REVIEW

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Subject: Dissertation of Dr. Milko Dimitrov Milev, doctor at Acibadem City Clinic - Tokuda Hospital EAD, Sofia, on the topic "Multimodal intraoperative electrophysiological neuromonitoring in neurosurgical operative interventions" for the award of the Educational and Scientific Degree "Doctor" in the field of higher education 7. Healthcare and sports, professional field 7.1. Medicine, PhD program "Neurosurgery", with supervisor Dr. Vladimir Stefanov Nakov, MD, PhD

The neurosurgical specialty has undergone revolutionary changes in recent decades, and from the stage of “structural determination of areas of functional significance” it has already moved to a new stage, with the registration of "functionally active areas of the nervous system". From many years of experience, it is known that the preservation of a specific nervous structure responsible for a given function during operative intervention does not always mean the preservation of this function for the body, due to the existence of phenomena associated with dynamic change in the location and interrelation of structures and changes in the normal relations and courses of nerve elements as a result of pathological formations and processes. The purpose of registration of functional activity with electrophysiological monitoring is to prevent the development of persistent or transient neurological deficit during neurosurgical interventions. This requires the formation and development of modalities throughout the complex neurosurgical treatment, including the construction of algorithms for assessing the risk of postoperative deficit based on electrophysiological indicators. This brief exposé clearly conveys the essence of Dr. Milev's work, emphasizes its relevance and social significance.

Dr. Milko Dimitrov Milev was born in 1986 in Chirpan, and in Sliven he completed his secondary education with excellent grades. He acquired a master’s degree in medicine at the Medical University in Sofia in 2010, in 2011 he started specializing in neurosurgery at the University Hospital for Active Treatment "N. I. Pirogov”, and since 2015 he has been a resident at the University Hospital "Tokuda", where he completed his specialization in 2016. Completed the course "EFIC - European Pain School 2007" in Siena, Italy; “Pain Medicine" course at MU Sofia; Research Course - EANS, Krakow, Poland. He has participated in several research projects in 2006, 2007, 2008, 2009 and 2010 in the study of neuropathic pain. A list of 22 full-text publications in domestic and foreign journals, 58 abstracts from participation in scientific congresses and other forums is presented. He is a member of the Bulgarian and European Association of Neurosurgery, uses written and spoken English, his computer literacy is inimitable.

With this dissertation, Dr. Milev aims to analyze the importance of different electrophysiological criteria in neuromonitoring, to study their interactions with other clinical features of the individual case and specifics of the course and nature of the exact

surgical intervention and to filter the complex of the most essential indicators that allow the practical application of risk assessment models for neurological damage.

The dissertation is written on 177 pages in a consistent Bulgarian language, with a 26-page literature review covering 189 literature publications, with 12 publications by Bulgarian authors. The literature publications are relevant in time and topic of development. The dissertation is richly illustrated with 91 graphs, 4 figures and 2 tables. An abstract, produced according to the requirements, accompanies the dissertation. The dissertation is complemented with 6 full-text publications and 5 abstracts of participations in congresses in Bulgaria and abroad. Extreme attention is paid to some biophysical processes determining the reactivity and behavior of nerve tissue in the CNS when subjected to external electrical stimulation. A systematic analysis of the available literature data on the reliability of the different electrophysiological criteria applied in intraoperative diagnostics and prevention of damage to the primary motor cortex and cortico-spinal tracts was conducted. A review of the methodologies for monitoring of oculomotor nerves, as well as the possibilities for registration of the activity of the external eye muscles, was carried out. The review of the literature is complete and summarizes the currently available information on the specifics of electrophysiological neuromonitoring of the somatomotor system and oculomotor nerves in neurosurgical practice. It establishes the problematic aspects of the matter and the need for additional analysis of the electrophysiological criteria in terms of their informativeness for differentiation of risk events and actions during surgical interventions. The literature analysis allows for a clear and specific objective to be set: To establish a set of electrophysiological criteria in order to ensure timely and reliable identification of an increased risk of damage to the motor cortex and cortico-spinal tracts and to oculomotor nerves.

To achieve this goal, the author sets himself the following specific tasks:

1. To identify factors modifying the postoperative functional status.
2. To identify the factors modifying the electrophysiological criteria.
3. To identify the interconnections between electrophysiological criteria and postoperative functional status.
4. To generate multifactorial predictive classification machine models.
5. To perform optimization of multifactorial models by eliminating low-information factors and reducing information noise.
6. To generate a final oligofactorial machine model and to analyze critical values of electrophysiological criteria for the risk assessment for the development of neurological damage to the systems as well as the effects of the modifiers in task 1. and 2. on the criteria and on the postoperative result in the model.

The material on which the dissertation is based covers 174 surgical interventions performed with the direct participation of the author at Tokuda Hospital for the period

2016 - 2021, divided into two main groups. In the first group are included 130 clinical cases for which, in the course of the surgical intervention, were examined electrophysiologically the spatial relations of the interventional area to the primary motor cortex and cortico-spinal tracts or an electrophysiological assessment of the functional status of the above structures has been performed. The second group was composed of 44 operative cases in which electrophysiological localization and assessment of the functional integrity of 61 oculomotor nerves in cranial base and brain stem operations were performed intraoperatively. Three systems with different ranges of programmable assignments and available modalities - NIM Eclipse E3, NIM Eclipse E4 and NIM Neuro 3.0, the selection of the apparatus for each case is dictated by the number of types of modalities required and the number of required channels. The technical support of all operations is made almost as a user manual, which is especially important for the implementation of such an apparatus. Described in this spirit also are the techniques for direct cortical stimulation, mapping of the cortex, monitoring of the somatomotor system. Of great interest is the monitoring of the ocular muscles /m. rectus inf.; m. obliquus sup.; m. rectus lateralis/, for which the corresponding eye muscles and respectively structures of the brain stem and cranial base are responsible /m. oculomotorius; n. trochlearis; n. abducens/. In view of the precise selective insertion of these electrodes, an ultrasonic control technique has been developed.

The statistical analysis provokes admiration. The primary analysis of the data in a graphical environment is conducted with the help of Microsoft Excel 365, and the subsequent statistical analysis is realized through the «script notebooks» of the extension of the interactive development environment JupyterLab. For the purpose of complex data processing, descriptive and statistical analysis and respectively generation of illustrative graphics, modules of the Python programming language and the JupyterLab development environment were used. The analysis of the distribution of cases by nominal categories was conducted using Fisher's exact test. Student’s t-test was used for comparison of averages and distribution of the quantitative variables. For comparison of the values of ordinal variables, or upon rejection of the normal distribution of quantitative variables by the test of D'Agostino and Pearson, the nonparametric U-test of Mann-Whitney-Wilcoxon was applied. Comparison of quantitative variables between three or more groups was conducted using analysis of variance (ANOVA), which was conducted in its one- and two-factor subtypes. To identify significant differences between pairs of groups in a significant ANOVA test, a post-hoc HSD (honestly significant difference) Tukey’s test was applied. The comparison of values of ordinal variables between three or more groups, as well as of quantitative variables in case of inapplicability of ANOVA according to the above conditions was conducted by means of the H-test of Kruskal and Wallis, a post-hoc analysis for differences between groups in pairs by Dunn's test. Pearson’s coefficient was used to correlate two quantitative variables, and in the case of ordinal variables Spearman and Kendall’s rang correlation coefficients were used. P-values less than or equal to 0.05 were taken as statistically significant.

Of the patients in the first group - 130 with the average age of 55,7, 66 were men and 64 - women. The predominant diagnosis is volume occupying processes /118 patients, 90,9%/, and in a smaller part of them 12 /9,23%/ - a cerebrovascular disease. In the tumor

group predominantly mapping and monitoring of supratentorial sensorimotor zones and tracts was performed, the majority of the processes involved Sulcus centralis, Sulci et Giri pre- et postcentralis – 35 /29,5%/ cases. In 75% of the operated patient's radical resection was reported, and in 23,3% subtotal and in 1,7% - partial. In 28 cases, changes in electrophysiological parameters were reported that were categorized as indicating risk of damage to a functionally active area and the course of the surgical intervention was changed. In 47 of the cases, direct cortical stimulation of the motor cortex was performed. Overall, there was no significant difference in functional status – pre- and postoperatively, which confirms the efficacy of electrophysiological control. 44 surgical interventions were performed with localization and monitoring of cranial nerves in surgical interventions at the cranial base - 9/14.8%/ cases for n. oculomotorius, 12 /19.7%/ for n. trochlearis and 40 /65.6%/ for n. abducens. The mean age of the patients was 50 years, with 65,9% of the patients being female and 15 /34,1%/ male. In most patients the electrodes were implanted under ultrasound and electrophysiological control.

The conclusions are logically defined by the analysis of the literature review and the statistical processing of the results achieved and are defined both with regard to the electrophysiological examination of the motor cortex and corticospinal tract, as well as that of the oculomotor nerves. Summarized conclusions look like this: 1. The monofactorial analysis of electrophysiological criteria does not provide a sufficiently reliable assessment of the risk of neurological damage, unlike multifactorial machine learning models, which can successfully classify cases in which damage to the somatomotor system will occur. 2. Multifactorial classification models can be optimized by selecting the variables that are actually significant for the classification process, simplifying their application while maintaining or increasing the accuracy of the prediction. 3. Analysis of the model for the direction for classification of cases to the positive or negative class at different values of electrophysiological criteria, in the context of concomitant modifiers and risk factors, can identify threshold values for electrophysiological indicators in terms of the risk of damage to the somatomotor system. 4. An amplitude of cortical MEP below 50% is associated with neurological deficit, and between 50 and 100% there is an increased risk of deficit, with the result being determined by additional modifying factors: preoperative status, intensity of stimulation, age and inability to conduct a total resection of the solid tumor. 5. The combination of the registration of suprathreshold motor response to subcortical monopolar stimulation with an intensity below or equal to 5mA with a drop in the percentage amplitude of transcranial MEP below 50% of the baseline value is associated with risk of late moderately severe or severe postoperative motor deficit. With regard to the application of electrophysiological studies of the oculomotor cranial nerves the conclusions are seven: 1. Ultrasound control over the position of intraorbital electrodes allows their accurate positioning and leads to lower impedances in anatomically difficult localizations. 2. Impedance control on the electrode positioning is associated with more frequent registration of responses to direct nerve stimulation. 3. The combination of ultrasound and impedance control allows the recording of high-quality responses to n. trochlearis responses. 4. Machine learning classification models successfully identify cases at risk of development of postoperative oculomotor nerves deficit, as well as the values of electrophysiological criteria associated with an increased risk of deficit. 5. The latency of the response to direct nerve stimulation is a stable indicator correlated to the location of

the stimulation zone and can serve to differentiate nonspecific responses and artifacts. 6. An elevated risk of damage to the abducent nerve is registered during operations on basal meningiomas with exposed cisternal segment of the nerve. 7. A decrease in the amplitude of the compound muscle potentials from direct stimulation of n. abducens below 100 microvolts is associated with postoperative deficit.

The dissertation is notable for the extremely precise documentation, accurate analyses with the help of magnificent statistical processing and the contributions are essential and correctly formulated. The contributions are well formulated in three aspects:

Theoretical:

1. The literature review presents the current trends and the practical results of electrophysiological intraoperative monitoring of the primary motor cortex and corticospinal tracts and of oculomotor nerves.

2. The detailed analysis of the methods for localization of the primary motor cortex and corticospinal tract and the electrophysiological criteria for risk assessment allow the proposition of appropriate sets of electrophysiological tests to prevent their damage through the course of the surgical intervention.

Methodical:

1. The established relationships between postoperative status, clinical case characteristics and electrophysiological findings of intraoperative monitoring for cases with interventions in the supratentorial space with danger to the somatic motor function, and near the oculomotor nerves and their nuclei, provide the basis for conducting a selective analysis of the complex interrelations.

2. A machine learning model based on an algorithm for gradient boosted decision trees is created for the first time in the areas of neuro-oncology, operative neurosurgery, intraoperative neurophysiology.

3. For the first time, an assessment of the accuracy of the prediction of classification models has been made on the basis of indicators resistant to oversight of the importance of false-positive and false-negative results, which allows the abolition of the effect of imbalance of the classification classes.

4. The defined threshold values of the examined electrophysiological criteria, as well as the variations of these threshold values upon changes of concomitant modifiers, risk factors and other electrophysiological indicators, allow an assessment of the risk of damage to the primary motor cortex and corticospinal tracts and to the abducent nerve.

Practical:

1. The created oligomodal classification models for assessment of risk of damage

to the primary cerebral cortex and corticospinal tract during interventions for supratentorial tumors based on patient characteristics, tumor, surgical intervention, and electrophysiological criteria are routinely applicable in the neurosurgical operative practice.

2. An algorithm was developed for generation of individually calibrated curves of the values of electrophysiological criteria against the risk of primary motor cortex and corticospinal tract damage for the purpose of dynamic assessment of intraoperative neuromonitoring findings.

3. A technique for accurate, ultrasound- and impedance-controlled positioning of flexible intraorbital electrodes for the purpose of monitoring eye-motor nerves with generally available equipment is created and described.

4. For the first time in the literature, a protocol for ultrasound assisted positioning of intraorbital electrodes for monitoring m. obliquus sup. is given.

In conclusion: In the conduction of the defense of Dr. Milko Milev, all legal deadlines and requirements have been met. The dissertation of Dr. Milko Milev is fully completed, contains noteworthy contributions that significantly improve the quality and safety of surgical treatment of tumors in the CNS motor zone and the cranial base. From my personal impressions and the professional activity of Dr. Milev, I think that he is an established neurosurgeon, meticulous and consistent in his scientific and practical work. The dissertation works meet all the conditions and requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Rules of Acibadem City Clinic University Hospital Tokuda Sofia. This allows me to vote with pleasure for the award of the educational and scientific degree "Doctor" to Dr. Milko Milev.

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