REVIEW

by

Prof. Nelly Petkova Sivkova, MD, PhD, FEBO

Department of Ophthalmology, Medical University of Plovdiv

Regarding

Dissertation thesis on theme "Screening program for retinopathy of prematurity – regional application, analysis of results and perspectives"

By

Anna Nedyalkova Ilieva-Krusteva, MD

for the acquisition of the educational and scientific degree

"Doctor" in the field of higher education in scientific specialty "Ophthalmology", code 03.01.36

Research supervisor: Assoc. Prof. Yana Manolova, DM, PhD

Brief biographical data:

Dr. Ilieva was born in 1991. In 2009 she completed her secondary education at the First Language School with intensive study of English in Varna. In 2015 she graduated with honors from the Master's Degree in Medicine at MU-Varna. The following year she started her specialization at the University Specialized Hospital of Eye Diseases for Active Treatment - Varna. In 2019 Dr. Ilieva was enrolled as a full-time PhD program in the scientific specialty "Ophthalmology" at the Department of Eye Diseases and Visual Sciences of MU-Varna with research supervisor Assoc. Prof. Dr. Yana Manolova. In 2021 she acquired a specialty in eye diseases. At present, Dr. Ilieva works as an ophthalmologist at medical centers "Sanita" and "Heilan 4" in Varna. She is also a member of the Bulgarian Society of Ophthalmology and the Bulgarian Medical Association. Her scientific interests are in the field of paediatric ophthalmology and diseases of the posterior segment of the eye. She has participated in congresses of the Bulgarian Society of Ophthalmology and in the symposia of the Bulgarian Glaucoma Society.

Teaching work:

Dr. Ilieva teaches classes on eye diseases to medical, dental, medical optics and optometry students.

Relevance of the problem

The present dissertation is devoted to a disease of national and international relevance: retinopathy of prematurity (ROP). It is a multifactorial vasoproliferative disorder affecting children born prematurely before 32 gestational weeks and weigthing less than 1500g. Firstly described in the 1940s, it has become a leading cause of preventable childhood blindness worldwide. It has been estimated that as of 2010, almost 185,000 preterm infants worldwide have developed ROP with 20,000 losing vision and 12,300 developing mild to moderate visual impairment. The majority of children with visual impairment from ROP are in

developing economies, which includes Bulgaria. Medical progress in recent years in relation to ROP is undeniable. Different treatment approaches are being developed with the aim of intervening as early as possible. The natural course of the disease is being studied by searching for the pathophysiological mechanisms that suppress abnormal processes without affecting the normal maturation of the ocular structures. The development of digital technology offers new rapid and convenient methods of diagnosis, including remote diagnosis. However, there are still many problems facing the medical community: a small number of specialists trained to deal with this specific pathology; organizational and logistical problems - the distance between the intensive care units for premature babies and the ophthalmology units, the need for coordination between specialists from separate medical structures, the increasing number of children affected, a number of legal aspects concerning claims by parents in the event of an adverse outcome. All this makes the topic of the screening programme for ROP particularly current for our country.

Structure of the dissertation

The dissertation has volume of 202 pages and is illustrated with 34 figures and 17 tables. The dissertation includes the following sections: Abbreviations used - 4 pages; Contents - 4 pages; Introduction - 2 pages; Literature review - 54 pages; Aim and objectives - 1 page; Materials and methods - 8 pages; Results - 36 pages; Discussion - 41 pages; Conclusions and conclusion - 4 pages; Contributions - 1 page; Publications and scientific communications related to the dissertation - 1 page; Appendices - 4 pages; References used - 40 pages; Acknowledgements - 1 page. The bibliography includes 481 references - 13 in Cyrillic and 468 in Latin. The research related to the dissertation work was conducted in "University Specialized Hospital of Eye Diseases for Active Treatment - Varna" Ltd. and "Specialized Hospital of Obstetrics and Gynecology for Active Treatment Prof. D. Stamatov - Varna" Ltd.

From the literature review presented, it is evident that there is very good knowledge of the problem. The **literature review** is comprehensive and includes both publications of historical value and contemporary publications on the topic from the last 5 years. The aim of the dissertation is logically derived and correctly formulated.

The **aim** of the dissertation is to establish the epidemiological and clinical characteristics of ROP among premature infants in Varna region according to the current screening program for ROP adopted in the Republic of Bulgaria, as well as to propose a platform for improving the awareness of parents and medical professionals about this disease. For its implementation **six tasks** have been set as follows:

1. To determine the frequency and characteristics of ROP of premature infants screened in the Neonatology Department of the Specialized Hospital of Obstetrics and Gynecology "Prof. Dimitar Stamatov" - Varna and the University Specialized Hospital of Eye Diseases for Active Treatment - Varna;

2. To analyze the risk factors on the fetal side, which could be related to the development and progression of the disease;

3. To analyze the maternal risk factors that could be relevant to the development and progression of the disease;

4. To monitor the early post-therapeutic effect of intravitreal administration of anti-VEGF medication;

5. To determine the place of ROP as a cause of severe visual impairment and blindness among the students at the Special School for Students with Visual Impairment "Prof. Dr. Ivan Shishmanov", Varna;

6. To offer an internet-based information portal for ROP.

The **clinical material** includes the premature infants who were screened for ROP in the Hospital "Prof. Dimitar Stamatov" - Varna and followed up in the Specialized Hospital of Ophthalmology for Active treatment - Varna for the period January 2017 - December 2020: a total of 124 premature infants. For the purpose of the study, the patients were divided into two groups: first group - children who did not develop ROP and second group - children who developed ROP. The second group was divided into two subgroups: patients with spontaneously regressed ROP (untreated) and patients with progressive ROP requiring treatment (treated). The inclusion criteria for the study were consistent with the standard adopted at the National Workshop on Screening and Treatment of ROP in Bulgaria in 2009.

In the study concerning the incidence of ROP in the "Prof. Dr. Ivan Shishmanov" School for visually impaired students, Varna, included 145 children. The study was conducted between August 2022 and November 2022, after obtaining permission from the school principal. Data was collected on the age, gender and cause of visual impairment according to the available medical information of the visually impaired students attending the school in the school year 2022/2023.

The conduct of the study was approved by the Research Ethics Committee of MU-Varna.

The **statistical methods** are well chosen. Statistical analysis was performed using SPPSS V 26.0 statistical package. Descriptive, comparative, linear and regression analyses were used.

Results

The epidemiological characteristics of ROP among patients undergoing a mandatory screening program at the Hospital "Prof. D. Stamatov" Ltd. Varna have been investigated with a sample of 124 children. During the study period, signs of ROP were detected in 86 children (69.4% of all examined children), and in 25 of them (20.2% of all examined children) the disease progressed to ROP requiring treatment. The remaining 61 children (49.2% of all children studied) showed signs of spontaneous disease regression.

Twenty fetal risk factors and 10 maternal risk factors for the development and progression of ROP were analyzed.

The early posttherapeutic effect of intravitreal administration of anti-VEGF medication was also evaluated.

From the survey conducted among the students at the school for children with visual impairment "Prof. Dr. Ivan Shishmanov", Varna, the etiological factors for impaired visual function were identified and the place of ROP among them was determined - second only to optic nerve atrophy, responsible for 8.6% of cases of vision loss.

A web-based information portal is proposed, aiming to improve the awareness of parents and medical professionals at a national level, summarizing the facts and presenting them in an adapted form suitable for a mass audience.

The results are very well illustrated. They are compared with similar ones from the available literature cited.

The conclusions are properly formulated. They are 10 in number, grouped in three sections: cognitive, applied and confirmatory.

1. Contributions of a cognitive nature

1.1 An in-depth literature review on the incidence, pathogenesis and risk factors of ROP has been conducted;

1.2 Current trends in the diagnosis, treatment and follow-up of children with ROP are updated;

2. Contributions of scientific and applied nature

2.1 For the first time in Northeastern Bulgaria, a study of the clinical and epidemiological characteristics of ROP was conducted, involving 124 premature infants;

2.2 The long-term effects of ROP were analyzed in a study of 145 schoolchildren attending a specialized school;

2.3 An in-depth analysis of maternal and fetal risk factors involved in the development and progression of ROP was carried out, confirming the findings of other researchers at major university centers in Sofia and Plovdiv;

2.4 Evidence has been collected on the beneficial early post-therapeutic effect of intravitreal administration of anti-VEGF drugs;

2.5 For the first time in Bulgaria, an online-based information portal dedicated to ROP has been proposed and implemented to support parents and medical professionals.

3. Contributions of a confirmatory nature

3.1 The effectiveness of the screening programme for ROP adopted and operating in Bulgaria has been confirmed;

3.2 Confirmed the role of risk factors in the development and progression of ROP;

3.3. Confirm the efficacy of anti-VEGF drugs used for the treatment of ROP.

Of these, the most significant is conclusion 2.5, namely that **for the first time in Bulgaria** an on-line-based information portal for ROP has been proposed and implemented in order to support the awareness of parents and the work of medical professionals.

The author's **conclusion** is that retinopathy of prematurity is a disease with severe consequences that can be fatal for the child's visual function. Among the measures that are capable of limiting the adverse outcome are high quality neonatal care, strict adherence to the recommendations of the National Strategy for the Screening and Treatment of ROP, and improved awareness of both parents and medical professionals.

The abstract is presented in 80 pages. It meets the requirements and reflects the main results achieved in the thesis.

Dr Ilieva has submitted eight full-text publications.

There are **4 publications and one scientific communication related to the thesis.**

In **conclusion**, the presented dissertation represents a complete and well-constructed scientific work with authorial contributions. It fully complies with the requirements of the Academic Staff Development Act of the Republic of Bulgaria and the Regulations of MU-Varna for its application. This gives me a reason to give **my positive assessment and to propose to the members of the esteemed scientific jury to vote positively for the award of the educational and scientific degree "Doctor" to Dr. Anna Nedyalkova Ilieva-Krusteva.**

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679

19.12.2024 Signature: .....

Plovdiv Prof. Nelly P. Sivkova, MD,PhD,FEBO