Review

on dissertation for award on educational and scientific degree "DOCTOR" in scientific specialty " Ophthalmology " at topic :

Approach to uveitis in Bulgaria

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Brief autobiographical data

Dr. Sylvia Nikolaeva Nikolova was born in 1983 in the town of Aytos . She graduated at the Secondary School "Ivan Vazov " in the city of Burgas in 2001. Studied medicine (2002-2009) at the Medical University "Prof. Dr. Paraskev" Stoyanov " – Varna. After graduation, she acquired experience in pharmaceutical sector as medical representative (2009-2018) to Libra EAD, Finohelt EOOD and PHOENIX Pharma EOOD, as well as in the field on Obstetrics and gynecology as doctor resident at the Burgas Hospital . After specialization by " Eye " diseases " in SBOBAL - Varna , in 2018 acquired specialty in eye diseases. Since 2021. is part-time assistant to "Department of Ophthalmology and Vision Sciences " of MU- Varna , followed by full-time assistant at "Medical optician" specialty and ophthalmologist at SBOBAL- Varna. Her scientific interests are directed to treatment and follow-up on patients with uveitis, surgically treatment on anterior ocular segment and eyelids, treatment and follow-up on glaucoma patients. Dr. Nikolaeva continuously increases the qualification, participating in courses and conferences , for which she presented detailed list . Member of Bulgarian medical Union and Bulgarian ophthalmological society . She fluently speaks Russian and English language. .

Problem overview

Uveitis includes big group infectious and non- infectious diseases with variable etiology. In many from the cases the inflammatory process engage not only the uveal tract, but also the neighboring structures: including retina, optic nerve and vitreous body and can result in semi-permanent or irreversible disruption of structure and function. The distribution of the disease depends on multitude demographic factors as age, gender, race, geographic location, heredity, influence on the environment and even social habits. For the last years ommune-mediated uveitis has a predominance over infectious uveitis. The clinical picture on uveitis also tolerate dynamics in connection with new trends in the course of diseases and their treatment. All these facts give rise to necessity from continuously renewal of knowledge about uveitis and its epidemiological characteristics. Comparing on epidemiological data provides opportunity for the disclosure on predisposing factors in the different regions and gives new insights into pathogenesis on the disease, as well as outlines

the road for future studies. Uveitis affects basically the working population and generates social and economic problems for the health system and society. Patients suffering uveitis, often have systematic disease and their conditin requires interdisciplinary approach. New diagnostic capabilities require rethinking and reworking of the algorithms applied in real clinical practice. It is especially important for the differential diagnosis to perform serological tests, imaging and other investigations in order to clarify the overall picture of the disease and to take diagnostic and preventive steps. Last but not least, new technologies and the implementation of artificial intelligence would contribute to a precise diagnosis and prognostic algorithm for the disease. That is why Dr. Nikolaeva's dissertation is a timely addressing of the problem and represents a very serious step in the unexplored field of this polyetiological , complex and multidisciplinary disease.

The dissertation labor contains 212 pages , distributed as follows: overview, goals and objectives, materials and methods, results, discussion, conclusions and contributions. The text includes 22 tables and 60 figures . Cited are 217 literary sources , only in English. The probable explanation for this is that after the 1970s there have been almost no publications in Bulgaria (except for clinical cases) on the topic and the first monograph of the new millennium will soon be published by Dr. Mitkova in Plovdiv. The thesis is amalgamated in 5 chapters according to the requirements.

The aim of the thesis is well formulated: "The study is an assessment of socio-demographic characteristics, diagnostic and therapeutic algorithms, and complications in patients with uveitis, based on retrospective analysis and prospective follow-up for a period of 8 years."
To achieve the goal, the author sets himself 6 precisely thought-out tasks:
- To present an overview on publications in the literature and assessment on modern diagnostic approaches in patients with uveitis and therapeutic approach;
- To study and analyze the socio-demographic characteristics and etiology of patients with uveitis for a period of 8 years;
- To analyze the course of uveitis, diagnostic approaches and therapeutic algorithms in patients with uveitis who underwent treatment at USBOBAL-Varna;
- To assess the complications of the course of the disease, concomitant diseases and side effects of the therapy;
- To analyze the duration and course of the disease (relapses, remission intervals);
- Creating a risk profile of the studied patients with uveitis and predicting the risk of recurrence and behavior algorithm for patients with infectious and non-infectious uveitis.

Materials and methodology:
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 - 2014-2018 and 2019-2021. 219 patients who underwent treatment in hospital and outpatient care were evaluated. The selection of patients was based on precisely defined criteria - patients with uveitis as an independent or accompanying disease in patients, under and over 18 years of age and who completed an informed consent.

Exclusion criteria were patients without uveitis, patients with other ophthalmological diseases not accompanied by uveitis, patients with uveitis and mental disabilities, and those

who did not fill out an informed consent. The study methodology included a documentary method through research and analysis of the published scientific literature on the prevalence and risk factors of the disease, diagnostic methods and therapeutic algorithms. The sociological method included the creation of a questionnaire that met the objectives of the study and the conduct of a survey among patients. Clinical methods included performing clinical tests including high-tech ones (optical coherence tomography and fluorescein angiography). The collected data were processed using the following statistical methods – analysis of variance (ANOVA, MANOVA), variation, correlation, regression and comparative analysis and risk assessment analysis (OR, RR) .

In the author's study, the treatment was etiological - according to the etiology, symptomatic - in idiopathic uveitis, systemic in systemic diseases and according to the site of administration - systemic, local and intravitreal. Initiation of treatment with topical corticosteroids and cycloplegics is important after the diagnosis of uveitis. In recent years, biologic agents, biologic response modifiers, anti-TNF-alpha necrotizing factor therapies, anti-IL-6 therapies and next-generation calcineurin inhibitors have provided new options for the treatment of uveitis , but they have been applied in isolated cases.

Results

The author conducted his analyses including 219 patients with uveitis in two time periods 2014-2018 and 2019-2021. For the first period, 12,906 patients passed through SBOBAL - Varna, with the relative share of patients with uveitis being 0.9%, and for the second period, 8,704 patients passed, of which the relative share of patients with uveitis was 1.2%. The results show that the number of people suffering from uveitis is increasing , probably related to the COVID-19 pandemic. The average age of the studied 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 was a trend towards rejuvenation of patients with uveitis (respectively 56.04 years for the period 2014-2018 and 52.07 years for the period 2019-2021). The analysis of the results by gender shows that there is a slight preponderance of men (57.3% for men and 42.7% for women, respectively). No significant difference by gender was found during the two periods studied.

The majority of patients with uveitis are from cities (85.3%), with the urban:rural ratio remaining the same in both periods (83.9% for cities in 2014-2018 and 86.9% for 2019-2021, respectively). No difference in place of residence was found by gender. The analysis of patients with uveitis by place of residence and age shows that patients from villages are younger than those from cities (49.3 years for villages and 55.0 for cities, respectively). No significant difference was found in the average age of patients according to the type of uveitis, with the average age of patients with acute uveitis being 52 years and chronic uveitis being 55.5 years. No difference in age was found in relation to the affected eye, with patients with unilateral eye involvement having an average age of 54.6 years and those with bilateral involvement having an average age of 48.1 years. A significant difference was also found in relation to the type of uveitis according to the studied period (p<0.001), with the chronic form of uveitis prevailing in 2014-2018 (66.4%), and the acute form in 2019-2021 (65.2%). A significant difference was also found in terms of the severity of uveitis and the place of residence of the patients (p=0.047), with patients from cities being predominantly those with moderate severity of uveitis (52.2%), while 46.9% of patients from villages had

severe uveitis . A significant difference was also found in terms of the localization and severity of uveitis (p<0.001), with anterior uveitis being predominantly moderate (54.8%), while posterior uveitis was predominantly severe (89.5%). The most common are idiopathic uveitis (42.2%), followed by etiological causes such as herpes zoster , ankylosing spondylitis , herpes simplex and rheumatoid arthritis. The author identifies and analyzes clinical signs and symptoms, both according to etiology and depending on the period.

When comparing the use of local and systemic corticosteroids, no significant difference was found. Systemic NSAIDs were used significantly less than local NSAIDs (p<0.001), on the other hand, systemic and local antibiotics for 2019-2021. maintained a high frequency of use, while for 2014-2018. a lower frequency of use of systemic antibiotics was observed compared to local ones (p<0.001). The frequency of use of antiviral medications remained below 10% for both local and systemic administration for both studied periods. A higher frequency was also observed for the administration of parasympathomimetics and sympathomimetics for 2019-2021, but the difference was not statistically significant. Antiglaucoma medications were more commonly used in therapy for 2014-2018, and the difference was again not significant. The use of systemic corticosteroids, antivirals, and antibiotics was most common in patients with moderate uveitis . The use of systemic NSAIDs increased with the severity of uveitis , and immunosuppressants were only used in patients with severe uveitis .

The author finds that there is no significant difference; it can be said that in 2014-2018, uveitis recurrences occurred in younger people. No significant difference in the occurrence of relapses was found according to gender, with men predominating in both studied periods.

Dr. Nikolaeva has developed a "risk profile" of patients with uveitis and an algorithm for a systematic course of eye examination and overall clinical activity in making a diagnosis. The systematic approach developed for outpatient ophthalmologists is especially important, since interest in uveitis is low and knowledge is often lacking, which disrupts the diagnostic and treatment process.

Discussion

In her work, Dr. Nikolaeva considers uveitis as a diagnostic and therapeutic challenge and a complex disease that can occur differently in each patient. Due to its polyetiological nature, the disease creates many differential diagnostic problems, and often and therapeutic ones. The author also pays special attention to the impact of this chronic disease on the social status of patients and their quality of life, as well as the psychological and economic burdens on patients, their relatives and society. The prevalence of the disease depends on a number of factors - gender, age, place of residence, race , environmental influences , genetic factors , social habits , health status, state of the health system .

Particular emphasis is placed on integrated care and collaboration not only with the GP but also with other specialists involved in the overall approach to a patient diagnosed with

uveitis . The author rightly emphasizes that knowledge of the symptoms of the disease by the GP can shorten the response time and improve the outcome of uveitis .

In the end, Dr. Nikolaeva draws particular attention to the need for reference centers for uveitis , as there are none in Bulgaria. The discussion is rightly aimed at outlining good practices on a European and global scale.

The author has formulated 10 conclusions, of which the following are particularly valuable:

- Idiopathic uveitis predominate, followed by syndromatic disease, the most common being herpes zoster (6.9%), ankylosing spondylitis (5.1%), herpes simplex (4.6%) and rheumatoid arthritis (2.3%). The location of uveitis correlates with the age of the patients and the severity of the disease.
- A significant difference has been found in the drug treatment of uveitis , with biologic medications being used primarily in patients with moderate to severe disease. The use of systemic NSAIDs increases with the severity of uveitis , and immunosuppressants are used only in patients with severe disease.
- Causes of uveitis have been identified for the Bulgarian population : rheumatoid arthritis, herpes simplex and ankylosing spondylitis. spondylitis , with their severity decreasing during the second study period, which can be explained by improved disease control through the use of biological therapy.
- The risk profile of patients with uveitis 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 this extremely important work for practice are divided into three groups, there are 12 of them and are distributed according to their scientific-applied, practical and cognitive nature, and the most important of them are as follows:

- uveitis in Northeastern Bulgaria has been performed , focusing on epidemiology, diagnostics, treatment, and complications. This complex analysis was performed in the context of the capabilities of artificial intelligence.

- Based on a detailed literature analysis, it has been proven that the trends related to the prevalence of uveitis in Northeastern Bulgaria correspond to data from other sources for other countries.

- Algorithms have been created for the diagnosis and treatment of patients with infectious and non-infectious uveitis , as well as a risk profile of patients with uveitis and prediction of recurrence.

- Guidelines have been created for general practitioners with the aim of early diagnosis of uveitis , raising awareness, initiating effective treatment and improving the quality of life of patients.

The author there is the necessary publications related to the dissertation work that is innovative approach based on modern trends for the use of artificial intelligence, but also with a practical focus on improving the work of GPs and integrated care. For first time has been explored uveitis in the Northeast Bulgaria , as are made analyzes and conclusions which will contribute for better diagnostics and effective treatment .

I know Dr. Nikolaeva as student , resident , lecturer and colleague ophthalmologist and always I am was delighted from her systematicity and readiness yes do personal sacrifices in the name of on our noble profession .

On base on the analyses of the comprehensive work, critical look to publications and evaluation on role and importance on the topic " uveitis " in regional and national context, I do recommend on the esteemed scientific jury to vote positively for awarding of the educational and scientific " Doctoral " degree to Dr. Silvia Nikolaeva Nikolova .

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