

PEER REVIEW

OF A DISSERTATION WORK

of **Krasimira Ivanova Koleva, MD**, entitled **‘Some contemporary diagnostic aspects of inflammatory bowel diseases in children and adolescents’** for the acquisition of the educational and scientific degree of **‘Doctor’** in the field of higher education **No 7 ‘Public health and sports’**, professional direction **No 7.1 ‘Medicine’** and scientific speciality of **‘Pediatrics’**

Scientific adviser: Assoc. Prof. Miglena Dimitrova Georgieva, MD, PhD

Reviewer:

Prof. Valeria Ignatova Kaleva ,MD, PhD

pediatrician, Professor at the Department of Pediatrics, Medical University of Varna

By decision of the Chairman of the Scientific Jury and according to Order No R109-105/March 17, 2021 of the Rector of Medical University of Varna, I have been defined to submit the present peer review.

Concise biographical and professional data about the PhD student:

Krasimira Ivanova Koleva, MD, has been trained at Fifth secondary school of Varna. She graduates in the speciality of medicine from the Professor Paraskev Stoyanov Medical University of Varna in 1994. She has acquired the specialities of ‘pediatrics’ in 2009 and ‘pediatric gastroenterology’ in 2016. Since 2017 until presence, she works as assistant in the Department of Pediatrics of the Faculty of Medicine at Professor Paraskev Stoyanov Medical University of Varna. She is a member of the Academic Council of the Medical University of Varna and also a member of ESPGHAN and ECCO.

1. Actuality of the problem

Inflammatory bowel diseases are, most commonly, diagnosed in adolescence and young age as during the recent years, an increase of the relative number of the newly-diagnosed cases in children has been observed. Early and precise diagnosis is a serious

challenge taking into consideration the great variety of the clinical symptoms, the dynamics of the laboratory parameters and the results from the imaging examinations. The lack of an universal diagnostic algorithm, the risk of occurrence of complications of different kind and severity in case of delayed diagnosis and the serious health-related consequences in at a more mature age pose the problem of the early and precise diagnosis in the focus of research in the field of pediatric gastroenterology.

The dissertation theme chosen is actual and useful not only in an experimental aspect but also for the clinical practice. In our country, there are single publications dealing with this problem.

2. Characteristics, volume and structure of the dissertation work

The dissertation work is elaborated in 183 pages and illustrated with 99 tables, 12 figures and one supplement. Style is good, clear and with a correct discussion of data and results.

The contents is properly structured and balanced in single parts. It is presented with introduction (2 pages), literature survey (53 pages), purpose, tasks and working hypothesis (one page), material and methods (7 pages), own results (47 pages), discussion (34 pages), concluding remarks (2 pages), conclusions (one page), contributions (one page), references (27 pages), supplements (5 pages), and list of publications related to the dissertation work (one page). The reference list contains 227 titles, 15 of which are Cyrillic and 212 in Latin alphabet. The list of scientific publications includes 5 articles published in 2020. The PhD student is the only author in one and the first author - in four articles. Research activity during the period of preparation of the dissertation work meets the normative requirements.

2.1. Literature survey

The literature survey defines the clinical importance of the inflammatory bowel diseases (IBD) in children and adolescents and provides actual and comprehensive information related to the social epidemiology and contemporary methods of diagnosis of Crohn's disease, ulcerative colitis and unspecified colitis.

In terms of IBD epidemiology, a main place is devoted to the problem of the stable tendency towards the increasing incidence rate in childhood and the greater frequency of relapses during the first year in cases with an earlier disease onset. Attention is paid to the most common clinical manifestations associated with the beginning of the diseases in childhood as well as to the greater frequency of the gastrointestinal malignant diseases in patients who have been diagnosed at a younger age. A special part of the literature survey is devoted to the diagnosis of 'unspecific colitis' and to the ongoing discussion in the literature whether this clinical and morphological phenotype is a distinct nosological unit, or it reflects the difficulties when defining IBD type as ulcerative colitis or Crohn's disease.

In the second part of the survey, the modern methods for IBD diagnosis in children and adolescents, their significance concerning the sensitivity and specificity and the real possibilities for application in the clinical practice are presented. They are divided into three groups and include laboratory markers, imaging examinations and microribonucleic acids. Every method or marker is classified as routine or innovative and is analyzed in terms of its diagnostic value.

The literature survey ends with a critical appraisal of the comparativeness of the diagnostic methods used by different authors and the conclusions related to that which are of varying directions, often fragmentary and not always convincing. This circumstance as well as the lack of a systematic investigation of the importance of the complex application of some modern diagnostic methods in pediatric IBD in Bulgaria represents the grounds for the PhD student to perform the present study.

2.2. Purpose, tasks and working hypothesis

The purpose of the dissertation work is clearly and exactly formulated: 'To analyze the individualized diagnostic behaviour in children and adolescents with inflammatory bowel diseases with of view to its perfectioning'. In order to achieve it the PhD student has defined five main tasks which logically follow the purpose. The last task includes the elaboration of an algorithm for IBD diagnosis in childhood and adolescence, and, in practice, is the approval of the working hypothesis which supposes that 'The elaborated original constellation of modern methods for the diagnosis and differential diagnosis is

sufficiently effective and applicable in children and adolescents with inflammatory bowel diseases’.

2.3. Material and methods

For the purposes of the scientific investigation, Dr. Koleva analyzes 76 children with IBD, 41 boys and 35 girls at a mean age of $13,54 \pm 3,13$ years which does not differ between both sexes. All the children are diagnosed, treated and followed-up in the Second Clinic of Pediatrics at St. Marina University Hospital of Varna and include 27 patients with Crohn’s disease, 36 with ulcerative colitis and 13 with unspecific colitis. The study period lasts 12 years and 7 months (from January 1, 2008 to July 31, 2020).

There are numerous methods of examination and they are presented in 4 categories such as clinical, laboratory (hematological, biochemical and biological parameters) and imaging. Every category contains a definite number of diagnostic parameters which are read at least twofold - at the time of diagnosis and during the last discharge from hospital within the investigation. The clinical parameters are presented by severity of the disease, assessment of the pediatric activity index of Crohn’s disease and ulcerative colitis, number of hospitalizations, number of serious accompanying diseases and organ localization of the inflammatory process. The hematological and biochemical parameters are selected with the purpose for iron deficiency screening and assessment of inflammation presence while the biological ones - for the proof of the intestinal inflammation and the potential possibility of some of them to differentiate the single inflammatory diseases.

The imaging examinations include a routine panel of abdominal echography and x-ray, computed tomography of abdomen and small pelvis, irigography, fibrogastroduodenoscopy and fibrocolonoscopy.

Statistical methods are optimally selected and enable processing of the expected results.

2.4. Results

The results from the study are structured into five subsections and are well-illustrated with figures and a great number of tables.

In the first subsection, the results from the investigation of the clinical peculiarities in IBD children in terms of the severity of the diseases, comorbidity and organ localization of the disease are presented.

The second subsection includes the results from the laboratory examinations carried out for registration of the iron deficient anemia and as criteria for inflammatory activity. In order to assess these clinical conditions in all the patients, erythrocytes, hemoglobin, serum iron, leukocytes, fibrinogen, C-reactive protein and fecal calprotectin are examined.

In the same subsection, the results from the examination of the expression of 11 microribonucleic acids in a part of the examined patients with Crohn's disease and ulcerative colitis and in 20 healthy controls are presented. This examination is performed for the first time in the Bulgarian pediatric gastroenterological practice and the results obtained are very comprehensively and competently interpreted by the PhD student in the discussion section.

The results from the imaging diagnosis are placed in the third subsection. They are systematized according to the kind of the examinations carried out such as abdominal echography, CT, fibrogastroduodenoscopy, fibrocolonoscopy and pathohistology and to the preliminarily defined criteria for abnormality with the corresponding imaging examination.

The fourth and fifth subsections are the consequence of the information provided in the first three ones. In the fourth subsection, the identified correlation dependences between the single parameters analyzed have been presented while in the fifth final one, an original diagnostic algorithm for children and adolescents with IBD constructed on the grounds of the results obtained has been proposed. The identified and approved constellation of various and mutually complementing one another parameters presents with an objectively proved diagnostic and differential-diagnostic value in the children and adolescents with Crohn's disease, ulcerative colitis and unspecified colitis.

2.5. Discussion

This section of the dissertation works follows the logic of the investigation and adequately comments on the results received. Within three independent subsections, a comprehensive comparative analysis not only of PhD student's own results but also of

those reported by other authors on these concrete interdisciplinary problems has been carried out.

2.6. Concluding remarks

The concluding remarks are concise and clear and include a generalization of the most significant results from the dissertation work to the benefit of the clinical gastroenterological practice.

2.7. Conclusions

The dissertation work ends with seven concrete, well-formulated conclusions which correspond to the tasks set.

Contributions

I completely accept not only the three contributions of original nature but also the four contributions of confirmatory nature which support the significance of the dissertation work. It completely meets the requirements of the Law for academic staff career and objectively and adequately reflects the basic results and scientific contributions of the dissertation work.

I do not detect any omissions in Dr. Krasimira Koleva's documentation enclosed.

Critical remarks

There are no grounds for substantial critical remarks. Guided by the ambition to present and analyze all the publications related to IBD in children and adolescents in the literature available, the PhD student makes some reiterations from the literature survey into the discussion section which does not provide any additional information about the corresponding problem. Concerning the criteria used for the definition of the anemic syndrome in children and adolescents with IBD, it could be more appropriate to replace the serum ferritin by the examination of reticulocyte count and ferritin.

Publications and research activity

The PhD student has published 5 scientific articles on the theme of the dissertation work. She is the only author in one and the first author - in four articles. All the publications are dated in 2020. Research activity during the period of preparation of the dissertation work meets the normative requirements.

CONCLUSION

The dissertation work reviewed represents an authentic author's elaboration that deals with an actual problem in pediatric gastroenterology and it is characterized with originality and practical applicability. The PhD student demonstrates profound theoretical knowledge, professional skills in pediatrics and pediatric gastroenterology as well as qualities for independent performance of a scientific investigation.

Bearing in mind the aforementioned, I give my positive evaluation of the dissertation work presented and propose to the members of the honoured Scientific jury to award the educational and scientific degree "**Doctor**" in the scientific speciality of 'Pediatrics' to Krasimira Ivanova Koleva, MD.

May 16, 2021

Varna

Reviewer:

Prof. Valeria Kaleva, MD, PhD