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Macedonian Medical Doctor of Philosophy (PhD) Theses Defended in 2011

Macedonian Journal of Medical Sciences

Institute of Immunobiology and Human Genetics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, Republic of Macedonia

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Key words: Doctor of Philosophy (PhD); Medical research; Republic of Macedonia.

Correspondence: Macedonian Journal of Medical Sciences. Institute of Immunobiology and Human Genetics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of Macedonia. 50 Divizija No 16, PO Box 60, 1109 Skopje, Republic of Macedonia. Telephone: +389 2 3110556. Telefax: +389 2 3110558. EMail: mjms@ukim.edu.mk

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Abstract

We present English abstracts of PhD theses defended in 2011 at the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of Macedonia. English summaries are published as they are translated by authors and included in the final version of defended PhD. Macedonian Medical Doctor of Phylosophy (PhD) theses are deposited in the Central Medical Library and National and University Library "St. Kliment Ohridski" in Skopje.

At the Faculty of Medicine in Skopje 22 PhD theses there were defended in 2011, two of them wihout English abstract (9.09%): one from the Institute for Forensic Medicine and one from the University Clinic of Urology. Nine PhDs are without Key words (40.91%), and most of them (12) are with structured abstracts (54.5%).

Editorial Board does not take any responsibility either for the content, nor the quality of the abstracts.

Primary responsibility for the quality of the PhD theses belongs to the mentors, to the institutions they are representing, and to the Vice-Dean of science. They should be more actively involved in the preparation of Doctor of Phylosophy theses in order international standards to be achieved.

Defended PhDs can be cited as tey are published in this and in previous reports.

Emilija Cvetkovska. Clinical, neurophysiological and genetic study of patients with juvenile mioclonic epilepsy [PhD Thesis]. ***Skopje, Republic of Macedonia: University Clinic of Neurology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.*** Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Introduction: Juvenile myoclonic epilepsy (JME)-Janz syndrome is idiopathic, primarily generalized epileptic syndrome, genetically determined and age-dependent. There are a lot of ongoing neurophysiological, anatomomorphologic and genetic investigations in order to put insight in etiopathogenesis of disease and improve treatment and prognosis of the patients with JME.

Purpose: The aim of the study was to evaluate clinical and electroencephalographic (EEG) features, detect cognitive impairment, analyze pedigrees of families with JME proband and search for mutations in EFHC1 gene located on 6p12-p11 chromosome of patients with JME.

Patients and Methods: Sixty patients with JME, 22

members of their families and 30 healthy controls have entered the study. Diagnosis of JME was established folloving the ILAE Classification and diagnostic scheme. Exclusion criteria were coexistence of other neurological, psychiatric or somatic disorder other than JME. Detailed auto and heteroanamnesis and neurological examination, standard and sleep deprived EEG, as well as magnetic nuclear resonance imagings were done. Wisconsin card sorting test was used to assess frontal cognitive functions. Genetic investigation included pedigree analysis of familiar cases and molecular identification of mutations of EFHC1 gene by isolation of genomic DNA from leucocytes. Regions of EFHC1 gene were amplified by polimerase chain reaction (PCR). Detection of mutations was done by screening of venous blood samples of patients, family members and controls by molecular analysis SSCP (*Single-Stranded Conformation Polymorphism*). Precise determination of conformation polymorfism was done in positive samples with direct sequencening - Sanger technique with comercial set (Applied Biosystems) and automathic sequencionator (ABI Prism 307 Gene Analysator, Applied Biosystems). Nucleotide sequences were analyzed with software BioEdit and nucleotides were compared with referent sequences from GeneBank.

Results: The age of onset of seizures was 7-39 years (mean 14 ± 5. 6 years). There were three types of seizures: myoclonic jerks, generalized tonic-clonic seizures and typical absences. The most prominent and pathognomonic parts of the syndrome were the myoclonic seizures: early in the morning, immediately after walking, during the first half or an hour after walking. They appeared in the arms, legs or eye lids, involved more frequently the arms than the legs. Myoclonic jerks were bilateral and symmetrical in most of the patients, but 22% of patients reported unilateral domination. Absences were registered in 43% of the patients and 57 (95%) had generalized tonic-clonic seizures. Sleep deprivation and fatigue, especially after excessive alcohol abuse were the strongest precipitating factors, 10% of patients had seizures indused by photic stimulation in daily life and few by mental (cognitive) effort. Interictal discharges of spike-poly-spike-wave complexes with frequency of 3-6 Hz were registered in at least one EEG of almost all patients. Asymmetry, regional accentuation and focal abnormalities occured in 32% and photoparoxysmal responce in 58% of the patients. Standard magnetic resonance imagines were normal in all patients. Wisconsin card sorting test (WCST) was used to evaluate frontal (executive) functions. 42% of patients showed abnormalities on test in concordance with frontal cognitive deficit, while others achieved results within normal limits. Positive familiar history for seizures was obtained from 22 (37%) patients. Totally ten pedigrees with JME proband were further analyzed. Mean number of affected individuals per family was three. In half of families JME was the only clinical feature, while in others there were members with other forms of IGE (epilepsy with generalized tonic-clonic seizures on awakening, juvenile absence epilepsy and adult onset myoclonic epilepsy). In two three-generation families the phenomenon of genetic anticipation was observed, i.e. the onset of disease had a tendency to decrease in age which each successive generation. Molecular-genetic analysis of EFHC1 gene showed conformation polymorfism in one or several egzons in 12 patients and one family member with other form of IGE. Seizures were well controlled in more than 90% of patients with corresponding choice of antiepileptic drug (the commonly used drug in our patients was valproic acid; lamotrigine, topiramate and levetiracetam followed in order).

Conclusions: It is very important to stress the occurance of focal findings on EEG and asymmetry of seizures, because it could lead to misdiagnosis of syndrome, choice of inappropriate medication and poor seizure control and quality of life of affected individuals. Knowledge of focal predominance of epileptiform discharges and frontal neuropsychological deficit could lead to changing concepts of “generalized” epilepsies and understanding them as regional network epilepsies. Genetic and familiar studies elucidate aethyiology and knowledge about genotype/phenotype relations. Phenomenon of genetic anticipation, which was observed in two families with JME proband, suggests that nucleotide expansion mutations may be the possible genetic molecular mechanism involved in some cases of JME. Existence of conformation polymorphism in EFHC1 gene located on 6p12-p11 chromosome in about one fifth of our patients is important finding about genetic architecture of the disease, although their definitive role needs to be confirmed in further investigations.

Keywords: *juvenile myoclonic epilepsy; EEG; genetic analysis.*

Defended: March 29, 2011.

Mentor: Prof. Dr. Ilija Dzonov.

Crvenkova Simonida. Combinatoin of conformal radiotherapy and chemotherapy in the treatment of locally-advanced non-small cell lung cancer [PhD

Thesis]. ***Skopje, Republic of Macedonia: University Clinic of Radiotherapy and Oncology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.*** Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

During the period of the 1 October 2005 to the 31 of March 2008, at the Institute of Radiotherapy and Oncology, 110 patients with inoperable locally-advanced non-small cell lung cancer were randomized for chemoradiotherapy. Eighty five patients were evaluated. According the chemoradiotherapy method, patients were randomly assigned in two groups, concurrent and sequentional. Randomization was performed according the time when RT was starting. In concurrent chemoradiotherapy group, RT was starting at the same time with chemotherapy, following two cycles of consolidation chemotherapy. In sequentional group RT was giving after 4 cycles of chemotherapy. Tridimensional Conformal RT with Linear Accelerator was performed in the both groups, to a total dose of 60 Gy. Platinum based chemotherapy with etoposide was applied. Forty patients were treated with concurrent chemoradiotherapy method (CHRT), and 45 with sequentional method (SHRT).

Objective responce (complete+partial) was achieved in 83% in CHRT group, compare with 56% in SHRT group, statistical significant difference ($p<0.05$). Objective responce for all patients was 68%.

Median survival and disease free survival for CHRT group were 19 mounts and 16 mounts, and for SHRT group were 13 mounts and 9 mounts. There was statistical significant difference, between two groups ($p<0.001$). One year survival was achieved in 74.5% of the patients, two years survival was achieved in 36.6%, and three years survival in 26.6% patients in the CHRT group. For the SHRT group one year, two years, and three years survival were, 52.6%, 14.3% and 7.1%, respectively. Survival time was in significant correlation with local tumor control ($p<0.001$). Median survival for patients with complete response was 33 mounts, partial response 16 mounts and 6 mounts for patient without any responses.

Prognostic factors with significant influence on survival were: initial performance status according ECOG, initial weight loss, nodal involvement, tumor size and ages. Prognostic factors without any influence on survival were: gender, duration of symptoms, hemoglobin level and histological type.

Adverse effects of the both chemoradiotherapies schedules were mild and moderate. So, we recommended the both methods for NSCLC patients who were in good condition.

Keywords: Not available.

Defended: March 31, 2011.

Mentor: Prof. Dr. Cveta Tolevska

Agron Starova. Clinical, etiological and epidemiological aspects of dermatophytoses in R. of Macedonia [PhD Thesis]. ***Skopje, Republic of Macedonia: University Clinic of Dermatology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.*** Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Intoduction. Dermatophytoses involve the group of superficial fungal skin infections caused by dermatophytes. Traditionally infections caused by dermatophytes have been named according to their anatomical sites: tines capitis, tines barbae, tinea faciei, tinea corporis, tinea cruris, tinea manuum, tinea pedis and tinea ungium (onychomycosis). The aim of this study is to give an overview of the most commonly isolated dermatophytic spisies, and to present the clinical, etiological and epidemiological aspects in patients with certain types of dermatophytosis in the Republic of Macedonia.

Material and methods. The study was conducted in the Mycological Laboratory at the Clinic of Dermatology, at the Medical Faculty in Skopje. The Mycological Lab of the Clinic is specialized in objective diagnostics of dermatophytoses in the Republic of Macedonia and applies all conventional diagnostic methods of detection and identification of dermatophytic species. The research represents a prospective analitical study. In the period between June 2007 to January 2009, a sample was randomly taken out of 600 patients either examined or hospitalized. The main criteria of selection of the patients in the study, was a confirmed dermatophytosis with a direct microscopy and Wood light examination. In order to identify dermatophytes following Rebell and Taplin criteria, the respondents were submitted to a cultural examination of a Sabouraud medium with chloramphenicol, gentamycin and cycloheximide. All patients with dermatophytoses were given a structured semi-open questionnaire with 26 questions. The collected data were statistically processed with the software Statistics 5.

Results. Out of 1742 patients with suspected dermatophytosis, in 600 (34.44%) the dermatophytic infections of the skin, hair and nails was confirmed with a conventional paraclinic examination in

dermatomycology. 225 patients (37.50% of patients with dermatophytosis) had tinea ungium (onychomycosis). Onychomycosis is the most frequently diagnosed dermatophytosis followed by tinea pedis in 115 patients (19.17%), tinea corporis 92 (15.33%), tinea capitis 91 (15.17%), tinea cruris 44 (7.33%), tinea manuum 18 (3%), tinea faciei 13 (2.17%) and tinea barbae 2 (0.33%). Most commonly isolated dermatophytic species which in different prevalence causes dermatophytoses are: *Trichophyton rubrum* in 293 patients (48.83% of the patients with dermatophytosis) followed by *Microsporum canis* 120 (20%), *Trichophyton mentagrophytes var.interdigitale* 101 (16.83%), *Epidermophyton floccosum* 25 (4.17%), *Trichophyton verrucosum* 23 (3.83%), *Trichophyton mentagrophytes var.mentagrophytes* 18 (3%), *Trichophyton violaceum* 10 (1.67%), *Microsporum ferrugineum* 6 (1%) and *Microsporum gypseum* 4 (0.67%). Anthropophilic dermatophytes represent 72.5% of isolates. In female patients (57.33 of the sample) most often are diagnosed tinea corporis (69.57%), onychomycosis (68.89%) and tinea pedis (55.57%). Ethnic Macedonians prevail (before ethnic Albanians and Romas), from Skopje and rural areas around Skopje, with average social and economic status. The most affected patients are children from 3 to 10 and adults from 31 to 50. The most commonly clinic manifestation in children is *Microsporum canis* tinea capitis. It has been noted an increased number of *Microsporum canis* isolates (73.63%) in patients with tinea capitis, and according to anamnestic data, pets like cats and dogs are the main source of infection. The most commonly isolated anthropophilic dermatophytic species (*Trichophyton rubrum*) is most prevalent in tinea unguium (onychomycosis) (69.7%), tinea cruris (65.91%) and tinea pedis (64.35%). A concomitant (internal) disease is significantly more common then in other concomitant dermatosis is most commonly found in the same patients. From individual clinical variants of different types of dermatophytoses the most frequently noted are: tinea capitis superficialis (81.32% od cases with tinea capitis), disseminated annular eczematous tinea corporis on the arms, legs and trunk (31.52%), inguinal erythematosquamous tinea cruris (34.09%), intertriginous tinea manuum (33.33%), interdigital tinea pedis (54.78%) and distal lateral subungual onychomycosis (81.78%). Concomitant dermatophytosis in high percentage can be found in patients with tinea manuum (44.44% of cases), tinea cruris (36.36%) and tinea pedis (31.30%). Whereas, the other patients who have direct contact with already diagnosed dermatophytosis are found more frequently around patients with tinea capitis (58.24% of the cases), tinea corporis (33.70%) and tinea faciei (30.77%).

Conclusion. The average number of patients with dermatophytoses in the Mycological Laboratory at the Clinic of Dermatology stays approximately the same. The sex of the patient, the clinical forms and the age are closely related to the appearance of the dermatophytoses. Different dermatophytic species, which are pathogenic both for people and for animals, have each one an individual epidemiological and epizoological relevance. The distibution of dermatophytes in the Republic of Macedonia is similar to the one in the European countries. This stady shows that anthropophylic dermatophytic species and *Trichophyton rubrum* prevail as a most frequently isolated dermatophytes. As a result of hronicity and resistance of *Trichophyton rubrum* to the existig therapy, its affinity to nails, the higher standard and the benefits of modern civilization (the use of saunas, pools etc) the most common forms of dermatophytoses are tinea unguium (onychomycosis) and tinea pedis. In the course of the last decade the zoophilic microsporosis is reaching epidemic proportions. In children with tinea capitis there is a rise of *Microsporum canis* isolates and the *Microsporum canis* infection is becoming a serious epidemic issue in the Republic of Macedonia, which increasingly represents a financial burden to the health system.

Due to the need for a precise knowledge of the ecology and epidemiology of dermatophytes and dermatophytoses, which are essential to the identification of the type of infection and better understanding of the way of transmission, we consider that it is necessary to continue the monitorig of the incidence of dermatophytic superficial infections on the skin and registering every new case.

Keywords: *Dermatophytes; dermatophytoses; epidemiology; Republic of Macedonia.*

Defended: April 1, 2011.

Mentor: Prof. Dr. Margareta Balabanova-Stefanova.

Atanas Sivevski. Evaluation of effects of spinal and general anaesthesia for cesarean section in parturients and newborn infants [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Gynecology and Obstetrics, Department of Anaesthesia, Reanimation and Intensive Care, Medical Faculty, Ss. Cyril and Methodius University*

in Skopje; 2011. Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

According to majority of authors, hypotension develops in post dural puncture interval even in 80-100% of parturients who are administered spinal anesthesia for elective CS. The aim of this investigation was hypotension in parturient women undergoing general or (different types of) spinal anesthesia for Cesarean section as well as the influence of anesthesia on the short-term effect in newborn children (Apgar and gas parameters). At the same time, the option of hypotension prevention, i.e. its minimization by reducing bupivacaine dosage, administered alone or in combination with lipofil opioid (fentanyl) has been analyzed. The concept of "low-dose bupivacaine" spinal anaesthesia and its effect on hemodynamics in parturients as well as the short-term outcome in newborn children has been investigated.

Patients and method for work. The study included two hunderd (200) healthy (ASA I or II) parturients with similar demographics and similar indications for CS with strictly defined exclusion criteria, and the same number (200) of neonates. Parturients were divided randomly in five study groups: those who received general anesthesia (OA-group, 40 patients) and those who received spinal anesthesia (160 parturients), additionally divided into four equal groups: SA-group (spinal anesthesia with 13.5 mg isobaric bupivacaine, 2.7 ml, 40 patients); SA F10-group (spinal anesthesia with 12 mg bupivacain + fentanyl 10 μgr, 2.6 ml, 40 patients); SA F20-group (spinal anesthesia with 11 mg bupivacaine+fentanyl 20 μgr, 2.6 ml, 40 patients) and group SA LD (spinal anesthesia with 6-8 mg bupivacain + fentanyl 20 μgr, 1.6-2.0 ml), so called "low-dose bupivacaine-fentanyl" anesthesia (40 patients). The following issues have been observed: noninvasive maesurement of systolic, diastolic and mean arterial blood pressure; pulse frequency and Sat O_2; hypotension duration and the number of hypotensive measurements during the surgical intervention (1-60 min), the single and the total dose of ephedrine administered before and after giving birth; width and height of the sensor (motor) block. We have registered Apgar values in newborns (in the first and the fifth minute after delivery) along with gas analyses taken from umbilical artery (UA) by determinig acid-base status (pH, BE, PaO_2 $PaCO_2$).

Results. The most intensive reduction of systolic blood pressure, that is, hypotension (>30%) was found in clear spinal anesthesia (SA-gr., p<0.01), while the smallest evident reduction appeared in the group with low bupivacaine dose (SA LD gr.), i.e. mean 117.35 ± 22.12 mm Hg versus 87.38 ± 8.54 (p<0.001); ephedrine doses for hypotension correction were maximum in SA-group (21.08 ± 12.06 versus 4.75 ± 2.5 in SA LD-gr., p<0.05); the average values of blood pressure achieved with low doses (SA LD-gr.) were higher than spinal opioid groups (SA F10 and SA F20-groups) in spite of the stimulation with ephedrine from 19.09 ± 7.8 mg and 16.81 ± 5.6 mg. Also, there were no parturients who developed severe hypotension (SAP between 60-80 mm Hg) in SA LD-group while only 10.5% of parturients had mean hypotension between 80-90 mm Hg versus 44.7% in SA-gr. (p<0.01). Conventional spinal anesthesia (SA-gr.) led to increased risk of fetal acidemia (UApH=7.20 ± 0.06), while spinal anesthesia with "low bupivacaine doses" reduced the risk of fetal acidemia (pH=7.27 ± 0.05). General anesthesia (OA-gr.) had stable hemodynamics and satisfying acido-base ambient (UApH=7.24 ± 0.03), however the newborns were more depressed (Apgar <7 and pH>7.1) compared to those born with spinal anesthesia (27.5% versus 8.75%, p<0.01) and they had lower mean Apgar score (6.8 ± 2.5 against 7.8 ± 2.7 in SA-gr. and 8.3 ± 1.8 in SA LD-gr., p<0.01).

Conclusion. Conventional spinal anesthesia for Cesarean section which means (classical) dosage of 13.5 mg bupivacaine results in unacceptable degree of hypotension and possible risk for fetal acidemia in newborns. Modification from conventional into spinal anesthesia with "low doses" leads to hemodynamics with minimal variations of the blood pressure, minimal ephedrine demands and optimal pH values in newborn infants. General anesthesia leads to stable hemodynamics and satisfying acido-base ambient (pH) of newborn infants, however, it leads to more depressed newborns in comparison to those born with spinal anesthesia. Spinal application of "low bupivacaine doses" that includes from 6 to 8 mg plus 20 μgr fentanyl is an optimal choice, which does not threatens hemodynamics in parturients and has better short-term effects in newborns than general or other types of spinal anesthesia.

Keywords: *Cesarean section; anaesthesia; spinal; effects; parturients; newborn infants.*

Defended: April 11, 2011.

Mentor: Prof. Dr. Jordan Nojkov.

Biljana Ilievska-Poposka. Prognostic value of immunohistochemical expression of HER-2/neu, p53,

Bcl-2 and Ki-67 in patients with lung cancer [PhD Thesis]. *Skopje, Republic of Macedonia: Institute for Lung Diseases and Tuberculosis, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Background. Despite major advances in cancer treatment over the past two decades, prognosis of patients with lung cancer (LC) has improved only minimally, and the most significant prognostic factor both in patients with non-small cell lung cancer (NSCLC) and those with small-cell lung cancer (SCLC), the differences in survival within staging groups require new information about additional factors influencing the outcome, independent of the stage. The advance in molecular biology has provided clues to the pathogenesis of cancer and has shown the involvement of gene mutations (oncogene activation and tumor-suppressor gene inactivation) as well as the key role of apoptosis in the development of carcinomas. While the importance of gene mutations in the pathogenesis of lung cancer is clear, it is still not clear whether gene mutations affect individual patient's chances for survival, which requires further investigations.

Aim of the study. To evaluate the expression of protein products of four molecular markers: HER-2/neu gene, p53 gene, Bcl-2 gene and Ki-67 proliferative index in patients with different histological types of lung carcinoma (LC) and to assess their clinicopathological and prognostic significance.

Materials and Methods. A total of 127 patients with different histological types of LC were included in the study. They were diagnosed and followed-up between April 2003 and June 2008. HER-2/neu, p53, anti Bcl-2 and anti Ki-67 monoclonal antibodies. All patients were followed-up for 1 to 48 months. Survival curves time, the log rank test was used, and in the multivariate analysis, Cox's proportional hazard model.

Results. The overall expression of HER-2/neu, p53, Bcl-2 and Ki-67 in 127 patients with LC was 28.3%, 47.2%, 41.7% and 81.9%, respectively. These results showed that, with some exceptions, there were no correlations between the expression of investigated molecular markers and clinicopathological features in the examined patients. HER-2/neu expression was present in 36.78% of NSCLC patients, and only in 10% of patients with SCLC (p=0.004). Among NSCLC, HER-2/neu expression was seen more frequently (60%) in the patients with adenocarcinoma (p=0.031). Kaplan-Meier's survival estimates showed a significantly shorter survival for the patients with positive HER-2/neu expression in comparison with those with negative expression (Log Rank=8.228, p=0.004). We found no significant statistical differences of p53 between the patients with NSCLC, p53 expression was more frequent in the patients with squamous carcinoma (p=0.05). p53 positive expression in the patients with NSCLC was associated with a significantly shorter survival (Log Rank=6.534, p=0.011). Multivariate analysis showed that positive HER-2/neu (HR=1.686, p=0.032) and p53 expression (HR=1.549, p=0.049) were independent and statistically significant prognostic factors for worse prognosis, i.e. for shorter survival. HER-2/neu and p53 gene expression were not associated with statistically significant differences in suvival of the SCLC patients. Bcl-2 gene proved to be a highly selective marker with positive expression in 65% of patients with SCLC (p=0.000). Bcl-2 expression was in correlation with the stage of the disease (p=0.04), the time of occurance of metastasis (p=0.033) and recurrence of the disease (p=0.0001) in the SCLC patients. Bcl-2 expression was associated with a significantly shorter survival of the SCLC patients and it is a highly significant, independent prognostic factor for survival (HR=6.029, p=0.000). The results of this study revealed no statistically significant differences of Ki-67 expression in patients with NSCLC and SCLC. Ki-67 expression had no prognostic value in the examined patients.

Conclusion. Defining the gene alterations in patients with LC is of huge importance since it can be used as important prognostic information, i.e. it enables selection of patients who have these alterations and who have need of an adjuvant therapy and might have benefit from it. The results obtained from these kinds of investigations are an indicator for changing the current standardized therapeutic protocols and enable intoducing of individual tretment for each patient separately. The latest scientific achievments provide target therapy based on monoclonal antibodies which have effect on gene mutations. In fact, this is a new therapeutic approach, which promises longer survival rate as well as better quality of life for patients with lung carcinoma.

Keywords: *HER-2/neu; p53; Bcl-2; Ki-67 proliferative index; non-small cell lung cancer; small-cell lung cancer; immunohistochemical analysis; survival; prognostic value.*

Defended: April 12, 2011.

Mentor: Prof. Dr. Tome Stefanovski.

Branko Blazhevski. Influence of type of lumbar disc herniation and surgical tretament on predictive factors of functional outcome [PhD Thesis]. ***Skopje, Republic of Macedonia: University Clinic of Neurosurgery, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.*** Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

The aim of this study was to analyze the influence of the following factors on the functional outcome in patients operated for lumbar disc herniation: type of disc herniation, type of surgery, patient preoperative expectations, preoperative pain intensity, duration of sciatica prior to surgery and grade of disc degeneration. In addition, we wanted to define which of these factors have *predictive importance* in pursuing the selection of patients who would undergo surgical treatment.

This prospective study included 92 consecutive patients, who were examined and operated on for lumbar disc herniation at the University Clinic of Neurosurgery in Skopje in the period form 1998 to 2009.

Data for assessment of the functional outcome were recieved either during regular outpatient visits or telephone communication *12 months after surgery* when the examiner completed a specially-designed questionnaire.

Evaluation of the functional outcome was done by assessment of: ODI Scoring, activities of daily living, patient satisfaction, intensity of postoperative pain, withdrawal of sensibility impairment, withdrawal of motor deficits and recurrent disc herniation.

Based on the results obtained, we can draw the following conclusions:

- Lumbar discectomy is a safe and efficient method for treatment of lumbar disc herniation;

- Type of the lumbar disc herniation is a strong predictive factor for the functional outcome;

- Type of the surgery has no significant influence on the surgical outcome;

- Intensity of the preoperative pain is the strongest predictive factor for the functional outcome

- Duration of sciatica is a strong predictive factor for the functional outcome;

- Patient preoperative expectation of the surgical result is a predictive factor for the functional outcome;

- Patient satisfaction from the surgery has to be examined with the same seriousness as the objective methods for examination of the surgical results;

- Grade of the disc herniation is a predictive factor for the functional outcome;

- Indication for surgery is set on the basis of comparison and correlation between clinical signs and symptoms and diagnostic methods of examination.

Keywords: *lumbar disc herniation; sciatica; discectomy.*

Defended: June 07, 2011.

Mentor: Prof. Dr. Jovica Ugrinovski.

Brankica B. Mladenovik. The influence of psychosocial determinants upon adolescents' sexual conduct in the Republic of Macedonia (quantitative-qualitative study) [PhD Thesis]. ***Skopje, Republic of Macedonia: Department of social medicine, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.*** Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

The ***main objective*** of the study was to investigate the influence of psychosocial determinants upon adolescents' sexual conduct in Macedonia, and to identify risk and protective factors in order to obtain data for designing public health interventions aimed at their sexual and reproductive health.

Study context: The study consists of a quantitative and a qualitative part.

The main objective of the ***quantitative part*** of the study was to determine the influence of gender, place of living, family affluence, family culture and peer culture (as independent explanatory variables) upon the main components of sexual conduct-prevalence of sexual activity, age of sexual initiation, number of sexual partners and use of contraception during the first and recent sexual intercourse (as dependent variables).

The main objective of the ***qualitative part*** of the study was to obtain additional data about the influence of traditional cultural norms, media and gender roles upon adolescent sexual conduct.

Material and methods: Data was obtained through cross-sectional survey conducted among 1326 high-school students between February and May, 2009. Standardized paper-and-pencil self-administered

questionnaire prepared for the WHO "Health Behaviour in School-aged Children Study" was used for the quantitative part, while focus group discussion guide was used for the qualitative part of the study. The study population included students from 1st and 3rd year from 10 different high school in 8 different cities in 8 regions in Macedonia; 1226 students in the quantitative and 100 students in the qualitative part of the study.

Results

***Main results of the quantitative part of the study*:** High proportion of students (31.1%) started with sexual activity in high school. There was a significant difference of reported sexual activity between boys and girls: when entering the year 3 of study, 76.4% of the boys and 23.6% of the girls had already started with sexual activity. The median age of onset of sexual activity is 14.9 years for boys and 15.5 years for girls. The difference between the two was also demonstrated in the number of sexual parners and in the use of contraception. The place of living (rural-urban) has no influence on sexual conduct. The father's level of education and his employment status have no influence on sexual conduct, while the mother's level of education is an important protective factor for contraception use. The level of family affluence has significant influence on the age of sexual initiation and on the number of sexual parners, and no influence on the prevalence of sexually active adolescents and use of contraception. Adolescents whose families are higher on the family affluence scale (FAS) started with sexual activity earlier and have more sexual partners. Family stucture has proved to be a strong protective factor; children from two-parent families started later with sexual activity and have smaller number of different sexual partners. Although adolescents find it more difficult to talk to their fathers, communication with the father is a strong protective factor and exerts influence on the prevalence of sexual activity and the use of contraception, while those who communicate with their mothers start later with sexual activity. Mother's and father's monitoring are strong protective factors, especially in relation to the prevalence of sexual activity. The study showed that good emotional bonding with both parents is a strong protective factor; bonding with the mother has proved to be significant in relation to the prevalence of sexual activity, while bonding with the father is a protective factor in relation to all components of sexual activity. Frequency of day and evening times spent with peers proved to be a protective factor in relation to the age of onset of sexual activity and the use of contraception, a risk factor in relation to the prevalence of sexual activity, and with no influence on the number of partners. Type of activities with friends has no influence on the prevalence of sexual activity and the use of contraception, while 'face to face' conversation is a protective factor in relation to the age of onset of sexual activity and the use of contraception. Chatting through the Internet proved to be a risk factor as these respondents tend to change sexual partners, while 'hanging around with friends' and social competence have no influence whatsoever on any of the components of sexual conduct. Logistic regression analysis confirmed the individual characteristics of participants like age and gender as predictive risk factors, while communication with the mother is the strongest predictive protective factor.

Main results of the qualitative part of the study: The study has shown elements of risky sexual behaviour: early onset of sexual activity, high proportion of sexually active students, high numbers of different sexual partners, unplanned sexual activity, insufficient knowledge and use of modern methods of contracepton, and insufficient negotiation skills for introducing contraception. Peers, gender stereotypes and media have strong influence on sexual conduct, while the influence of traditional cultural norms has been weakening. Despite the strong influence of gender roles on many components of sexual conduct, its influence has become less important; earlier onset of sexual activity among girls, higher proportion of sexually active girls, premarital sexual activity of girls, and the attitude that both partners are equally responsible for contraception use, are widely accepted by both-boys and girls. Media stimulate the early sexual initiation and create atmosphere that sexual activity is desirable and approved, as well as important for social adjustment. Parents were designated as the most important source of information and support.

Conclusion: The study results confirmed the importance of family support, especially parental monitoring and communication within the family, which strengthen the adolescent resilience and enable them to overcome the negative effects of risk exposure. Peer influence has shown to be a protective factor, which implies that this influence is more complex than our stereotype of the negative influences by friends. Study results imply that there is a process of "social equalization" in adolescent behaviour when the influence of some social determinants is diminishing, while other social determinants like individual factors, family support and peer influence are prevailing. Therefore, it is of utmost importance to better understand the determinants which influence the sexual conduct of adolescents in order to overcome the existing

stereotypes, to design appropriate public health interventions and to assess the success thereof.

Keywords: not available.

Defended: June 08, 2011.

Mentor: Prof. Dr. Mome Spasovski.

Jasmina Pluncevik Gligoroska. Neurophysiological and psycological estimation of cognitive functions in participants with different level of physical activity [PhD Thesis]. *Skopje, Republic of Macedonia: Department of ME Physiology and Antropology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

In this Thesis were estimated the cognitive functions as attention, concentration, psychomotor speed, visuomotor tracking, working memory, learning and cognitive adaptation during the electroexpectogram's paradigm in healthy young population regarding their level of physical activity. The enrolled population example was consisted of 90 participants, age range from 16 to 35 year, mean age 21.2 years old. Regarding the data based on self-reported physical history activity, participants were divided into three groups balanced for age, gender and educational level: group of sedentary individuals (a low level of PA); a group of participants involved in leisure-time physical activities (a moderate level of PA); a group of athletes (a high level of PA).

Neurophysiological testing was made with EXG (electroexpectogram) paradigm which is dynamic experimental environment during which the electrophysiological indicators of level of expectation were measured. The examination of the attention and learning is based on the concept of adaptation of the subjects to the experimental conditions. Electrophysiological parameters of the EXG paradigm such as amplitude of CNV potential and duration of EXG oscillations were analyzed. The results obtained in EXG testing showed that subjects involved in long term physical activity (moderate and high level) had a better capability for cognitive adaptation then sedentary subjects. These results support a hypothesis that physical activity has a beneficial impact on cognitive functions in young healthy adults.

Psychological estimation of cognitive functions was made with: TMT (Trial Making Test); Digit Span Test; and RAVLT (Ray's auditory verbal learning test). The obtained cognitive parameters for short term memory, working memory, psychomotor speed and verbal learning showed a statistically significant trend of increasingly higher mean scores of cognitive parameters in the participants with a higher level of long-term physical activity. These results are contributing to the growing body of literature that highlighted that the physical activity participation may influence cognitive functioning in young adults.

Our data suggest that regular physical activity in adolescence and young adult age may have beneficial influence on certain aspects of cognitive functioning. The active style of life should be promoted between young population because of its multifactorial positive impact on somatic and mental health, in the present and future time in their lifespan.

Keywords: *physical activity; cognition; attention; memory; learning CNV potential; EXG - elektroexpectogram.*

Defended: June 09, 2011.

Mentor: Prof. Dr. Liljana Bozinovska.

Arben Taravari. Clinical and genetic findings in patients with idiopathic Parkinson's disease [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Neurology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Parkinson's disease is a neurodegenerative disease which predominantly appears within the period of 20 to 60 years of age, and which, at the end, brings to patients' disability to perform their everyday activities.

Essential change in Parkinson's disease is the impaired dopaminergic neurotransmission of basal ganglia. Idiopathic Parkinson's disease (IPD) is the most frequent type of parkinsonism, being present in about 70% of the patients with parkinsonism.

In recent years, there is no doubt, that genetic factor has an important role in the etio-pathogenesis of the idiopathic form of Parkinson's disease.

This study comprised a total of 32 subjects with clinically verified diagnosis for idiopathic Parkinson's disease, 18 men and 14 women (with mean age of 52.7 years). Control group consisted of 31 randomly selected, literally healthy persons, at similar age, with similar gender representation without clinical and anamnestic data for parkinsonism and similar clinic entities.

This study has been prospective, clinically genetic one, which has been lasting for whole 2 years.

The clinical part of this study was made at the University Clinic of Neurology in Skopje, Unit for extrapyramidal diseases. The laboratory-genetic part of the study was elaborated at the Laboratory for molecular biology at the Institute for Biology, the Faculty of Sciences, University "Ss Cyril and Methodius".

All 32 investigated persons were with verified IPD. At the same time, vein blood samples were also analysed of 2 volunteers from the families of these patients. By molescular-genetic analyses of the patient and his family members genetic researches were made (presence or absence of mutations and expressions of the investigated gene for protein á-synuclein).

The persons investigated had idiopathic Parkinson's disease (IPD), in whom IPD was verified by means of: detailed anamnesis, detailed clinical neurologic examination, strictly keeping to Brain Bank Criteria, and by means of neurophysiologic investigations made, such as: electroencephalography, electromyography, visual evoced potentials; neuroimaging investigations: computer tomography and magnetic resonance imaging of the brain; Doppler of extracranial and neuropsychologic investigations.

Objective neurologic result of all 32 investigated subjects (100%) showed presence of rigor, tremor and bradykinesia.

Minimal symptoms of IPD after UPDRS were present in 34.4% of the examinees, there were 40.6% with slight signs, while equal number of the examinees 4 (12.5%) had pronounce and very expressed symptoms of Parkinson's disease after UPDRS.

In my study, investigated mutations G88C in exone 3 and G209A in exone 4 from SNCA gene were not detected in all 32 examinees with IPD. Multiplication of the number of SNCA gene copies were not found in any of these examinees.

It could be concluded with a great statistical significance that deletion 4977 in mitochondrial genome has been registered more frequently in the group of patients with IPD. The difference tested between the investigated and control group, concerning the present or absent deletion and heteroplasmia, has been highly statistically significant (p=0.001).

Results from therapeutic effects in optimal doses of levodopa in the treatment of IPD patients were: weak reaction of the optimally administered therapy 12.5% of the examinees 20 (62.5%) manifestered very good therapeutic effect of the optimal dose of the substitution-levodopa therapy.

Relationship between the examinees' age and response to the optimal dose of the therapy with levodopa, by using the Spearman's coefficient of correlation has been analyzed. Its value of p=0.39 speaks that there is a positive i.e. a direct correlation between these two correlations.

Keywords: not available.

Defended: June 13, 2011.

Mentor: Prof. Dr. Vera Petrova.

Vesna Kotevska. Resistance of *Streptococcus pneumoniae* strains to penicilin with respondents of children's age: genes of resistance and serogroups [PhD Thesis]. *Skopje, Republic of Macedonia: Institute for Microbiology and Parasitology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Mutations of genes *pbp2x/pbp2b/pbp2a/pbp1b/pbp1a/pbp3* of PBP (penicillin-binding proteins) are the cause for apperance of penicillin-resistant pneumococci (PRP). The aims of this study were to determine the presence of PRP in the nasopharyngeal region with healthy children and children having infections of the respiratory tract and the role of socio-demographic factors (age, antibiotic treatment, previous infections, number of family members) regarding their onset. For the purpose of PRP detection we used oxacillin screening test and agar dilution test (MIC: sensitive (S) >0.06 µg/ml, moderately sensitive (MS) of 0.12-1 µg/ml and resistant (R)< 2 µg/ml). PRP apperance significant genes were detected by a polymerase chain reaction (PCR) and then they correlated with the phenotype resistance of pneumococci to penicillin. Also, we proved the most frequant vaccinal groups/types of pneumococci present in the 23-valent polysaccharide vaccine and non-vaccinal groups/types and their resistance to penicillin. Resistance of *S. pneumoniae* types was examined to: beta-lactam, macrolides, quinolones, tetracycline, co-trimoxazole, lincosamides. A total of 145 pneumococci (27 isolates of nasal pneumococci from 95 healthy children, group I) and (118 isolates of pneumococci from children having infections: 76 nasal and 42 from tracheal aspirates, group II). Pneumococcal carriage with healthy children

was 28.4%. *S. pneumoniae* most frequently was found with children coming from families having more than 4 members (92.3%), then with children aged 1-3 years (44.1%), with children having more than two infections (71.4%) and children having used more than two antibiotics (66.6%) over the last three months.

According to the agar dilution method (MIC), PRP were 14.8%/22.0% (group I/II). PCR detected 29.5% mutations of genes (group I), and 36.4% in group II. There were 75.0%/25.0% single/combined mutations in group I, while 34.8%/65.1% were in group II. Mutation of *pbp2x* gene was the most frequent with both groups (I/II): 62.5%/23.4%. In group I and II pneumococci combination of genes *pbp2x/pbp2b/pbp1a* was 25.0%/30.0%. The combination *pbp2x/pbp2b* was proved only in I group of pneumococci having 35.0% presence. As to the origin of pneumococci (tracheal aspirates/nose) and sensitivity to penicillin, there was no statistically significant difference shown between P (22.3%/21.4%), MS (42.1%/42.8%) and S (35.5%/35.7%). Serogroup with polyvalent sera (P; Q; R; S; T) revealed that 63.5% of pneumococci were vaccinal groups/types (23-valent polysaccharide vaccine) and 36.4% were non-vaccinal. With Q serum were typified 41.3% of pneumococci, with P 30.6%, with R 14.6%, with S 9.3% and with T 4.0%. All 26 P of pneumococci belonged to 23 valent polysaccharide vaccine. Non-vaccine groups/types didn't show resistance to penicillin (36 S / 7 MS). The examination of pneumococcal resistance (disc diffusion method) to some groups of antibiotics in group I/II was: tetracyclines 66.6%/64.4%, cotrimoxazole 51.8%/60.1%, cefixime 48.1%/47.4%, clindamicin 29.6%/48.3%, erythromycin 29.6%/37.2%, azithromycin/clarithromycin 25.9%/ 34.7%, penicillin 29.6%/38.1%. Pneumococci of group I showed no resistance to: ceftriaxone/cefotaxime, ciprofloxacin, levofloxacin and vancomycin, and of the group II to levofloxacin and vancomycin. Age, close contact between the family members, respiratory infections during the last 3 months and number of antibiotics are relevant regarding the carrige of pneumococci. PRP percentage with healthy and children having infections of the respiratory tract was 14.8%/ 22.0%. Mutations of genes were found with all pneumococci (P/ MS/MS). Pneumococci showed no statistically significant difference in relation to the resistance of pneumococci (group I/II). Children aged 1-3 years should be the target group where precipitation and administration of antibiotics will be reduced, there will be an action regarding their mutual transmission of pneumococci, vaccination programs will be implemented (PCV7; 13; 23 polysaccharide vaccine), and pneumococcal disorders should be treated in accordance with the clinical manifestations and following a previous examination of the pneumococcal sensitivity to antibiotics.

Keywords: *Streptococcus pneumoniae; resistence; genes; serogroups/serotypes.*

Defended: June 14, 2011.

Mentor: Prof. Dr. Milena Petrovska.

Biljana Gerasimovska Kitanovska. Integrated prognostic model, prognostic score and prediction of individual risk for preeclampsia [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Nephrology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Intoduction. Preeclampsia is defined as a pregnancy-specific condition, characterized by placental dysfunction, systemic inflammatory response and andothelial activation and coagulation on maternal side and is one of the categories of hypertensive disorders of pregnancy. There are numerous definitions and subclasifications which entail different conditions and severity of the conditions through clinical and research perspectives.

The aim of this study is to provide prediction of preeclampsia through prospective longitudinal follow-up of patients with hypertensive disorders in pregnancy and provide prediction of preeclampsia through an integrated prognostic model and calculation of individual risk of preeclampsia.

Material and methods. A total of 120 gravid and 30 non-gravid patients were comprised in our study.

A total of 120 gravid patients, reffered to the University Department of Nephrology in Skopje for preexisting or newly discovered hypertension in pregnancy were followed in the period 2008-2010. Patients that were included during pregnancy were followed in several gestation weeks from the moment they were reffered to the Department (08, 18, 23, 28, 32, 36 gw and 2-6 months after delivery), they were later on systemized in trimesters. At the first control, anamnestic data on previous medical conditions, family history, smoking, previous pregnancies were obtained, while during following controls, data on values of blood pressure and subjective symptomes were recorded, including data on use of antihypertensives and renal function. At every control, body height, body weight were measured, and

24 hour blood pressure monitoring and D-dimers and hemostasis were made. In 32nd gestation week, an analysis of the resistance index of the Doppler of umbilical artery was made at the Department of Gynecology. Biochemical data included a hematology pannel, metabolic pannel, transaminases, electrolyte pannel, urea, creatinine, uric acid. Outcome was defined as proposed by NHBPEP in 5 subgroups: normotensive, preexisting hypertension, gestational hypertension, preeclampsia and superimposed preeclampsia. In the final analysis the groups were dichotomized into a group with and a group without preeclampsia. Subclasification was made when possible into groups with early/late preeclampsia and mild/severe preeclampsia. Laboratory results and 24 hour monitoring of blood pressure were presented as means and standard deviation, and differences between groups were calculated by the use of ANOVA. Categorical variables (risk factors) are presented as numbers and percents, and the difference between them was calculated by a chi-square. D-dimers, GFR and blood pressure values were analysed by trimesters and ROC curves were made in order to determine the cut-off values predictive of preeclampsia. The integrated prognostic model was processed by the method of determination of apriori and aposteriori risk and the principle of calculation of individual risk. Statistical analyses were made by the use of the SPSS 13.0 software.

Results. From the total number of 148 followed patients, 28 were excluded because they came only once and no data were obtained on the outcome of the pregnancy. The examined population, after delivery was divided into 5 groups and consisted mainly of gravidas with preexisting hypertension (48 gravidas), and preeclampsia -27 gravidas, while superimposed preeclampsia SP was registered in 24 gravidas, gestational hypertension in 11, and 10 patients were normotensive. At the first control, the group with superimposed preeclampsia was the oldest-33.2 ± 4.7 years, had the highest BMI- 31.6 ± 5.04 and highest values at 24 hour blood pressure monitoring (134 ± 13.4 mmHg for daily systolic, 115.9 ± 11.6 for night systolic, 88.7 ± 11.07 for daily diastolic and 72.2 ±11.1 for night diastolic blood pressure. With regards to the gestational week, delivery occurred very early in the patients with preeclampsia, and the newborns had small gestational weight. The groups with newly discovered and superimposed preeclampsia, when merged, had seven-fold risk of delivery with cesarean section -OR=7 (1.07-45), 4-fold risk of delivery before 37 gw - OR=4 (0.69-23), and the risk of low birthweight was10-fold - OR=10 (0.89-119). When assesing the apriori risk of preeclampsia, according to the risk factors estimated in the first trimester, out of those that were significant at the univariant analysis by the use of multivariant logistic regression, the following were determined as predictors of preeclampsia-age above 35 years and use of dual antihypertensive therapy (p=0.09 and p=0.032 respectively). In these patients, the risk of preeclampsia is increased by 3.95%. Predictive biochemical parameters for preeclampsia in the first, second and third trimester according to the multivariable logistic regression were identified. Cutoff values for biophysical parameters -D-dimers, GFR and 24 hour blood pressure monitoring were defined for the first, second and third trimester. All parameters obtained from the 24 hour blood pressure monitoring were associated with low birthweight of the fetus. The integrated prognostic model for each trimester was calculated and a-priori risk for the first trimester defined the final risk and the individual risk for the patient.

The group of 30 non-pregnant women, consulting at the Department 2-28 years after delivery, had one control and 71% of patients had hypertension, 32% had proteinuria and 22.6% had decreased renal function. Women with previous preeclampsia had 28.5-fold risk of developing decreased renal function in the period of 1-5 years after delivery (OR=28.5, 95%, CI = 2.7-309).

Conclusion. The integrated prognostic model offers possibilities for an a-priori assessment of risk in patients with hypertensive disorders in pregnancy as well as calculation of an individual risk of every patient. The endothelial dysfunction does not end with the delivery and is a cause for hypertension and decreased renal function in later life.

Keywords: not available.

Defended: June 20, 2011.

Mentor: Prof. Dr. Katica Zafirovska.

Roza Krsteska. Risk factors for late-life depression [PhD Thesis]. ***Skopje, Republic of Macedonia: Psychiatric Hospital "Skopje", Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.*** Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Introduction: The aims of this research are the risk factors for late life depression, which are in significant association with the onset and development of depression in elderly persons.

The aims of the research was to analyze the difference between some demographic, psychological,

enviromental and physical factors in the older adults with or without depressive disorder.

Material and Methods: We studied 120 subjects, divided in two groups:

-60 patients diagnosed by ICD 10 with depressive disorder (a depressive episode or recurrent depressive disorder), treated at the Department for Geriatric Psychiatry in the Psychiatric Hospital "Skopje", represented the experimental group.

-The control group is consisted of 60 persons without depressive disorder.

The following instruments for investigation were used: standardized clinical interview, the list of possible risk factors in the persons with risk for depression, the Geriatric Depression Scale, Hamilton Scale for Anxiety, Scaling of Life Events, the COOP for adult primary care practice, SASS-Social Adaptation Self evaluation Scale and Non standardizied sociological-demographic questionnare.

Results: The results were statistically analysed with the following statistical methods: percents, arithmetic mean and standard deviation, independent samples t-test, Mann-Whitney U test, Pearson's coefficient.

The results indicated that female gender, age, living in the urban area and low level of education were demographic factors of risk for late-life depression.

Our results confirmed that severe financial difficulties in childhood were risk factors for depression in the elderly. Subjects who had estimated their mother or father with negative personality were at significantly greater risks for late-life depression development. Conflictual family relations, the father's alcocholism in childhood were in association with depression in the elderly.

Lack of retirement income significantly increases the risk of late life depression.

The state of housewife in life regarding any other profession brings higher risk for development of late-life depression.

Living in a geriatric institution is a risk factor for late-life depression.

Our investigation has proved the association of physical, mental and social inactivities with late-life depression.

Our findings proved the role of some characteristics of the person, such as low self-esteem, big depedence on other people and pessimisam, which are psychological factors of risk for appearence of late-life depression. The existence of characteristics of dependent structure of personality and avoidant personality disorder were common findings in the examinees of the experimental group.

We confirmed that poor marital relation was a risk factor for late-life depression, and it also could be an important predictor of depression. The results showed that conflictual family relations, the feeling of not being wanted by the family, lack of family support and help, were more common in patients in the experimental group against examinees in the control group.

There was a significant association between the appearance of depression in older adults and a family history for depressive disorders.

The chronic medical illnesses in older adults represent risk factors for late-life depression and may be predictors for occurence and further development of late-life depression.

Older adults who have difficulties to adapt to aging are with higher risk for depression development.

The quality of patient-physician communication in patients with late-life depression was poorer against older sdults without depressive disorder.

Our investigation proved the importance of stressful life events like psychological risk factors in the appearance of late-life depression. The cumulative burden with life events was in association with depression in older adults.

71.67% of examinees had prior depressive episodes, which proved that prior depressive episodes were risk factors for late-life depression.

Prior to the occurence of the first depressive episode in life, all examinees had experienced some stressful life event, which proves that psycological factors have a big role in the etiology of depression in older adults. The influence of life stressful events in older age is of huge importance not only for occurance, but also for triggering provocation and streghtening late-life depression.

More than 20% of examinees had prior suicidal attempts, which represent a risk factor for depression and suicide in older adults. A low risk for suicide was present in 33.33% of examinees, a moderate risk in 5% and a high risk in 16.66% of examinees. This shows that older adults with late-life depression should be carefully

monitored and evaluated for the risk of suicide.

25% of the patients with depressive disorder were not treated aldough they had the illness for many years. 73% of the patients who did not have remission since the first episode of depression, actually did not receive any treatment (were untreated). This fact indicates that detection of depression is insufficient and older adults do not receive adequate therapy.

Disability was more frequent in patients with late-life depression than in the examinees of the control group.

Family members of the patients significantly more often experience stress because of the patients' illness than family members of the health examinees.

Conclusion: Our research proved the relevance of some demographic, psychological, social and physical risk factors in older age. The knowledge of risk factors could help in identification of subjects with greater risk for depression and give opportunity for designing a strategy for prevention of onset of depressive symptoms in late life, earlier detection and an optimized well-timed treatment.

Keywords: *late-life depression; risk factors; older adults; demographic; psychological; enviromental; physical factors; family relationship; suicide.*

Defended: June 28, 2011.

Mentor: Prof. Dr. Vesna Pejoska Gerazova.

Risto Colancevski. Evaluation of the value of particular surgical procedures in treatment of fibrino-purulent stage of pleural empyema [PhD Thesis]. *Skopje, Republic of Macedonia: Clinic for Thoracic and Vascular Surgery, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Introduction. The choice of a method of a surgical treatment of pleural empyema depends on the stage of development of the disease. The success of the different surgical methods in the treatment of the fibrino-purulent pleural empyema speaks that there are many differences between clinical and pleural findings at patients, although, according to the classification, belonging to the same stage of disease.

The **aim** of this stady is to show, analyze and to interpret the pre and postoperative differences of the general clinical and pleural findings at the patients with fibrino-purulent stage of pleural empyema at each and every single used clinical method. Based upon the successfulness of the surgical methods on the right time for right reason in surgical treatment of the fibrino-purulent stage of pleural empyema.

Methods. This dissertation represents a scrotal study, where the patients with fibrino-purulent stage of pleural empyema were include out of the subpopulation of all patients surgically treated for pleural empyema. 80 adult patients male and female were divided in four groups of 20 patients according to the successfulness of the type of the operation used in their surgical treatment and according to the algorithm. Group 1 with pleural drainage, group 2 with pleural drainage and intrapleural usage of Streptocinase, group 3 Video assisted thoracoscopical decortications of the biological, morphological and biochemical finding of the pleura and the pleural space were performed pre and postoperatively. The function of the lungs were performed, pre and postoperatively after 3 and 6 months. The kind and the way of performing the surgical methods and also the inclusive and exclusive factors of patient's selection are described.

Results. Statistically significant differences of mean values of the examined parameters are established between the groups preoperatively and among the groups pre and postoperatively. The linear multiple regression analysis of every single preoperative examined parameter and it's relation to variable group are shown. Statistically significant preoperatively examined variables with their Y values in relation with variable Group are also shown. The equation of the linear multiple regression analysis of influence of the all preoperative examined variables on variable group is established. The results are numerically and graphically shown.

Conclusion. There are, pre and post operational, significant differences in clinical picture, morphological, biological and biochemical characteristics of the pleura and the pleural space among patients surgically treated in fibrino-purulent stage of pleural empyema with: thoracic drainage, thoracic drainage with intrapleural use of streptokinase, VATS and opened decortications. There is a correlation of pre and post operational values of the clinical picture, morphological, biological and biochemical characteristics of the pleural effusions for every single operation in surgical treatment of fibrino-purulent stage of pleural empyema. Adequate indication for optimal surgical treatment of fibrino-purulent stage of parapneumonic pleural empyema can be established based on pre operational values of the clinical picture, morphological, biological and biochemical characteristics

of the pleural space.

Keywords: *Pleural empyema; VATS decortication; open decortication; thoracic drainage.*

Defended: June 29, 2011.

Mentor: Prof. Dr. Goran Kondov.

Izabela Filov. Assessment of the risk of violence between individuals with mental disorders [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Psychiatry, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Introduction. The epidemiological stydies conducted in various regions through the world point out of increase risk of violence between individuals with mental disorders. Violence behavior occurs in certain social system that involves a whole person with certain history of life, with certain state of health or disease and interaction with other social circumastances. There are different methods for risk assessment, but basically two wide categories of methods determine assessment of the risk: clinical and statistical. The main purpose of the investigation is by using the both methods to determine risk factors of psychopathological and social nature as well as individual traits that determine violent behavior.

Material and methods. The investigation has been conducted in Psychiatric hospitals in Macedonia. The experimental group - perpetrators of criminal act (PCA) encompasses 89 patients, admitted in Psychiatric hospitals in Macedonia as forensic patients. These patients have commited criminal act. According to the forensic expertise they have had diagnose of psychiatric disorders (ICD 10). The investigation was conducted in two control groups - control group-without violence (*CG WV*) patient with mental disorders who didn't commited criminal act and didn't expressed violent behavior 60 patients that encompasses 60 patients. Other control group encompasses 60 patients and they were involuntarily addmited in Psychiatric hospital (Contoril group-involuntarily hospitalized CG IH). Methodologically in the investigation is used the following instruments: *Leading interwiev for sociodemografic characteristics, Violence Risk Assessment Guide (VRAG), Brief psychiatric rating scale (BPRS), Psychopathy chleclist revised Hare (PCL-R Hare), HCR-20*.

Results and conclusions. Psychiatric disorder doesn't have predictive value per se, but assossiated with other factors as co morbidity with antisocial personality disorder, alcohol abuse, violent behavior during developmental period of life and treatment's problem is considerable predictive base for prevention and managing with further violence between individuals with mental disorders.

Keywords: *mental disorder; risk of violence; prediction; risk managament.*

Defended: November 07, 2011.

Mentor: Prof. Dr. Marija Raleva.

Zlatko Jakovski. Application of the alalysis of the autosome and Y-chromosome short tandem repeat's (STR's) in forensic-medicine practice [PhD Thesis]. *Skopje, Republic of Macedonia: Institute of Forensic Medicine, Criminalistics and medical deontology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Not available.

Keywords: not available.

Defended: November 09, 2011.

Mentor: Prof. Dr. Biljana Janevska.

Antigona Hasani. Evaluation of the analgetic effect of midazolam used in preemptive analgesia [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic Center-Prishtina, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* **Maced J Med Sci.**

Introduction: Preemptive analgesia sugests that the application of analgesic in prior to proceeding of noxious stimuli prevent the sensibility of the central nervous system which provokes the pain. The aim of this study was to investigate preemptive analgetic effects of intraperitoneally administrated midazolam in different doses and midazolam with morphine and diclofenac, in rat model.

Material and Methods: After Institutional Ethics Committee approval, 240 male, Sprague Dawley rats, weighing 250-300, were included in the study. The rats are divided in five groups. In group I, midazolam group, midazolam is applied in 0.1, 1.5 and 10 mg/kg ip; group II diclofenac in doses 10 mg/kg ip; group III, morphine 10 mg/kg ip, and in group IV and V, morphine and diclofenac

was added to midazolam. Saline was used as control. The hot plate test, model of acute pail and formalin test, model of inflammatory pain were performed 10 minute after the drug administration. Paw withdrawal in response to thermal stimulation and or paw fliching and shaking in response to sc hind paw formalin injection were measured. Behaviour side effects and motor disturbances were also examined.

Results: In hot plate test and formalin test, midazolam produced significant preemptive analgetic effects with the 50% effective dose (ED50) of 2.82 mg/kg (CI95%=-1.85-5.1 mg) and 1.6 mg/kg (CI95%=-0.81-4.04 mg) in phase I and 1.1 mg/kg (CI95%=0.67-5.03 mg) in phase II. Antinociceptive effects of midazolam enhanced with morphine, in hot plate test and formalin test. ED50 of midazolam with morphine was 0.91 mg/kg (CI95%=-0.51-3.7 mg) in hot plate test and 0.8 mg/kg (CI95%=-0.66-3.07 mg) in phase I and 0.5 mg/kg (CI95%=0.13-4.53 mg) in phase II, in formalin test. Midazolam with diclofenac also exprerssed increased antinociceptive effects, in both tests, The ED50 of midazolam (with diclofenac) 1.0 mg/kg (CI95%=-1.37-5.01 mg) in hot plate test and 0.9 mg/kg (CI95%=-0.87-4.09 mg) in phase I and 0.7 mg/kg (CI95%=0.48-6.63 mg) in phase II, in formalin test.

Conclusion: Systemically administered midazolam had preemptive analgesic effects on acute thermal, and acute inflammatory induced nociception in rats. The antinociceptive potency of midazolam enhanced with morphine and diclofenac.

Keywords: not available.

Defended: November 10, 2011.

Mentor: Prof. Dr. Marija Sholjakova.

Mila Polazarevska. Certain epidemiologic characteristics of the attempts for suicide in Skopje and the possibilities of prevention [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic for Psychiatry, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Attempted suicide and completed suicide are human reactions or responses to the exogenous and endogenous factors that trigger them like any other psychological and psychopathological reaction. Although essentially destructive, both attempted and completed suicides have bio-psycho-social grounds.

Depression, anxiety, aggressivness and impulsivity as psychological factors play a key role in the suicidal behavior.

In psychiatric interpretation of the etiology of suicide the most frequently described disorders are depressive and bipolar affective ones or other psychiatric disorders, but very often suicide is not a consequence of psychiatric disorder alone.

Psychiatric-psychological investigations have to includebroader analysis of extreme attitudes that suicidology is not solely psychiatric observation, but etiological component and treatment have to be taken into consederation.

Sociological, philosophical, religious dimensions, etc. along with the extreme attitudes of suicide as an artistic performance also deserve their different discourse in controbution to the understandidng of the complexity of the motives and methods of self-destruction.

In general, disregarding the research focus, all these dimensions are aimed at reducing the suicide rate and the number of suicide attempts.

Interdisciplinary activity and multidisciplinary team would result in greater efficacy of prevention and treatment of this problem.

This investigation was performed in the period between 1999 and 2009, which was a period of social transition in R. Macedonia and was characterized with turbulent social, political, socio-economic and cultural changes.

The retrospective analysis of the research yielded the following results:

- During the period of 1999-2008, a significantly larger number of suicide attempts were registered among females than among males in the city of Skopje.

- Older males predominated over females.

- Seasonal index in the attempted suicides had the highest values in July and June and the lowest values in November and December.

- The mean monthly index in the attempted suicides was x=14.03 for the period of 1999-2008.

- The biggest increase in the number of attempts was registered in 2007 (compared with 2006) and the increase trend was 68.87%.

- The smallest number of attempted suicides was registered in 2004 (compared to 2003) and in 2006

(compared to 2005), the decrease trend being 23.98%.

- During the period of 1999-2008 attempted suicides showed a decreasing tendency.

- In attempted suicides, women of Christian religion were prevailing over women with Muslim religion. There was no significant difference in the number of attempted suicide among men with different religious affiliation.

- Both men and women predominantly chose intoxication with medications as a method of attempted suicide.

The prospective analysis yielded the following results:

- There were a significantly larger number of attempted suicides among women in the examined group.

- The largest number of attempted suicides was registered in February and the smallest in July.

- With regard to place of birth of the patients with attemted suicides, the predominant place was the city against the village.

- Following attempted suicide the largest number of patients spent one day in a hospital. Former suicidal attempts were registered in 22.5% of the patients.

- Concerning temporary diagnosis of patients with attempted suicide, moderately severe depressive spisode prevailed (F=32.1).

Total score on the Hamilton Rating Scale for Depression varied in the interval 17.71 ± 6.91 points, ± 95.0% confidance int.16.17-19.25, minimal value of 4 points and maximal of 39 points.

Total score on the Hamilton Anxiety Rating Scale varied in the interval 17.49 ± 8.84 points, ± 95.0% confidance int.15.52-19.45, minimal value of 1 point and maximal of 47 points.

Difference between the examined and experimental groups:

Total score on the Hamilton Rating Scale for Depression was significantly higher in patients with attempted suicide (17.71 ± 6.91 points) in comparison with the subjects from the control group (4.51 ± 2.84 points).

Total score on the Hamilton Rating Anxiety Scale was significantly higher in patients with attempted suicide (17.49 ± 8.84 points) in comparison with the subjects from the control group (6.09 ± 4.91 points).

From psychiatric-psychological aspect the prospective study gave evident data about the importance of the role of depressive and anxiety disorders. However, this aspect was not sufficient to comprise entirely the complex human psychology and unpredictable reactions in certain circumstances that would induce the complex process of the suicidal behavior, attempted suicide or suicide.

Guided by the humanistic approach to each and every individual as well as the endeavor of the civilized societies to achieve the same goal, primary, secondary and tertiary prevention of the attempted suicides and suicides is a leading premise, and in general maintenance and enhancement of mental health.

Keywords: not available.

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Mentor: Prof. Dr. Vesna Pejoska Gerazova.

Violeta Anastasovska. Molecular characterization of CYP21A2 mutations in the congenital adrenal hyperplasia (CAH) [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Pediatrics, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Congenital adrenal hyperplasia - CAH is a group of autosomal recessive disorders. Deficiency of 21-hydroxylase is present in 90-95% of all cases with CAH. The discovery of the gene and the mutations, which are responsible for these disorders, enabled the diagnosis at the genetic level and prenatal diagnosis as a possibility for prevention and control of all three clinical form of the disease: salt loosing (SL), SV-simple virilizing (SV) and late onset (LO).

The aim of this study is molecular characterization of CAH in Macedonian patients, as a group of congenital disorders causing mortality in the early neonatal period and morbidity in the childhood.

We have studied 71 patients with 21-hydroxylase deficiency (53 Macedonian patients and 18 patients from R. Serbia) and 109 family members (parents and siblings). The methods use for the molecular characterization included: differential Polymerase Chain Reaction (PCR), ACRS (Amplification Created Restriction Site), restrictional endonuclease digestion, agarose and polyacrilamide gel electrophoresis.

Molecular analysis in the Macedonian patients revealed six CYP21A2 point mutations in 73.6% of the alleles with following distribution: IVS2 (37.7%, P30L (17.9%), Q318X (10.4%), V281L (4.7%), I172N (3.8%) and R356W (1.9%).

In our population of patients with different ethnical origin, IVS2 mutation is the most frequent (100% in Gypses, 57.1% in Albanians and 20.6% in Macedonian patients). Our data support the thesis that the IVS2 (656 nt.) mutation may be a hot spot in different populations all over the world. Among the patients with different clinical presentation of CAH, mutations are present in 87% of the SL, 87.5% SV and 47.2% LO alleles. IVS2 mutation is the most frequent in the SL alleles (71.7%), whereas P30L is the most common in the SV (33%) and LO alleles (30.6%). Among 62.3% of Macedonian patients with completely defined genotype, 52.8% are homozygotes for one mutation and 9.4% are compound heterozygotes. The most common genotype is IVS2/IVS2, detected in the 34% of the patients. Genotype-phenotype correlation was observed in all SL and LO patients and 90% of the SV patients. In 26.4% of the alleles no mutation was detected.

Molecular analysis in the patients from R. Serbia showed CYP21A2 point mutations in 69.4% of the alleles with the following distribution: P30L (30.6%), IVS2 (22.2%), Q318X (11.1%), R356W (5.6%) and I172N (5.6%). Mutations were detected in all of the SL, 80% of SV and 50% of the LO alleles. IVS2 mutation is the most common in the SL alleles (62.5%), whereas P30L is the most common in the SV (40%) and LO (27.8%) alleles. In 66.7% of the Serbian patients complete genotype was revealed, 38.9% were homozygotes for one mutation and 27.8% were compound heterozygotes. The P30L/P30L genotype was the most frequent, detected in the 16.7% of the patients. Genotype-phenotype correlation was observed in all SV, 75% SL and 50% of the LO patients. In 30.6% of the alleles no mutation was detected.

The results of this study support the theory that specific CYP21A2 mutations are involved in the three different clinical forms of CAH with good genotype-phenotype correlation. However, mutations associated with milder form of CAH may also occur in severe classical forms of the disease. Thus, the high prevalence of P30L mutation, mostly associated with NCAH was found in both Macedonian and Serbian patients with classical SV form of the disease. The delineation of the types and frequency of the most common CYP21A2 point mutations showed that there are ethnic specific differences in the mutations distribution. Our genotyping approach, aplicable for routine analysis in the clinical laboratory, allowed accurate and sensitive identification of the most common CYP21A2 point mutations in CAH patients and their relatives and offered reliable information needed for diagnostics, treatment, prognosis and adequate genetic conselling, as a first step to prenatal diagnosis.

Keywords: *Congenital adrenal hyperplasia; 21-hydroxylase deficiency, CYP21A2 gene.*

Defended: December 29, 2011.

Mentor: Prof. Dr. Mirjana Kocova.

Oliver Stankov. Surgical approach in resolving opstructive azoospermia: Evaluation of the macrosurgical technics with clack and compatison with the clasical macrosurgical technics [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Urology, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Not available.

Keywords: Not available.

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Mentor: Akademik Prof. Dr. Zivko Popov.

Katarina Stavrik. Asssociation of the polymorphism of cytokine genes with atopic dermatitis in chlidren [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Pediatrics, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Introduction: AD is a compex disease due to interaction between genes, defective skin barrier and enviromental factors. Knowledge of the dynamic of IgE sensitization and the most common allergens in the population can help us in provideng prevention of our patients. Avoidance of trigger factors can immrove the severity of AD. To date, there have been five genom wide linkage studies performed on AD. Only the 3p24 locus has been truly replicated. 111 published studies reported association of AD and 81 candidate genes from which 13 genes were positively associated in at least one other independent study. Only filagrin gene has been associated with AD in more than 20 studies. Some polymorphisms are associated with some ethnical groups, so that way the data can be generalised.

Aim: Increased prevalence of AD, chronic character and its association with other allergic diseases there is a pressing need for earlier detection, treatment and prevention. Taking in to account the contemporary

scientific knowledge about the role of polymorphism of cytokine genes in the pathogenesis of AD we established the following odjectives:

· Assessment of the severity of AD in children younger than 5 years

· Laboratory characterististics and allergic sensitization in children with AD

· Establishment of the presence and frequency of cytokine gene polymorphism interleukin IL-1 alfa (IL-1α), IL-1 beta (IL-1β), IL-1R receptor (IL-1R), IL-1R antagonist (IL-1RA), gamma-interferon (INFγ), IL-2 (IL-2), IL-4 (IL-4), IL-4 receptor alfa (IL-4Rα), IL-6 (IL-6), IL-10 (IL-10), IL-12B (IL-12-B), TGF beta 1 (TGF-β1) and TNF alfa (TNF-α) in children with AD

· Association of each single cytokine gene polymorphism (susceptible or protective) in children with AD and control group of healthy Macedonian population.

Material and methods: 118 children with AD at age from 6 months to 60 months (mean 24 ± 20 months) who attended the Imunologic outpatient ambulance in University Children Hospital Skopje were evaluated. 60 were male and 58 were female. In the study were involved children with AD according the diagnostic criteria of Hanifin and Rajka, who had increased serum IgE according the age. Each patient was interviewed and standard questioner was fulfil. SKORAD index was used for assessment of the severity of the disease. Inclusion criteria: children aged less than 5 years, SKORAD >15, increased serum IgE according the age, and/or one or more positive IgE specific antibodies to nutritive (egg and milk) or airborne allergens (home dust mite, grass and tree pollens, animal dandruff and mould). Detection of allergen specific IgE were measured with the CAP system fluorescent enzyme immunoassay. Specific IgE >=0.35 kUA/L was considered positive. Absolute number of eosinophilis, total serum IgE, specific IgE to nutritive and airborne allergens and 13 cytokine genes [(interleukin IL-1 alfa (IL-1α), IL-1 beta (IL-1β), IL-1R receptor (IL-1R), IL-1R antagonist (IL-1RA), gamma-interferon (INFγ), IL-2 (IL-2), IL-4 (IL-4), IL-4 receptor alfa (IL-4Rα), IL-6 (IL-6), IL-10 (IL-10), IL-12B (IL-12-B), TGF beta 1 (TGF-β1) and TNF alfa (TNF-α)], were evaluated. Cytokine gene polymorphism was performed by polymerase chain reaction with sequence-specific priming (PCR-SSP) Heidelberg kit) at the Institute of Immunology and human genetics, Medical Faculty Skopje. The control group were 301 unrelated individuals at age from 20 to 40 years born in different parts of Macedonia. From 118 children in 80 was performed specifitic IgE measurement and 69 of them cytokine gene polymorphism was done.

Results: In 30% of children severe form of AD was found, with predominance in second born children and infants. All children with AD have increased level of absolute number of eosinophyls (1086 ± 1009) and serum level of total IgE (280 ± 433 kU/L) there is no statistical significance between group of children with mild and severe form of AD classified by SKORAD index ($p>0.05$). Children with severe form of AD had significantly lower level of serum proteins ($p<0.01$), albumin ($p<0.003$) and haemoglobin ($p<0.004$). Severe form of AD is more common in younger children mean age 18 ± 15 months ($p<0.02$). Breastfeeding during the first 4 months has protective role (OR=0.026, 95% CI=0.79-0.88) p=0.03. Expose to cigarette smoke (OR=4.44, 95% CI=1.75-11.22) p=0.02, house mould (OR=5.07, 95% CI =1.58-16.25) p=0.06 and second born children (OR=5.34, 95% CI=1.54-18.53) p=0.008 increased the risk for severe form of AD. Association of other risk factors with the severity of AD: born pattern, solid food introduction, positive family history for allergic diseases, positive personal history for allergy there was not found. Positive association of total IgE and age was found Children with IgE level >30kU/L had statistically significant higher level of SKORAD (p=0.01) and they are older (p=0.02). Sensitization is present in 62 patients (77.5%). Fifty six patients (70%) with mean age of 16 ± 14 months become sensitized to food allergens and 33 patients (46%) with mean age of 24 ± 18 months to airborne allergens (p=0.02). Sensitised children had increased level of total IgE compared with children with AD who are still unsensitised ($p<0.05$). The most commonly food allergens were egg white in 46 children (60%) and milk in 39 children (49%) and from airborne allergens home dust mite in 8 children (10%) pollens in 6 children (8%), animal in 6 children (8%) and mould in 4 children (5%). Egg white sensitization is not associated with severity of AD, age or total IgE $p>0.05$. Egg white sensitization was significantly highest in breast feed children ($x2=17.8$, $p<0.001$) in our study. 44 children (91%) sensitized to egg white and 16 children (50%) without egg white sensitization were breastfeed. In all 14 children with significant egg allergy open food challenge test was performed. Nine children with history of mild allergic reaction had negative food challenge test and immunisation with MMR were performed without adverse reaction. Two children with severe allergic reaction to egg in infancy and negative food challenge test were also immunised without adverse reaction. Three of them had positive food challenge test with urticaria, itching, vomiting and wheezing and due to anxiety of the parents

the immunization was dallied at age of 2 years. One of them had worsening of the eczema with itching; the two other had no adverse reaction.

Increased level of total IgE in children older than 24 months was found (p=0.09). Children younger than 12 months had higher SKORAD index (p=0.0007). In infants IgE sensitization to food allergies egg white (60%) milk (50%) egg yolk (23%) and animal (9%) were most common. In children age 12 to 24 months increased prevalence to egg white (89%), milk (67%), egg yolk (22%) and mould (22%) sensitization was found. In children older than 24 months prevalence of IgE sensitization to nutritive allergens egg white (33%) milk (25%) egg yolk (25%) were diminished and airborne sensitization animal (12.5%) home dast mite (37.5%), grass pollen (37.5%), tree pollen (37.5%), mould (11%) and weed (11%) were shown.

In 8 (28.5%) with severe form of AD and 10 children (20%) with mild form of AD IgE sensitization was not found.

Highest number of cytokine genotypes (11 of them) are susceptible for AD with biggest odds ration of 18.173 for *IL-4 -33/T:T*, and more than three times bigger risk (p<0.001) for *IL-4 -1098/G:G* (OR=10.962), *TGFbeta1 cdn25/C:G* (OR=5.653); *IL-4 -1089/T:T* (OR=5.518), and *IL-1alfa -889/C:T* (OR=5.250). *IL-2 +166/T:T, IL-1beta -511/C:T, IL-12 -1188/C:T, IL-10 -1082/A:G, IL-1beta +3962/C:T, INFgamma +874/A:T* also increased the risk for AD. Five cytokine diplotypes, six cytokine haplotypes, and four cytokine alleles were found to be positively (susceptible) associated with AD. At the same time protective cytokine polymorphisms regarding atopic dermatitis for seven cytokine genotypes (*IL-4 -1089/G:T, TGFbeta cdn25/G:G, IL-4 -33/C:C, IL-1alpha -889/C:C, INFgamma +874/A:A, IL-10 -1082/A:A, IL-1beta -511/C:C*), one cytokine diplotype, two cytokine haplotypes, and four cytokine alleles were found. Most of the negative (protective) associations with AD were at very high protective levels (p<0.001).

***Conclusion*:** Severe form of AD was present in 30% of our study group and it was more common in infants associated with poor nutritive status. Breastfeeding has protective role, while passive smoking and home mould increased the risk of severe form of AD. Sensitization to nutritive allergens is more common in infants and egg white and milk are the most common allergen, while sensitization to airborne allergens is shown after age of 2 years. Sensitization to egg white is not risk factor for MMR immunization.

Cytokine gene polymorphism showed that Macedonian healthy population have protective alleles and genotypes of cytokine genes that are involved in innate immune response (IL-1A and IL-1B) as well as Th2 immune response (IL-4) and T regulatory cytokines (TGF beta). All those protective alleles have frequency higher than 70% as well the protective genotypes (frequency >65%). Although A allele of *IL10 -1089* gene is balanced, the protective AA genotype is less frequent in our healthy population. The polymorphism of Th1 citokine genes shows higher frequency of p-rotective allele and genotype of *IL2-166*, and lower frequency of protective genotypes of *IL12* and *IFN-gamma* genes. Inconsistent results obtained from various authors highlight the importance of gene-environment interaction and the genetic role among different ethnic groups.

Keywords: Not available.

Defended: December 29, 2011.

Mentor: Prof. Dr. Sonja Peova.

Tatjana Zorchec. Psychological and neurophysiological evaluation of executive functions in children with obsessive-compulsive disorder and attention deficit hyperactivity disorder [PhD Thesis]. *Skopje, Republic of Macedonia: University Clinic of Pediatrics, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Intoduction: In the past decade researches and clinicians, have become more involved in defining and evaluating executive functions [EFs] in children. Those functions are connected with the cortical network in the prefrontal cortex and are involving a hige number of processes who are responsible for self-regulation of the behavior and development of social and codnitive abilities in children. EFs, as the highest cognitive processes in the hierarchy, are involving information from the working memory, inhibition of the inappropriate bahavior, as well as directing and sustaining the attention, towards the goal-oriented behavior.

Aim of the study: neurophysiological and psychological evaluation of EFs in children with obsessive-compulsive disorder [OCD] and attention deficit hyperactivity disorder [ADHD].

Subjects and methods: in each group we have included 30 subjects, as well as 30 healthy subjects as a control group. Neurophysiological assessment was performed

with Visual Continous Performance Test [VCPT] from which Event Related Potentials [ERPs] were extracted. Psychological assessment was performed with Stroop Color Word Task [SCWT] and Wisconsin Card Sorting Test [WCST]. Additional psychological scales were implemented for the assessment of some other psychological functions.

Results: ADHD children make more perseverative and non-perseverative errors, need more cards per category and have severe difficulties in the mental flexibility, while the OCD children have only perseverative errors and mild difficulties in the mental flexibility. VCPT and ERPs in ADHD children confirmed serious difficulties in executive functioning, while in OCD children it is in much lover extend.

Conclusion: ADHD children from this study have serious problems in EFs, while for the OCD children this is not the case.

Keywords: *OCD; ADHD; EFs; children.*

Defended: December 30, 2011.

Mentor: Prof. Dr. Nada Pop Jordanova.

Katerina Tosheska-Trajkovska. Association of the lipid transfer proteins and enzymes with atherosclerosis [PhD Thesis]. *Skopje, Republic of Macedonia: Institute for Medical and Experimental Biochemistry, Medical Faculty, Ss. Cyril and Methodius University in Skopje; 2011.* Maced J Med Sci. 2012 Mar 15; 5(1):114-134.

Reverse cholesterol transport is a multi-step process resulting in the net movement of cholesterol from peripheral tissues back to the liver via the plasma.

Lecithin-cholesterol acyltransferase (LCAT) is an enzyme that converts free cholesterol into cholesteryl ester. The enzyme is bound to high-density lipoproteins (HDLs0 in the blood plasma.

Cholesteryl ester transfer protein (CETP) promotes an equimolar exchange of cholesteryl esters (CE) and triglyceride between lipoproteins. It collects triglycerides from very-low-density (VLDL) or low-density lipoproteins (LDL) and exchanges them for CE from high-density lipoproteins (HDL), and vice versa.

For the first time in Republic of Macedonia determination of CETP and LCAT concentration was done in healthy subjects as well in patients with coronary artery disease (CAD).

HDL and LDL subclass phenotyping was done using 3-31% gradient polyacrilamide gel electrophoresis.

In healthy subjects large LDL subclasses (26.08±0.86 nm) and large HDL subclasses (9.78±0.96 nm) were dominant.

Small LDL subclasses were dominant in 60% of CAD whereas its percent was 11% in healthy population. The frequency of LDL3 subclasses was 58%.

Polydisperse LDL profile was dominant in 68% of patients with CAD. The incidence of small HDL subclasses was significantly higher in patients with CAD compared with healthy subjects.

The CETP concentration determined in 100 patients with CAD was statistically significant higher than in the control group ($p<0.05$).

In patients with CAD monodysperse profile is characterised with higher CETP concentration compared to polydisperse profile.

There was no difference in LCAT concentration between healthy subjects and patients with CAD.

Age, diastolic blood pressure, CETP concentration and LDL particle size were independent factors for determing IMT by multiple linear regression analysis. They accounted for 35% of the observed variability in IMT. The present study shows that increasing CETP levels are associated with an increased risk of future CAD. Those in the highest CETP quartile had an OR of 1.44 (95% CI, 1.06 to 2.00, p=0.03) compared with those in the lowest quartile.

Keywords: *CETP; LCAT; HDL; reverse cholesterol transport.*

Defended: December 30, 2011.

Mentor: Prof. Dr. Sonja Alabakovska.