OPINION

From Prof. Vasil Hristov Karakostov, MD, PhD

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SUBJECT: Dissertation of Dr. Milko Dimitrov Milev, PhD student at the Clinic of Neurosurgery of "Acibadem CityClinic University Hospital Tokuda" on the topic "Multimodal intraoperative electrophysiological neuromonitoring in neurosurgical operative interventions" for the award of the educational and scientific degree "Doctor" in the scientific specialty of "Neurosurgery"

In connection with the Order of the Executive Director of "Acibadem City Clinic Tokuda University Hospital and Decision of the Scientific Council (protocol No. 43/29.09.2022r.), I am appointed to give an Opinion of the dissertation of Dr. Milko Dimitrov Milee for the award of the educational and scientific degree "**Doctor**" in the scientific specialty of neurosurgery on the topic: "Multimodal intraoperative electrophysiological neuromonitoring in neurosurgical operative interventions".

Scientific advisor:

Associate Professor Dr. Vladimir Stefanov Nakov, MD, PhD

Dr. Milko Dimitrov Milev was born on 07.02.1986. In 2010 he graduated medicine at MU-Sofia. He started working as a resident-neurosurgeon at the Clinic no Neurosurgeon of Tokuda Hospital Sofia in 2015. After a series of training courses, as well as a course for neurosurgical specialization at UMHATEM ,,N. I. Pirogov", he successfully passes exams and acquires specialty in neurosurgery. He is fluent in written and spoken English language.

The dissertation work is presented on 177 pages, contains 95 figures and 4 tables, the literature sources include 189 literary sources, of which 12 by Bulgarian authors and 177 - by foreign ones. The dissertation paper was discussed and preferred for public defense from an extended scientific committee at the Neurosurgical Clinic at Acibadem City Clinic University Hospital Tokuda.

The literature review, which consists of 18 pages of the dissertation , is pragmatically concise but sufficient and thorough to give a clear picture of the issues the author works upon. A short historical review on the development of intraoperative neuromonitoring in the world is presented in a comprehensible, accessible and contemporary way, while at the same time particular attention is paid to the current situation and what has been done on the subject at national level. The anatomy and physiology of the central brain region, the pyramidal pathway and the various motor cortical representations are discussed in detail as the main subject of study of the dissertation. In the literature review, a good comparative analysis of the different techniques for electrophysiological mapping and monitoring of the central brain region and the pyramidal pathway, with highlight on their advantages and limitations. The modern use of intraoperative monitoring of oculomotor muscles is discussed in detail as a diagnostic technique in nosological entities related to surgery near the oculomotor nerves. Based on the literature review the author successfully defines the most important and unsolved problems in the field at present time.

The aim that the author sets: To establish a complex of electrophysiological criteria with the purpose to provide timely and credible identification of increased risk of damage to the motor cortex and cortico-spinal pathways and oculomotor nerves", is clearly defined, and the 6 tasks are sufficient, well formulated and specifically aimed at its solution. As an editorial note I would mention my disagreement with the content of the concept „machine models", which is present in problems No 4 and 6, which the author later in his dissertation fills with meaning, corresponding to the methodological facts set out, namely "computer-generated models''.

The clinical material, on which the dissertation is based, includes clinical, medical imaging and electrophysiological material from 174 surgical interventions in the period 2016-2021 year in which intraoperative electrophysiological neuromonitoring was performed.

The clinical study by its design is prospective and covers a 6-year period. The design of the study is well formulated in a quite detailed graphic scheme at the very beginning of the chapter "Materials and methods", although it is not labeled as a graph.

The scientific work describes in detail the studied parameters and periods of follow-up, and 2 independent, nosological groups are formulated in accordance with the two directions of the

aforementioned aims and tasks. The first group consists of 130 clinical cases in which, in the course of neurosurgical interventions, the spatial relations of the surgical intervention area to the primary motor cortex and cortico-spinal pathways were electrophysiologically investigated or an electrophysiological assessment of the functional status of the above structures was performed.

The second group consisted of 44 operative cases (for the period 2018-2021) in which electrophysiological localization and functional integrity assessment of 61 oculomotor nerves in cranial base and brain stem operations were performed intraoperatively.

The methodology for the two nosological groups of the study is very well described and illustrated in detail with the author's own photographs and direct recordings from the intraoperative monitoring equipment.

The results of the study are presented comprehensively enough, illustrated with a large number of figures, photographs, graphs and tables. Sufficiently informative methods, formulas and correlation methods are used for the processing of the obtained results, which impart the necessary statistical credibility to the criteria. Based on these results and indicators, the author defines with high level of certainty the parameters of relative safety based the amplitudes of cortical motor evoked potentials.

1.) which at values less than 50% are associated with the development of neurological deficit ($\leq 4/5$ p., MMT), and at amplitudes between 50 and 100% are at increased risk of deficit, with the end result being determined by additional modulating factors: preoperative status, intensity of stimulation, age, as well as the inability to perform a total resection of the solid tumor (which is not a small part of the cases is also related to the subjective factor of the surgeon's skills and experience).

2.) The combination of a suprathreshold motor response to subcortical monopolar stimulation with intensities of ≤ 5 mM with a drop in the percentage amplitude of transcranial MEP < 30% or of cortical MEP < 50% from baseline is related to the development of moderate or severe postoperative motor deficit ($\leq 3/5$ MMT).

In the discussion, the author very thoroughly and critically subjects to analysis all of the significant results of the study, comparing them impartially with the available data from similar series in the specialized literature. Of particular importance for the value of scientific work is the special attention that the author pays to the discussion about intraoperative monitoring of the two different nosolorical groups.

The conclusions of the study are structured in two parts that correspond to the two independent nosological groups in the design of the study.

A total of 13 conclusions made for the two independent nosological groups from the design of study, corresponding to a greater degree to the 6 set tasks and are analytically deduced and justified by the results and discussion.

In general, I believe that the ideas and methodologies presented in the current work have a rational and innovative prognostic character, some of which contain the signs of scientific and practical contributions. As contributions with greater significance I would would indicate:

First of all, the introduction and validation of the electrophysiological monitoring of the oculomotor muscles with the assistance of ultrasound positioning.

The reasoned assertion that an analysis only on the basis of electrophysiological techniques and criteria in intraoperative monitoring does not provide a sufficiently reliable assessment of the risk of postoperative neurologic deficit, I consider very practically credible and filled with meaning, unlike multifactorial machine learning models, which can successfully classify the cases with expected damage to the somatomotor system.

In relation to the dissertation the doctoral student presents 5 full-text articles (one of which has IF) and 5 abstracts from participations in scientific forums that deal with some important parts of the dissertation.

The content and layout of the proposed abstract of the dissertation correspond, in synthesized form, to the full text of the dissertation. The abstract is written on 95 pages and is illustrated with a sufficient number of tables and figures, which include sufficiently informative, author's own image material.

In conclusion, I believe that on the basis of the above, the dissertation presented by Dr. Milko Dimitrov Milev: "**Multimodal intraoperative electrophysiological neuromonitoring in neurosurgical operative interventions**" meets the quantitative and qualitative criteria for acquiring of the educational and scientific the degree of "**Doctor**". For this reason, I vote positively /for/ and I call on the members of the Scientific Jury to award the educational and scientific degree "Doctor" to Dr. Milko Dimitrov Milev.

28.12.2022r.   Prof. Vasil Karakostov, MD, PhD