REVIEW

by

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regarding a dissertation thesis on the topic

"Approach to uveitis in Bulgaria"

by Silvia Nikolaeva Nikolova, MD

for the awarding of the educational and scientific degree "Doctor" in the scientific specialty "Ophthalmology", code 03.01.36

Research supervisor: Assoc. Prof. Binna Nikolaeva Nencheva, MD. PhD

The presented set of materials on paper and electronic media is in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

Brief biographical data

Dr. Silvia Nikolaeva Nikolova was born in 1983 in the city Aitos. In 2009 she graduated medicine at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. After graduating, she gained experience in the pharmaceutical sector as a medical representative (2009-2018), as well as in the field of Obstetrics and Gynecology as a resident physician at MBAL-Burgas. In 2018, she acquired a specialty in ophthalmology diseases, after specialization at SBOBAL-Varna. Since 2021, she has been a part-time assistant at the Department of Eye Diseases and Vision Sciences of the University of Varna, a full-time lecturer at the department for "Medical Optician" and a specialist ophthalmologist at USBOBAL-Varna. Her scientific interests are focused on the treatment and follow-up of patients with uveitis, surgical treatment of the anterior eye segment and eye appendages, treatment and follow-up. Dr. Nikolova actively participates in both research and clinical work, annually attending courses and conferences, for which she presented a detailed list. She is a member of the Bulgarian Medical Association and the Bulgarian Society of Ophthalmology. She speaks Russian and English and has very good computer literacy.

Teaching work

Dr. Nikolova teaches classes on eye disease to medical, dental, medical optics and optometry students.

Relevance of the problem

Uveitis represents a large group of diseases. The inflammatory process often involves not only the uvea, but also adjacent structures, including the retina, optic nerve and vitreous body. It may cause permanent and irreversible damage to the visual function. Its distribution depends on many demographic factors, influence of the environment, social habits, health care and health care system in the country. Uveitis affects both working-age patients and the non-working population. This is a prerequisite for many socio-economic problems for the health system and society. These changes, the complex etiology and multifaceted nature of the

disease, give rise to the need to continuously update the knowledge of uveitis and its characteristics, as well as epidemiological data. The analysis of the latter helps to reveal the predisposing factors and the pathogenesis of the disease. Uveitis often presents as an element of a systemic disease requiring an interdisciplinary approach. New diagnostic technologies and the implementation of databases through artificial intelligence would contribute to making a precise diagnosis. That is why Dr. Nikolaeva's dissertation is up-to-date and draws attention to the need to study this complex and multidisciplinary disease.

Structure of the dissertation

The dissertation contains 212 standard typewritten pages, distributed as follows: literature review (88 pages), aim and objectives (1 page), materials and methods (17 pages), results, discussion, conclusions and contributions (73 pages). They are illustrated with 22 tables and 60 figures. 217 literary sources are cited, but there are no Bulgarian authors included.

The presented literature review shows a good knowledge of the problem. The aim and objectives are correctly formulated.

The **aim** of the dissertation is to study and evaluate the sociodemographic characteristics, diagnostic and therapeutic algorithms, as well as complications in patients with uveitis based on a retrospective analysis and prospective follow-up over a period of 8 years.

To achieve the aim, the author sets herself 6 tasks:

- To conduct a review of the publications in the literature and an evaluation of the modern diagnostic approaches in patients with uveitis and the therapeutic approaches applicable to them;
- To investigate and analyse the socio-demographic characteristics and etiology of patients with uveitis for a period of 8 years;
- To analyse the course of uveitis, diagnostic approaches and therapeutic algorithms in patients with uveitis who underwent treatment at USBOBAL-Varna;
- To evaluate the complications of the course of the disease, concomitant diseases and side effects of the therapy;
- To analyse the duration and course of the disease (relapses, remission intervals);
- To create a risk profile of the studied patients with uveitis and to predict the risk of recurrence in patients with infectious and non-infectious uveitis.

Material and methods

The present study was conducted on the territory of the University Specialized Hospital for Eye Diseases for Active Treatment - Varna for a period of 8 years in two time periods from 2014 to 2018 and from 2019 to 2021. 219 patients who underwent treatment in hospital and pre-hospital care were studied. The selection of patients is based on previously defined criteria: patients with uveitis as an independent or accompanying disease, under and over 18 years of age and who, have completed an informed consent form. Exclusion criteria were: patients with other ophthalmic diseases not accompanied by uveitis, patients with uveitis and with mental disabilities and those who did not complete an informed consent form. The research methodology includes a documentary method, diagnostic methods and therapeutic algorithms. The sociological method included establishing a survey card corresponding to the objectives of the study and conducting a survey among patients. Clinical methods include the performance

of specialized tests, including high-tech ones (optical coherence tomography and fluorescein angiography). The collected data was processed using the following statistical methods analysis of variance (ANOVA, MANOVA), variation, correlation, regression and comparative analysis and risk assessment analysis (OR, RR).

The carried out treatment is etiological according to the etiology, symptomatic in case of idiopathic uveitis and systemic in case of systemic diseases. Initiation of treatment with topical anti-inflammatory agents and cycloplegics is important after diagnosis of uveitis. In recent years, biologic agents, biologic response modifiers, anti-TNF-alpha necrosis factor therapies, anti-IL-6 therapies and next-generation calcineurin inhibitors have provided new options for the treatment of uveitis. The same have been applied only in isolated cases.

Results

The results obtained during the study are presented in an appropriate form, illustrated with a sufficient number of figures and tables. The author analysed data from 219 uveitis patients in two time periods retrospectively for 2014-2018 and prospectively for 2019-2021. The average age of the examined patients for both periods was 54.21 years. ± 17.66 years, with the minimum age being 6 years and the maximum being 92 years. The study of the age indicator shows that during the second studied period there is a tendency towards rejuvenation of uveitis patients (respectively 56.04 years for the period 2014-2018 and 52.07 years for the period 2019-2021). The analysis of the results according to gender shows that there is a slight predominance of men (respectively 57.3% for men and 42.7% for women). No significant gender difference was found in the two studied periods.

The majority of patients with uveitis are from the cities (85.3%), and the urban: rural ratio is preserved during both periods (83.9% for the cities for 2014-2018 and 86.9% for 2019-2021, respectively). The analysis of uveitis patients according to place of residence and age shows that patients from villages are younger than those from cities (respectively 49.3 years for villages and 55.0 for cities). No significant difference was found in the average age of the patients according to the type of uveitis, with the average age of the patients with acute form of uveitis being 52 years and the chronic form being 55.5 years.

Patients with unilateral ocular involvement had a mean age of 54.6 years and those with bilateral involvement had a mean age of 48.1 years. A significant difference was found regarding the type of uveitis according to the studied period ($p<0.001$), as in 2014-2018. the chronic form of uveitis prevails (66.4%), and in 2019-2021 is the acute form (65.2%). A significant difference was also displayed regarding the severity of uveitis and the place of residence of the patients ($p=0.047$), with the majority of patients from cities having moderate severity of uveitis (52.2%), while 46.9% of patients from villages had severe uveitis. A significant difference was also found regarding the localization and severity of uveitis ($p<0.001$), with anterior uveitis being mostly of moderate severity (54.8%), while posterior uveitis was more often severe (89.5%). The most common are idiopathic uveitis (42.2%), followed by etiological agents such as herpes zoster, ankylosing spondylitis, herpes simplex and rheumatoid arthritis.

When comparing the use of topical and systemic corticosteroids, no significant difference was found. Systemic NSAIDs are applied significantly less compared to local NSAIDs ($p<0.001$), on the other hand systemic and local antibiotics for 2019-2021 maintain a high frequency of use. The frequency of use of antiviral medications remained below 10% for both topical and systemic use for both periods studied. In the administration of parasympathomimetics and sympathomimetics, a greater frequency was also observed for the second studied period, but

the difference was not statistically significant. Anti-glaucoma medications are more widely used in therapy for 2014-2018, with no significant difference between the two periods. The use of systemic corticosteroids, antivirals, and antibiotics is most common in patients with moderately severe uveitis. The use of systemic NSAIDs increases with the severity of uveitis, and immunosuppressants are used only in patients with severe uveitis.

The dissertation student establishes that in 2014-2018 uveitis recurrences occurred in younger patients. No significant difference was found in the occurrence of relapses according to gender, with males predominating in both studied periods.

Dr. Silvia Nikolaeva Nikolova has developed a "risk profile" of patients with uveitis and an algorithm for the systematic course of the eye examination when making the diagnosis. The systematic approach developed for pre-hospital ophthalmologists is particularly important, since knowledge is often lacking, which disrupts the diagnostic and therapeutic process.

Discussion

In Dr. Nikolova's dissertation work, uveitis is considered as a multifactorial, multifaceted disease that can progress differently in each patient. Because of this, the disease creates many differential-diagnostic and often therapeutic problems. In the chapter "Discussion", the good practices in European countries, as well as on a global scale, are thoroughly followed by analysing how far they have been adopted in the country. The own results are consistently examined and compared with the studies of a number of foreign authors, analysing the similarities and the differences in the indicated data. Attention is paid to the need for integrated care and collaboration not only with general practitioners, but also other specialists regarding the multidisciplinary disease. The dissertation emphasized the need to know the symptoms of the disease from the general practitioner in order to have a faster reaction time and start timely treatment.

Dr. Nikolova draws attention to the fact that Bulgaria lacks reference centres for patients with uveitis, stressing the need for them.

10 conclusions have been formulated, of which the following are most significant:

- Idiopathic uveitis predominates with the most common causes being herpes zoster (6.9%), ankylosing spondylitis (5.1%), herpes simplex (4.6%) and rheumatoid arthritis (2.3%). The localization of uveitis correlates with the age of the patients and with the severity of the disease.
- A significant difference was observed in the medical treatment of uveitis, with biological medications being used primarily in patients with moderate and severe forms of the disease. The use of systemic NSAIDs increases with the severity of uveitis and immunosuppressants are used only in patients with a severe form of the disease.
- For the Bulgarian population, the following risk factors for recurrence of uveitis were identified: rheumatoid arthritis, herpes simplex and ankylosing spondylitis and their severity decreased during the second study period, which can be explained by improving the control of the disease through the application of biological therapy.
- The risk profile of uveitis patients for disease recurrence and development of severe disease includes the presence of systemic diseases (psoriasis vulgaris), autoimmune diseases (ankylosing spondylitis and rheumatoid arthritis) and viral agents (herpes zoster), binocular involvement and residence in a rural area.

The contributions of the dissertation work are 12 in number, divided into three groups with a scientific-applied, practical and cognitive nature. I consider the following to be the most important of them:

- For the first time, an analysis of patients with uveitis in North-Eastern Bulgaria was performed with an emphasis on epidemiology, diagnosis, treatment and complications. This complex analysis is done in the context of the capabilities of artificial intelligence.
- Algorithms for diagnosis and treatment in patients with infectious and non-infectious uveitis and risk profile of patients with uveitis and prediction of recurrences were created.
- Guidelines have been created for general practitioners with the aim of early diagnosis of uveitis, raising awareness, starting effective treatment and improving the quality of life of patients.

IN CONCLUSION: The presented dissertation work is a complete and well constructed scholarly work with significant author's contribution. It fully meets the requirements of the Law on the Development of the Academic Staff of the Republic of Bulgaria and the Regulations of the University of Varna for its application. This gives me the reason to give my positive assessment and to suggest to the members of the respected scientific jury to vote positively for awarding the educational and scientific degree "Doctor" to Dr. Silvia Nikolaeva Nikolova.

20.12.2024. Signature:

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