

## **R E V I E W**

By Assoc. Proff Dimitar Georgiev Nikolov, MD, PhD

Department of Nephrology, II Department of Internal Medicine, Medical  
University of Plovdiv

On the dissertation of Dr. Iskui Mnatsakan Erkanyan for awarding the degree of Doctor, field of higher education 7, health and sports, professional field -7.1-medicine, scientific specialty 03.01.15-Nephrology, Medical University of Plovdiv

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**Topic: "IgA NEPHROPATHY – CLINICAL, IMMUNOLOGICAL AND PATHOMORPHOLOGICAL CRITERIA FOR DIAGNOSIS AND THERAPEUTIC APPROACH"**

**Doctoral Program in Nephrology**

**Author:** Dr. Iva Krasimirova Kostadinova

**Supervisors: Assoc. Prof. Dr. Eduard Tilkian, PhD**

**Prof. Dr. Iliyan Doykov, MD**

Second Department of Internal Medicine, Department of Nephrology,  
Medical University - Plovdiv

## **1. Biographical data.**

Brief biographical information

In 2010, Dr. Iskui Erkanyan graduated from the Medical University of Plovdiv

Since 2010 he has been a doctor at the Clinic of Nephrology at the University Hospital "Kaspela" Plovdiv

Since 2015 she has a recognized specialty in Nephrology and over 10 years of experience in the specialty.

Since 2018 she has been a regular assistant professor in Nephrology at MU-Plovdiv.

She is a member of the BMA and BDN

She speaks English.

The presented set of materials, Dissertation and Abstract is in accordance with the Law on the Acquisition of a Scientific Degree and the Rules of Procedure for Acquiring a Scientific Degree and Occupying Academic Positions at MU – Plovdiv.

**General characteristics of the presented dissertation.** The dissertation is properly structured, in a volume of 113 typewritten pages, contains 10 main tables, each of which has a different number of additional subheadings and 35 figures. The bibliographic reference covers a total of 178 literary sources, 23 of which are from the last five years. Their numbering is in the order of citation in the literature review.

### **Relevance of the topic.**

The history of IgA nephropathy (IgAN) is associated with many famous names - Heberden, Johann Schönlein and Eduard Henoch, the French pathologist Jean Berger, who in 1968 revealed the pathogenic role of IgA deposits. Nephropathy is the most common primary glomerulonephritis worldwide and is one of the leading causes of chronic kidney disease. The frequency of the disease is influenced by different factors: Socioeconomic status, genetic predisposition, ethnic, geographical,

and others. It is noted that in Asian patients, the frequency of manifestation is higher and the course of the disease is more aggressive.

Despite serious scientific discoveries in the field of genetics, epigenetics and pathogenesis of the disease, as well as novelties in the treatment of the disease, the clinical course is progressive and a large percentage of patients reach the final stage of kidney disease. There are still no algorithms approved by clinical practice that allow timely detection and treatment of the disease. Often, the diagnosis is late, which does not allow optimal therapeutic control and a favorable outcome of the disease.

In view of all this, I believe that the dissertation topic chosen by Dr. Iva Kostadinova is extremely relevant and contemporary.

### **Structure of the dissertation**

The presented dissertation is developed on 113 pages and is illustrated with 10 tables, 35 figures, and 8 microscopic photographs. It is structured correctly, in accordance with generally accepted requirements.

From the presented **Literature Review** , consisting of 178 sources, /176 in Latin and 2 in Cyrillic/ most of which are in the period of the last five years, it can be seen that the author is familiar with the current state of the problem. It presents the current knowledge regarding epidemiology, genetics, the role of microRNAs and the pathophysiological aspects of the disease, histopathological variants and the various classifications proposed so far. with the main conclusions from the analyzed scientific literature.

In relation to the literature data, the **purpose of the dissertation is to** *investigate the clinical, immunological and pathomorphological criteria for diagnosis and differential diagnosis of patients with IgA nephropathy and their importance for the therapeutic approach.*

The goal is clearly and precisely formulated and fully corresponds to the thesis set in the title of the dissertation.

To achieve this goal, Dr. Iskui Erkanyan sets **an optimal number of 8 tasks:**

1. To study the frequency of patients with IgAN, the diagnosis of which is specified by puncture renal biopsy.
2. To specify the frequency of secondary IgAN.
3. To specify the possibilities for the use of other biomarkers in the diagnosis and therapeutic approach of IgAN.
4. To investigate the diagnostic significance of serum and tissue IL-6 levels, as well as the difference between primary and secondary IgAN.
5. To investigate the relationship of pathomorphological changes with clinical presentation.
6. To investigate the role of immunological tests for diagnosis, activity monitoring and therapy.
7. To monitor the clinical course of IgAN in different age groups.
8. To give recommendations for therapeutic behavior in patients depending on clinical presentation, immunological and pathomorphological changes.

The tasks are specific, doable and meet the defined goal in the dissertation.

Methodically, the scientific research is **well planned**.

The study included **110 patients, 84 men and 26 women**, with biopsy-proven IgA nephropathy, treated at the Clinic of Nephrology at Kaspela University Hospital for a period of 13 years (2010-2023). All patients underwent a puncture renal biopsy, clinical and laboratory tests of blood and urine, immunological tests - autoantibodies and C3+C4 complement fractions, Glomerular filtration was examined, interleukin 6 levels were examined.

The obtained data were analyzed using modern statistical methods using standard statistical packages.

In **the statistical study** of the data obtained, the statistical programs IBM SPSS, version 27 (2020), Minitab version 19 (2020) and MedCalc, version 20.008 (2021) were used, through which it is possible to completely reliably objectify the results obtained.

**The results** are presented clearly and are well illustrated with tables and graphs. Of interest is the combination of IgA nephropathy with immune arthropathy, psoriasis, hepatitis B. The biopsy finding is illustrated with its own histological images, including immunofluorescence and conventional light microscopic examination.

The role of interleukin 6 has been evaluated, which has been shown to be higher in women and correlated with more pronounced tubulo-interstitial inflammatory infiltrates.

Dr. Erkanyan also presents the main therapeutic strategies for patients with IgA nephritis: 1. Therapy with only a RAAS inhibitor is available in 11 patients, all of them have a level of proteinuria below 500 mg/24h; 1 of the CD. 2. Methylprednisolone – pulse therapy was performed in 82 patients. 3. Cyclophosphamide. 4. IMF – 11. 5. Azathioprine – 10. 6. Advagraf – 1. 7. Budesonide – 24, of which only 1 as initiating therapy. 8. Dapagliflozin received 17 patients.

For the first time in Bulgaria, the dissertation describes a systematic treatment of the disease with Budesonide – in a total of 24 patients. Treated for a period of between 3 and 20 months with good tolerance.

Dr. Erkanyan also evaluated the effect of the gluten-free diet in the patients studied and reported a good effect on clinical and laboratory signs in the patients followed, emphasizing that at the beginning of this dietary regimen the patients were without significant proteinuria, nitrogen retention or systemic manifestations. These data raise the question of the importance of a gluten-free diet as an additional means of influencing mild forms of IgA nephritis.

**The discussion** is presented on page 6 and clearly emphasizes the significance of the results obtained against the background of the data in the literature so far.

**There** are a total of 8 conclusions and fully correspond to the tasks:

1. The study confirms the data that IgAN is the most common glomerulopathy in patients up to 60 years of age with predominantly male involvement.

2. The results show a similar profile of light microscopic diagnoses to those in most large studies, but also some differences in immunofluorescence examination - low percentage of IgG and C4 deposition.

3. Elevated serum IgA levels are proven in only 2 patients and cannot be a diagnostic criterion.

4. The study of IL-6 showed significantly higher serum levels among patients compared to healthy controls. Comparison with histological changes shows that patients with higher levels of IL-6 exhibit more pronounced levels of interstitial infiltrates, mesangial hypercellularity, as well as higher levels of fibrosis compared to patients with lower levels.

5. The effect of the treatment shows very good results in patients with medium and high risk, especially with early diagnosis and initiation of therapy.

6. In patients treated with Budesonide, the data from the studies conducted so far for a good effect on renal function are confirmed. None of them have proven IBD and no positive antigliadin antibodies have been found.

7. It is confirmed that the leading renal pathology in Ps/PsA is IgAN

8. Therapy for IgAN should be refined according to the leading immune cause, respectively primary or secondary.

The dissertation presents a total of 5 **contributions**, of which the assessment of the level of interleukin 6 and their relationship with the signs of IgA nephritis activity and the presented therapeutic experience with

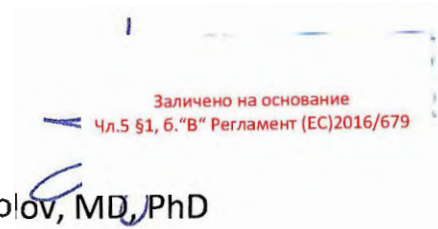
budesonide are perhaps indicative. An algorithm for early diagnosis of IgA nephritis and therapeutic options depending on the pathohistologic finding and concomitant/underlying diseases and conditions have been created.

Dr. Erkanyan presents three publications in connection with the dissertation, incl. in journals indexed in Scopus, as well as two participations in scientific forms.

The abstract is written in correct Bulgarian and compiled according to the generally accepted requirements.

**Conclusion:** Based on the above, I consider that the dissertation of Dr. Iskui Mnatsakan Erkanyan is a fully completed work. The scientific work is properly constructed, with a precisely selected methodology, completed tasks and reliable scientific and applied results and meets the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its Implementation and the Regulations of MU – Plovdiv.

Therefore, **I give my positive assessment and confidently propose to the honorable scientific jury to award the educational and scientific degree "Doctor" to Dr. Iskui Mnatsakan Erkanyan**, PhD student of independent training in "Nephrology" at the Department of Internal Medicine, Medical University - Plovdiv.



16.11.2024 г.