

Review

Regarding dissertation for the acquisition of the educational and scientific degree

"Doctor" on topic:

"Screening program of retinopathy of prematurity - regional application, analysis of results and perspectives"

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By Corresponding Member Prof. Christina Nikolova Grupcheva, MD, PhD, FEBO, FICO, FBCLA, FIACLE (internal reviewer), appointed by Order № R-109-405/ 20.11.2024 of the Rector of MU-Varna

Brief biographic information: Dr. Ilieva was born in 1991. She graduated in 2009 from the First Language School in Varna with intensive study of English. In 2015 she graduated from the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna with honors and began specialization in "Specialized Hospital of Eye Diseases for Active Treatment" - Varna. In 2019, after a competitive exam, Dr. Ilieva was enrolled in a full-time PhD program in the scientific specialty "Ophthalmology" at the Department of "Eye Diseases and Visual Sciences" of MU-Varna with scientific supervisor Assoc. Prof. Yana Manolova, MD, PhD. During her doctoral studies she participated in the teaching activities of the department, conducting exercises of students. She has participated in two structural projects:

1. Establishment of a structure to perform precise topography of the anterior segment of the eye for early diagnosis of corneal diseases, as well as in patients with cataract and glaucoma, 2017.
2. Establishment of a station for static and dynamic examination of the posterior ocular segment with a large and small fundus camera, 2018.

Dr. Ilieva has eight publications, four of which are related to this dissertation. She received her specialty training in ophthalmology in 2021, after which she turned to pediatric ophthalmology, as well as the diagnosis and treatment of diseases of the posterior ocular segment. At present, Dr. Ilieva is part of the specialist teams of MC Sanita and MC Heilan 4, in Varna.

Relevance of the problem: Retinopathy of prematurity is one of the major interdisciplinary challenges of pediatric ophthalmology. Survival of children with low body weight and preterm birth leads to structural immaturity of the eye, which in turn is the basis for rapidly developing pathological processes. The disease has been called "retrolental fibroplasia" for a reason in the past-it reflects the fatal end of untreated vascular proliferation with tractional retinal detachment. Over the years, therapeutic approaches have moved from cryo- to laser therapy, and then came the era of anti-vascular proliferative injections. Of course all this is only possible based on precise screening and follow-up criteria. The problem is relevant not only nationally but also globally with the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) reporting 13.4 million children born prematurely (before 37) in 2020 or 1 in every 10 live births, and 1 million of them dying due to complications of prematurity or 1 baby every 40 seconds. Premature babies are at a huge risk of developing a range of complications from different organs and systems, with vision being one of the key issues and its preservation is a primary concern globally, in Europe and nationally. In Bulgaria there are several centres for the management of premature babies, such as "Specialized Hospital of Obstetrics and Gynecology for Active Treatment prof. Dimitur Stamatov- Varna" Ltd. is the leading

hospital in North-Eastern Bulgaria. The dissertant had the chance to work in collaboration with this center and to make an interesting work with practical benefit.

Dr Ilieva discusses retinopathy of prematurity (ROP), a multifactorial vasoproliferative disorder affecting children born prematurely, especially before 32 weeks gestation. Her thesis is based on worldwide statistics that by 2010, globally, almost 185,000 preterm children had developed ROP, 20,000 had lost vision, and another 12,300 had developed mild to moderate visual impairment. 65% of children with visual impairment are in developing economies, which includes Bulgaria. It is alarming that there are 50 000 children under the age of 15 worldwide who have lost their sight due to this disease.

Realizing the complexity of the problems of premature children, the author concentrates on eye problems and their potential for visual impairment. The research related to the dissertation was conducted at the "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.

Characteristics of the dissertation:

The dissertation has volume of 202 pages and is illustrated with 34 figures and 17 tables. 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.

Review

The author has provided an up-to-date review of the literature, emphasizing that the struggle of ophthalmologists with ROP has been ongoing for more than 80 years. The advances of medicine in this period are, of course, undeniable. Whereas in the 1940s and 1950s, the disease was simply described in its terminal phase and vision was irretrievably lost, in the following decades, treatment techniques were tried with the aim of intervening as early as possible, the natural course of the condition was studied, and the pathophysiological mechanisms that suppress abnormal processes without affecting the normal maturation of ocular structures were sought. Developments in digital technology offer new rapid, convenient methods for diagnosis and follow-up and the implementation of telemedicine. The author correctly notes that the difficulties also come from the small number of specialists willing to engage and train to deal with this specific pathology, as well as purely logistical difficulties. The fact that fewer and fewer practicing ophthalmologists are willing to work in this field, and a number of them are planning to quit, is extremely alarming, according to the American Ophthalmological Association (AOA).

At the end of her review, Dr Ilieva stresses that in Bulgaria, there is an urgent need to ensure a certain level of communication between the different treatment centers in the country, which would standardize the approach to the disease and ensure access to consultative or curative care. It is imperative that an electronic registry that contains information about the ocular status of premature children with signs of ROP, to facilitate the transfer of information between different specialists and medical institutions.

The aim is correctly formulated as follows: "To establish the epidemiological and clinical characteristics of ROP among premature infants in the Varna region according to the current screening program for ROP adopted in the Republic of Bulgaria, and to offer a platform to improve the awareness of parents and medical professionals about this disease."

To achieve this ambitious goal, the following tasks have been set:

1. To determine the incidence and characteristics of ROP in preterm infants screened at the Neonatology Department of the Specialized Hospital of Obstetrics and Gynecology "Prof. Dr. 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 propose an internet-based information portal for ROP

Materials and methods

The author included in her study a total of 124 premature infants divided into two groups: group I - patients who did not develop ROP; group II - patients who developed ROP. The second group was divided into two subgroups: group II A - patients who developed ROP and had spontaneous regression (untreated); group II B - patients with progressive ROP requiring treatment (treated). Inclusion criteria are according to the standard adopted at the National Workshop on Screening and Treatment of ROP in Bulgaria in 2009: live, preterm infants born before 32 years and/or weighing less than 1500 g; all preterm infants weighing 2000 g or less in the presence of any of the following factors: ventilator failure, severe intrapartum asphyxia, intracranial haemorrhage, exchange transfusions; sepsis, and at the discretion of the neonatologist. All investigations, too, are consistent with the standard.

For the study of morbidity, 145 children were enrolled in the "Prof. Dr. Ivan Shishmanov" in the city of Varna. Data on age, gender and cause of visual impairment were collected according to the available medical information of the visually impaired students attending the school in the school year 2022/2023.

Results and discussion

The study covered a period of 4 years (January 2017-December 2020) and followed 124 preterm infants, finding 86 children (69.4% of all children studied) with retinopathy. The author emphasizes that the data for the Varna region, exceeds the frequency reported by other Bulgarian authors in different regions of Bulgaria - 30.3% for the Plovdiv region, 22.8% for the Sofia region and 5.4% for the Stara Zagora region. Of the children diagnosed with retinopathy, 25 (20.2% of all studied children) were treated due to disease progression. In the study for the Varna region, the mean birth weight of premature infants was 1106 (\pm 254.4) g and the mean gestational age was 28.3 (\pm 2.3) g.w. The author emphasizes that over the last 20 years in Bulgaria there has been a trend towards a decrease in neonatal mortality - from 13.3/1000 in 2000 to 5.6/1000 in 2021 (according to the National Statistical

Institute), which allows the survival of increasingly immature children, with extremely low weight (the smallest child in the study weighed only 580 g), who are at the highest risk of developing the disease.

The presence of lung injury in preterm infants is associated with an increased need for oxygen therapy, and this is a major pathogenetic factor in the development of retinopathy. Therefore, the author analyzes the most common pathological conditions of the respiratory system associated with preterm birth - hyaline membrane disease, respiratory distress syndrome, neonatal pneumonia and bronchopulmonary dysplasia. On this basis, the author demonstrates that hyaline membrane disease is a statistically significant factor in the development and progression of retinopathy of prematurity in the univariate analysis applied. It is interesting to note that after the logistic regression analysis, hyaline-membrane disease dropped as an independent risk factor. Surfactant therapy is the standard of care for children with respiratory distress syndrome, and it results in a decreased need for prolonged mechanical ventilation in these children, as well as with a reduction in mortality and pulmonary complications of prematurity. Dr. Ilieva's data indicate the significance of this factor in the development and progression of retinopathy, but it also drops out as an independent factor in the regression model.

The author's approach to investigate 11 potential maternal risk factors is interesting, looking for a correlation between these and the development and progression of ROP. A significant association was found between the factor in vitro fertilization and the development of the disease, which was explained by a higher frequency of smaller and more immature children. Regarding the other 10 risk factors - mechanism of delivery (by Caesarean section or vaginal delivery), maternal age, hypertensive conditions during pregnancy, placental abruption, premature rupture of the amniotic sac, cervical surgery, chorioamnionitis, maternal-fetal infections, gestational diabetes, antenatal corticosteroid prophylaxis - the study found no significant association for the development and progression of retinopathy of prematurity.

One of the important tasks that Dr. Ilieva has set herself is to evaluate the early post-therapeutic effect of anti-VEGF drugs used to treat retinopathy. In the study that is the subject of this thesis, monotherapy with anti-VEGF medication was administered to 19 children (36 eyes in total).

In 5 children (10 eyes), treatment was performed combining intravitreal administration of anti-VEGF drugs with ablative therapy (8 eyes were treated with laser therapy and 2 eyes with cryotherapy).

In two of the treated children (4 eyes) the process progressed to stage 4b and they were referred for pars plana vitrectomy. Regression of the ophthalmoscopic finding was observed in the remaining 22 children (42 eyes), representing 91.7% of the children who received anti-VEGF drug therapy and 81.5% of all children treated. Based on these results, the author concludes that monotherapy with anti-VEGF medication is elegant, specific, and not associated with destruction, and does not result in anterior segment ischemia of the iris and lens. Another advantage is preservation of the visual field, especially in zone 1, and a lower rate of refractive abnormalities (myopia and astigmatism) compared with laser therapy.

Dr. Ilieva, does not miss the discussion of complications of anti-VEGF therapy. Local ones are related to the risks of intravitreal injections - endophthalmitis, retinal hemorrhage, cataract and retinal detachment. The author points out that there are concerns in the literature about negative effects on the neuropsychiatric development of children treated with anti-VEGF medications, but the conflicting opinions in the analyzed literature indicate that it is currently extremely difficult to draw a line of demarcation between the complications accompanying prematurity and the side effects of the conducted treatment for retinopathy.

In the process of analyzing the situation with retinopathy of prematurity, the author also set himself an important task to determine the role of the disease as a cause of severe visual impairment and blindness among the students in "Prof. Dr. Ivan Shishmanov" school in the city of Varna. In this part of the study, 143 students were included, of which 88 boys (61.5%) and 55 (38.5%) girls. The age ranged from 6 to 20 years and the mean age for the whole group was 12.5 ± 3.7 years. In all age groups, a higher prevalence of males was found. Optic nerve atrophy (74.8%) proved to be the leading cause of impaired visual function among the children studied. Retinopathy of prematurity was the second most common disease (8.6%). The author also performed a retrospective analysis of the characteristics of ROP among students with visual impairment due to this disease. It was found that the mean birth weight was 1033 g (range 610 - 1750 g) and the mean gestational age was 34.4 weeks (range 31 - 36 g). The ratio of boys: girls was 2:1. The majority of cases were treated for retinopathy (83.3%) with cryotherapy (41.7%) and surgery (41.7%). Almost all children (91.7%) were found to have neuro-psychiatric retardation, and hearing impairment was diagnosed in 41.7%.

An important practical task is to work to improve awareness of parents and medical professionals at a national level, summarising the facts and presenting them in an adapted form suitable for a mass audience, for which the author has developed a website at: www.rop-info.com. The creation of a digital information portal in Bulgarian is a modern solution, providing visibility and easy access to systematized information throughout the country, not only in large university centers. The website includes data regarding the epidemiology, pathogenesis, diagnosis and current therapeutic options for the treatment of retinopathy of prematurity and can serve the general public and medical professionals in the ongoing care and rehabilitation of our youngest and most vulnerable patients.

The author concludes his work with 10 well-articulated conclusions, the more important of which are:

- Incidence of ROP among premature infants treated in the Intensive Neonatology Unit at the Hospital "Prof. Dimitar Stamatov" - Varna. 69.4% compared to the rates in Plovdiv region (30.3%), Sofia region (22.8%) and Stara Zagora region (5.4%).
- Low birth weight, invasive ventilatory support, grade III IVH and the presence of neonatal anemia are significant and independent risk factors for the development and progression of the disease.
- Timely treatment with intravitreal administration of anti-VEGF medication for type 1 prethreshold disease has a good early anatomic outcome.

The dissertation has 10 contributions of a cognitive, scientifically applied and confirmatory nature, of which I rate the highest:

- The analysis of current trends concerning the diagnosis, treatment and follow-up of this rare disease.
- For the first time in Northeastern Bulgaria, a study of the clinical and epidemiological characteristics of ROP disease was conducted involving 124 premature infants and a survey of 145 students attending a specialized school for visually impaired students;
- An in-depth analysis of maternal and fetal risk factors involved in the development and progression of retinopathy and the beneficial early post-treatment effect of intravitreal administration of anti-VEGF medication was demonstrated;
- 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.

Conclusion

The author concludes that retinopathy of prematurity continues to be a leading cause of irreversible vision loss worldwide. Knowledge of the disease, its pathogenesis and natural course continues to improve, and technological advances provide opportunities for early diagnosis and telemedicine consultation. Hopes are pinned on relatively new treatment modalities, but more studies and results are needed to answer questions concerning the safety and long-term effectiveness of these drugs. Retinopathy of prematurity is a condition whose consequences can be devastating for the child, his or her relatives and society. In order to avoid them, it is necessary to ensure the highest quality of neonatal care, to strictly follow the recommendations of the National Strategy for the Screening and Treatment of ROP, to improve the awareness of parents and medical professionals involved in the care of premature infants and to work towards eliminating the problems in this respect of the health system in Bulgaria.

Dr. Ilieva has listed 4 publications related to her dissertation, one in English, one bilingual and two in Bulgarian.

I know Dr. A. Ilieva as a student, graduate student, lecturer and fellow ophthalmologist and I have always admired her perseverance, collegial approach and especially her willingness to work with children, which is rare among young ophthalmologists.

On the basis of the analysis of the dissertation, the critical look at the publications and the evaluation of the role and importance of the topic "retinopathy of prematurity" in the regional and national context, I recommend the esteemed scientific jury to vote positively for the award of the educational and scientific degree "Doctor" to Dr. Anna Nedyalkova Ilieva-Krusteva.

01.12.2024

Cor. Member Prof. Ch. Grupcheva

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