

**To The Chairman of the Scientific Jury,  
appointed by Order No.RD-38-297/21.06.2022  
of the Rector of Sofia University "St. Kliment Ohridski"**

**REVIEW**

from

Prof. Dr. Dobrin N. Konstantinov, PhD,  
Head of the Children's Clinical Hematology and Oncology Clinic, "Tsaritsa Yoanna-ISUL"  
UMBAL, Sofia, Professor, Department of Paediatrics, MF, MU - Sofia, external member of the  
Scientific Jury,

for a dissertation on:

**"Macrophage activation syndrome in childhood - analysis of clinical laboratory changes,  
assessment of diagnostic approach and therapeutic effectiveness"** for awarding the  
educational and scientific degree "DOCTOR"

of Dr. Kalin Yordanov Lisichki,

free doctoral student in a doctoral program 7.1. Medicine (03.01.50) "Paediatrics" at the  
Department of "Internal Diseases, Pharmacology and Clinical Pharmacology, Paediatrics,  
Epidemiology, Infectious and Skin Diseases", Faculty of Medicine, SU "Kliment Ohridski".

**Biographical data**

Dr. Kalin Yordanov Lisichki was born in Sofia in 1958. He completed his secondary education in the year of 1976. In 1984 he graduated with honours as a doctor at the Medical Academy, MA, Sofia. From 1984 to 1987, he was a paediatrician at the Regional Hospital - Dupnitsa. In the period from 1987-2007, he was successively an assistant, senior assistant and chief assistant in the Paediatric Rheumatology Clinic at the Scientific Institute of Paediatrics, MA, Sofia, (currently - SBALDB, Sofia). From 2007 to 2013, he worked as a resident physician at Tokuda General Hospital, Clinic for paediatrics, and after 2013 until now he is the head of the same department. He acquired a specialty in paediatric diseases in 1991 and a second one in paediatric rheumatology in 1997.

During the entire period of his medical career, Dr. Lisichki has shown to have a fully active commitment not only to the medical point of view but the diagnostic, teaching and research component.

**Importance of the topic.**

The topic of the dissertation work "Macrophage activation syndrome (SMA) in childhood - analysis of clinical and laboratory changes, evaluation of the diagnostic approach and

therapeutic effectiveness" is undeniably significant and relevant, given the life-threatening nature of SMA, the difficulties in recognizing it in daily paediatric practice and the need for a wide range of differential diagnostic search, with a real risk of high mortality among affected children in case of delayed diagnosis and untimely or inadequate treatment.

### **Structure of the dissertation.**

The submitted dissertation contains 123 standard typewritten pages. The introduction and literature review are presented on 30 pages; purpose, tasks, materials and methods occupy 10 pages; results - 41 pages, discussion, conclusions and contributions - 20 pages; literary sources - 20 pages.

The exhibition includes 37 graphic figures and 8 graphic tables. In connection with the dissertation work, Dr. Lisichki has 6 publications, of which 4 in the Bulgarian specialized press and 2 in foreign journals. He is the first author in five of the six publications. As the first author, he participated in 4 presentations on the subject of the dissertation in congresses and conferences in our country.

**The written dissertation** is comprehensive. It contains 203 literary sources, of which 2 in Cyrillic and 201 in Latin, with over 16% published in the last 5 years and the majority - in the last 15 years. The overview itself is structured thematically, in directions that allow the clarification of the essence of the SMA. The different characteristics of the lymphohistiocytic model are discussed in depth. An independent review was made of the information on serum ferritin with its biological nature and the justified possibility of being a reliable marker for evaluation in prominent inflammatory processes, in that number including SMA. Reviewed and commented on are the various diagnostic criteria and clinical manifestations and the proposed combinations. Different treatment approaches are widely advocated. The summaries made at the end of the overview are a good basis for building the plan of the dissertation work.

### **Purpose and tasks.**

The aim of the presented work, formulated by the dissertation, is to describe in detail patients with macrophage activation syndrome in childhood in Bulgaria, to analyze the established clinical and laboratory changes and to evaluate the applied diagnostic approach and the effect of the treatment. Presented in this way, the goal is clear, but it also includes some of

the tasks to achieve it. The tasks themselves, eight in number, are aligned with the main target guidelines and include dividing patients by gender and age, distinguishing the triggers of the main disease, presenting data for the clinical characteristics and laboratory parameters, assessment of the dynamics of their changes, as well as analysis of the effect of the applied medications in their control. In addition, the author sets himself the task of offering a modern diagnostic approach and an effective therapeutic strategy for SMA.

### **Research Material and methods.**

The data of 20 children with macrophage activation syndrome, diagnosed and treated in the period from 2013 to 2019, were analyzed, including a contingent from the unit where Dr. Lisichki works - Children's Clinic, "Acibadem City Clinic Tokuda Hospital" - Sofia, as well as patients from the main specialized paediatric structures for Bulgaria, among them, the Paediatric Rheumatology Clinic at UMBALDB "Prof. Ivan Mitev" - city, Sofia, Children's Clinic at the UMBAL "St. Georgi" - the city of Plovdiv and the Children's Clinic at the UMBAL "St. Marina" - city of Varna.

All patients were diagnosed with SMA in accordance with the current EULAR/ACR 2016 diagnostic criteria for this disease, namely:

Presence of:

- Fever
- Ferritin > 684 ng/ml

and at least two of the indicators:

- Platelets < 181x10<sup>9</sup>/l
- AST > 48 UI/l
- Triglycerides >1.76 mmol/l
- Fibrinogen <3.6 g/l

The patients are carefully divided and studied in several groups, according to the performance of the tasks, such as: distribution by gender and age; according to the triggers of the macrophage activation syndrome (cases with juvenile idiopathic arthritis, dermatomyositis and infectious provoked SMA are included here); by clinical appearance (fever, rashes, lymphadenomegaly, CNS manifestations); by paraclinical results - hematological indicators, markers of inflammation, biochemical indicators, ferritin, coagulation status, microbiological tests, imaging, bone marrow aspiration biopsy results. To the main criteria of EULAR/ACR from 2016, the dissertation student also applies those generally valid for Hemophagocytic

Lymphohistiocytosis. All clinical and laboratory parameters were assessed repeatedly, both at diagnosis and during treatment and observation.

Dr. Lisichki's approach to include a control group of 21 patients is authentic. This allows comparison and conclusions on a number of parameters in the main group and in children with other diseases, occurring with a pronounced inflammatory clinical-laboratory syndrome and with diagnostic criteria different from those generally accepted for SMA.

The therapy of the followed patients started with corticosteroid - methylprednisolone in pulse doses on three consecutive days. When considering the effect on disease control, an additional medication (cyclosporine, intravenous immunoglobulins, etoposide or anti-interleukin 1 antibody) is included, if necessary. For the assessment of the therapeutic results, the patients were divided into subgroups, respectively - only with high-dose corticosteroid, in combination or not with cyclosporine and with an added third medication.

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### **Results and discussion.**

Dr. Lisichki presents the results of his development in a systematized form and with appropriate visualization in figures and tables. The order of the presentation follows the set goals and objectives and each group of results is accompanied by a commentary by the author. Here the personal attitude of Dr. Lisichki and his shared clinical experience is evident. Dr. Lisichki follows the recommended in the scientific literature and practice and current diagnostic criteria for SMA, and the majority of the results obtained by him confirm the published data. At the same time, the author offers a convincing thesis in assessing the significance of some parameters and their applicability in practice. For example, starting from the information in his literature

review and based on his own results, Dr. Lisichki pays special attention to serum ferritin, as a defining marker with a leading role in the diagnosis and follow-up of SMA cases. Examining in detail the role of ferritin, the dissertation uses a comparative study of a control group with diseases with high inflammatory activity with the patients diagnosed for SMA. The author proposes the ferritin / ESR ratio as a reliable and easily accessible laboratory indicator. Based on reports in the literature and the results obtained by him, the dissertation assesses the sensitivity and specificity of the ferritin / ESR ratio and reports an impressive (100%) sensitivity and specificity in cases with SMA.

Dr. Lisichki also systematized his observations on the dynamic influence of the laboratory parameters by the therapy. The data is precisely registered, as according to the individual therapeutic approaches and clinical course, they are tracked in a long time range. The author also describes the first experience in our country with the use of an anti-IL-1 receptor antagonist in two of the children. Dr. Lisichki demonstrated high competence in discussing the results. His interpretations are convincing and testify to the maturity of a well-rounded clinician who knows the methods of scientific research and analysis.

The conclusions drawn by the author are clearly formulated. They are based on actual achieved results and provide answers to the goals and tasks set in the development. Despite the limited clinical material, Dr. Lisichki's work justifiably claims to be a contribution to the field of SMA. The most significant contribution to the Bulgarian paediatric practice is the comprehensive description of the characteristics of the patients registered in the country with an analysis of their treatment approach and the proposal to introduce the ferritin / ESR ratio as a fast and effective method for differentiating SMA from non-SMA patients.

### **Abstract.**

The proposed abstract is written on 50 pages and in terms of form and content it fully meets the requirements and gives a clear and complete idea of the essence of the dissertation work.

### **Recommendations.**

The layout of the dissertation - structurally, linguistically and graphically - deserves a very good evaluation. I have no significant remarks that would affect my personal positive assessment of the dissertation work.

In **conclusion**, on the basis of the above, I believe that the dissertation fully meets all the requirements of the regulatory framework and I would confidently recommend to the respected Scientific Jury to award Dr. Kalin Yordanov Lisichki the scientific and educational degree "Doctor".

**Signature:**