REVIEW

From: Corr. Member of BAS, Prof. Dr. Nikolay Gabrovsky, DSc, Head of Neurosurgery Clinic, University Hospital for Active Treatment "N.I. Pirogov" – Sofia.

Subject: doctoral thesis by Dr. Milko Dimitrov Milev, neurosurgeon at the Neurosurgery Clinic of Acibadem City Clinic University Hospital Tokuda EAD, on the topic: "Multimodal electrophysiological neuromonitoring in neurosurgical operative interventions" for the award of the educational and scientific degree "Doctor“ in the scientific specialty Neurosurgery, CODE 03.01.41 in professional field 7.1. Medicine, field of higher education 7. Health and sports.
Scientific director: Assoc. Vladimir Stefanov Nakov, MD, PhD
The procedure was announced by Order No 15-03-393#1 of 18.11.2022. of the Executive Director and the Procurator of Acibadem City Clinic University Hospital Tokuda.

Dr. Milko Dimitrov Milev was born on February 7, 1986. He graduated from the HSNM - Sliven in 2004. In 2010 graduated as a Master in Medicine at the Faculty of Medicine at the Medical University - Sofia with excellent grades. For the period 2010-2016 specializes in neurosurgery at the UMHATEM "N.I. Pirogov" and in the Clinic of Neurosurgery of "Acibadem City Clinic University Hospital Tokuda". In 2016 successfully passes the neurosurgery specialty exam.

Dr. Milko Milev has conducted numerous additional courses and trainings related to the topic of the dissertation: Research Course of the European Association of Neurosurgical Societies (2011); three-year cycle of the Educational Course of the International Society of Intraoperative Neurophysiology (2018-2021); IRCAD Masterclass – 360-Degree Skull Base Surgery (2021). For the period 2006-2010 he

has participated in five research projects focused primarily on neuropathic pain. The total number of his actual publications is 22, the participations in scientific congresses and forums with published abstracts – 58.

Dr. Milko Milev is a member of the Bulgarian Society of Neurosurgery, the European Association of Neurosurgical Societies and the International Society of Intraoperative Neurophysiology. He speaks English at level C1.

The doctoral thesis of Dr. Milko Dimitrov Milev on the topic: "Multimodal electrophysiological neuromonitoring in neurosurgical operative interventions" is presented in 177 pages and contains 2 tables, 4 figures, 91 graphs. The literature references include 189 titles, of which 12 are in Cyrillic. The structure of the dissertation is: a literature review – 25 pages; research methodology – 23 pages; results and discussion – 104; conclusions and contributions — 4. The structure is well balanced and per the requirements.

The struggle to reduce the risk of postoperative complications has always accompanied the development of neurosurgery. The anatomical features of the central nervous system, the lack of clear, easily distinguishable anatomical landmarks during surgical interventions, as well as the extremely complex balance between surgical radicality and the risk of iatrogenic damage are the basis of numerous surgical methods and techniques introduced in neurosurgery over the last decades. Undoubtedly, one of the most important and powerful tools introduced and improved in recent years is intraoperative neurophysiological monitoring. For this reason, the topic "Multimodal electrophysiological neuromonitoring in neurosurgical operative interventions" is relevant, important and interesting.

The literature review is comprehensive and describes the current level of development, the advantages and disadvantages, as well as the main unresolved issues in intraoperative monitoring of the motor cortex, cortico-spinal pathways and oculomotor nerves. Special attention is paid to the biophysical processes determining the reactivity and behavior of nerve tissue in the CNS upon subjection under of external electrical stimuli. The necessary conditions for the application of

subcortical monopolar stimulation for cortico-spinal pathways localization and the limiting circumstances within which the principle of millimeter distance to excited nerve fibers for each milliampere of stimulation intensity required for a suprathreshold response are also discussed.

A systematic analysis of the available literature data on the reliability of the various electrophysiological criteria applied in the intraoperative diagnosis and prevention damage to the primary motor cortex and cortico-spinal pathways was conducted. The need to combine the different criteria to increase the credibility of the results has been identified and the conclusion is made about the necessity for a complex analysis of clinical, operative, and electrophysiological findings.

Based of the literature review, the aim of the scientific work is also formulated: To establish a complex of electrophysiological criteria capable of ensuring prompt and reliable identification of increased risk of damage to the motor cortex and cortico-spinal pathways and oculomotor nerves. For the achievement of this aim six clearly formulated and feasible tasks are defined.

The clinical material of the dissertation included 174 cases, and the analysis performed was retrospective. The patients were divided into two groups – cases with monitoring of motor cortex and cortico-spinal pathways in interventions in the supratentorial space (130 cases) and cases with monitoring of oculomotor nerves (44 cases and 61 nerves). The functional outcome for the first group was assessed in the late postoperative period according to the manual muscle testing scale, and for the second group – based on the presence of postoperative oculomotor deficit.

The results of the cases in the first clinical group revealed statistically significant lower end percentage values of the amplitudes of motor evoked potentials from transcranial and direct cortical stimulation in the group of patients with moderate or severe late postoperative deficits for the affected extremities. Graphic representations of the change in the risk of postoperative motor deficit of different degrees with changes in the values of one or more predictive factor have been developed, which give patient-individualized information and allow analysis of

the findings in the course of the operative intervention. A comparative analysis with the available literature data was conducted and it was found that the proposed classification machine learning models yielded predictions at reliably higher levels of confidence (positive predictive value and sensitivity, with low rates of false positive and false negative results) compared to previously published monofactorial studies.

Analysis of the results of oculomotor nerve monitoring shows the importance of ultrasound assistance in the positioning of intraorbital electrodes, especially for the early cases in the series and those requiring access to the hard-to-reach muscles (m. obliquus superior in the monitoring n. trochlearis). The proposed original electrode placement technique for n. trochlearis monitoring allows selective, reliable and quality recording of electromyographic responses from this nerve, comparable to those elicited by the more accessible lower and lateral straight muscles. Analogously to the first clinical group, a multifactorial classification machine learning model was generated, which was subsequently optimized by eliminating the uninformative predictors until reaching a four-factor model for classification on the development of postoperative motor deficit with a high sensitivity of 0.8 and a positive predictive value of 0.79.

The results and the conducted analysis allow the author to reach 5 conclusions in the field of primary motor cortex and cortico-spinal pathways monitoring and 7 conclusions in the field of monitoring of oculomotor nerves. The conclusions are important, practical and consistent with the set tasks. The doctoral thesis has two theoretical, 4 methodological and 4 practical contributions. There are 6 publications related to the dissertation work, one of which is in English. Presentations at scientific forums and conferences are five.

In conclusion, the doctoral thesis of Dr. Milko Dimitrov Milev: "Multimodal electrophysiological neuromonitoring in neurosurgical operative interventions" is an important, current topic for neurosurgery, with the purpose of increasing the safety of interventions and reduce the risk of iatrogenic injury to the patients. The study is

retrospective, it is approached consistently and systematically, the aims are feasible, and the conclusions have a clear practical orientation and value.

Based on the above, I find that the **doctoral thesis** by Dr. Milko Dimitrov Milev: "Multimodal electrophysiological neuromonitoring in neurosurgical operative interventions" has the necessary qualities and **meets all criteria for the award of the educational and scientific degree "Doctor".**

30.12.2022

Sofia (N. Gabrovsky)