All patients had ANA, ENA profile, ANCA, aCL IgG and IgM, C3, C4, CH50, anti-TPO, AST and RF antibodies tested.

RESULTS: From 726 patients with CIS that were reviewed, the complete battery of immunological tests was performed in 418 of them (57.6%), representing our cohort. Altered tests were found in 235 patients (56.2%); 73 (17.4%) had positive antinuclear antibodies, 14 (3.3%) had positive ENA, 47 (11.2%) had positive aCL IgG, 83 (19.8%) had positive aCL IgM, and 13 (3.1%) had anti TPO antibodies. We found no correlation between ANA, aCL IgG or IgM positivity (ANA vs aCL IgG $p=0,554$; ANA vs aCL IgM $p=0,19$; aCL IgG vs aCL IgM, $p=0,155$). None of the patients had any clinical manifestations other than MS symptoms.

CONCLUSION: These results indicate that significant number of patients with CIS have altered immunological tests but nevertheless none of them had clinical expression of

any other autoimmune disease making them clinically insignificant. In conclusion there is no need to perform extensive immunological work-up in all patients with CIS. Contrary, our results argue for more focused testing rather than a battery of screening tests.

Cvitković A, Vuković-Lela I, Edwards KL, Karanović S, Jurić D, Cvorišćec D, Fuček M, Jelaković B. Could Disappearance of Endemic (Balkan) Nephropathy Be Expected in Forthcoming Decades? Kidney Blood Press Res. 2011 Nov 23;35(3):147-152.

Institute for Public Health, County Brodsko Posavska, Slavonski Brod, Croatia.

Background/Aims: An epidemiological survey of endemic nephropathy (EN) was performed in endemic Croatian areas and the current prevalence was compared to that reported for the same villages several decades ago. **Methods:** A total of 2,487 adult farmers from 6 endemic villages and 3 non-endemic villages were enrolled. An extensive epidemiological questionnaire, clinical examination and laboratory analyses of blood and urine were performed. According to the modified WHO criteria, participants were classified into diseased, suspected of having EN, and those at risk of developing EN. **Results:** The overall prevalence of EN in the Croatian areas was 1.0%, ranging between 0.3 and 2.3% in different villages. Those suspected of having EN amounted to 3.9%. In the endemic villages a decreasing trend in the prevalence of EN was observed comparable to the results obtained in previous surveys. It is interesting to note that no EN patients were recorded in the endemic village of Dubočac. **Conclusion:** The prevalence of EN in the endemic Croatian areas appears to be decreasing. For the first time, we failed to detect any EN patients

in a village that was previously considered endemic, which might indicate that EN is diminishing.

Trbušić M, Riederer M, Vučić M, Lovričević I, Krušlin B, Gauster M, Mohrenz S, Berghold A, Tiran B, Degoricija V, Frank S. Increased expression of endothelial lipase in symptomatic and unstable carotid plaques. J Neurol. 2012 Mar;259(3):448-56.

University of Zagreb School of Medicine, Zagreb, Croatia.

The aim of this study was to evaluate endothelial lipase (EL) protein expression in advanced human carotid artery plaques (HCAP) with regard to plaque (in)stability and the incidence of symptoms. HCAP were collected from 66 patients undergoing carotid endarterectomy (CEA). The degree of plaque (in)stability was estimated by ultrasound and histology. In HCAP sections, EL expression was determined by immunostaining and the intensity was assessed on a semi-quantitative scale (low: <25%, high: >25% positive cells). Monocytes and macrophages in adjacent HCAP sections were stained with a CD163 specific antibody. High EL staining was more prevalent in histologically unstable plaques (in 33.3% of fibrous plaques, 50% of ulcerated non-complicated plaques and 79.2% of ulcerated complicated plaques; χ^2 test, $p = 0.004$) and in the symptomatic group (70.8 vs. 42.9% in the asymptomatic group; χ^2 test, $p = 0.028$). The majority of EL immunostaining was found in those HCAP regions exhibiting a strong CD163 immunostaining. EL in HCAP might be a marker and/or promoter of plaque instability and HCAP-related symptomatology.

Jelaković B, Karanović S, Vuković-Lela I, Miller F, Edwards KL, Nikolić J, Tomić K, Slade N, Brdar B, Turesky RJ, Stipančić Ž, Dittrich D, Grollman AP, Dickman KG. Aristolactam-DNA adducts are a biomarker of environmental exposure to aristolochic acid. Kidney Int. 2012 Mar;81(6):559-67.

School of Medicine, University of Zagreb and Department for Nephrology, Arterial Hypertension and Dialysis, University Hospital Center Zagreb, Zagreb, Croatia.

Endemic (Balkan) nephropathy is a chronic tubulointerstitial disease frequently accompanied by urothelial cell carcinomas of the upper urinary tract. This disorder has recently been linked to exposure to aristolochic acid, a powerful nephrotoxin and human carcinogen. Following metabolic activation, aristolochic acid reacts with genomic DNA to form aristolactam-DNA adducts that gener-

ate a unique TP53 mutational spectrum in the urothelium. The aristolactam-DNA adducts are concentrated in the renal cortex, thus serving as biomarkers of internal exposure to aristolochic acid. Here, we present molecular epidemiologic evidence relating carcinomas of the upper urinary tract to dietary exposure to aristolochic acid. DNA was extracted from the renal cortex and urothelial tumor tissue of 67 patients that underwent nephroureterectomy for carcinomas of the upper urinary tract and resided in regions of known endemic nephropathy. Ten patients from nonendemic regions with carcinomas of the upper urinary tract served as controls. Aristolactam-DNA adducts were quantified by $(32)\text{P}$ -postlabeling, the adduct was confirmed by mass spectrometry, and TP53 mutations in tumor tissues were identified by chip sequencing. Adducts were present in 70% of the endemic cohort and in 94% of patients with specific A:T to T:A mutations in TP53. In contrast, neither aristolactam-DNA adducts nor specific mutations were detected in tissues of patients residing in nonendemic regions. Thus, in genetically susceptible individuals, dietary exposure to aristolochic acid is causally related to endemic nephropathy and carcinomas of the upper urinary tract.

Zagorac GB, Mahmutefendić H, Tomaš MI, Kučić N, Le Bouteiller P, Lučin P. Early endosomal rerouting of major histocompatibility class I conformers. J Cell Physiol. 2012 Jul;227(7):2953-64.

Department of Physiology and Immunology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia.

Major histocompatibility class I (MHC-I) molecules are present at the cell surface both as fully conformed trimolecular complexes composed of heavy chain (HC), beta-2-microglobulin ($\beta 2\text{m}$) and peptide, and various open forms, devoid of peptide and/or $\beta 2\text{m}$ (open MHC-I conformers). Fully conformed MHC-I complexes and open MHC-I conformers can be distinguished by well characterized monoclonal antibody reagents that recognize their conformational difference in the extracellular domain. In the present study, we used these tools in order to test whether conformational difference in the extracellular domain determines endocytic and endosomal route of plasma membrane (PM) proteins. We analyzed PM localization, internalization, endosomal trafficking, and recycling of human and murine MHC-I proteins on various cell lines. We have shown that fully conformed MHC-I and open MHC-I conformers segregate at the PM and during endosomal trafficking resulting in the exclusion of open MHC-I conformers from the recycling route. This segregation is associated with their par-

titoning into the membranes of different compositions. As a result, the open MHC-I conformers internalized with higher rate than fully conformed counterparts. Thus, our data suggest the existence of conformation-based protein sorting mechanism in the endosomal system.

Gunjaca I, Zunic J, Gunjaca M, Kovac Z. Circulating Cytokine Levels in Acute Pancreatitis-Model of SIRS/ CARS Can Help in the Clinical Assessment of Disease Severity. Inflammation. 2012 Apr;35(2):758-63.

Division of Gastroenterology, Department of Medicine, University Hospital Dubrava

The aim of our study was to evaluate the pro- and anti-inflammatory cytokine response during acute pancreatitis and its predictive value on severity of disease. A hospital-based prospective clinical study was conducted. Twenty patients with acute pancreatitis were enrolled during a 12-month period. Plasma concentrations of TNF- α , IL-1 β , IL-6, and IL-10 were determined at days 1, 2, 3, 6, and 9. The patient population was analyzed by type of acute pancreatitis. Severity was defined according to the Atlanta criteria for assessing severity of acute pancreatitis. Clinical variables were recorded to patients classified in one of two groups: severe acute pancreatitis (SAP group) and mild acute pancreatitis (MILD group). Patients with SAP had significantly higher average levels of IL-6 compared to the MILD group patients (539.2 pg/L vs. 23.4 pg/L, $p < 0.0001$). Also, the values of IL-10 were significantly higher in patients with SAP (242.4 pg/L vs. 8.1 pg/L, $p = 0.003$). The values of TNF- α were not significantly different in both groups. The value of IL-6 and IL-10 showed a positive correlation ($r = 0.7964$, $p < 0.0001$). Although a relatively small sample of patients was used, we can conclude that the determination of the value of IL-6 and IL-10 can help in the clinical assessment of disease severity.

Vuk T, Barišić M, Očić T, Mihaljević I, Sarlija D, Jukić I. Error management in blood establishments: results of eight years of experience (2003-2010) at the Croatian Institute of Transfusion Medicine. Blood Transfus. 2012 Feb 22:1-10.

Croatian Institute of Transfusion Medicine, Zagreb, Croatia.

BACKGROUND: Continuous and efficient error management, including procedures from error detection to their resolution and prevention, is an important part of quality management in blood establishments. At the Croatian In-

stitute of Transfusion Medicine (CITM), error management has been systematically performed since 2003.

MATERIALS AND METHODS: Data derived from error management at the CITM during an 8-year period (2003-2010) formed the basis of this study. Throughout the study period, errors were reported to the Department of Quality Assurance. In addition to surveys and the necessary corrective activities, errors were analysed and classified according to the Medical Event Reporting System for Transfusion Medicine (MERS-TM).

RESULTS: During the study period, a total of 2,068 errors were recorded, including 1,778 (86.0%) in blood bank activities and 290 (14.0%) in blood transfusion services. As many as 1,744 (84.3%) errors were detected before issue of the product or service. Among the 324 errors identified upon release from the CITM, 163 (50.3%) errors were detected by customers and reported as complaints. In only five cases was an error detected after blood product transfusion however without any harmful consequences for the patients. All errors were, therefore, evaluated as "near miss" and "no harm" events. Fifty-two (2.5%) errors were evaluated as high-risk events. With regards to blood bank activities, the highest proportion of errors occurred in the processes of labelling (27.1%) and blood collection (23.7%). With regards to blood transfusion services, errors related to blood product issuing prevailed (24.5%).

CONCLUSION: This study shows that comprehensive management of errors, including near miss errors, can generate data on the functioning of transfusion services, which is a precondition for implementation of efficient corrective and preventive actions that will ensure further improvement of the quality and safety of transfusion treatment.

Suton P, Lukšić I, Müller D, Virag M. Lymphatic drainage patterns of head and neck cutaneous melanoma: does primary melanoma site correlate with anatomic distribution of pathologically involved lymph nodes? Int J Oral Maxillofac Surg. 2012 Apr;41(4):413-20.

University of Zagreb School of Medicine, University Hospital Dubrava, Zagreb, Croatia

The aim of this study was to analyse patterns of metastatic spread from cutaneous head and neck melanoma, which are said to be highly variable. The medical records of 145 patients with pathologically proven metastatic melanoma were reviewed retrospectively. The lo-

cation of pathologically positive lymph nodes was compared with clinically predicted spread, and patients with metastatic disease in areas outside of predicted drainage patterns were considered aberrant. There were 33 curative and 73 elective neck dissections. 21 of 77 patients undergoing parotidectomy had positive results for metastases. Clinical prediction proved to be correct in 33 of 45 cases (73.3%). Two patients with lateralized melanomas were initially seen with contralateral metastases. Six of 45 patients (13.3%) developed contralateral metastases after neck dissection. Patients with clinical involvement of the parotid gland were at high risk of occult neck disease (40%). Patients undergoing neck dissection for primaries originating in face, forehead, coronal scalp, periauricular

area, and upper neck should be considered for parotidectomy. Patients with posterior scalp and posterior neck primaries should be considered for selective neck dissection in conjunction with posterior lymphadenectomy. In patients with coronal scalp and periauricular primaries, a complete neck dissection including parotidectomy is the recommended approach.