Macedonian Medical Doctor of Philosophy (PhD) Theses Defended in 2007

Faculty of Medicine, University “Ss Kiril and Metodij”, Skopje, Republic of Macedonia

Doctor of Philosophy, abbreviated Ph.D. or PhD for the Latin *Philosophiæ Doctor*, meaning “teacher of philosophy”, (or, more rarely, D.Phil., for the equivalent *Doctor Philosophiæ*) is an advanced academic degree awarded by universities. In Republic of Macedonia it has become the highest degree one can earn and applies to graduates in a wide array of disciplines in the medical fields. The Ph.D. has become a requirement for a career as a university professor or researcher in many fields of medicine.

Candidates are submitting PhD under the guidance of mentor, the proposal is reviewed by 3 university professors for applicability, final submission is accepted by reviewer commision of 5 university professors, and publically defended.

Macedonian Medical Doctor of Philosophy (PhD) Degrees are deposited in the Central Medical Library and National and University Library “St. Kliment Ohridski” in Skopje.

English summaries are published in Macedonian Journal of Medical Sciences as they are translated by authors and included in the final version of defended PhD. Editorial Board do not take responsibility either for the content, nor for the quality of the abstracts. At the Faculty of Medicine there are defended seven PhD theses in 2007 and one of them is without the abstract (14.3%).

Igor Petrov. Evaluation of neurophysiologic and morphologic findings in patients with particular types of parkinsonism and parkinson plus syndrome and cognitive disorders [PhD thesis]. Skopje, Republic of Macedonia: University Clinic of Neurology, Faculty of Medicine, University “Ss Kiril and Metodij”; 2007. E-mail: neuromed2m@yahoo.com

Importance of the quick diagnosing and differentiation of patients with parkinsonism from those with parkinson plus syndrome (PPS) has been referred in the fact that correct classification and adequate treatment is needed. The most problematic points in the above mentioned efforts are: quick detection of specific neurologic signs in the clinical picture of patients with PPS; involvement of pyramidal, cerebellar and other systems in pathogenetic degenerative process except the extrapyramidal syndrome, which is mutual characteristic of these patients. Of particular significance is the quick distinction of patients with incipient dementia from the patients with depression, representing a real difficulty even for the skilled neurologist. Due to all these mentioned problems, the purpose of this doctoral dissertation was to make an assessment of clinical, neurologic, psychologic, physiologic and morphologic examination.
Dissertation comprised 110 patients with parkinsonism, 55 of which with idiopathic parkinsonism, 20 with secondary parkinsonism of vascular etiology, 5 patients had normal pressure hydrocephalus (HNP), 30 patients were with PPS, 14 of which with progressive supranuclear palsy (PSP), 9 with multiple system atrophy (MSA) and 7 with corticobasal ganglionic degeneration (KBGD).

These patients were diagnosed and treated at the Clinic for Neurology, Clinical Centre in Skopje, at the Unit for Extrapyramidal Disorders. Patients were divided according to age, sex, 59 men and 51 women, aged 35 to 75 years (mean age 68 years). The onset of the disease at the first hospitalization ranged from 6 months to 2.5 years (average 18 months), with an average disease time duration of 3.2 years. Except anamnesis and detailed neurologic finding, a unified assessment scale (UPDRS-Unified Parkinson Disease Rating Scale) was used for the assessment of disability degree.

Neurophysiologic investigations comprised: EEG, EVP (SEP, SEP, VEP, BAEP and CM measurement). Neuropsychophysiologic analysis included a battery of psychologic testing and electroexpectogram (EXG). EXG was made at the Institute of Physiology and Antropology, Faculty of Medicine in Skopje. Motor evoked potentials (MEP) analysis and central motor conduction time (CMT) measurements were made by means of TMC. Results were analysed in patients with idiopathic parkinsonism, vascular, HNP and in patients with PSP, MSA and KBGO. Paralysis of vertical gaze, blepharospasm, extrapyramidal syndrome, pyramidal syndrome, ataxia and definitively cognitive-mnestic disorder going to affective incontinence dominated in patients with PSP.

Dominant symptomatology in patients with KBGD were: extrapyramidal syndrome, tremor, pyramidal deficiency, “strange hand phenomenon (hand ataxia). Mental-cognitive disorders were discrete at the beginning, but the psychoorganic syndrome was progressing.

MCA – was diseases. PPS where dominated extrapyramidal syndrome and vegetative dystonia (disuria hypotony), stridor as well as cerebral dysfunction, psychosyndrome, but dementia was at subcortical dementia level with slow thinking and impaired concentration.

Analysis and statistical computation of data demonstrated that patients with idiopathic parkinsonism were represented with 50%, with vascular 18%, with HNP 4.5% and there were 27.5% patients with PPS.

Depression dominated in patients with parkinsonism, cognitive disturbances were less represented, in contrast to the patients with HNP, PSP and KBGD in whom extrapyramidal, pyramidal and cognitive-mnestic dysfunctions dominated. Cognitive dysfunctions were represented in 100% of the KBGD patients, while depression was absent.

In PPS patients dominated decreased learning ability for new events in 100%, decreased ability in 92.9%; dyspraxia in 92.9%; and in MSA dominated decreased concentration and decreased learning ability in 100%. EXG analysis showed changes in sense of decreased number of cycles and decreased amplitude Amax in MSA, decreased number of cycles, decreased Amax, Amin, prolonged Pbmax and increased number of errors in PSP, and decreased Amax, decreased number of cycles, prolonged PBmax and decreased amplitude in KBGD.

Finding from the MEP prolonged latency of the upper and lower limbs and prolonged CMT in patients showed involvement of the pyramidal system in PPS pathology, and they are presented as a sensitive indicator for a proof of pyramidal lesion.

Key words: Parkinsonism, progressive supranuclear palsy, multiple system atrophy, cortico-basal ganglionic degeneration, motor evoked potential, electroexpectogram.

Mentor: Prof. Dr. Vera Daskalovska.

Konstandina N. Kuzevska-Maneva. Evaluation of heart rhythm disturbances in children operated from different congenital heart diseases using Holter 24 hour electrocardiographic monitoring [PhD thesis]. Skopje, Republic of Macedonia: University Children's Hospital, Faculty of Medicine, University „Ss Kiril and Metodij”; 2007. E-mail: manevakostandina@hotmail.com

We have analyzed the type, frequency and severity of heart rhythm disturbances and conduction abnormalities in 178 patients-children aged from 3.5 to 21 years, who was operated in the early childhood, from various congenital heart defects(CHD): atrial septal defect, ventricular septal defect, atroventricular septal defect, Tetralogy of Fallot, transposition of the great arteries, Single ventricle and other more rare congenital heart defects (pulmonary atresia, double outlet right ventricle and tricuspid atresia). Also we
have analyzed heart rhythm in 30 healthy children, who constituted the control group.

The main method that has been applied during the study was the Holter 24 hour electrocardiographic monitoring. The other applied methods were: anamnestical data, objective findings, electrocardiogram before the operation, electrocardiogram before Holter application and echocardiogram.

With all our patients we have carried two Holter monitorings and we have analyzed the following heart rhythm disturbances and conduction abnormalities: sinus nodus dysfunction, premature atrial contraction (significant and nonsignificant), sinus tachycardia, supraventricular paroxysmal tachycardia, nodal rhythm, atrial flutter, ventricular premature contraction (Lown gr. I-III and Lown gr. IV), atrioventricular blocks of I, II or III degrees, right bundle branch block complete and incomplete, left anterior haemiblock. The analysis of the Holter 24 hour ECG has been done on computer software designed for this purpose.

Holter analysis have been carried out in 178 operated patients, but serious arrhythmias and conduction abnormalities have been found in 47/178 (26.4%). 25 children of 178 needed antiarrhythmic therapy, the effect of which was later monitored. Two children of 178 were in need of pacemaker application. The other arrhythmias required permanent monitoring, to enable timely inclusion of therapeutic treatment, to avoid more serious complication – life threatening arrhythmias and sudden death.

There were not any significant statistical difference in the types of arrhythmias between the first and the second Holter analysis among the studied groups, except for the group of children operated from atrioventricular septal defect were, it has been found significant statistical difference in the appearance of premature ventricular contraction Lown gr I-III and transient nodal rhythm.

The correlation of the findings among the studies groups of surgically treated children with the control group of healthy children showed significant difference in the occurrences of specific arrhythmias in the operated versus the healthy children: in the atrial sepal defect typ secundum- right bundle branch block complete and incomplete and premature ventricular contractions Lown gr I-II; in ventricular sepal defect- right bundle branch block complete and incomplete; in atrioventricular sepal defects - atrioventicular block gr I, right bundle branch block complete and incomplete and left anterior haemiblock; in Tetralofy of Fallot- right bundle branch block complete, left anterior haemiblock and also premature ventricular contractions Lown gr I-III; in transposition of the great arteries- supraventricular paroxysmal tachycardia, sinus tachycardia, complete right bundle branch block and also premature ventricular contractions Lown gr I-III; in single ventricle-complete right bundle branch block; and in the complex congenital heart diseases- premature ventricular contractions Lown gr IV and complete right bundle branch block. The special surgical techniques used in specific congenital heart diseases, had contributing to the appearance of specific types of heart arrhythmias and conduction abnormalities.

Comparing the findings of the standard methods (especially the12 channel ECG) with Holter ECG analysis results it was shown that the level of discovering of arrhythmias and conduction abnormalities using Holter ECG is much higher especially in the patients without subjective difficulties, but with serious rhythm disturbances.

The value of Holter 24 hour electrocardiographic monitoring, as a non invasive method for discovering arrhythmias and conduction abnormalities in our pediatric patients operated from different congenital heart defects, is in precise prognosis of these heart diseases, it allows us to set up the way of every day life and level of over usage i.e. physical activities for every individual patient.

Key words: Surgery; Congenital heart defects; Pulmonary atresia; Double outlet right ventricle; Tricuspid atresia; Holter 24 hour electrocardiographic monitoring; Children; Republic of Macedonia.


Mentor: Not available.

Igor Kaftandzhiev. Algorithm for treatment of open fractures of tibial diaphyses [PhD thesis]. Skopje, Republic of Macedonia: Traumatology Clinic, Faculty of Medicine, University „Ss Kiril and Metodij”; 2007.

The definition of the AO group in which the notion of the open fractures evidences that the communication between the fracture and the outward district persists, what doubtless includes skin injuries and tender tissues in the broken bone’s area, is generally accepted. The most frequently injuries are caused by the effect of severe trauma which causes considerable damages.

The open fractures on the diaphysis of the tibia are the most frequently in the whole skeleton trauma.
and therefore they are still challenge for the surgeons and the way of their treatment cause determined hesitations. The open fractures present complicated surgical problem on account of their cure which needs reachable approach, because of the complications that aren’t rare at all, and they influence on the final outcome. The universal accepted principle of treatment includes primary surgical treatment of the whole devitalize tissues, abundant irrigation, stability of the fracture and covering the defect of the tender tissue. The methods of the bone’s stabilization cause determine controvert. Up to now the use of the external fixation has been counted as a standard in the surgical treatment. But, the occurrence of complications bound with this way of treatment that aren’t exceptional, imposed the use of the unreamed intramedullary fixation as a method of stabilization of the grade II and III open fractures according Gustilo classification. The advantages of this method and preservation of the osseous blood flow and the stable fixation, that origin the main factors for faster bone’s healing.

Base on that point, the main target of this abstract is to evaluate the results and complications from the operative treatment of the grade II and III open fractures of the tibial diaphysis, to compare the results with those which are obtained from the treatment with the external fixation and in the end, based on the obtained results and eventual complications to fortify the worth of the method of the unreamed intramedullary fixation in the treatment of the open fractures of tibial diaphysis. Algorithm for surgical treatment is recommended in the end of the study.

Clinical material from the Traumatology Clinic, Clinic Center, Skopje is used in the study, which is divided into groups according grade of injury (Gustilo classification) and into subgroups by the surgical manner of bone stabilization. 96 patients were examined, 66 male and 30 female, middle age of 35, 97 years. The most frequent mechanism of injury was high energy trauma at 77 patients. 56 patients were treated in group A and 40 in group B. The examinations were performed following the determined criteria. At all of the patients the exact protocol were performed following the determined criteria. At all of the patients the exact protocol were conducted which included preoperative, operative (consist of two different parts: primary surgical treatment of traumatized soft tissue and bone stabilization, in subgroup 1 with external fixateur and in subgroup 2 with unreamed interlocking intramedullary nail) and postoperative part. Few parameters were examined in the study such as: radiological evaluation (new bone formation, time of union, problems of union), soft tissue condition, infection, problems with the implant, other complications connected with the operative treatment and functional outcome. The results were statistically evaluated.

The results from the study showed shorter time of union with statistical signification in the groups of patients treated with intramedullary fixation. The degree of the injury influenced the time of union. Statistically significant difference is noticed in the examined complications of the union compare the both manner of bone stabilization. The results from the examinations of the infection, showed lower percent in the superficial and deep infection in the groups treated with intramedullary nails. The results showed different type of complications in connection of different manner of bone stabilization. The examination included also the need for covering the soft tissue defect with skin transplant, the use of bone graft, correction of the frame of the external fixateur or its conversion, implant failure, dynamisation of the intramedullary nail or its conversion. Some of the complications from the examination in the study is specific and depends on the different way of fracture fixation. The functional outcome according Olerud score system showed statistically significant better results in the groups of patients treated with intramedullary fixation.

Summarize the results of this clinical study and evaluation of the followed complications allows recommending the surgical method of unreamed interlocking intramedullary fixation for the open fractures of the tibial diaphysis. This method of treatment offers stable fixation of the fracture and lower percentage of complications and it can be recommended as the treatment of choice for grade II, III A and B open fractures of the diaphysis of the tibia. The imperative is still the adequate treatment of soft tissue injuries which influences over the final outcome of the whole treatment. The recommended working protocol can decrease the eventually present mistakes in the surgical approach.

Key words: Not available.


Mentor: Not available.

Gjorgji Jota. Rectal carcinoma-degree of loco regional recidivism and quality of life in three possible therapeutic modalities [PhD thesis]. Skopje, Republic of Macedonia: Clinic for Abdominal Surgery, Faculty of Medicine, University „Ss Kiril and Metodij“; 2007.

Abstract not available.
Sashko Jovev. The effects of the lung resections on heart-lung haemodynamics [PhD thesis]. Skopje, Republic of Macedonia: Clinic for Thoracic and Vascular Surgery, Clinical Center - Skopje, Faculty of Medicine, University „Ss Kiril and Metodij”; 2007.

The aim was to identify the effects of pulmonary resection on right ventricular performance and the possible contribution to mortality and morbidity. We examined the patients with Doppler Echocardiography before the operation and 4 months after the pulmonary resection. Systolic, diastolic and stroke volumes as well as right ventricular ejection fraction were estimated. Pulmonary arterial pressure was calculated using the level of tricuspid regurgitation and subtracting method. Right ventricular end diastolic volume (RVEDV) and volume index increased, the heart rate (HR) also increased and the ejection fraction (EF) decreased in patients after the lung resections. We evaluated 80 patients with major pulmonary resection due to carcinoma of the lung. We divided the patients in 2 groups: the first contains 40 patients with previous complications such as myocardial infarct, arrhythmias, pulmonary hypertension or COPD, the second also contains 40 patients but without complications. We concluded that there were changes in the parameters (sPAP, RVEDV, RVEDD, HR, EF) in both groups. The main parameters to predict the postoperative haodynamic status and cardiac complications after the resection were: TPVRI, mPAP and CI. Pulmonary resection causes dilatation on right ventricle in the early postoperative period. Early detection can provide the chance for interventional therapy.

Key words: pulmonary resection, right ventricular volumes, right ventricular volume index, right ventricular ejection fraction.

Mentor: Prof. Dr. Zoran Spirovski.

Anita A. Arsovska. Transcranial color Doppler sonography in the patients with ischemic cerebrovascular insult: Clinical-radiological investigation with magnetic resonant angiography [PhD thesis]. Skopje, Republic of Macedonia: University Institute of Radiology, Faculty of Medicine, University „Ss Kiril and Metodij”; 2007. E-mail: anita70mk@yahoo.com

Cerebrovascular diseases are among the most frequent diseases of the central nervous system. Steno-occlusive diseases of the intracranial arteries are responsible for stroke appearance in 5-10% of the population. Such patients are at very high risk for recurrent stroke and lethal outcome. Transcranial color duplex sonography (TCDS) and magnetic resonance angiography (MRA) are noninvasive methods for evaluation of intracranial blood vessels. In the foreign literature there are several authors that have compared the efficacy of TCDS and MRA in the evaluation of morphologic and hemodynamic changes of cerebral blood vessels. So far in R Macedonia there have not been any comparative studies between these two methods, in order to prove which method could be more or less applied in the diagnosis of intracranial arteries diseases.

Aim of this study was to show whether there is a significant difference in the certainty of detection of different pathological changes with the transcranial color-duplex sonography (TCDS) and magnetic resonance angiography (MRA) method and whether the results obtained with the duplex method could allow more rational use of the MRA diagnostics.

Fifty patients, aged 58-76 years, with ischemic cerebrovascular insult in the anterior circulation were evaluated, hospitalized at the Department for Urgent Neurology, Clinic of Neurology, during the period from March 2004 until March 2006.

All patients were clinically evaluated with the following order: history of the disease, risk factors for cerebrovascular insult, age, gender, physical examination, neurological status and consciousness, laboratory analysis of blood and urine, computerized tomography of the brain (CT), carotid arteries evaluation (with extracranial color duplex sonography device TOSHIBA SSH-140A, with linear array of 7.5 MHz and/or magnetic resonance angiography), transcranial color duplex sonography (TCDS) with device TOSHIBA SSH-140A, with linear array of 2 MHz (native or with contrast application with Levovist-Schering), nuclear magnetic resonance (NMR) of the brain and magnetic resonance angiography (MRA) of brain blood vessels at the Institute of Radiology.

TCDS examination was performed in the period of 24-48 hours after hospitalization at the Clinic of Neurology, Clinical Center, Skopje. For each intracranial artery the following hemodynamic parameters
were evaluated: peak systolic velocity-PSV; end diastolic velocity-EDV; mean velocity-MV, flow direction (anterograde or retrograde); pulsatility index-PI and asymmetry index-AI, on the symptomatic and asymptomatic side.

MRA examination was performed at the Institute for Radiology, Clinical Center, Skopje, with the device Philips Gyroscan T10-NT, with the magnetic strength of 1 Tesla. MRA examination was performed 1-5 days after the TCDS examination and it was considered as a “golden standard” to which TCDS findings were compared.

The results were statistically analyzed with the statistical program Statistica for Windows 7.1/2005 and EPI 6.0.

According to the TCDS method, the patients were divided into 4 groups: 1) normal findings; 2) occlusion of ACM branches; 3) stenosis of ACM main stem and 4) occlusion of ACM main stem. These findings were compared with the findings of MRA.

In the first group the following results were obtained: sensitivity 77,8%, specificity 93,8%, positive predictive value 87,5% and negative predictive value 88,2%.

In the second group, sensitivity was 87,5%, specificity 97,6%, positive predictive value 87,5% and negative predictive value 97,6%.

In the third group sensitivity was 81,3%, specificity 94,1%, positive predictive value 86,7% and negative predictive value 91,4%.

In the fourth group sensitivity was 88,9%, specificity 92,7%, positive predictive value 72,7% and negative predictive value 97,4%.

Obtained results show that certainty of TCDS method in the diagnosis of steno-occlusive diseases of the intracranial arteries is at risk level less than 1%.

As a general conclusion one can bring out that TCDS is a safe and secure diagnostic modality that serves for fast and recurrent analysis of the intracranial arteries patency in the acute stroke phase; TCDS can predict clinical evolution and can contribute for more rational use of MRA technique, in order to adequately modulate the therapeutic approach.

Key words: transcranial color duplex sonography, magnetic resonance angiography, cerebral arteries, ischemic cerebrovascular insult.
early puberty), than the other groups. The growth velocity significantly decreased in the first and second year of the evaluation period, as well as the pubertal stage. The bone age during the evaluation time slowed down. The levels of the hormone LH were significantly higher in this group than in the others. In the group with infantile mammoplasia, growth velocity significantly decreased through time, as well as the values of the bone age. The weight of the children did not increase. In the group with early puberty, bone age significantly increased, the weight was advanced, while growth velocity significantly decreased. The pubertal stage advanced. In the group with premature thelarche, bone age significantly increased during evaluated time period, while growth velocity in the second and third year significantly decreased. Positive correlations were found between chronological age and weight, so those children were not heavier in comparison to the other groups.

The xenoestrogen, p,p'-DDE was not elevated in the group of 56 girls with premature sexual development in comparison to the control group of 26 healthy children. Unexpectedly, the presence of the pesticide lindane was discovered in both groups. IGF1 and IGFBP3 were not elevated enough according to the pubertal stage. Negative correlations were found between IGFBP3 and growth velocity, and positive between height and weight of the girls, as well as the age.

In the cross-sectional study 928 girls were evaluated. Rome, Turkish and Serbian nationality was very rarely represented, while a detailed analysis was performed on the Macedonian and Albanian population which were in greater number. The Macedonian girls were significantly higher and heavier than the Albanian girls. The pubertal stage was also more advanced in the Macedonian girls.

**Conclusion:** The longitudinal study showed that the group with central precocious puberty is more different then the rest of the groups. The treatment with a LH-RH agonist contributes to improvement of auxologic and pubertal parameters. The group with early puberty deserves constant follow-up due to the danger of fast progressing puberty which may compromise final height. The groups with infantile mammoplasia and premature thelarche represent benign conditions, and in our case there was not a progression into central precocious puberty. IGF1 and IGFBP3 in our evaluation did not show as a significant tool for diagnosis of premature development. The xenoestrogens present in our population, are probably not a possible reason for premature sexual development, however a lager investigation of the involved regions is necessary, as well as their prohibition in the agricultural use.

**Key words:** Premature sexual development, xenoestrogens, IGF1, IGFBP3.

**Defended:** July 2, 2007.

**Mentor:** Prof. Dr. Mirjana Kochova.