lek. Magdalena Maria Bazewicz

Współczesne metody diagnozowania zapaleń błony naczyniowej.

Contemporary methods of diagnosing uveitis.

Rozprawa na stopień naukowy doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

Promotor: dr hab. n. med. Janusz Skrzypecki

Zakład Fizjologii i Patofizjologii Eksperymentalnej, Wydział Lekarsko-Stomatologiczny, Warszawski Uniwersytet Medyczny

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych Warszawskiego Uniwersytetu Medycznego

Warszawa 2023

Streszczenie w języku angielskim

Contemporary methods of diagnosing uveitis.

Uveitis encompasses a diverse array of eye diseases with various etiologies, which can result in permanent severe visual impairment or even blindness. Treatment success hinges upon timely diagnosis and the administration of appropriate medications. Accurate diagnoses can be achieved through understanding the clinical and multimodal imaging features of different uveitis types, as well as employing diagnostic tests.

Uveitis is classically divided into noninfectious, which requires immunosuppressive treatment, and infectious, where determining the etiology is necessary to administer appropriate causal treatment. It should also be mentioned that the causes and course of uveitis are different in adults and children. In adults, noninfectious uveitis is most often associated with the presence of the HLA-B27 antigen (23% in the Netherlands), while in children it is often associated with juvenile idiopathic arthritis (JIA)(20% in the Netherlands). Despite the significant development of diagnostic methods, the etiology of uveitis remains unknown in 30-60% of cases.

The aim of this dissertation is to improve comprehension of contemporary uveitis diagnostic methods and to attempt to analyze the mechanisms leading to noninfectious uveitis development. Understanding the molecular pathways involved in uveitis development may lead to the discovery of more effective diagnostic methods.

The experimental study focuses on the mechanisms of autoimmune uveitis. The study was performed in vitro on retinal pigment epithelium (RPE) cells. The study shows that RPE cells overexpressing Suppressor Of Cytokine Signaling 1 (SOCS1) may inhibit IFNγ-based

signal transduction pathways. Overexpression of SOCS1 in RPE cells inhibits the IFNγ-induced decrease in IL-8 secretion and prevents the IFNγ-induced increase in MHC II and ICAM1/CD54 expression. Furthermore, SOCS1 overexpression does not affect TNFα-induced IκBα degradation or block IL-8 secretion induced by TNFα or IL-17. Instead, IL-17-induced IL-8 secretion is increased by SOCS1 overexpression. The results of the above experimental study elucidate some molecular mechanisms in autoimmune uveitis that could potentially serve as novel targets for diagnosing or treating noninfectious uveitis.

The subsequent two clinical studies focus on uveitis diagnostics in clinical settings. Both are retrospective studies that include patients with rare uveitis types. The first evaluates the utility of FDG PET/CT in the diagnosis work-up of pediatric idiopathic uveitis, showing that FDG PET/CT provided crucial information for final diagnosis in 33% of children with bilateral uveitis. The second clinical study explores neurosyphilis cerebrospinal fluid (CSF) findings and initial ophthalmic manifestations in patients with ocular syphilis. It indicates that only 57% of patients with syphilis-related uveitis met the CDC criteria for definite neurosyphilis. However, CSF abnormalities suggestive of central nervous system involvement were more frequent, present in the majority of patients (71%), supporting the treatment of ocular syphilis using the neurosyphilis protocol.

The last publication addresses diagnostic concerns pertinent to uveitis specialists in clinical settings. The article emphasizes differences in the course of ocular sarcoidosis among adults, children over five years old, and in patients with Blau syndrome/Early-onset sarcoidosis (BS/EOS), in whom ocular symptoms most often begin before the age of 5. The review not only delves into existing diagnostic tools but also considers potential future advancements in ocular sarcoidosis diagnosis. The analysis of various diagnostic modalities, including chest X-ray and CT, FDG PET-CT, gallium-67 scintigraphy, bronchoalveolar lavage

fluid, genetic testing for NOD2 mutations, and numerous serum biomarkers such as ACE, lysozyme, and IL2R.

In conclusion, this dissertation addresses current diagnostic challenges in infectious and non-infectious uveitis and highlights mechanisms associated with autoimmune uveitis that could potentially serve as new targets for diagnosis or treatment. The original clinical studies focus on modern diagnostic methods: FDG PET/CT in the diagnosis of pediatric idiopathic uveitis and examination of cerebrospinal fluid in patients with uveitis in the course of ocular syphilis. Moreover, the review outlines dynamically developing diagnostic methods in ocular sarcoidosis.