

STATEMENT

by **Assoc. Prof. Georgi Stoyanov Nikolov, MD, PhD**

National Center for Infectious and Parasitic Diseases, Sofia,

Department of Immunology

for awarding the scientific degree of Doctor of Medical Sciences

in professional direction: 7. "Health care and sports"

Field of higher education: 7.1. "Medicine"

Scientific specialty "Immunopathology and allergology"

Candidate: **Assoc. Prof. Svetlan Mihov Dermendzhiev, MD, PhD**

Department: Second Department of Internal Medicine, Faculty of Medicine,
Medical University - Plovdiv

Subject: **Angioneurotic edema - epidemiology, etiology, pathogenesis, forms,
clinical course, diagnostic and differential diagnostic criteria,
therapeutic approaches**

1. General presentation of the procedure and the candidate

The presented set of materials on paper and electronic media is in accordance with Art. 123 (1) of the Procedure for achieving the scientific degree of Doctor of Sciences in Medical University - Plovdiv and the Regulations of Medical University - Plovdiv from 06/11/2014, and includes all required documents.

Copies of 32 publications were presented in relation to the subject of dissertation.

Assoc. Prof. Svetlan Dermendzhiev was born on 26/02/1962. In 1988, he graduated his higher education in Medicine at the Higher Medical Institute, Plovdiv.

During the period 1988 - 1990 he worked as a therapist in Karlovo.

From January 1991 till 2006 he was a doctor at the Clinic of Occupational Diseases and Toxicology, Department of Toxicology and Intensive Care at the Higher Medical Institute - Plovdiv. And from May 2006 to August 2011 he was a doctor at the Clinic of Occupational Diseases and Toxicology, Department of Toxicology and Intensive Care of the "St. George"

University Hospital, Plovdiv. From September 2011 until now he is a Head of Department at the Clinic of Occupational Diseases, Department of Occupational Diseases and Allergology.

During the period February 1996 to 2014 he was Senior Assistant Professor, and since 2014 he has been an Associate Professor in the Second Department of Internal Medicine, Department of Occupational Diseases of the Medical University - Plovdiv. Since 2012 - until now he is the Head of the Section of Occupational Diseases.

In 1994 he acquired a degree in Internal Medicine.

In 1996 he acquired a degree in Clinical Toxicology.

In 2006 he acquired a degree in Clinical Allergology.

In 2008 he acquired a degree in Occupational Diseases

In 2010 he graduated with a Master's Degree in "Health Management" at the Faculty of Health Sciences of the Medical University of Plovdiv.

In 2012 he achieved the scientific degree of PhD defended with doctoral thesis on "Comparative analysis of allergic diseases of general and occupational nature for a 10-year period in the Plovdiv region" in the scientific specialty Social Medicine and Organization of Health and Pharmacy.

Assoc. Prof. Dermendzhiev was a member of the Faculty Council of the Faculty of Public Health of Medical University of Plovdiv (2009-2010). Since 2018 he has been a member of the National examination committees in the specialties "Clinical Allergology", "Occupational Diseases" and "Clinical Toxicology".

He is a member of a number of national and international scientific communities: Bulgarian Society of Allergology; Bulgarian Clinical Toxicology Association (until 2016); Bulgarian Scientific Society of Occupational Diseases, of which he has been chairman since 2018; European Academy of Allergology and Clinical Immunology (EAACI); World Allergological Association (WAO); International Conference on Rare Diseases & Orphan Drugs (ICORD).

The scientific output of Assoc. Prof. Dermendzhiev includes a total of 82 publications (1 dissertation for the scientific degree of PhD, 6 monographs, one of which is published in English. He has published over 70 articles in national and international journals; 4 publications in educational manuals).

Conducts theoretical and practical training of doctors in the specialties "Clinical Allergology" and "Occupational Diseases" with 5 graduates.

He was a Scientific Consultant of 1 PhD student. Now he is the Supervisor of 1 PhD student.

The candidate has participated in 2 scientific projects in Bulgaria.

The scientific indicators of Assoc. Prof. Dermendzhiev are in accordance with the national requirements for the academic degree "Doctor of Sciences" in Professional field 7.1. Medicine.

2. Relevance of the subject

Angioneurotic edema is a disease with a wide range of etiological, pathophysiological factors and mechanisms, which makes it incompletely studied and poorly understood. The clinical manifestations are diverse, and hence the diagnostic and therapeutic algorithms are subject to constant updating.

In this regard, the doctoral thesis of Assoc. Prof. Dermendzhiev examines: the frequency, etiology, clinical manifestation, course, comorbidities and therapy in patients with angioedema in the Department of Occupational Diseases and Clinical allergology at the "St. George" University Hospital, Plovdiv.

The influence of occupational environment factors, whose role in the etiology and pathogenesis of angioneurotic edema has not yet been well elucidated, is assessed. The clinical manifestations are systematized and the different clinical forms are differentiated. Diagnostic-therapeutic algorithms are introduced, analyzed and attempting to individualize the therapeutic approach in different forms of this disease.

The original results of the doctoral thesis have been published in Bulgarian and international scientific journals.

3. Knowledge on the subject

Assoc. Prof. Dermendzhiev demonstrates a good knowledge of the problem. The literature review has a volume of 69 pages. Detailed information is provided on the etiology, genetics and epidemiology of angioneurotic edema. The classification, clinical picture and differential diagnosis are described. New approaches in the treatment and prevention of this common allergic disease are discussed. A special place is given to hereditary angioedema. The modern knowledge about the disease and its treatment is presented, as well as the new researches in the direction of development of drugs aimed at prevention and treatment of its

acute phase.

The main text of the review has been published in three separate monographs.

4. Objective and methodology of the dissertation

The objective and tasks of the dissertation are thoroughly and expertly set. The doctoral thesis aims to assess the significance of angioneurotic edema as a serious, often life-threatening problem by analyzing the epidemiology, etiology, clinical picture and diagnostic criteria of the disease.

For the implementation of the set aim Assoc. Prof. Dermendzhiev has focused his efforts on solving 5 tasks that structure a sound approach to the study.

During the study period, 2211 patients treated in the Department of Occupational Diseases and Allergology of "St. George" University Hospital, Plovdiv were observed for a period of 4 years. 10.9% of patients have an unspecified allergy, and angioneurotic edema is diagnosed in 3.9% of cases. The number of patients with hereditary angioedema followed in the study was 8.

Assoc. Prof. Dermendzhiev used modern clinical and laboratory diagnostic methods and immunological approaches to assess patients' sensitization to a range of conventional allergens, as well as some key indicators of their immunological reactivity.

The results are statistically analyzed with appropriate methods and are illustrated with a sufficient number of figures and tables.

5. Characteristics and evaluation of the dissertation

The dissertation is written on 171 pages and is formed according to the generally accepted academic form. It is illustrated with 38 diagrams and 35 tables. The bibliography contains 287 literature sources, 18 in Cyrillic and 269 in Latin.

Data on the frequency of angioneurotic edema and its forms are provided, and an increasing trend of hospitalized patients with angioneurotic edema over the age of 50 years has been established. A higher incidence of the disease has been found among women who are engaged in a certain profession.

The spectrum of etiological factors that trigger the clinical manifestation of angioedema is characterized by diversity and variety. Medicament intake and the impact of trauma are leading causes of angioneurotic edema. The pharmacological agents and substances that most often

trigger the onset of the disease are: acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, antibiotics and chemotherapeutics, analgesics, topical preparations, hormones.

In the studied patients with hereditary angioedema it was found that the leading factor in triggering edema are food allergens and insects, followed by the frequency of trauma, and medicaments, such as analgetics, anesthetics and antipyretics. Trauma stands out as a leading factor triggering angioedema attacks in patients with HAE type 1. Mechanical trauma is the most common provoking factor in the combined type of HAE, and surgery is the cause of swelling in the group of patients with HAE type 1.

The results of the study indicate diversity both in terms of clinical forms and clinical picture of angioneurotic edema, as well as in terms of the presence of other concomitant diseases with allergic and non-allergic etiology and pathogenesis. In 84.1% of cases, edema is accompanied by other symptoms, the most commonly reported concomitant clinical manifestations being itching, rash and erythema. The examination revealed that angioedema is often combined with other allergic syndromes, among which urticaria predominates (in 46.6%).

Almost half of patients with angioneurotic edema have at least one concomitant disease. The most common among the accompanying and socially significant are diseases of the cardiovascular, endocrine, musculoskeletal, nervous and respiratory systems. People with HAE type 1 have the most concomitant suffering.

The leading role in the diagnosis of angioneurotic edema has the clinician-allergist, while for the correct and accurate diagnosis in patients with hereditary angioedema an immunological laboratory tests are important.

Having in mind the specifics of the etiology and pathogenesis of HAE, the results of the study confirm the ineffectiveness of conventional antiallergic therapy with antihistamines, corticosteroids and adrenaline in patients with HAE. A good therapeutic response and beneficial response to HAE is achieved by the administration of specific therapy with a recombinant C1 esterase inhibitor or fresh frozen plasma.

The obtained results are appropriately illustrated, which makes their perception easy and convincing.

The summarizing conclusions are formulated according to the performance of each specific task and reflect the essence of the obtained results. They emphasize the relevance of research and

can serve as a theoretical justification and practical application of an individualized therapeutic approach in various forms of this disease.

The doctoral thesis is precisely structured and I have no significant remarks on the methodology, presentation of the results and their analysis.

6. Assessment of dissertation contributions, publications and the candidate's personal contributions

I accept the formulated original scientific and confirmatory contributions from the doctoral thesis and I believe that they objectively reflect the real results of the conducted research.

I consider the following contributions to be more significant:

- A thorough analysis of the etiology of the disease was performed and were examined and analyzed a wide range of factors that trigger and provoke the manifestation of angioedema (drugs, food, insects, trauma, invasive manipulations, occupational factors et ctr.).
- It has been established the importance of blood eosinophils and the levels of total IgE as biomarkers that can be implemented as a routine and widely available method for the differentiation of allergic from non-allergic forms of angioedema.
- The immunological panel used for the study, including the determination of C4 levels, the amount and quality of C1-INH, can be used to differentiate the unclear and unresponsive edema cases.
- The results and conclusions of the survey can be used to optimize public spending on diagnosis and treatment of different types of angioedema.

Assoc. Prof. Dermendzhiev has published 32 scientific papers related to the dissertation: 3 author's monographs, 1 Guide for theoretical and practical training of students, postgraduates, doctoral students, general practitioners and 28 articles in Bulgarian and foreign scientific journals. There are 19 scientific communications, of which 7 participations in scientific forums abroad and 12 participations in scientific forums in Bulgaria.

The quantity and quality of the publications related to the doctoral thesis exceed the requirements for awarding the scientific degree of Doctor of Medical Sciences, as set by Medical University - Plovdiv.

7. Abstract

The abstract has been prepared according to the requirements and written on 81 pages, and accurately reflects the dissertation studies, results and conclusions.

CONCLUSION

In conclusion, I would like to summarize that the presented doctoral thesis of Assoc. Prof. Svetlan Dermendzhiev has significant scientific and practical value and fully meets all requirements for achieving the degree of Doctor of Medical Sciences, regulated by the Academic Staff Development Act (ASDA) in the Republic of Bulgaria, the Regulations for the implementation of the ASDA and the corresponding Regulations of Medical University - Plovdiv. The presented materials and dissertation results fully correspond to the specific requirements of Medical University - Plovdiv.

Because of the above, I confidently give my positive assessment of the conducted research and recommend to the members of the honorable scientific jury to vote positively for awarding the scientific degree of Doctor of Medical Sciences to Assoc. Prof. Svetlan Mihov Dermendzhiev.



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Assoc. Prof. Georgi Nikolov, MD,PhD

26.10.2020