REVIEW

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Regarding dissertation for the acquisition of the educational and scientific degree "Doctor"
in the field of higher education "7. Healthcare and Sports"
professional direction "7.1. Medicine"
scientific specialty "**Ophthalmology**"

to Dr. Maria Rumenova Boyadzhieva MD- PhD student in regular form of study

Topic of the dissertation:
"LIVE MICROSTRUCTURAL ANALYSIS OF RARE EYE DISEASES WITH MODERN TECHNOLOGIES"

Research supervisor:
Corresponding member Prof. Dr. Hristina Nikolova Grupcheva, MD, FEBO, FICO(Hon), FBCLA, FIACLE

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Basis for drawing up the review: Order No. R-109-1 /05.01.2023. of the Rector of the Medical University - Varna for determining the composition of the Scientific Jury and Protocol No. 1/ 16.01.2023. from the first held meeting of the Scientific Jury.

Brief biographical data about the author of the work

Dr. Maria Boyadzhieva was born on 30.12.1983. in Sofia. She finished her secondary education in 2002 in the Science and Mathematics High School "Acad. Sergey P. Korolev", city of Blagoevgrad with intensive study of biology and English language. In 2009 graduated in "Medicine" at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. Since 2009 she has worked at the Center for Emergency Medical Assistance - Varna and the Emergency Department, and a year later became part of the team of the Intensive Respiratory Department of the University Hospital UMBAL "St. Marina" - Varna (now the Department for Invasive Treatment and Non-Invasive Ventilation).

In 2016 Dr. Boyadzhieva started her specialisation in "Ophthalmology" at the Specialized Hospital for Eye Diseases for Active Treatment (SBOBAL) - Varna. Since 2017 she has worked as a part-time assistant-professor at the Department of Ophthalmology and Visual Sciences at Medical University - Varna, and since 2018, after a competition, she has been appointed as a full-time assistant at the same department. In 2018 she is enrolled as a full-time PhD student at the University of Medicine - Varna with the topic of her dissertation work "Live Microstructural

Analysis of Rare Eye Diseases with Modern Technologies". In 2020 acquired a specialty in ophthalmology.

Dr. Boyadzhieva continuously improves her qualifications by annually attending scientific meetings and conferences in the country and abroad. She has participated in numerous courses and specializations, including: Orthokeratology Course - Paris (2019), Summer School in Lincshoppin under the guidance of Prof. Nil Lagali (2017), as well as numerous trainings in Bulgaria. She has over 17 scientific publications in national and international journals, three of which are related to her dissertation work. There are 19 citations to scientific publications. She is part of the author's collective of a textbook on eye diseases. She currently works as an ophthalmologist at SBOBAL - Varna. As a full-time assistant in the Department of Ophthalmology and Vision Sciences, she has an intensive teaching activity, conducting practical classes on eye diseases for students in the specialties of "Medicine" (including in the English-language study program), "Dental Medicine", "Nursing", "Midwife" and "Medical Optician".

Relevance and significance of the dissertation work

The topic of the dissertation is aimed at the extremely current direction in medicine and health care - rare diseases and opportunities for their management. Rare eye diseases are a challenge that is yet to be solved. They affect about 6% of the world's population and have a negative effect on the lives of patients, their relatives and society as a whole, which determines their great importance. Many of them are the result not only of genetic mutations, but also of the influence of various environmental factors.

The study of rare eye diseases will open new horizons, both in diagnosis and in their treatment. Most patients with a rare disease have a long and complicated journey to the correct diagnosis. Approximately half of people with a suspected rare disease are undiagnosed, and at the same time, the diagnosis process takes an average of 5-6 years. The result is wasted time, inappropriate therapy, and irreversible vision damage.

The lack of epidemiological, scientific and clinical data on rare eye diseases is at the root of the delay in diagnosis, wrong treatment, impaired quality of life and suffering not only of the patients themselves, but also of their families.

This study is the first in the country, aimed at improving the management of rare eye diseases, by promoting the preparation of a registry for rare eye diseases, the creation of an expert center and a model of a rare eye disease for inclusion in the list of rare diseases of the Republic of Bulgaria.

Structure and content of the dissertation

The presented dissertation has a total volume of 157 pages and is illustrated with 14 tables and 46 figures. Its structure is logically constructed and balanced and includes: introduction- 3 pages; Literature review- 36 pages; purpose and objectives – 1 page; materials and methods- 31 pages; results- 38 pages; discussion- 7 pages; conclusion- 1 page; contributions- 1p.; conclusions – 2p.; bibliography – 8 pages and appendices – 14 pages. At the beginning of the dissertation work are placed: a summary, a list of figures and tables and a list of abbreviations used, and at the end - publications related to the dissertation work.

The literature used is precisely described in the bibliographical reference. 142 literary sources are cited, of which 17 are in Cyrillic and 125 are in Latin.

The literature review is targeted, thorough and well structured. The PhD student demonstrats a broad and up-to-date awareness of the dissertation, as well as an ability to generalize, systematize, bring out significant issues, thoroughly analyze and interpret the scientific literature in the researched field. An analysis and overview of Bulgarian and foreign scientific publications regarding rare eye diseases is presented. A definition of rare diseases is given according to the European Union, WHO, as well as in different countries. The sources of information were considered - online platforms, patient communities, international reference database (Orphanet). Within the EU, the European Commission is creating a European reference network, the Clinical Patient Management System (CPMS). It is important to direct the attention of the public and patients to sites with regulated and high-quality information. A unique and innovative platform for cross-border cooperation between specialists for the diagnosis and treatment of rare diseases, called the European Reference Network, has been created. cross-border healthcare in action.

The purpose of this platform is to connect clinicians, patients and researchers across Europe to facilitate the exchange of experience in the presence of complex and difficult cases. This exchange is made even easier by creating a web-based application.

Emphasis is placed on the role of screening, in particular mass neonatal screening, as one of the most effective forms of secondary prevention, which enables early diagnosis and treatment of a number of serious diseases. Children are examined a few days after birth, before symptoms of the disease appear. More than 50 diseases can be detected at an early stage through neonatal screening and timely treatment can be started. Mass neonatal screening is currently carried out in Bulgaria for 3 diseases - phenylketonuria, congenital hypothyroidism and congenital adrenal hyperplasia. In the study - Current Status of Newborn Screening in Southeastern Europe from 2021. the lack of financial resources, organization and political will are indicated as obstacles to the expansion of newborn screening programs among the countries of North-Eastern Europe (including Bulgaria).

Secondary prevention also includes prenatal screening and prenatal diagnostics, regulated in Ordinance No. 9 of 2019 on determining the package of health activities guaranteed by the NHIF budget and Ordinance No. 8 of 2016 on preventive examinations and dispensation. In the context of rare diseases, the aim of prenatal screening and early diagnosis is to identify mothers at high risk of transmitting a rare disease (based on family history - birth of a child with a rare disease, a relative with a known or suspected genetic disease) or the detection of a fetus with a rare disease.

Due to the low prevalence of these diseases, knowledge is scarce, research is limited, access to medical expertise is rare, and the care offered is often inadequate. Dr. Boyadzhieva also presented the difficulties associated with the development of safe and effective drugs, biological and medical devices for the prevention, early diagnosis and treatment of these conditions.

In Europe, rare eye diseases (RODs) are the leading cause of reduced vision and blindness in children and young people. To date, according to Orphanet, more than 900 rare eye diseases have been described.

Rare eye diseases are often bilateral, asymmetric and progressive. Early and correct diagnosis of rare eye diseases is essential for their prognosis. Timely intervention has a significant impact on the prognosis of many diseases, which can lead to blindness. Innovations in the treatment of rare diseases of the eye are related to the discovery of the genetic defect and the possibility of creating a treatment that can affect the progression of the disease or even a definitive cure.

The need of Bulgarian patients with rare eye diseases for adequate access to the achievements of modern pharmaceutical and molecular investigational medicine and orphan drugs, the definition of national centers of expertise and the construction of a national strategy for

people with rare diseases, based on the full scope of their needs and consistent with the values of the European Action Plan for Rare Diseases are drawn up.

The purpose of the scientific work is clearly and precisely defined. Six main tasks, logically consistent are derived that are aimed at achieving the main goal, "tracking the path of patients with rare eye diseases, evaluating the registration regime, including eye diseases in the National Register of Rare Diseases and creating a model for a clinical register in benefit of daily ophthalmic practice'.

The methodology includes documentary, survey, modeling and clinical method.
The instrument (questionnaire) for the survey among ophthalmology specialists and specialising physicians was developed by the doctoral student for the purposes of the scientific study.
The clinical part of the methodology is based on analyzes made with modern high-tech methods for microstructural analysis of the anterior and posterior eye segments, including:
- Optical coherence tomography performed with a Zeiss Cirrus 5000 HD-OC with appropriate scanning protocols for anterior and posterior eye segment;
- Live laser-scanning confocal microscopy with HRT Rostock Cornea module with presented algorithm;
- Examination of the visual field with the Humphrey® Field Analyzer 3 with a presented algorithm;
- Photo documentation of with Zeiss Digital Fundus Camera - Visucam 524;
- Electroretinography (ERG).

In addition to the studies, the results of visual acuity and color perception and anterior eye segment biomicroscopy and fundobiomicroscopy with a +90 D lens are attached.
Detailed algorithms for the clinical evaluation of anterior and posterior eye segment diseases are presented. Multidisciplinary teamwork for follow-up and treatment in syndromic rare diseases is also proposed.

Results

The results are grouped and presented in six sections.

- 1st section – overview of the European rules and registration regimes for rare diseases and rare eye diseases. Overview of the National Registry for Rare Diseases.

- 2nd section - evaluation of knowledge about rare diseases among ophthalmologists through a survey, in which 51 specialists and 23 specialising physicians participated. Nearly half of the participants reported seeing patients with rare eye diseases. More than half of the respondents do not treat or refer such patients. Of those who treat rare eye diseases (39.5% of all respondents) - 42.1% indicated that they treat all types of rare diseases, 30.3% - diseases of the anterior segment of the eye, 10.5% noted that they treat rare eye diseases on posterior eye segment.

- 3rd section – clinical assessment of rare eye diseases according to the Orphanet classification. For the purposes of the study, 39 patients with a rare eye disease were followed for the period 2017-2022. in SBOBAL-Varna, which are divided into five groups according to the Orphanet classification. The average age of the followed patients was 37 years, with the youngest patient being 12 years old and the oldest being 62 years old. The female gender prevails in rare diseases of the anterior eye segment, and the male in rare diseases of the posterior eye segment.

- 4th section, in which the author creates a model for registration of the rare eye disease aniridia, following the algorithm for registration of a rare disease and with the support of the

Association in Aniridia Bulgaria. Documents have been submitted for the entry of the disease Aniridia in the National List of Rare Diseases, as in November 2022 approval was obtained from the Commission for Rare Diseases and the disease was included in the National Register of Rare Diseases. Along with Aniridia, Leber's hereditary optic neuropathy is also included in the list.

- 5th section includes the development of a plan to create an expert center for rare eye diseases in Bulgaria. It has been established that as of 01.05.2022 20 expert centers for rare diseases are registered on the territory of our country. SBOBAL - Varna, as a high-tech base, has been proposed as an expert center for rare eye diseases. The preparation of a self-assessment and the submission of an application, according to Ordinance No. 16 of 2014 of the Ministry of Health, are the initial documents for starting this process.

- 6th section - Creation of a model for a publicly available national register for rare eye diseases in Bulgaria. On the basis of the analysis and accumulated data, a project of a model for a register of rare eye diseases was created in the SBOBAL - Varna. The goals of this model are to create a replicable data base that will serve to support the registration of rare eye diseases in the National Register of Rare Eye Diseases, to improve diagnosis and treatment, clinical trials and the creation of good practice. To this end, a template will be created - a cloud-based file customized to the requirements of the individual disease, including demographics, clinical history, diagnoses, medications, medical and surgical procedures, tests and research results, imaging and other documentation that can to be necessary for the individual condition.

Discussion

Although Bulgaria is one of the first countries with an adopted national plan/strategy, today there is still a lack of a comprehensive and clear health policy regarding rare diseases. Issues related to the prevention, diagnosis and treatment of some rare diseases are partially represented in various national programs and laws, but without a comprehensive solution to the many problems of a medical, social and ethical nature. Dr. Boyadzhieva also presented the factors that limit patients' access to specialized laboratory tests. Bulgaria is seriously lagging behind in the development of its expert activities and capacity in the field of rare diseases compared to the EU countries - among the 1500 expert centers approved by the EC on the territory of the EU and Norway, Bulgaria has only 7. The absence of Bulgarian medical facilities in 19 of the total of 24 therapeutic areas within the scope of the European Reference Networks, deprives the Bulgarian specialists - clinical doctors and researchers - of cooperation with the expert centers in the composition of the ERM. Our country is one of the three countries (along with Luxembourg and Malta) officially named by the European Commission that did not participate in 2019 in the process of joining medical facilities, healthcare providers, hospitals within the European reference networks (Bulgaria does not broadcast a single hospital for participation in these 24 areas within the invitation to join issued by the European Commission in 2019).

Dr. Boyadzhieva also examines the role of electronic health records - part of the National Health Information System. Electronic medical records provide an easy and affordable way to collect a wide range of data and enrich information about most diseases, including rare ones. Having electronically stored and coded data will provide an opportunity to improve medical care and service.

Conclusions of the dissertation

10 conclusions have been drawn, which are clearly formulated and logically follow from the obtained results.

Particularly valuable of practical importance are the conclusions related to: the creation of an accessible and functional registry for rare eye diseases in our country, the creation of an expert reference center for rare eye diseases in Bulgaria and its participation in the European reference networks for improving the care and diagnosis of rare eye diseases; the need to include more rare eye diseases in the National List of Rare Diseases; the need to create algorithms for good practices and care for patients with rare eye diseases and to increase the awareness of the population and specialists, as well as the need to update the Medical Genetics standard, Ordinance No. 26 of the Ministry of Health and the diagnostic algorithms and indications for conducting genetic and genomic studies.

The creation of an up-to-date, accessible and functional registry for rare eye diseases in our country is realistically feasible and can represent a step forward in epidemiological and clinical studies in this area. The lack of reliable epidemiological and clinical data generated in local settings is a significant obstacle to effective planning and management of health care costs.

It is necessary to update the standard on "Medical genetics", Ordinance No. 26 of the Ministry of Health and the diagnostic algorithms and indications for conducting genetic and genomic research. Establishing a precise molecular diagnosis for any genetic eye disease can only be achieved through genetic testing, and this will allow the clinician to stratify clinical risk in terms of prognosis, comorbidities, treatment options, and/or participation in clinical trials. The financing of diagnostic genetic tests now only takes place within the framework of Ordinance 26 of the Ministry of Health - children up to 18 years old age are examined free of charge. For patients over 18 years of age with rare diseases, genetic diagnosis is practically not provided within the current clinical pathways, and these patients remain in a large number of cases undiagnosed and inadequately treated.

Dissertation Contributions

The contributions are predominantly original in nature - with theoretical and practical-applied significance.
For the first time in Bulgaria, a comparative study was conducted on the European and national policy for rare eye diseases. For the first time, an algorithm has been developed for the diagnosis and follow-up of patients with a rare eye disease. For the first time, an algorithm has been developed to include a rare eye disease in the National List of Rare Diseases in Bulgaria. For the first time, the need to create a registry for rare eye diseases in our country, as well as an expert center for rare eye diseases, has been proven. The developed methodology for creating and registering an expert center for rare eye diseases has an original contribution character with great potential for practical applicability.

A very good impression makes the synthesis of the limitations of the research at the end of the dissertation.

Publications on the issues of the dissertation work

In connection with the dissertation work, the doctoral student presents three full-text publications, two of which are in international journals. A participant in a scientific conference in our country is also mentioned.

Conclusion

The dissertation is an up-to-date, complete and in-depth scientific work. It is well structured, with clearly defined goals and objectives. The design of the scientific research is adequately selected. The methodology is complex and competently applied. The results are presented correctly and comprehensively. The conclusions are clearly formulated and are the basis of the dissertation contributions. The contributions are predominantly original in nature and have a high potential for practical applicability.

The dissertation fully meets the requirements of the Law on the Development of the Academic Staff of the Republic of Bulgaria, the Regulations for its Application and the Regulations for the Development of the Academic Staff of the Medical University - Varna for the acquisition of the educational and scientific degree "Doctor"

The work represents an important step towards updating and improving the approach to an extremely significant health problem. Although rare in terms of prevalence, these diseases significantly alter the lives of affected individuals and their loved ones. The creation of work algorithms, the creation of an expert center for rare eye diseases, as well as the request for participation is ERN-EYE is an important direction in improving the care of these patients and their well-being.

The current topic, the in-depth nature of the conducted research, the applied complex innovative methodology, the results obtained, the conclusions drawn and the contributions of a mostly original and applied nature, give me the reason to give a positive assessment of the dissertation work and to confidently propose to the Scientific Jury d-r Maria Rumenova Boyadzhieva to be awarded the educational and scientific degree "Doctor" in the scientific specialty "Ophthalmology" in professional direction 7.1. "Medicine".

04. 06. 2023г.
Varna

Member of Scientific Jury:
Prof. Dr. Albena Kerekovska, MD, PhD