CROATIAN INTERNATIONAL PUBLICATIONS

by Dunja Gorup

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Ostojic A[1], Markotic A[2], Kelava T[3,4], Mrzljak A[1]. Implementation of quality assurance program in radiography-2-year experience of collaboration with public health institutions in west region of Croatia. Medicine (Baltimore). 2019 Feb;98(8):e14612. doi: 10.1097/MD.0000000000014612.

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While increased serum concentrations of CXCL9/10 are associated with acute cellular rejection (ACR) occurrence, the association between CXCL9/10 single nucleotide polymorphisms (SNPs) and ACR after liver transplantation (LT) remains unknown.In the present case-control study, polymorphisms of CXCL9 (rs10336) and CXCL10 (rs3921) were determined by polymerase chain reaction in 215 liver transplant recipients. ACR was defined as biopsy proven within 6 months after LT. As selected SNPs were in 3'-UTR region, their possible association with protein synthesis was assessed by measuring the plasma concentration of CXCL9/10 in a cohort of 40 new transplant patients using ELISA.There was no association between CXCL9/10 genotypes and overall incidence of ACR. However, patients with CXCL9 genotype AA developed ACR earlier than patients with GG genotype (P=.003), with similar results for CXCL10 gene (CC vs GG; P=.005). There was no statistically significant difference in plasma concentrations of CXCL9/10 between the rejectors and the non-rejectors. Of note, patients with AA CXCL9 genotype had significantly higher CXCL9 plasma concentrations than patients with AG (P=.01) or GG genotype (P=.045).In conclusion, the SNPs of CXCL9 (rs10336) and CXCL10 (rs3921) are not associated with the incidence of ACR. However, patients with CXCL9 genotype AA developed ACR earlier and the same genotype was associated with greater plasma concentrations suggesting the involvement of CXCL9 mediated processes in ACR development.

Gawish R[1], Bulat T[1], Biaggio M[1], Lassnig C[2], Bago-Horvath Z[3], Macho-Maschler S[2], Poelzl A[1], Simonović N[1], Prchal-Murphy M[4], Rom R[1], Amenitsch L[1], Ferrarese L[1], Kornhoff J[1], Lederer T[1], Svinka J[5], Eferl R[5], Bosmann M[6], Kalinke U[7], Stoiber D[8], Sexl V[4], Krmpotić A[9], Jonjić S[9], Müller M[10], Strobl B[11]. Myeloid Cells Restrict MCMV and Drive Stress-Induced Extramedullary Hematopoiesis through STAT1. Cell Rep. 2019 Feb 26;26(9):2394-2406.e5. doi: 10.1016/j.celrep.2019.02.017.

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Cytomegalovirus (CMV) has a high prevalence worldwide, is often fatal for immunocompromised patients, and causes bone marrow suppression. Deficiency of signal transducer and activator of transcription 1 (STAT1) results in severely impaired antiviral immunity. We have used cell-type restricted deletion of Stat1 to determine the importance of myeloid cell activity for the defense against murine CMV (MCMV). We show that myeloid STAT1 limits MCMV burden and infection-associated pathology in the spleen but does not affect ultimate clearance of infection. Unexpectedly, we found an essential role of myeloid STAT1 in the induction of extramedullary hematopoiesis (EMH). The EMH-promoting function of STAT1 was not restricted to MCMV infection but was also observed during CpG oligodeoxynucleotide-induced sterile inflammation. Collectively, we provide genetic evidence that signaling through STAT1 in myeloid cells is required to restrict MCMV at early time points post-infection and to induce compensatory hematopoiesis in the spleen.

Mészner Z[1], Wysocki J[2], Richter D[3], Zavadska D[4], Ivaskeviciene I[5,6], Usonis V [5], Pokorn M[7], Mangarov A[8], Jancoriene L[6,9], Man SC [10], Kristufkova Z[11], Jesenak M[12], Tešović G[13], Pluta J[14], Wolfson LJ[15]. Burden of varicella in Central and Eastern Europe: findings from a systematic literature review. Expert Rev Vaccines. 2019 Feb 27:1-13. doi: 10.1080/14760584.2019.1573145.

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Vaccination against varicella rapidly reduces disease incidence, resulting in reductions in both individual burden and societal costs. Despite these benefits, there is no standardization of varicella immunization policies in Europe, including countries in Central and Eastern Europe (CEE). Areas covered: This systematic literature review identified publications on the epidemiology of varicella, its associated health and economic burden, and vaccination strategies within the CEE region, defined as Albania, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Serbia, Slovakia, and Slovenia. Twenty-six studies were identified from a search of PubMed, Embase®, and MEDLINE® biomedical literature databases, supplemented by gray literature and country-specific/global websites. Expert commentary: Limited information exists in published studies on the burden of varicella in CEE. The wide variability in incidence rates between countries is likely explained by a lack of consistency in reporting systems. Funded universal varicella vaccination (UVV) in CEE is currently available only in Latvia as a one-dose schedule, but Hungary together with Latvia are introducing a two-dose strategy in 2019. For countries that do not provide UVV, introduction of vaccination is predicted to provide substantial reductions in cases and rates of associated complications, with important economic benefits.

Gorup D[1], Škokić S[1], Kriz J[2], Gajović S[1]. Tlr2 Deficiency is Associated with Enhanced Elements of Neuronal Repair and Caspase 3 Activation Following Brain Ischemia. Sci

Rep. 2019 Feb 26;9(1):2821. doi:10.1038/s41598-019-39541-3.

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The aim of this study was to apply multimodal in vivo imaging to assess the influence of altered innate immunity on brain repair after ischemic lesion. Tlr2-deficient mice were compared to wild type controls, as they lack Tlr2-mediated pro-inflammatory signalling triggered by post-ischemic necrosis. The ischemic lesion was induced by transient middle cerebral artery occlusion for 60 min, followed by brain imaging and analysis at four time points until 28 days after ischemia. Multimodal in vivo imaging involved a combination of 3 modalities: (1) magnetic resonance imaging by T2-weighted scans to assess brain lesion size, (2) bioluminescence imaging of Gap43-luc/gfp transgenic mice to visualize the axonal remodelling, and (3) caged-luciferin bioluminescence imaging of DEVD-luciferin allowing for visualization of caspase 3 and 7 activity in Gap43-luc/gfp mice. This enabled innovative correlation of the MRI-determined lesion size to photon fluxes obtained by bioluminescence imaging. Our data revealed that following ischemia, Tlr2-deficient mice had higher Gap43 expression and higher levels of caspases 3 and 7 activity, which was accompanied by enhanced levels of synaptic plasticity markers DLG4 and synaptophysin when compared to wild type controls. Altered inflammation in Tlr2-deficient mice was accompanied by enhanced elements of post-stroke repair, in particular during the chronic phase of recovery, but also with delayed final consolidation of the brain lesion.

Mulac-Jeričević B[1], Šućurović S[1], Gulic T[1], Szekeres-Bartho J[2,3,4,5]. The involvement of the progesterone receptor in PIBF and Gal-1 expression in the mouse endometrium. Am J Reprod Immunol. 2019 Feb 25:e13104. doi: 10.1111/aji.13104.

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PROBLEM: The progesterone regulated genes; PIBF and Gal-1 are key players in the feto-maternal immunological interaction. This study aims to investigate the expression of PIBF and Gal-1 in WT and progesterone receptor KO models as well as subsequent effects of PIBF on decidualization of stromal cells. METHOD OF THE STUDY: PRAKO, PRBKO and PRKO BALB/c mice were used for assessing the role of PR isoforms in PIBF induction. PIBF- and Gal-1 mRNA expression in the uterus was tested by real-time PCR. The effect of PIBF on decidualization of endometrial stromal cells was verified by anti-desmin immunofluorescence. Immunohistochemistry was used for testing PIBF expression in the uterus. Gal-1, ERα and PR positive decidual NK cells were detected by immunofluorescence. RESULTS: PIBF mRNA was significantly increased in progesterone treated WT mice, but not in PRKO and PRAKO mice. PIBF protein expression was reduced in the endometria of PRKO and PRAKO, but not in PRBKO mice. During a 6 day culture PIBF induced decidual transformation of endometrial stromal cells. PIBF expression in the mouse uterus was highest during the implantation window, while Gal-1 mRNA expression continuously increased between day 2.5 and day 11.5 of gestation. Decidual NK cells express Gal-1 and ERα, but not PR at day 7.5 murine pregnancy. CONCLUSION:PIBF produced via engagement of PRA, is highly expressed in the endometrium during the implantation window, and plays a role in decidualization. The concerted action of PIBF and Gal-1 might contribute to the low cytotoxic activity of decidual NK cells.

Civljak R1, Tot T[2], Falsey AR[3], Huljev E[1], Vranes J[4,5], Ljubin-Sternak S[4,5]. Viral pathogens associated with acute respiratory illness in hospitalized adults and elderly from Zagreb, Croatia, 2016 to 2018. J Med Virol. 2019 Feb 22. doi: 10.1002/jmv.25437.

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Dentistry, 425 Portland Avenue, Rochester, NY, USA; [4]Clinical Microbiology Department, Dr. Andrija Stampar Teaching Institute of Public Health, Mirogojska 16, Zagreb, Croatia; [5]Department of Medical Microbiolog, University of Zagreb School of Medicine, Rockefellerova 4, Zagreb, Croatia.

AIM: To investigate the viral aetiology of acute respiratory infection (ARI) in hospitalized adults and elderly patients in Croatia, compare the prevalence of detected viruses, and to determine clinical characteristics and seasonal occurrence of investigated infections. METHODS: From January 2016 to June 2018, a total of 182 adult patients presented with symptoms of ARI and admitted to the hospital were tested for 15 respiratory viruses by multiplex RT-PCR. Clinical data were collected by retrospective analysis of the patient's chart. RESULTS: A virus was identified in 106 (58.5%) of the patients. The most commonly detected virus was influenza virus (41.5%), followed by respiratory syncytial virus (13.8%), human metapneumovirus (13.0%), parainfluenza viruses (12.2%), rhinoviruses (11.4%), adenovirus and coronaviruses with equal frequencies (3.3%), and enterovirus (1.6%). The serum level of C-reactive protein and white blood cell count were significantly lower in patients with respiratory viruses identified when compared to those in whom no virus was detected (P>0.001 and P=0.007 respectively). There were no differences in clinical symptoms according to the type of the detected virus, except for more frequent illness exposure recall for influenza infection (P=0.010). Influenza, parainfluenza and pneumoviruses were detected mostly in winter months, while rhinoviruses in autumn and spring. CONCLUSIONS: In addition to influenza, pneumoviruses, rhinoviruses and parainfluenza viruses play an important role in aetiology of ARIs in adults. Fast and accurate laboratory diagnosis for respiratory viruses in routine practice is needed for clinicians optimally manage patients with ARI and potentially avoid the unnecessary use of antimicrobial drugs.

Stojanovic B[1,2], Milovanovic J[1,3], Arsenijevic A[1], Stojanovic B[4], Strazic Geljic I[5], Arsenijevic N[1], Jonjic S[5], Lukic ML[1], Milovanovic M[1]. Galectin-3 Deficiency Facilitates TNF-α-Dependent Hepatocyte Death and Liver Inflammation in MCMV Infection. Front Microbiol. 2019 Feb 8;10:185. doi: 10.3389/fmicb.2019.00185. eCollection 2019.

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Galectin-3 (Gal-3) has a role in multiple inflammatory pathways. Various, opposite roles of Gal-3 in liver diseases have been described but there are no data about the role of Gal-3 in development of hepatitis induced with cytomegalovirus infection. In this study we aimed to clarify the role of Gal-3 in murine cytomegalovirus (MCMV)-induced hepatitis by using Gal-3-deficient (Gal-3 KO) mice. Here we provide the evidence that Gal-3 has the protective role in MCMV-induced hepatitis. Enhanced hepatitis manifested by more inflammatory and necrotic foci and serum level of ALT, enhanced apoptosis and necroptosis of hepatocytes and enhanced viral replication were detected in MCMV-infected Gal-3 deficient mice. NK cells does not contribute to more severe liver damage in MCMV-infected Gal-3 KO mice. Enhanced expression of TNF-α in the hepatocytes of Gal-3 KO mice after MCMV infection, abrogated hepatocyte death, and attenuated inflammation in the livers of Gal-3 KO mice after TNF-α blockade suggest that TNF-α plays the role in enhanced disease in Gal-3 deficient animals. Treatment with recombinant Gal-3 reduces inflammation and especially necrosis of hepatocytes in the livers of MCMV-infected Gal-3 KO mice. Our data highlight the protective role of Gal-3 in MCMV-induced hepatitis by attenuation of TNF-α-mediated death of hepatocytes.

Ribić R[1], Meštrović T[2], Neuberg M[1], Kozina G[1]. Proposed dual antagonist approach for the prevention and treatment of urinary tract infections caused by uropathogenic Escherichia coli. Med Hypotheses. 2019 Mar;124:17-20. doi: 10.1016/j.mehy.2019.01.010. Epub 2019 Jan 11.

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Urinary tract infections are among the most common infectious diseases worldwide, primarily caused by uropath-

ogenic Escherichia coli (UPEC) strains that harbor type I pili and P pili on the surface. Standard E. coli therapy still entails antibiotic consumption, but urinary tract infections tend to recur at a very high rate. Due to the emergence of antibiotic resistant strains of UPEC, as well as high infection recurrence rates, there is a need for new approaches to efficiently treat and prevent urinary tract infections. Since aforementioned adhesive organelles are the principal virulence factors in UPEC, anti-adhesion strategy seems to be the most promising (and hitherto unexplored) treatment option. Here we propose an antiadhesive dual targeting approach towards FimH and PapG adhesive proteins placed on two key virulence factors for UPEC - type I fimbriae and P pili. Such dual antagonists will contain appropriate pharmacophores (mannose and natural cranberry-containing polyphenol) joined together and will more efficiently block the infection and prevent the progression of the disease in comparison to FimH and PapG as isolated targets. More specifically, polyphenol mannosides (due to the structural similarities with the most potent biaryl inhibitors) can act as high-affinity FimH ligands, while cranberry-associated polyphenol moiety can additionally inhibit the PapG-mediated adhesion. Proposed compound may also contribute to the antioxidant capacity of the human organism. In conclusion, this dual-target hypothesis for the prevention and treatment of UPEC infections represents an important foundation for further research on this topic.

Vrdoljak J[1], Boban T[2], Petrić Miše B[2], Boraska Jelavić T[2], Bajić Ž[3], Tomić S[4], Vrdoljak E[2]. Efficacy and safety of TC dose-dense chemotherapy as first-line treatment of epithelial ovarian cancer: a single-institution retrospective cohort study. Jpn J Clin Oncol. 2019 Feb 23. pii: hyz011. doi: 10.1093/jjco/hyz011.

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BACKGROUND: The optimal first-line therapy of advanced ovarian cancer still remains questionable: standard paclitaxel-carboplatin (TC), dose-dense TC, intraperitoneal chemotherapy or TC plus bevacizumab. In this study, we present the real-life results of dose-dense treatment of the single-institution on Caucasian population. METHODS: A retrospective cohort study was used on consecutive samples of 74 patients treated with the conventional 3-weekly TC protocol (2008-11) and on 70 treated with TC dose-dense protocol (2012-16). The primary endpoint of this study was overall survival (OS). Secondary endpoints were progression free-survival (PFS) and toxicity. We made adjustments for age, pathohistological type, tumor grade, stage and postoperative residual disease by Cox regression. RESULTS: After adjustment for pre-planned clinical and sociodemographic factors, patients treated with dose-dense protocol showed a significantly lower hazard for dying from any cause, than patients treated with conventional protocol (HR = 0.50; 95% CI 0.26-0.98; P = 0.042). Median OS, at 60 months follow-up had not been reached in the dose-dense group, while in the standard treatment group was 48 months (95% CI 33-62). Unadjusted PFS was significantly longer in the dose-dense group (HR = 0.58; 95% CI 0.38-0.88; P = 0.011), but not after the adjustment (P = 0.096). Generally, the level of toxicity was similar in both groups of patients. The need for blood transfusions and usage of filgrastim was significantly higher in the TC dd group. The incidence of neutropenia and thrombocytopenia Grade 3 or 4 were not significantly different in both regimens. CONCLUSIONS: Our retrospective study has shown the superior efficacy and comparable toxicity of dose-dense chemotherapy regimen over the conventional regimen in treatment of ovarian cancer on Caucasian population at a single-institution.

Pavičić Žeželj S[1], Kenđel Jovanović G[2], Krešić G[3]. The association between the Mediterranean diet and high physical activity among the working population in Croatia. Med Pr. 2019 Feb 21. pii: 95029. doi: 10.13075/mp.5893.00773.

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BACKGROUND: Unhealthy eating habits and physical inactivity constitute an emerging public health problem. The working population is of special interest for public health monitoring and evaluation because workers' unhealthy lifestyles may lead to reduced work ability. The aim

of this study was to determine diet quality and adherence to the Mediterranean diet (MD), according to the level of physical activity, and to detect variables associated with the working population's being highly physically active. MATERIAL AND METHODS: At the Institute for Occupational Medicine 400 full-time workers were examined for obesity factors, filled in the short version of International Physical Activity Questionnaire (IPAQ-short) and a validated food frequency questionnaire for adherence to the Mediterranean diet using Mediterranean Diet Score (MDS). The workers were divided into low, moderate and high physical activity groups according to the IPAQ-short scoring protocol. Hierarchical linear regression was performed to determine the variables associated with being highly active. RESULTS: One-third of the participants were highly physically active and their diet adhered to the MD (Me_{MDS} = 7). Significant variables associated with a high level of physical activity were gender ($p < 0.001$), age ($p = 0.02$), waist-to-hip ratio (WHR) ($p < 0.001$), sitting level ($p = 0.044$) and occupational type ($p < 0.001$). CONCLUSIONS:It was found that the participants displaying a high level of physical activity had a better quality diet that adhered to the Mediterranean diet but not to a significant degree. The variables associated with a high level of physical activity were male gender, younger age, normal WHR, non-sedentary occupation and reduced sitting time. The study findings could serve the purpose of improving future public health promotion of physical activity and the Mediterranean diet.

Radman M[1], Babic A[2], Runjic E[3], Kadic AJ[3], Jeric M[4], Moja L[5,6], Puljak L[7]. Revisiting established medicines: an overview of systematic reviews about ibuprofen and paracetamol for treating pain in children. Eur J Pain. 2019 Feb 21. doi: 10.1002/ejp.1380

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BACKGROUND AND OBJECTIVE: We explored how systematic reviews evaluated paracetamol and ibuprofen for treating pain in children, as these two nonopioid analgesics are well-established medicines included in most national essential medicines lists. DATABASES AND DATA TREATMENT: We carried out an overview of systematic reviews (SRs) of randomized controlled trials (RCTs) of interventions (PROSPERO registration: 42016045367). We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR) and Database of Reviews of Effects (DARE) up to August 23, 2017. We used AMSTAR checklist to analyze methodological quality of included SRs. RESULTS: We found 17 SRs with 72 unique RCTs; the majority of those trials included under 100 children. Positive conclusive evidence was found in only one SR, regarding safety of paracetamol. Conclusions of other SRs for efficacy and safety of ibuprofen and paracetamol were inconclusive, unclear, or there was no opinion. Only one SR analyzed efficacy of ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) in chronic pain and the conclusion was that there was no evidence from RCTs that NSAIDs were effective for chronic noncancer pain in children and adolescents. Most of the SRs addressed very narrow questions, included few trials, with few children and were of low or medium methodological quality. CONCLUSIONS: Most SRs on two relevant medicines have inconsistent conclusions and doubt upon their effectiveness. Instead of focusing on very narrow questions, SRs should examine more comprehensive research topics to obtain a general sense of consistency, particularly when analyzing established medicines.

Rusic D[1], Bozic J2, Bukic J[1], Seselja Perisin A[1], Leskur D1, Modun D[1], Tomic S[1,3]. Evaluation of accordance of antibiotics package size with recommended treatment duration of guidelines for sore throat and urinary tract infections. Antimicrob Resist Infect Control. 2019 Feb 11;8:30. doi: 10.1186/s13756-019-0495-5. eCollection 2019.

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BACKGROUND: The aim of this study was to investigate whether marketed antibiotics package sizes are in accordance with treatment durations recommended in guide-

lines for prescribing antibiotics in sore throat and urinary tract infections. METHODS:National drug database was searched with limitation to Antibacterials for systemic use. Formulations which did not have pre-specified dosage unit by the manufacturer were excluded (e.g. powders for oral solutions). The final list contained 94 drugs with 23 different active substances. This list was then cross-referenced with selected antimicrobial prescribing guidelines provided by Intersectoral Society for Antibiotic Resistance Control (ISKRA), National Institute for Health and Care Excellence (NICE) and The Infectious Diseases Society of America (IDSA). RESULTS: Seven packages matched ISKRA guidelines on sore throat while 16 were mismatched. Considering drug packages under reimbursement, 3 matched ISKRA guidelines and 8 were mismatched. Only 3 packages matched IDSA guidelines for comparable indications, and 18 were mismatched. When considering NICE guidelines there were 5 mismatched and only one package that was in accordance with the guidelines. ISKRA guidelines for urinary tract infections matched 23 packages and mismatched 58 packages. IDSA guidelines for urinary tract infections matched one package and were mismatched in 15 cases. CONCLUSIONS: One of the causes of leftover antibiotics is poor accordance of antibiotic package size with treatment recommendation duration. This should be identified as a potential target for reduction of excess antibiotics in the community. Measures that promote patient adherence to therapy and patient education should be considered essential to manage proper handling of leftover antibiotics.

Knezović V[1], Kasprian G[2], Štajduhar A[1], Schwartz E3, Weber M[3], Gruber GM[4], Brugger PC[4], Prayer D[3], Vukšić M[1]. Underdevelopment of the Human Hippocampus in Callosal Agenesis: An In Vivo Fetal MRI Study. AJNR Am J Neuroradiol. 2019 Feb 21. doi: 10.3174/ajnr.A5986.

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BACKGROUND AND PURPOSE: In subjects with agenesis of the corpus callosum, a variety of structural brain alterations is already present during prenatal life. Quantification of these alterations in fetuses with associated brain or body malformations (corpus callosum agenesis and other related anomalies) and so-called isolated cases may help to optimize the challenging prognostic prenatal assessment of fetuses with corpus callosum agenesis. This fetal MR imaging study aimed to identify differences in the size of the prenatal hippocampus between subjects with isolated corpus callosum agenesis, corpus callosum agenesis and other related anomalies, and healthy controls. MATERIALS AND METHODS: Eighty-five in utero fetal brain MR imaging scans, (20-35 gestational weeks) were postprocessed using a high-resolution algorithm. On the basis of multiplanar T2-TSE sequences, 3D isovoxel datasets were generated, and both hippocampi and the intracranial volume were segmented. RESULTS: Hippocampal volumes increased linearly with gestational weeks in all 3 groups. One-way ANOVA demonstrated differences in hippocampal volumes between control and pathologic groups (isolated corpus callosum agenesis: left, $P = .02$; right, $P = .04$; corpus callosum agenesis and other related anomalies: $P < .001$). Differences among the pathologic groups were also present for both sides. Intracranial volume and right and left hippocampal volume ratios were different between corpus callosum agenesis cases and controls ($P < .001$). When we corrected for intracranial volume, no differences were found between corpus callosum agenesis and other associated anomalies and isolated corpus callosum agenesis (left, $P = .77$; right, $P = .84$). Hippocampal size differences were more pronounced at a later gestational age. CONCLUSIONS: Callosal agenesis apparently interferes with the normal process of hippocampal formation and growth, resulting in underdevelopment, which could account for certain learning and memory deficits in individuals with agenesis of the corpus callosum in later life.

Babić Božović I[1], Stanković A[2], Živković M[2], Vraneković J[1], Mahulja-Stamenković V[3], Brajenović-Milić B[1]. Maternal LINE-1 DNA Methylation and Congenital Heart Defects in Down Syndrome. Front Genet. 2019 Feb 6;10:41. doi: 10.3389/fgene.2019.00041. eCollection 2019.

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Background: Down syndrome (DS) is one of the most common chromosomal abnormalities associated with congenital heart defects (CHD), with approximately 40 to 60% of cases showing cardiac defects. This study assessed (i) the association between maternal LINE-1 methylation and the occurrence of CHDs in children with DS and (ii) the impact of endogenous maternal factors (MTHFR C677T polymorphism and maternal age) and exogenous maternal factors (cigarette smoking, alcohol intake, medication use, body mass index and dietary habits such as folate intake) on maternal LINE-1 methylation and on the occurrence of CHD in children with DS. Patients and Methods: The study included 90 mothers of children with DS of maternal origin (49% DS-CHD+ mothers/51% DS-CHD- mothers). LINE-1 DNA methylation was analyzed in peripheral blood lymphocytes by quantification of LINE-1 methylation using the MethyLight method. MTHFR C677T polymorphism genotyping was performed using PCR-RFLP. Results: LINE-1 methylation was not significantly different between DS-CHD+ and DS-CHD- mothers (P = 0.997). Combination of MTHFR C677T genotype/diet and BMI were significant independent predictors of LINE-1 DNA methylation in DS-CHD+ mothers (β -0.40, P = 0.01 and β -0.32, P = 0.03, respectively). In the analyzed multivariate model (model P = 0.028), these two factors explained around 72% of the variance in LINE-1 DNA methylation in mothers of children with DS and CHD. The group with the highest BMI (≥30 kg/m2) had significantly lower LINE-1 methylation than the group with normal BMI (Bonferroni post hoc P = 0.03) and the overweight group (Bonferroni post hoc P = 0.04). The lowest LINE-1 DNA methylation values were found in DS-CHD+ mothers with the CT+TT genotype and a low-folate diet; the values were significantly lower than the values in mothers with the CC genotype and a folate-rich diet (Bonferroni post hoc P = 0.04). Conclusion: Association between maternal LINE-1 methylation and CHD in children with DS was not found. Study showed that the MTHFR genotype/diet combination and BMI were significantly associated with LINE-1 methylation in mothers of children with DS-CHD+. These results highlight the need for a multifactorial approach to assess the roles of endogenous and exogenous maternal factors in maternal LINE-1 DNA methylation and the consequent pathologies in children. More extensive studies in a larger sample may help elucidate these relationships.

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Key regulators of the Wnt signalling, DVL1, DVL2 and DVL3, in astrocytomas of different malignancy grades were investigated. Markers for DVL1,DVL2 and DVL3 were used to detect microsatellite instability (MSI) and gross deletions (LOH), while immunohistochemistry and immunoreactivity score were used to determine the signal strengths of the three DVL proteins and transcription factors of the pathway, TCF1 and LEF1. Our findings demonstrated that MSI at all three DVL loci was constantly found across tumour grades with the highest number in grade II (P = 0.008). Collectively, LOHs were more frequent in high-grade tumours than in low grade ones. LOHs of DVL3 gene were significantly associated with grade IV tumours (P = 0.007). The results on protein expressions indicated that high-grade tumours expressed less DVL1 protein as compared with low grade ones. A significant negative correlation was established between DVL1 expression and malignancy grades (P < 0.001). The expression of DVL2 protein was found similar across grades, while DVL3 expression significantly increased with malignancy grades (P < 0.001). The signal strengths of expressed DVL1 and DVL3 were negatively correlated (P = 0.002). However, TCF1 and LEF1 were both significantly upregulated and increasing with astrocytoma grades (P = 0.001). A positive correlation was established between DVL3 and both TCF1 (P = 0.020) and LEF1 (P = 0.006) suggesting their joint involvement in malignant progression. Our findings suggest that DVL1 and DVL2 may be involved during early stages of the disease, while DVL3 may have a role in later phases and together with TCF1 and LEF1 promotes the activation of Wnt signalling.