CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Bohaček
ibohacek@hiim.hr

Petković G, Barišić I. Prevalence of fetal alcohol syndrome and maternal characteristics in a sample of schoolchildren from a rural province of Croatia. Int J Environ Res Public Health. 2013;10(4):1547-61.

Children's Hospital Srebrnjak, Srebrnjak 100, Zagreb 10000, Croatia.

Fetal alcohol syndrome (FAS) is a congenital syndrome caused by maternal alcohol consumption during pregnancy and is entirely preventable by abstinence from alcohol drinking during this time. Little is known about the prevalence of FAS and maternal alcohol consumption during pregnancy in Western countries. We present the results of FAS/partial fetal alcohol syndrome (PFAS) prevalence study and maternal characteristics in a sample of schoolchildren from a rural province of Croatia. This study involved seven elementary schools with 1,110 enrolled children attending 1st to 4th grade and their mothers. We used an active case ascertainment method with passive parental consent and Clarified IOM criteria. The investigation protocol involved maternal data collection and clinical examination of children. Out of 1,110 mothers, 917 (82.6%) answered the questionnaire. Alcohol exposure during pregnancy was admitted by 11.5%, regular drinking by 4.0% and binge drinking by 1.4% of questioned mothers. Clinical examination involved 824 (74.2%) schoolchildren and disclosed 14 (1.7%) with clinical signs of FAS and 41 (5.0%) of PFAS. The observed FAS prevalence, based on 74.2% participation rate, was 16.9, PFAS 49.7 and combined prevalence was 66.7/1,000 examined schoolchildren. This is the first FAS prevalence study based on active ascertainment among schoolchildren and pregnancy alcohol drinking analysis performed in a rural community of Croatia and Europe. High prevalence of FAS/PFAS and pregnancy alcohol consumption observed in this study revealed that FAS is serious health problem in rural regions as well as a need to develop future studies and preventive measures for pregnancy alcohol drinking and FASD.

Ruljancic N, Mihanovic M, Cepelak I, Bakliza A. Platelet and serum calcium and magnesium concentration in suicidal and non-suicidal schizophrenic patients. Psychiatry Clin Neurosci. 2013;67(3):154-9.

Department of Laboratory Diagnostics, Psychiatric Hospital 'Sveti Ivan', Zagreb, Croatia.

AIM: The main processes modulated by Ca and involved in the cause of schizophrenia are alteration in the dopamine and glutamate neurotransmitter system. Intracellular effects of Mg-ions are opposite to Ca-ions in competition at K-ion channels, in Na/K-ATP-ase activity, cAMP/cGMP concentration and Ca-ion currents in pre- and postsynaptic membranes. We conducted this research due to the incongruent results on Ca and Mg concentration that have been published until now and to determine platelet Mg concentration in suicidal and non-suicidal schizophrenic patients.

METHODS: A group of schizophrenic patients consisted of 23 patients with attempted suicide (S-SCH) and 48 patients without suicidal behavior (K-SCH) diagnosed according to ICD-10 diagnosis (F20.0) with or without intentional self-harm (X60-X84). The control group (K) included 99 healthy voluntary blood donors. The Mg and Ca concentration in platelets and serum was determined by atomic absorption spectrophotometry on the AAnalyst 200.

RESULTS: Using one-way anova test and manifold application of the Student-Newman-Keuls post-hoc test we established that there were higher concentrations of platelet Mg (μmol/109 platelets) ($P = 0.009$, $F = 4.89$) and lower concentrations of serum Ca (mmol/L) ($P < 0.001$, $F = 19.18$) in the S-SCH group of patients and higher concentrations of platelet Ca/Mg ratio in the K-SCH group of patients ($P = 0.006$, $F = 5.37$).

CONCLUSION: A higher Ca/Mg ratio in the platelets of non-suicidal patients confirms indirect higher Ca concentra-

tion. Higher Mg concentration in the platelets of suicidal patients, considered a Ca antagonist, may represent a compensatory attempt to restrain Ca activity.

Ivankovic M, Radman M, Gverovic-Antunica A, Tesanovic S, Trgo G, Demarin V. Influence of hypertension and type 2 diabetes mellitus on cerebrovascular reactivity in diabetics with retinopathy. Ann Saudi Med. 2013;33(2):130-3.

Department of Internal Medicine, Clinical Hospital Centre Split, Croatia.

BACKGROUND AND OBJECTIVES: Cerebrovascular reactivity (CVR) provides information on the intracerebral arterioles capacity to react to vasodilatory stimuli. The current study aimed to investigate the influence of hypertension and type 2 diabetes mellitus on CVR in diabetics with retinopathy.

DESIGN AND SETTING: Retrospective analysis of data prospectively collected over a 1-year period.

SUBJECT AND METHODS: Subjects were classified into four groups each comprised of 30 participants: diabetic retinopathy with hypertension (DRH), diabetic retinopathy without hypertension (DR), hypertension without diabetes mellitus (H), and healthy controls without diabetes and hypertension (C). CVR was estimated in relation to the increase in the mean flow velocity compared with the basal velocity in both middle cerebral arteries during hypercapnia.

RESULTS: In the DRH group, the mean (SD) increase in CVR was 8.8 (2.49) cm/s, in the H group 14.4 (2.59) cm/s and in the DR group 9.7 (2.97) cm/s. The analysis of variance showed significant differences among the groups in blood flow velocity after a breath-holding test ($F=89.83$; $df=3.116$; $P < .001$).

CONCLUSIONS: Diabetes mellitus influences CVR more than hypertension.

Brinar M, Cukovic-Cavka S, Bozina N, Ravic KG, Markos P, Ladic A, Cota M, Krznaric Z, Vucelic B. MDR1 polymorphisms are associated with inflammatory bowel disease in a cohort of Croatian IBD patients. BMC Gastroenterol. 2013;13:57.

Division of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Croatia.

BACKGROUND: Inflammatory bowel diseases (IBD) are chronic diseases of unknown etiology and pathogenesis in which genetic factors contribute to development of disease. MDR1/ABCB1 is an interesting candidate gene for IBD. The role of two single nucleotide polymorphisms, C3435T and G2677T remains unclear due to contradictory results of current studies. Thus, the aims of this research were to investigate the association of MDR1 polymorphisms, C3435T and G2677T, and IBD.

METHODS: A total of 310 IBD patients, 199 Crohn's disease (CD) patients and 109 ulcerative colitis (UC) patients, and 120 healthy controls were included in the study. All subjects were genotyped for G2677T/A and C3435T polymorphism using RT-PCR. In IBD patients, review of medical records was performed and patients were phenotyped according to the Montreal classification.

RESULTS: Significantly higher frequency of 2677T allele ($p=0.05$; OR 1.46, 95% CI (1.0-2.14)) and of the 3435TT genotype was observed among UC patients compared to controls ($p=0.02$; OR 2.12; 95% CI (1.11-4.03). Heterozygous carriers for C3435T were significantly less likely to have CD ($p=0.02$; OR 0.58, 95% CI (0.36-0.91)). Haplotype analysis revealed that carriers of 3435T/2677T haplotype had a significantly higher risk of having UC ($p=0.02$; OR 1.55; 95% CI (1.06-2.28)).

CONCLUSION: MDR1 polymorphisms are associated with both CD and UC with a stronger association with UC.

Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Arriola L, Bergman J, Bianca S, Boyd PA, Draper ES, Gatt M, Haeusler M, Khoshnood B, Latos-Bielenska A, McDonnell B, Pierini A, Rankin J, Rissmann A, Queisser-Luft A, Verellen-Dumoulin C, Stone D, Tenconi R. Fraser syndrome: epidemiological study in a European population. Am J Med Genet A. 2013;161(5):1012-8.

Children's Hospital Zagreb, Clinical Hospital Centre Sisters of Charity, Medical School University of Zagreb, Zagreb, Croatia.

Fraser syndrome is a rare autosomal recessive disorder characterized by cryptophthalmos, cutaneous syndactyly, laryngeal, and urogenital malformations. We present a population-based epidemiological study using data provided by the European Surveillance of Congenital Anomalies (EUROCAT) network of birth defect registries. Between January 1990 and December 2008, we identified 26 cas-

es of Fraser syndrome in the monitored population of 12,886,464 births (minimal estimated prevalence of 0.20 per 100,000 or 1:495,633 births). Most cases (18/26; 69%) were registered in the western part of Europe, where the mean prevalence is 1 in 230,695 births, compared to the prevalence 1 in 1,091,175 for the rest of Europe (P = 0.0003). Consanguinity was present in 7/26 (27%) families. Ten (38%) cases were liveborn, 14 (54%) pregnancies were terminated following prenatal detection of a serious anomaly, and 2 (8%) were stillborn. Eye anomalies were found in 20/24 (83%), syndactyly in 14/24 (58%), and laryngeal anomalies in 5/24 (21%) patients. Ambiguous genitalia were observed in 3/24 (13%) cases. Bilateral renal agenesis was present in 12/24 (50%) and unilateral in 4/24 (17%) cases. The frequency of anorectal anomalies was particularly high (42%). Most cases of Fraser syndrome (85%) are suspected prenatally, often due to the presence of the association of renal agenesis and cryptophthalmos. In the European population, a high proportion (82%) of pregnancies is terminated, thus reducing the live birth prevalence to a third of the total prevalence rate.

Brkljacic J, Pauk M, Erjavec I, Cipcic A, Grgurevic L, Zadro R, Inman GJ, Vukicevic S. Exogenous heparin binds and inhibits bone morphogenetic protein 6 biological activity. Int Orthop. 2013;37(3):529-41.

Laboratory for Mineralized Tissues, Center for Translational and Clinical Research, School of Medicine, University of Zagreb, Croatia.

PURPOSE: The purpose of this study was to explore the effect of heparin on bone morphogenetic protein 6 (BMP6) osteogenic activity.

METHODS: Western blot analysis was used to confirm the binding of BMP6 to heparin and to observe its effect on BMP6 signaling in C2C12-BRE-Luc myoblasts. Real-time RT-PCR was performed for the expression analysis of alkaline phosphatase (ALP) and osteocalcin (OC) in C2C12 myoblasts treated with BMP6 and heparin for 72 hours. Rat ectopic bone formation assay was performed to explore the effect of heparin on BMP6 osteogenic activity. Two weeks following implantation the implants were analysed morphologically and histologically. A mouse osteoporotic model was used to test the ability of BMP6 to improve the bone quality in vivo in the presence of heparin, followed by DEXA and μCT analyses. Blood coagulation was tested in rats previously treated with BMP6.

RESULTS: BMP6 specifically bound to heparin and induced Smad1/5/8 phosphorylation which was inhibited by heparin. After 48 and 72 hours of treatment, heparin inhibited BMP6-induced ALP and OC expression in C2C12 cells. Heparin dose dependently inhibited BMP6-induced new bone and cartilage formation in the rat ectopic bone formation assay, while in osteoporotic mice heparin inhibited the BMP6 potential to improve the bone quality as evidenced by decreased bone mineral density and trabecular bone parameters. Interestingly, BMP6 prevented the effect of heparin on the blood coagulation parameters.

CONCLUSION: The interaction of BMP6 with heparin might contribute to the heparin-induced osteoporosis and blood coagulation.

Miletić A, Krmpotić A, Jonjić S. The evolutionary arms race between NK cells and viruses: Who gets the short end of the stick? Eur J Immunol. 2013;43(4):867-77.

Department of Histology and Embryology, Faculty of Medicine, Rijeka, Croatia; Center for Proteomics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia.

NK cells are innate lymphocytes that play a key role in the control of various viral infections. Recent studies indicate that NK cells may acquire some features of adaptive immune cells, including the formation of long-lived memory cells. A large and growing body of data indicates that NK cells regulate the adaptive immune response as well. The function and the activation status of NK cells are tightly regulated by signals induced by a broad range of inhibitory and activating cell surface receptors and cytokines released by other immune cells. Here, we review the function of mouse NK-cell receptors involved in virus control and in the regulation of the adaptive immune response. In addition, we discuss viral strategies used to evade NK-cell-mediated control during infection. Finally, the role of several activating Ly49 receptors specific for mouse cytomegalovirus (MCMV), as well as some controversial issues in the field, will be discussed.