

REVIEW

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Subject: Dissertation paper for the acquisition of the National Doctor of Sciences, entitled "Ocular changes and vasography in patients with psoriasis", by Zdravka Velichkova Chalmanova - Demerdjieva, MD, Head of the Clinic of Dermatology and Venereology at Acibadem City Clinic Tokuda Hospital.

I have been appointed a member of the Scientific Jury in the procedure for public defense of the submitted dissertation work with Order No. Order No. 46 of 23.01.2020 of the Executive Director and procurator of Acibadem City Clinic Tokuda hospital. At the first meeting of the Scientific Jury, I was selected as a reviewer. The documentation provided to me is in accordance with the requirements of the Academic Staff Development Act of the Republic of Bulgaria, the Regulations for its implementation and the Regulations for the development of the academic staff in the above-mentioned academic institution.

Psoriasis is a genetically determined and immunomedicated systemic inflammatory disease affecting up to 3% of the Bulgarian population. In recent years, it has been found that, in addition to skin and joint syndrome, dermatosis is also combined with a number of comorbid conditions associated with disorders of lipid and glucose metabolism, increased risk of cardiovascular and cerebrovascular accidents, COPD, some neoplasms, psycho-emotional deviations, poor quality of life. The contribution of the Bulgarian Dermatological School to the definition of

the modern concept of disease system is well known to dermatologists and globally recognized, a fact reflected in dignity in the dissertation.

So far, no studies have been conducted in the Republic of Bulgaria to determine the condition and changes in the microcirculation of the conjunctiva in the different clinical forms of dermatosis, and correlations between them have been sought through vasography of lymphatic and blood vessels. The insufficient information on the problem at the moment determines both the author's motivation for carrying out this scientific work and the contribution character of the thesis.

Assoc. Prof. Zdravka Demerdjieva's dissertation is written on 115 printed pages and includes the usual sections for scientific development: title page, content, abbreviations used - 5 pages; introduction and literature review - 39 pages; purpose and tasks of the study - 1 page, materials and methods - 3 page, results of own studies - 30 page; discussion of the results - 16 pages; conclusions and contributions - 3 pages; bibliography - 15 pages. The text is illustrated with 12 tables, 41 photos and 9 diagrams, the bibliography is from 202 literary sources, 11 in Cyrillic and 191 in Latin.

The literature review presents summary data from the scientific periodicals related to the psoriasis-associated microbiome and the mechanisms of microbial pathogenesis of dermatosis, and the changes in the various anatomical structures of the eye analyzer recorded in patients are described in detail. In the light of current genetic studies and knowledge about the immunopathogenesis of psoriatic disease, T-cell alterations and the resulting expression of cytokines, chemokines, growth and hormonal factors, vasoactive substances as a reference to microcirculation are analyzed in detail.

The review concludes with an emphasis on contemporary aspects of the problem, emphasizing Assoc. Prof. Demerdjieva's own view that analysis of changes in permeability as a symptom is part of the comorbid conditions in psoriasis. This fact represents an ambitious request on the part of the author, exploring the conjunctiva, to develop a model for the observation and detailed study of many systemic diseases associated with various vascular symptoms.

The purpose of the dissertation is to clearly formulate and concretise a study of ocular changes in psoriatic disease and to identify and analyze the condition and changes in the microcirculation of the conjunctiva in guttate, pustulosus and arthroparasis by vasodography with Patentblau V on blood and lymph vessels. The dissertation student has set 8 tasks, the consistent implementation of which logically leads to the achievement of the goal.

The study material is a clinical contingent of 148 patients with psoriasis - 67 hospitalized and 81 outpatients at the clinic, selected for a five-year period (2014 - 2019). 16 healthy subjects were the control group used to compare the results of the studies. A sufficient number of patients studied suggests correct conclusions and conclusions.

Classical and modern medical methods (clinical, diagnostic, laboratory, quality of life assessment) were used to carry out the research. The collected information from the studies was introduced and processed with the statistical software SPSS ver.23 for Windows. Statistical methods for hypothesis testing (parametric and non-parametric), descriptive and estimation methods (correlation and graphical analysis), regression analysis were used to process the obtained results. A $p \leq 0.05$ coefficient was chosen for the significance level, which rejects the null hypothesis.

The results of our own studies are published on 35 pages. I believe that the data obtained are convincing of the merits of scientific development.

36 patients with Psoriasis guttata, 32 with Psoriasis arthropathica, 34 with Erythrodermia psoriatica and 30 with Psoriasis pustulosa were examined, describing the clinical symptoms and ophthalmic diagnoses for each of them. Contrast vasography was performed, incl. and 16 healthy controls.

The vasographic findings of the eruptive psoriasis group show that the permeability of the lymphatic vessels (shortened penetration time, shortened diffusion time, diffusion rate) is significantly increased, blood vessels too, and the dye diffusion time in the depot in the depot is 3.75 min., compared with 4.33 min. in healthy controls. In 13 of 32 cases of arthropathy, the dye does not penetrate the lymphatic vessels, and accordingly they remain without visualization. The study for the group shows that with the progression of the disease, the time it takes to notice the diffusion of the dye outside the lymphatic vessels increases.

For patients with pustular dermatosis, the degree of diffusion from the blood vessels varies from weak to medium, regardless of the age and gender of the person. The type of lymphatic vessels in the group deviates significantly from those of healthy controls, most often single, pale and short, and with the progression of the disease, the time it takes to notice diffusion outside the lymphatic vessels is prolonged.

The discussion of the obtained results is on 17 pages, and it is indisputable that the dissertation student demonstrates skills for reasoned analysis. Prof. Demerdjieva makes a comparison between the data she has received for psoriatic patients, correctly pointing out the fact that such data are missing in the world scientific literature, and for some of the studies are single. Existing discrepancies, quite permissible

in any scientific study, show critical thinking and provide logical explanations. The statement also makes its own claims as a query for future searches of an applied nature, which I greatly appreciate.

Conclusions are 11, which I accept with one note - conclusion # 6 can be removed, but if it is an authoritative assessment of the diffusion intensity introduced for the purposes of scientific development, it should be emphasized as an original contribution. I also accept the aforementioned 10 contributions (in total) to the dissertation, usually divided into "original" (6) and "applied" (4).

The thesis contains a list of scientific papers related to the topic. They are a total of 12 - 4 publications in English (in the WOS / S databases), 6 in Bulgarian medical periodicals and 2 publications in monographs (one abroad - published by Lambert Academic publishing). The abstract for the dissertation is from 52 pages and adequately reflects the main points of scientific development.

Critical notes:

- The tasks set in the dissertation are 8 (eight), but in the abstract there are 9 (nine), which I take as a technical pass.
- Vasography is a method and a description and should be in the chapter "Material and methods" and not in "Results of own studies" (pages 52 and 53)
- Diagnosis, written in both Latin and Bulgarian languages, should be avoided by applying only one option in the text (preferably in Latin).
- The list of scientific papers on the topic is correct to be applied in the dissertation itself (not only in the abstract), as proof of the realization of the scientific claim.

- Critical notes of a technical nature (misspellings, dots, commas, and spaces between them) are not material.

The remarks made do not diminish the scientific and contribution value of the dissertation.

In conclusion, I positively appreciate the dissertation work of Assoc. Prof. Demerdjieva. My grounds for positive assessment are some truly up-to-date and up-to-date studies on some aspects of the clinical picture, the pathophysiology and comorbidity of psoriatic disease. Vasography studies of changes in the microcirculation and permeability of conjunctival blood and lymphatic vessels in patients with various clinical forms of psoriasis are pioneering in Bulgaria. I agree that the tasks assigned have been adequately fulfilled.

17.02.2020 г.
PhD

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