



To the Chairman of the Scientific Jury

Nominated by order No P -1684/ 30.09.2020

of the Rector pa MU – Plovdiv

REVIEW

by Prof. Dr. Hristo Borisov Taskov, DSc.

Scientific Specialty "Immunopathology and Allergology", Medical University of Plovdiv, Department of Microbiology and Immunology member of the scientific jury, nominated by order of the Rector of the University of Plovdiv

Regarding: Procedure for defense of the dissertation on the topic: " ANGIONEUROTIC EDEMA – EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS, FORMS, CLINICAL COURSE, DIAGNOSTIC AND DIFFERENTIAL DIAGNOSTIC CRITERIA, THERAPEUTIC APPROACHES" for obtaining a scientific degree "Doctor of Sciences"

Author of the dissertation: Assoc. Prof. Dr. SVETLAN MIHOV DERMENDZHIEV, MD

The review was prepared in accordance with the requirements of the Law on Progress of Academic Staff in the Republic of Bulgaria, its Implementing Regulations, and the Rules of Procedure for acquiring scientific degrees and holding academic positions at the Medical University of Plovdiv.

The materials presented on paper/electronic form are in accordance with the procedure for acquiring the scientific degree "DOCTOR OF SCIENCES" and the rules of the University of Plovdiv.

When reviewing the dissertation submitted to me, I found no evidence of plagiarism. I declare the lack of common scientific works with the Assoc. Prof. Dermendzhiev and a potential conflict of interest as well.

I. Biographical data and career development of the candidate

Assoc. Prod. Svetlan Dermendzhiev MD, is born on 26.02. 1962 in Plovdiv. He graduated from the Medical University of Plovdiv between 1982 and 1988. In 2012 he acquired an educational and scientific degree "Medical Doctor". Between 2000 and 2013 he completed

16 postgraduate courses. His academic career began in 1991. at the Clinic of Occupational Diseases and Toxicology at MU-Plovdiv. Here he grew up as a Chief Assistant, Associate Professor (2014) and Head of the Department of Occupational Diseases and Allergology.at University Hospital Sent Georgi.

II. Topicality and importance of the thesis

The dissertation is dedicated to the modern aspects of angioedema, its epidemiology clinic and treatment. Angioedema is a disease whose medico-social significance is constantly increasing. This is because in clinical practice cases with an acquired form of the disease, especially after administration of ASE, tend to increase. Another indisputable fact that provokes interest for clinicians of various medical specialties is the multi-face clinical manifestation of the disease and its difficult primary diagnosis. The fact that hereditary angioedema is among allergic diseases associated with a high risk of fatal outcome should also not be overlooked. . In general, angioedema leads to a number of adverse physical, mental and socio-economic consequences and ultimately - to a poor quality of life with suboptimal therapeutic response. Therefore, timely, precise, multidisciplinary therapy is especially important. .

In general, the theme of the dissertation is contemporary and with increasing scientific and clinical significance. Assoc prof. Dermendzhiev knows the problem well, as evidenced by the well-structured review of literature and the bibliography used.. The professional analysis logically indicates the relationship between theory and practice. The aim and tasks of this dissertation are well formulated and are able to answer the questions raised in the literature analysis. They focus is on practical issues related to epidemiology, etiology, diagnosis and treatment of various forms of angioedema.

III. Research work

III. 1. Structure of the dissertation work.

The scientific work of Assc. Dermendzhiev meets the requirements for the development of dissertation: way of structuring, presentation the problem, analysis the data and defense the thesis of the author. The submitted material is written on 200 standard pages and contains 39 figures, 35 tables and 20 photographs. The literary reference numbered 287 titles, including 18 in Cyrillic and 269 in Latin. The bibliography is up-to-date and comprehensive, with the sources selected thematically as close as possible to the dissertation. The technical layout

complies with the requirements. The structure is executed in the required standard form - title page; abbreviations used (2 p.); introduction (1 p.); review of literature (69 pp.); aim and tasks (1 p.); material and methods (15 p.); own results and discussion (88 pp.); conclusions, contributions and recommendations (23 p.); (40 p) bibliography (19 p.).

The theme of the dissertation " Angioneurotic edema - epidemiology, etiology, pathogenesis, forms, clinical course, diagnostic and differential diagnostic criteria, therapeutic approaches" is appropriately selected in terms of importance of the problem and topicality at the present time.

The overview of the scientific literature is targeted and informative, providing an up-to-date overview of the modern problems of angioneurotic edema. Well described are the clinic, classification, clinical forms, etiology and medical treatment. The overview of literature contains sufficient data to motivate the author to choose the topic, explains the issues and provides basic theoretical data. Ass. Dermendzhiev has been able to define the problems and make a summary of the outstanding problems, which leads to the aim of the dissertation.

Objectives and tasks.

The well-formulated conclusions of the literary review create a prerequisite for correctly defining the objectives of the dissertation work: to analyze the prerequisites for the increasing importance of angioneurotic edema with its epidemiology, diagnostic criteria and clinical picture. The tasks of the dissertation are clearly formulated and demonstrate the main design of the working hypotheses.

The material and methods describe the structure of the clinical material and the methods of analysis. The survey was done between 2010 and 2016 on patients who have admitted to the Department of Occupational Diseases and Allergology at University Hospital Sent Georgie-Plovdiv. The dissertation included 2,211 cases, subdivided in 927 men and 1,284 women. A detailed clinical questioner is presented for collection very detailed information about patients and on the basis of which inclusive and exclusionary criteria are defined. The laboratory diagnostic methods used are presented in the results, but are not described in the section "Materials and methods", which I consider an omission of the dissertation.

Modern statistical methods are used for processing the results obtained: variation analysis of variants, dispersion analysis., non-parametric analysis. This combination of statistical methods makes it possible to thoroughly analyze the data and make solid conclusions. I

believe that, in this respect, the dissertation work would have had even greater value if a multi-factor correlation and regression analysis had also been used for the analysis.

In this part of the dissertation work, it is seen that Assacs. Dermendzhiev has correctly selected methodical approaches to resolve the objective set in order to ensure the reliability and reliability of the reported results.

The results and their discussion are presented on 88 p., with the data logically following the order of the tasks of the dissertation work. The text is illustrated 39 figures, 35 tables, which give synthesized information and facilitate the perception of the material. The results obtained are convincing and presented clearly and accurately, which creates excellent review and documentation of scientific facts.

In the first part of the results, Assoc.Prof. Dermendzhiev analyzes the epidemiology and profile of angioedema patients admitted in the Department of Occupational Diseases and Allergology for a 6-year period. With a admission diagnosis, angioneurotic edema are 58 patients or 2.6%. 29 cases were diagnosed the course of the treatment process and the total number reached 87 persons. The vast majority (82%) were with unknown etiology. It is found that the most common trigger of edema (42%) is a drug, most often estrogen. Injuries cause swelling to unlock in about 30% of cases. Food products as a reason for unlocking are indicated in 9% of cases. Of the drugs most likely provocateurs are acetylsalicylic acid (15.9%), antibiotics and chemotherapists (11%), analgesics (8%), preparations for local use (6.8%), hormones (4.5%).

It is interesting that the diagnosis is mainly based on anamnesis, clinical symptoms and allergological status, while laboratory tests contribute only 53% to diagnosis.

In the period of observation, a tendency to increase the number of cases with angioedema has been identified. In three-quarters of (71%) of the patients studied the edema was self-limiting, In about half of cases (44%) the localization of edema is on the soft tissues of the face, lips and eyelids, which corresponds to literary data. In 25% of cases redness was observed, which do other authors support. In the majority of patients (94%) treatment has resulted in complete resolution of edema.

The second section of the results is devoted to hereditary angioedema. In my opinion, this is the right approach because this form is less common and has specific pathogenesis. The results in this section are presented and illustrated very well. They basically coincide with

data published by other authors. Assoc. Prof. Dermendzhiev found that the leading cause in HAE type 1 were food allergens (45.5%), as well as in the combined type (27.3%). Analgesics, anesthetics and antipyretics that cause attacks in one third (33.3%) of patients with HAE type 1, while other groups of drugs are more common triggers in the combined form (37.5%) and in HAE type 2 (62.5%).

While in the scientific literature trauma is cited as a factor in unlocking attacks in a high percentage – 54%, Dr. Dermendzhiev describes this in 33.3% of patients. According to his observations, provoking factors are both the number of injuries and their nature: mechanical trauma surgical interventions, invasive manipulations on the larynx, etc. In patients with HAE, comorbidities were found in about twice as often (36.4%) then published by other authors. Despite the difficulty of proving, the familial predisposition, it was found in 60.6% of patients, best expressed in HAE type 1 and 2.

As the main biomarkers for HAE Dr Dermendzhiev brings out the C1 esterase inhibitor, inflated IgE levels, blood eosinophils and positive skin-allergic samples for various allergens.

Conclusions. Due to the large volume of data, each section of the results ends with conclusions. These conclusions are a total number of 52 and give in synthesized form the most significant results. This approach allows the reader to navigate more easily the multiple data and more clearly perceive the main results. The dissertation ends with summary conclusions that are allocated to each task. They are 30 in total and are clearly and precisely formulated. I accept the conclusions, as they follow from the results obtained and the discussion made.

Recommendations. The dissertation work ends with the "Recommendations" section. Based on the results guidelines have been proposed for future action for improving clinical and laboratory diagnostic criteria in angioedema. It is right to suggest that the results and conclusions obtained serve as a basis for the development, discussion and adoption of a National Consensus guidelines for the Diagnosis and Treatment of Angioedema.

Critical remarks and recommendations to the dissertation

- As I have already noted, I consider as a omission the lack of detailed presentation of laboratory methods in the chapter "Material and methods". Indeed, they are indicated in the results, but in my opinion they should be described in the chapter "Material and methods".

- Laboratory tests for exclusion of HAE were performed only in 23.9% of the patients. The motives are a lack of means and laboratory conditions. My recommendation is in the future, Dr. Dermendzhiev to apply for additional funding in the form of scientific projects in order to have patients processed in full.
- There is an imbalance between the chapter „Review of Literature " (69 pp.) and "Results and discussion" (88 p.) in the sense that the results and their discussion are usually two-thirds, up to three-quarters of the dissertation.
- Another omission, in my view, is the insufficient discussion of the results. A more detailed comparison should be made with the published literature data in order to more clearly outline the contributions of the dissertation.
- Many of the publications related to the dissertation are clinical cases. My recommendation is in the future Dr Dermendzhiev to make standard publications in international referred journals. This would contribute to a substantial improvement in its indicators as researcher.

These critical notes and recommendations do not change the value of the presented dissertation, but aim to improve the scientific work of Dr. Dermendzhiev for his academic development.

III.2. Contributions

The successful solution to the assigned tasks is projected in the chapter of contributions – a total of 41. They are formulated as being of a scientific and theoretical character (7); applied-science character (7); of an original (14) and of a confirmatory character (13). I definitely think the contributions are unnecessarily fragmented. Therefore, some of them do not correspond to the category in which they are placed. For example, as a contribution of a scientific and theoretical character, it is stated *"For the first time in our country, the problem of angioneurotic edema is considered in its comprehensiveness and diversity, and in addition to clinico-diagnostic indicators related to the socio-demographic characteristics of the surveyed contingent"*. In principle, this statement is true as a feature of the dissertation work, but it has no character of theoretical contribution. It is similar to the scientific and theoretical contribution: *'A special place in the study of the etiology of the disease is dedicated to the study and specification of the family preposition and encumbrivity, as well as the role of concomitant diseases as unlocking factors.'*

In my opinion, the main contributions of the dissertation work are as follows:

Contributions of an original character

- The results of the survey clearly outline the socio-demographic profile of persons with angioedema in Bulgaria over 50 years of age, mostly women, and among medical staff, the predominance of service personnel.
- An original contribution is the establishment of the combination of angioedema with other allergic diseases/syndromes: allergic asthma, allergic rhinitis, urticaria, contact allergic dermatitis and others. Of particular importance is the established association with urticaria in nearly half of the persons surveyed.
- The original contribution is also the unique cases described of a combination of patients with rare and congenital diseases, such as the case of a patient with HAE and Arnold-Chiari type 1 syndrome (malformation).
- From a practical point of view, the two-time major association of HAE with concomitant diseases is important. Further research will be needed in this direction to clarify this association in more detail.
- Another important contribution is the finding of a correlation in dynamics between the number of provoking events and bouts of angioedema. More future studies in this regard would contribute to studying the relationship of the disease with another type of pathology.

Contributions of an applied character

- As available indicators for most medical services in the country blood eosinophils and general IgE levels can be used as a first step to differentiate allergic from non-allergic forms of angioedema, As a second step, as more precisely specific allergic mechanisms of angioedema can be used skin-allergic samples and determine the levels of specific IgE.
- To this group of contributions I also refer to the recommendations for future action to improve clinical and laboratory diagnostic criteria in angioedema. It is right to suggest that the results and conclusions obtained serve as a basis for the development, discussion and adoption of a National Consensus guidelines for diagnosis and treatment of the disease.

I accept all the contributions made with a confirmatory character. They enrich existing knowledge and are essential for their application in clinical practice in Bulgaria. I definitely

believe that the practical value of the above data, conclusions and contributions is indisputable for routine practice.

III.3 Assessment of mandatory scientific indicators related to the dissertation work

The publications of Dr Svetlan Dermendzhiev are 28, published in national and international journals, and meet the requirement to be thematically related to the dissertation. Of these, seven are in international journals with impact factor, 4 publications are in Bulgarian journals, listed in Scopus and 17 of the publications are Bulgarian journals that are not listed in Scopus. Eleven of the articles are in English, the remaining 17 are in Bulgarian language. Ten abstracts of congresses and conferences have been published in journals, listed in Scopus, and 17 abstracts have been published in other collections and journals. The total impact factor of the publications is 11,441. I didn't include the impact factor in two journals with congressional abstract.

The list of scientific papers includes three monographs, which are on the subject of the dissertation. Two are in Bulgarian and one in English. Monographs have rather an overview character but they are useful for a wide range of medical professionals.

In the submitted documents, Assoc. Prof. Dermendzhiev has indicated 11 articles, for which he has found 23 citations. Of these, 5 publications with 6 citations are thematically related to the dissertation. In this sense, the citations presented rather reflect the general scientific activity of the candidate.

In conclusion, I believe that the main results of the dissertation have been published in accordance with the requirement of the law and its implementing rules. The number of publications and science indicators comply with the Rules of Procedure for acquiring scientific degrees and holding academic positions at the Medical University of Plovdiv. 4.

Extended summary of Dissertation

The author's content and quality of the proposed author's report meet the requirements of the respective regulations. It is formed on a good technical level. It is structured in full compliance with the text of the dissertation work and reflects the research, results, conclusions and contributions requested.

Conclusion

The dissertation work contains scientific and applied results, which represent an independent contribution and meets all the requirements of the Law on development of academic staff in the Republic of Bulgaria its Implementing Regulations and the Rules of Procedure for acquiring scientific degrees and holding academic positions) at the Medical University of Plovdiv. The dissertation on the topic: " ANGIONEUROTIC EDEMA – EPIDEMIOLOGY, ETIOLOGY, PATHOGENESIS, FORMS, CLINICAL COURSE, DIAGNOSTIC AND DIFFERENTIAL DIAGNOSTIC CRITERIA, THERAPEUTIC APPROACHES " is dedicated to an up-to-date clinical problem. Its scientific value stems from studies, discussions and contributions. The dissertation shows that Dr. Dermendzhiev possesses the necessary theoretical knowledge and professional skills in the scientific specialty "Immunopathology and Allergology", as well as that he demonstrates qualities and skills for organizing and conducting a complex scientific study.

In connection with all of the above, I give my positive assessment and propose to the esteemed members of the scientific jury to award a scientific degree "Doctor of Sciences" to Assoc. Prof. Dr. Svetlan Mihov Dermendzhiev in the field of higher education 7. "Health and Sport", in professional field 7.1 Medicine, in scientific specialty "Immunopathology and Allergology", code 03.01.27.

24.10.2020

Plovdiv

Signature:

Prof. Dr. Hristo Taskov DSc