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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

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Słowa kluczowe

zapalenie błony naczyniowej, supresor sygnałów przekazywanych przez cytokiny, nabłonek barwnikowy siatkówki, sarkoidoza oczna, FDG pozytonowa tomografia emisyjna/ tomografia komputerowa, kiła oczna, płyn mózgowo-rdzeniowy, kiła ośrodkowego układu nerwowego, metody diagnostyczne, dzieci, Blau Syndrome/Early Onset Sarcoidosis

Key words

uveitis, Suppressor Of Cytokine Signaling 1, retinal pigment epithelium, ocular sarcoidosis, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT), ocular syphilis, cerebrospinal fluid, neurosyphilis, diagnostic methods, children, Blau Syndrome/Early Onset Sarcoidosis

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SPIS TREŚCI

Wykaz stosowanych skrótów

ACE - Angiotensin converting enzyme - konwertaza angiotensyny

BS/EO - Blau Syndrome/Early Onset Sarcoidosis

CDC - Centers for Disease Control and Prevention

CSF - Cerebrospinal fluid - płyn mózgowo-rdzeniowy

CT - Computed tomography - tomografia komputerowa

18F-FDG PET/CT (**FDG PET/CT**) - 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) - FDG pozytonowa tomografia emisyjna/ tomografia komputerowa

FDG PET/ ultra low dose CT - FDG PET/CT z protokołem ultra niskiej dawki w tomografii komputerowej

HRCT - High-resolution computed tomography - tomografia komputerowa wysokiej rozdzielczości

ICAM1/CD54 - intercellular adhesion molecule 1/cluster of differentiation 54 -

IFNγ - Interferon gamma

IκBα - nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha

IL2R - interleukin-2 receptor - receptor interleukiny 2

IL-8 - Interleukin 8 - interleukina 8

IL-17 - Interleukin 17 - interleukina 17

MHC II - Major histocompatibility complex class II - główny układ zgodności tkankowej klasy II

NOD2 - nucleotide-binding oligomerization domain-containing protein 2

RPE - Retinal pigment epithelium - nabłonek barwnikowy siatkówki

SOCS1 - Suppressor Of Cytokine Signaling 1 - supresor sygnałów przekazywanych przez cytokiny

TNFα - Tumor necrosis factor alpha - czynnik martwicy nowotworu alfa

Streszczenie w języku polskim

Wśród przyczyn zapalenia błony naczyniowej znajdują się choroby o różnych etiologiach, które mogą prowadzić do trwałego, ciężkiego upośledzenia wzroku, a nawet do ślepoty. Sukces leczenia zależy od wczesnej diagnozy oraz od wprowadzenia odpowiednio dobranego leczenia. Precyzja diagnozy jest oparta na interpretacji badania podmiotowego, przedmiotowego oraz wyników badań dodatkowych obejmujących multimodalne obrazowanie i liczne testy dignostyczne.

Zapalenia błony naczyniowej klasycznie dzieli się na nieinfekcyjne, które wymagają leczenia immunosupresyjnego oraz infekcyjne, kiedy ustalenie etiologii jest konieczne dla wdrożenia prawidłowego leczenia przyczynowego. Należy jednocześnie nadmienić, że przyczyny oraz przebieg zapaleń błony naczyniowej są różne u dorosłych i u dzieci. Wśród nieinfekcyjnych zapaleń błony naczyniowej u dorosłych najczęściej występuje zapalenie błony naczyniowej związane z obecnością antygenu HLA-B27 (23% w Holandii), podczas gdy u dzieci najczęściej występuje zapaleń błony naczyniowej związane z młodzieńczym idiopatycznym zapaleniem stawów (JIA)(20% w Holandii).Pomimo znaczącego rozwoju metod diagnostycznych etiologia zapalenia błony naczyniowej pozostaje nieznana w 30-60% przypadków.

Celem niniejszej rozprawy jest poprawa naszego zrozumienia metod diagnostycznych stosowanych w zapaleniach błony naczyniowej, a także próba analizy mechanizmów prowadzących do rozwoju nieinfekcyjnego zapalenia błony naczyniowej. Zrozumienie molekularnych szlaków rozwoju zapalenia błony naczyniowej może przyczynić się do opracowania jeszcze dokładniejszych metod diagnostycznych.

Badanie eksperymentalne koncentruje się na mechanizmach autoimmunologicznego zapalenia błony naczyniowej. Badanie przeprowadzono in vitro na komórkach nabłonka barwnikowego siatkówki (RPE). Badanie wykazuje, że w komórkach RPE z nadmierną ekspresją supresora sygnalizacji cytokin 1 (Suppressor Of Cytokine Signaling 1 - SOCS1) może dojść do hamowania szlaków przekazywania sygnału opartych na IFNγ. Nadmierna ekspresja SOCS1 w komórkach RPE hamuje indukowane przez IFNγ zmniejszenie wydzielania IL-8 i zapobiega indukowanemu przez IFNγ zwiększeniu ekspresji MHC II i ICAM1/CD54. Ponadto, nadmierna ekspresja SOCS1 nie wpływa na degradację IκBα indukowaną przez TNFα ani nie blokuje wydzielania IL-8 indukowanego przez TNFα lub IL-17. Zamiast tego, wydzielanie IL-8 indukowane przez IL-17 jest zwiększone przez nadmierną ekspresję SOCS1. Wyniki powyższego badania eksperymentalnego wyjaśniają niektóre mechanizmy molekularne w autoimmunologicznym zapaleniu błony naczyniowej, które mogłyby potencjalnie służyć jako nowe cele dla diagnozowania lub leczenia niezakaźnych zapaleń błony naczyniowej.

Dwa kolejne badania koncentrują się na diagnostyce zapalenia błony naczyniowej w warunkach klinicznych. Są to badania retrospektywne, które obejmują pacjentów z rzadkimi typami zapaleń błony naczyniowej. Pierwsze z nich ocenia przydatność FDG PET/CT w diagnostyce pediatrycznego idiopatycznego zapalenia błony naczyniowej, pokazując, że FDG PET/CT dostarczyło kluczowych informacji do ostatecznej diagnozy u 33% dzieci z obustronnym zapaleniem błony naczyniowej. Drugie badanie kliniczne opisuje natomiast wyniki analiz płynu mózgowo-rdzeniowego (CSF) oraz początkowe objawy oczne u pacjentów z zapaleniem błony naczyniowej w przebiegu kiły ocznej. Badanie to pokazuje, że jedynie 57% pacjentów z zapaleniem błony naczyniowej w przebiegu kiły spełniało kliniczne kryteria rozpoznania kiły ośrodkowego układu nerwowego wg CDC (Centers for Disease

Control and Prevention). Jednakże, aż 71% pacjentów miało zmiany w płynie mózgowo-rdzeniowym charakterystyczne dla neuroinfekcji. Wyniki tego badania stanowią uzasadnienie dla leczenia kiłowego zapalenia błony naczyniowej według schematów opracowanych dla kiły ośrodkowego układu nerwowego.

Ostatnia publikacja dotyczy klinicznych zagadnień diagnostycznych istotnych dla lekarzy okulistów specjalizujących się w leczeniu zapalenia błony naczyniowej. Artykuł podkreśla różnice w przebiegu sarkoidozy ocznej u dorosłych, dzieci powyżej piątego roku życia oraz u pacjentów z Blau Syndrome/Early Onset Sarcoidosis (BS/EOS), u których objawy oczne rozpoczynają się najczęściej przed 5 rokiem życia. Praca przeglądowa opisuje nie tylko istniejące metody diagnostyczne, ale przedstawia także potencjalne przyszłe możliwości w diagnozowaniu sarkoidozy ocznej. Analizie poddane jest zastosowanie różnych metod diagnostycznych, w tym: badania rentgenowskiego, tomografii klatki piersiowej, FDG PET-CT, scyntygrafii z galem-67, badania popłuczyn oskrzelowo-pęcherzykowych, testów genetycznych w poszukiwaniu mutacji NOD2 oraz licznych markerów osoczowych w tym: ACE, lizozymu oraz IL2R.

Podsumowując, niniejsza rozprawa porusza współczesne wyzwania diagnostyczne w zakresie zakaźnych i niezakaźnych zapaleń błony naczyniowej, a także ukazuje mechanizmy związane z autoimmunologicznym zapaleniem błony naczyniowej, które mogłyby potencjalnie służyć jako nowe cele w diagnostyce lub leczeniu. Badania kliniczne skupiają się na współczesnych metodach diagnostycznych: FDG PET/CT w diagnostyce pediatrycznego idiopatycznego zapalenia błony naczyniowej oraz badania płynu mózgowo-rdzeniowego u pacjentów z zapaleniem błony naczyniowej w przebiegu kiły ocznej. Ponadto, praca przeglądowa przedstawia dynamicznie rozwijające się metody diagnostyczne w sarkoidozie ocznej.

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.

Wstęp uzasadniający połączenie wskazanych publikacji w jeden cykl

Cykl publikacji, których Doktorantka jest pierwszym autorem, obejmuje jedną pracę eksperymentalną, dwie oryginalne prace kliniczne oraz jedną pracę przeglądową. Łączny Impact Factor cyklu publikacji wynosi: 12,108.

Celem cyklu jest zbadanie skuteczności nowoczesnych metod diagnostycznych w nietypowych grupach pacjentów z idiopatycznym zapaleniem błony naczyniowej, zapaleniem błony naczyniowej w przebiegu kiły ocznej oraz w przebiegu sarkoidozy. Ponadto, w badaniu eksperymentalnym badano molekularne mechanizmy rozwoju nieinfekcyjnego zapalenia błony naczyniowej, które mogą w być w przyszłości wykorzystane diagnostyce zapaleń błony naczyniowej.

Szerokie spektrum możliwych przyczyn zapalenia błony naczyniowej powoduje, że diagnostyka tej choroby jest skomplikowana i czasochłonna, a pomimo istotnego postępu w zakresie diagnostyki zapaleń błony naczyniowej u 30-60% pacjentów przyczyna zapalenia błony naczyniowej pozostaje nieznana. Niniejszy cykl publikacji odzwierciedla konieczność poszukiwania coraz efektywniejszych metod diagnostycznych zapaleń błony naczyniowej.

Praca eksperymentalna zawarta w cyklu bada mechanizmy molekularne związane z autoimmunologicznym zapaleniem błony naczyniowej, które mogą odegrać w przyszłości rolę w diagnostyce zapalenia błony naczyniowej. Dwie prace kliniczne niniejszego cyklu prezentują rolę badania FDG PET CT w diagnostyce idiopatycznego zapalenia błony naczyniowej u dzieci oraz rolę badania płynu mózgowo-rdzeniowego u dorosłych pacjentów z zapaleniem błony naczyniowej w przebiegu kiły. Czwarta publikacja jest pracą przeglądową, która szczegółowo opisuje współczesne spojrzenie na diagnostykę zapalenia błony naczyniowej w przebiegu sarkoidozy u dzieci i dorosłych.

Założenia i cel pracy

Celem prezentowanego cyklu publikacji jest przedstawienie współczesnych metod diagnostycznych stosowanych w zapaleniu błony naczyniowej, a w szczególności:

- analiza molekularnych mechanizmów odpowiedzialnych za rozwój zapalenia błony naczyniowej
- ocena skuteczności FDG PET-CT jako narzędzia diagnostycznego w zapaleniach błony naczyniowej u dzieci
- ocena użyteczności analizy płynu mózgowo-rdzeniowego u pacjentów z kiłą oczną
- przegląd metodologii diagnozowania zapaleń błony naczyniowej w przebiegu sarkoidozy u dorosłych oraz dzieci.

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Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines

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Research article

Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines

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HIGHLIGHTS

- SOCS1 mRNA overexpression in RPE cells prevents IFNγ-induced SOCS1 mRNA increase.
- SOCS1 overexpression prevents IFNγ-mediated STAT1 phosphorylation.
- SOCS1 overexpression in RPE cells inhibits IFNγ-induced decrease of IL-8 secretion.
- SOCS1 overexpression in RPE cells prevents IFNγ-induced MHC II and CD54 expression.
- SOCS1 overexpression in RPE cells does not block TNFα- or IL-17 induced IL-8 secretion.

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ABSTRACT

The purpose of this study was to investigate the in vitro effect of Suppressor Of Cytokine Signaling 1 (SOCS1) overexpression in retinal pigment epithelium (RPE) cells on their activation by pro-inflammatory cytokines IFNγ, TNFα and IL-17.

Retinal pigment epithelium cells (ARPE-19) were stably transfected with the control plasmid pIRES2-AcGFP1 or the plasmid pSOCS1-IRES2-AcGFP1. They were stimulated by IFNγ (150 ng/ml), TNFα (30 ng/ml) or IL-17 (100 ng/ml). The levels of SOCS1 mRNA were measured by real-time PCR. Signal Transducer and Activator of Transcription 1 (STAT1) phosphorylation and IκBα expression were analysed by western Blot (WB). IL-8 secretion was analysed by ELISA and expression of MHCII molecules and ICAM-1/CD54 by flow cytometry.

Our data show that SOCS1 mRNA overexpression in RPE cells prevents IFNγ-induced SOCS1 mRNA increase and IFNγ-mediated STAT1 phosphorylation. Moreover, SOCS1 overexpression in RPE cells inhibits IFNγ-induced decrease of IL-8 secretion and prevents IFNγ-induced MHC II and ICAM1/CD54 upregulation. However, SOCS1 overexpression does not affect TNFα-induced IκBα degradation nor block TNFα-induced or IL-17-induced IL-8 secretion. On the contrary, IL-17-induced secretion is increased by SOCS1 overexpression.

In conclusion, SOCS1 overexpression in RPE cells inhibits some IFNγ-mediated responses that lead to uveitis development. This notion raises the possibility that SOCS1 overexpression could be a novel target for treating non-infectious uveitis. However, some proinflammatory effects of TNFα and IL-17 stimulation on RPE are not blocked by SOCS1 overexpression.

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1. Introduction

The retinal pigment epithelium (RPE) is a monolayer of cells in the outer retina situated between the neuroretina and the choroid [1]. It is a part of the blood retinal barrier (BRB) that limits the access of blood components to the retina. The BRB consists of an outer part – tight junctions of the retinal pigment epithelium (RPE) and an inner part – tight junctions of retinal endothelial cells enhanced by extensions of Muller cells and astrocytes [2]. It is worth noticing that RPE has been well documented to play an important role in the maintenance of the ocular immune microenvironment as well as in the pathogenesis of uveitis [1]. In normal conditions, the eye is isolated from the rest of the body by the blood retinal barrier (BRB). In uveitis conditions, the BRB is broken down, BRB cells are activated and express molecules implicated in recruitment and stimulation of inflammatory cells.

The major activators of BRB cells during experimental autoimmune uveitis (EAU) are the proinflammatory cytokines produced by Th1 and Th17 autoreactive lymphocytes. Th1 lymphocytes secrete interferon gamma (IFNγ) as well as Tumor Necrosis Factor alpha (TNFα) and Th17 cells secrete TNFα, IL17, IL21 and IL22. IFNγ, TNFα, IL-17 and IL-22 can modulate RPE cell function, leading to outer BRB rupture [1]. IFNγ stimulation of RPE cells results in upregulation of CD54/ICAM-1 expression, induction of MHC class II (MHCII), CD40 expression and proinflammatory cytokines secretion: IL-8, IL-6, MCP-1, GM-CSF, M-CSF, RANTES.

The IFNγ proinflammatory cascade is mediated by the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [3]. As a result of a series of phosphorylations initiated by JAK, STAT dimerises and migrates into the cell nucleus to activate transcription of various target genes such as proinflammatory cytokines, adhesion molecules (ICAM-1/CD54) and MHCII. Nevertheless, also negative regulators of JAK/STAT pathway are transcripted. They are called Suppressors Of Cytokine Signaling (SOCS), a family which consist of eight members, SOCS1-7 and CIS [3]. It has been shown that SOCS1, SOCS2, and SOCS3 mRNAs are induced in response to IFNγ stimulation [4]. Moreover, SOCS1 and SOCS3 but not SOCS2 inhibited the tyrosine phosphorylation and nuclear translocation of STAT1 in response to IFNγ stimulation in HeLa and MCF-7-derived stable cell lines expressing SOCS1, SOCS2, and SOCS3 proteins. Furthermore, SOCS1 exhibited a much stronger inhibition of the activation of STAT1 than SOCS3. These results suggest that SOCS1 and SOCS3 but not SOCS2 are inhibitors of IFN-mediated Janus-activated kinase/STAT signaling pathways [5].

SOCS family members are inhibiting the IFNγ proinflammatory cascade by different mechanisms [6]. First, they bind to JAKs, inhibiting cytokine receptor phosphorylation and STAT activation. Secondly, SOCS protein can bind to P-Tyr residues on receptor chains, preventing JAK interaction with receptor chains or STAT recruitment. A third mechanism is the competitive inhibition of Grb2 recruitment by SOCS and blockade of MAPK pathway. Finally, SOCS can also induce ubiquitination and subsequent proteasome degradation of JAKs and receptor.

SOCS immunosuppressive profile is consistent with the findings that SOCS1 local overexpression is protecting target organs in experimental models of autoimmune diabetes and pulmonary inflammation [7]. Since the latter diseases are mediated through multiple cytokines, those data strongly suggest that SOCS1 can interfere not only with IFNγ signaling. Yet, some studies show that in addition to its action on the JAK/STAT pathway, SOCS1 can inhibit other signaling pathways, including that of Nuclear Factor Kappa B (NFkB) used by TNFα [6]. This would have great relevance for the possible therapeutical possibilities of SOCS1 overexpression in the treatment of non-infectious uveitis. In this study, we have thus tested the hypothesis that overexpression of SOCS1 in RPE cells can modulate their activation by the pro-inflammatory cytokines IFNγ, TNFα and IL-17. We found that SOCS1 overexpression in RPE cells prevents IFNγ-mediated STAT1 phosphorylation and prevents MHCII and ICAM-1 upregulation. However, it does not affect TNFα-induced IκBα degradation, nor TNFα/IL-17 –induced IL-8 secretion.

2. Materials and methods

2.1. Plasmid construction and clone selection

American retinal pigment epithelium type 19 (ARPE-19) is a spontaneously arising human RPE cell line obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). ARPE cells were stably transfected using lipofection by Fugene (Roche Diagnostics) with the plasmid pSOCS1-IRES2-AcGFP1 or the control plasmid pIRES2-AcGFP1 (Clontech). The plasmid containing the SOCS1 gene (pSOCS1-IRES2-AcGFP1) was constructed in our laboratory by inserting the SOCS1 sequence from plasmid pORF5-hSOCS1v24 (InvivoGen) into multiple cloning sites of pIRES2-AcGFP1. Several cell clones containing plasmid pSOCS1-IRES2-AcGFP1 (SOCS1 clone) or control plasmid pIRES2-AcGFP1 (CTRL clone) were tested by flow cytometry (FACS) for green fluorescence. The highest expressing ones were selected and further tested by quantitative reverse transcription PCR analysis (qRT-PCR) for SOCS1 gene expression.

2.2. Cell culture and treatment

ARPE-19 cells as well as CTRL clone and SOCS1 clone were cultured in a 1:1 mixture of Dulbecco's modified Eagle's medium (DMEM; Invitrogen, Merelbeke, Belgium) and Ham's F12 with 2.5 mM L-glutamine (Invitrogen), supplemented with 10% fetal bovine serum (FBS), 100 IU/ml penicillin and 100 μg/ml streptomycin in a 5% CO2 and 95% humidity incubator at 37 °C. In CTRL and SOCS1 clone cultures, 1 mg/ml Gentamycin 418 (InvivoGen) was added in order to maintain antibiotics induced selection. ARPE-19 cells, SOCS1 clone or CTRL clone was seeded at 5×10^5 cells/well in 6-well plates (Fig. 1, Fig. 2C) or at 2.5×10^5 cells/well/ml (Fig. 2B, Fig. 3B, Fig. 3C). Recombinant human IFNγ, TNFα and IL-17 were purchased from Invitrogen and added to cultures as specifically indicated below. In the experiments, CTRL clone unstimulated and ARPE-19 cells unstimulated were used as controls.

2.3. Real-time PCR

ARPE-19 cells, CTRL clone or SOCS1 clone was seeded at 5×10^5 cells/well in 6-well plates. One day later, IFNγ (150 ng/ml), TNFα (30 ng/ml) or IL-17 (100 ng/ml) were added to the cultures for 24 h. Cells were collected for qRT-PCR analysis of SOCS1 gene expression. β-Actin was used as a non-modulated reference gene. The mRNA extraction and isolation were carried out using the automated MagNA Pure LC Instrument system (LightCycler® RNA Master) and the MagNAPure LC mRNA Isolation Kit II, following manufacturer's instructions (Roche Applied Science, Vilvoorde, Belgium). A one step real-time quantitative RT-PCR technique using the RNA Master Hybridization Probes Kit (Roche Applied Science) was used to quantify mRNA expression using specific primes and fluorescent probes for human SOCS1 (Primer and probe SOCS1 human, Applied Biosystems SOCS1 TaqMan) and β-actin (Primer and probe B-actine human, Applied Biosystems, TaqMan Gene Expression Assays). Data are presented as normalized expression of SOCS1 versus β-actin ($2^{-(Ct_{SOCS1} - Ct_{\beta actin})}$).

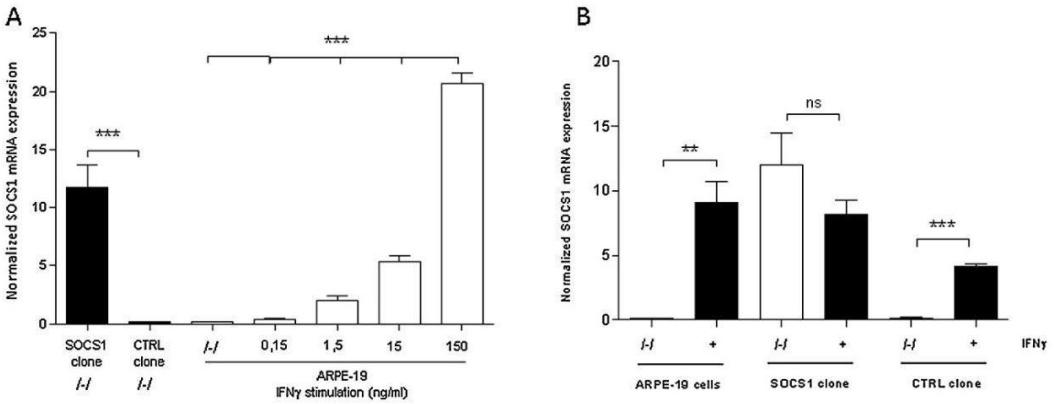

Fig. 1. SOCS1 mRNA expression. SOCS1 mRNA overexpression in RPE cells prevents IFNγ-induced SOCS1mRNA increase. ARPE-19 cells, SOCS1 clone or CTRL clone were seeded at 5 × 105 cells/well in 6-well plates. One day later, IFNγ was added to the cultures for 24 h, (A) IFNγ (at 150 or 15 or 1.5 or 0.15 ng/ml or none/-/) was added only to the ARPE-19 cell cultures. (B) IFNγ (at 150 ng/ml). Cells were collected for quantitative reverse transcription PCR analysis of SOCS1 gene expression./-/unstimulated,/+/IFNγ stimulated. Experiment was performed (A) three times in duplicates, n = 3 (B) three times in triplicates, n = 3. ***$p < 0.001$; **$p < 0.005$; ns: not significant (compared with unstimulated condition), mean ± SEM.

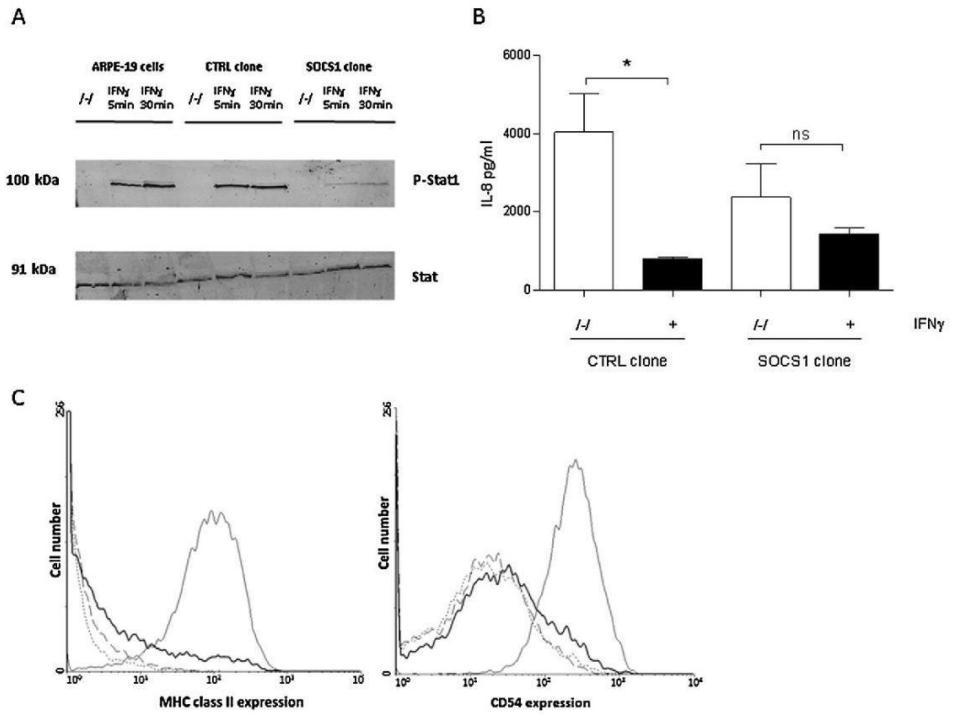

Fig. 2. SOCS1 overexpression in RPE cells affects IFNγ-induced responses. (A) SOCS1 overexpression prevents IFNγ-mediated STAT 1 phosphorylation. ARPE-19 cells, SOCS1 clone and CTRL clone cultures were stimulated with IFNγ (at 150 ng/ml). STAT1 phosphorylation and total STAT expression were analysed by Western Blot, 5 and 30 min after stimulation./-/unstimulated. Data are from one representative experiment out of three, n = 3. (B) SOCS1 overexpression in RPE cells inhibits IFNγ-induced decrease of IL-8 secretion. SOCS1 clone and CTRL clone were seeded at 2.5×10^5 cells/well/ml and stimulated for 24 h with IFNγ (at 150 ng/ml). IL-8 secretion in culture supernatants was analysed by ELISA./-/unstimulated. Experiment was performed three times in triplicates, n = 3. *$p = 0.011$, ns: not significant, mean ± SEM. (C) SOCS1 overexpression in RPE cells prevents IFNγ-induced MHC II and CD54 expression. CTRL clone and SOCS1 clone were plated at 5×10^5 cells/well in 6-well plates. One day later, IFNγ (at 150 ng/ml or none/-/) was added to the SOCS1 clone and CTRL clone cell cultures for 48 h. Membrane expression of CD54 and MCHII molecules was monitored by flow cytometry. Data are representative of three independent experiments, n = 3. – (bold) SOCS1 clone stimulated with IFNγ; – CTRL clone stimulated with IFNγ; . . . CTRL clone unstimulated; .-.-. SOCS1 clone unstimulated.

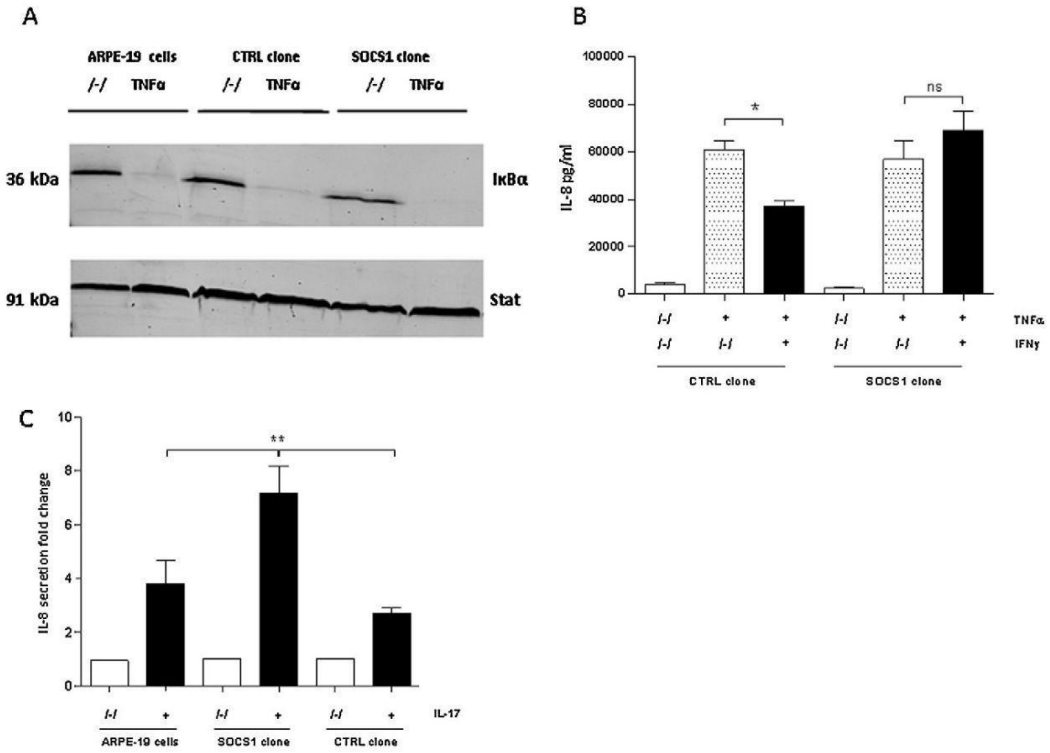

Fig. 3. SOCS1 overexpression in RPE cells does not affect TNFα- nor IL-17-induced responses. (A) SOCS1 overexpression does not affect TNFα-induced IκBα degradation. ARPE-19 cells, SOCS1 clone and CTRL clone cultures were stimulated with *TNFα* (at 30 ng/ml). IκBα expression was analysed by the Western Blot 30 min after stimulation./-/unstimulated. Data are representative of three independent experiments, n = 3. (B) SOCS1 overexpression in RPE cells does not block TNFα-induced IL-8 secretion. SOCS1 clone and CTRL clone were seeded at 2.5×10^5 cells/well/ml and stimulated for 24 h with TNFα (at 30 ng/ml) or TNFα (at 30 ng/ml) and IFNγ (at 150 ng/ml). IL-8 secretion in culture supernatants was analysed by ELISA./-/unstimulated. Data are representative of three independent experiments, n = 3. * p = 0.012, ns: not significant, mean ± SEM. (C) SOCS1 overexpression does not block IL-17-induced IL-8 secretion. ARPE-19 cells, SOCS1 clone and CTRL clone were seeded at 2.5×10^5 cells/well/ml and stimulated for 24 h with IL-17 (at 100 ng/ml). IL-8 secretion in culture supernatants was analysed by ELISA./-/unstimulated. Experiment was performed three times in triplicates, n = 3. **p = 0.004 (IL-17 stimulation compared with unstimulated condition for ARPE-19 cells, SOCS1 clone, clone CTRL respectively), mean ± SEM.

2.4. Western blot analysis

ARPE-19 cells, CTRL clone and SOCS1 clone were cultured and stimulated with IFNγ (150 ng/ml), TNFα (30 ng/ml) or IL-17 (100 ng/ml). STAT1 phosphorylation and IκBα expression were analysed by Western blot, 5 and 30 min after stimulation. The WB were performed as described by Makhoul M. et al. [8]. Briefly, specific primary antibodies used for immunodetection were anti-phospho-STAT and anti- total STAT (Cell Signalling) and anti-IκBα (Santa Cruz).

2.5. IL-8 ELISA

IL-8 secretion in culture supernatants of ARPE-19 cells, CTRL clone and SOCS1 clone was analysed by ELISA (HU IL-8 Cytoset, Invitrogen) following manufacturer's instructions. Cells were seeded at 2.5×10^5 cells/well/ml and stimulated for 24 h with IFNγ (150 ng/ml) or TNFα (30 ng/ml) or IL-17 (100 ng/ml).

2.6. Flow cytometry

CTRL clone and SOCS1 clone was plated at 5×10^5 cells/well/2 mL in complete medium and left overnight for adhesion. Then, the complete medium was changed and the cells were stimulated for another 48 h with IFNγ (150 ng/ml) or TNFα (30 ng/ml) or IL-17 (100 ng/ml). The cells were then recovered and washed by Phosphate Buffered Saline (PBS) containing sodium azide 0.1% and diluted in 100 μL of PBS-azide 0.1%. The expression of MHCII (MCHII BD mouse anti-human HLA-DR PE-conjugated) and CD54 (ICAM-1)(mouse anti-human BD CD54 PE-conjugated) molecules was quantified by flow cytometry using mouse anti-human specific antibodies comparatively to control isotypes (isotype control mouse IgG2a PE κ, BD). Labelled cells were analysed with a FACS Calibur cytometer and the Cell Quest Software (Becton-Dickinson). CTRL clone and SOCS1 clone were also controlled for the presence of FL1-H signal coming from Aequorea coerulescenes green fluorescent protein (AcGFP1).

2.7. Statistical analysis

The statistical significance between samples was established using the unpaired *t*-test with Welch's correction or Kruskal-Wallis test when 3 independent groups where compared. Data are expressed as means ±SEM.

3. Results

3.1. SOCS1 mRNA is constitutively expressed in SOCS1 clone

We first tested the levels of SOCS1 mRNA in ARPE-19 cells, CTRL clone and SOCS1 clone using qRT-PCR. As shown in Fig. 1A, SOCS1 mRNA levels were nearly undetectable in unstimulated ARPE-19 cells and in CTRL clone. In contrast, SOCS1 clone expressed constitutively large amounts of SOCS1 mRNA, significantly higher than in CTRL clone or in ARPE-19 cells. Similar high and dose-related expression of SOCS1 mRNA can be obtained in ARPE-19 cells by INFɣ stimulation. These data first confirmed that SOCS1 mRNA overexpression was achieved in SOCS1 clone as compared to CTRL clone and second, defined the experimental conditions for an inducible expression of SOCS1 in ARPE-19 cells. Those clones and culture conditions were thus used for further experiments.

SOCS1 mRNA overexpression in RPE cells prevents IFNγ-induced SOCS1 mRNA increase.

We thereafter investigated the influence of IFNγ stimulation on SOCS1 mRNA levels in CTRL and SOCS1 clones comparatively to ARPE-19 cells. The data from Fig. 1B shows an IFNγ-induced increase of SOCS1 mRNA levels in CTRL clone as in ARPE-19 cells, but not in the SOCS1 clone where the constitutive overexpression of SOCS1 prevented this inducing effect.

3.2. SOCS1 overexpression prevents IFNγ-mediated STAT1 phosphorylation

Next, we investigated the effect of SOCS1 stable overexpression on IFNγ-mediated intracellular signal transduction. One of the first steps of IFNγ signal transduction is STAT1 phosphorylation. We therefore tested by Western Blot the presence of phosphorylated STAT1 (P-STAT1) in ARPE-19 cells, CTRL clone and SOCS1 clone stimulated or not by IFNγ. As shown in Fig. 2A, in absence of IFNγ stimulation, P-STAT1 was undetectable, neither in ARPE-19 cells nor in CTRL clone or in SOCS1 clone. After 5 and 30 min of stimulation with IFNγ, P-STAT1 was detected in ARPE-19 cells, in CTRL clone and in SOCS1 clone but here at a largely lesser extent. These data thus demonstrate that SOCS1 stable overexpression prevents STAT1 phosphorylation induced by IFNγ stimulation.

3.3. SOCS1 overexpression in RPE cells inhibits IFNγ-induced decrease of IL-8 secretion

IL-8 production in RPE cells was shown to play an important role in different inflammatory retinal diseases. We thus measured by ELISA the level of IL-8 secretion in CTRL clone and SOCS1 clone. As shown in Fig. 2B, IL-8 secretion was strongly inhibited by IFNγ stimulation in CTRL clone but unchanged in SOCS1 clone.

3.4. SOCS1 overexpression in RPE cells prevents IFNγ-induced MHC II and ICAM-1 (CD54) expression

In addition to IL-8 production, MHCII and ICAM-1 (CD54) membrane expression are classically used as markers of RPE cell activation. We therefore assessed by flow cytometry the effect of the SOCS1 overexpression on the expression of ICAM-1 (CD54) and MHC II molecules. As illustrated in Fig. 2C, CTRL clone and SOCS1 clone expressed constitutively the same level of ICAM-1 (CD54) but no MHC II. IFNγ stimulation increased CD54 expression and induced MHCII expression in CTRL clone but not in SOCS1 clone. Isotype control was used showing no labeling.

3.5. SOCS1 overexpression does not affect TNFα-induced IκBα degradation

TNFα is another important cytokine involved in RPE cell activation during inflammatory retinal disease and has been shown to be modulated by SOCS family members [3,6]. We thus investigated if TNFα-mediated response may be affected by SOCS1 overexpression. TNFα stimulation leads to the phosphorylation and degradation of IκBα in cytoplasm which allows the release of the transcription factor NFκB and its translocation to the nucleus. We therefore tested by Western Blot the expression of IκBα in ARPE-19 cells, CTRL clone and SOCS1 clone either unstimulated or after TNFα stimulation. The data from Fig. 3*A* show that IκBα was similarly degraded in TNFα-stimulated ARPE-19 cells, CTRL clone and SOCS1 clone.

3.6. SOCS1 overexpression in RPE cells does not block TNFα-induced IL-8 secretion

Results from Fig. 3B show that, as expected, stimulation with TNFα increased very strongly the basal secretion of IL-8 in CTRL clone and SOCS1 clone. Thus, the stable SOCS1 overexpression did not prevent the TNFα-induced IL-8 secretion. However, simultaneous stimulation with TNFα and IFNγ inhibited the TNFα-induced IL-8 secretion in CTRL clone but not in SOCS1 clone.

3.7. SOCS1 overexpression does not block IL-17 induced IL-8 secretion

IL-8 secretion was significantly increased by IL-17 stimulation in ARPE-19 cells, CTRL clone and SOCS1 clone. As shown in Fig. 3C, SOCS1 overexpression does not prevent the induction of IL-8 secretion by IL-17 stimulation in RPE cells. Moreover, the fold increase of IL-8 secretion was significantly greater in SOCS1 clone than in CTRL clone or ARPE-19 cells ($p = 0{,}004$).

4. Discussion

During noninfectious uveitis, retinal pigment epithelium (RPE) cells undergo multiple stimulation by different cytokines secreted by autoreactive lymphocytes. Among all of them, IFNγ, IL-17 and TNFα appear to play a central role in RPE activation, a required step for inflammatory cell entrance into the eye and uveitis development.

The actual treatment of noninfectious uveitis in humans is based on the use of nonspecific immunosuppressive drugs that globally block the immune system [9]. More recently, with the development of biological drugs, a more specific approach has been proposed, and different cytokines can now be directly targeted in the whole organism [9]. A further step could be to act more locally in the eye, or even, more specifically by limiting the effect of the cytokine in cells involved in disease development, here the retina [10]. In this context, earlier works have explored the possibility to specifically block the NF-κB signaling pathway [11]. In this work, we have investigated if the IFNγ pathway could be similarly targeted by using SOCS1, a classical inhibitor of IFNγ signaling.

Our data first demonstrate how SOCS1 overexpression in RPE cells affects their response to proinflammatory cytokines involved in uveitis. We show that IFNγ stimulation in RPE cells increases SOCS1 mRNA expression, which is prevented by SOCS1 mRNA overexpression in RPE cells. SOCS1 overexpression also prevents the IFNγ-mediated STAT1 phosphorylation. These data are consistent with experiments on HeLa and MCF-7 cell lines showing that SOCS1 and SOCS3 are inhibitors of IFN-mediated Janus-activated kinase/STAT signaling pathways [5].

Furthermore, we demonstrate for the first time that SOCS1 overexpression in RPE cells inhibits the IFNγ-induced decrease of IL-8 secretion. Our results confirm the baseline secretion of IL-8 that has been described by other groups in human adult RPE cells as well as in the ARPE-19 cell line. Our data showing that IFNγ stimulation of RPE cells induces a decrease of IL-8 secretion are compatible with the described IFNγ-induced decrease of IL-8 gene expression in ARPE-19 [12]. However, in other cell types, IFNγ stimulation can have different effect on IL-8 secretion: either a decrease in IL-8 secretion like in endothelial cells [13], or no effect like in human bronchial epithelial cells or even an increase in IL-8 gene expression like in human monocytic cells. Such a variety of IL-8 responses to IFNγ stimulation in different cell types may explain the discrepancy between in vitro experiments and clinical data. On one hand, it has been shown that the IL-8 level increases in serum of patients with Bechet disease as well as in serum and intraocular fluid of patients with intermediate uveitis [14], but on the other hand, patients with autoimmune noninfectious uveitis presented a 3.4 fold decrease in IL-8 gene expression.

We also found that SOCS1 overexpression in RPE cells prevents the IFNγ-induced MHC II and ICAM-1/CD54 expression. Such an IFNγ-induced MHC II and ICAM-1/CD54 expression was also observed in human bronchial epithelial cells [15]. Both MHC II and ICAM-1/CD54 expression play an important role in the recruitment and activation of immunocompetent cells. ICAM-1/CD54 expression was shown to play a crucial role in passing leukocytes through the blood-retinal barrier during EAU and ICAM-1/CD54 expression was increased on human RPE cells in the presence of TNFα, IFNγ, and IL-1β. A high expression of MHC class II has been demonstrated to be required for uveitogenic lymphocytes activation [16].

Current evidence suggests that SOCS1 blocks in vivo multiple cytokine-mediated diseases. For example, SOCS1 was shown to ameliorate bleomycin-induced pulmonary inflammation, pulmonary fibrosis and mortality, mainly through its suppressive effect on TNFα secretion [7]. Furthermore, the group of Egwuagu demonstrated in mice that the forced transgenic retinal expression of SOCS1 protects them from developing severe experimental autoimmune uveitis [10]. Their model mimics a human noninfectious uveitis and implicates the activation of RPE cells by multiple cytokines including IL-17 and TNFα. However, in our study, we observe that SOCS1 overexpression in ARPE-19 cells do not affect the TNFα-induced IκBα degradation. Moreover, our results indicate that the SOCS1 overexpression in RPE cells does not block the TNFα-induced IL-8 secretion and neutralizes the inhibitory effect of IFNγ stimulation on the TNFα-induced IL-8 secretion.

We have next investigated a potential role of SOCS1 overexpression on IL-17 mediated RPE cell activation. The literature data concerning the role of IL-17 on activation of retinal pigment epithelium are inconsistent. One group showed that IL-17 significantly enhanced chemokine and IL-6 production [17], whereas another group has shown that RPE responds to IL-17 by increasing their levels of SOCS1 and SOCS3 proteins resulting in a limited production of proinflammatory cytokines and chemokines and an increased amount of suppressive cytokines, such as LIF [18]. Altogether, these data suggest a potential role of SOCS1 in modulating IL-17 activation of RPE cells.

However, unexpectedly, we could not find evidence in our study that SOCS1 overexpression in RPE cells affects negatively their response to IL-17 stimulation. The present data demonstrate that IL-17 stimulation increases the IL-8 secretion in RPE cells which is consistent with the described IL-17-induced IL-8 secretion in adherent cells like fibroblasts, keratinocytes, epithelial and endothelial cells [19]. Moreover, we demonstrate that SOCS1 overexpression does actually not block this IL-17 induced IL-8 secretion but even maybe increases it. This is however surprising considering that in SOCS-Tg rat and mice, stimulation of retinal cells by IL-17 decreases levels of IL1b and RANTES in comparison to wild types littermates [10].

5. Conclusions

In conclusion, our results indicate that SOCS1 overexpression in RPE cells inhibits some IFNγ-mediated responses that lead to uveitis development. This notion raises the possibility that SOCS1 overexpression could be a novel target for treating non-infectious uveitis. However, some proinflammatory effects of TNFα and IL-17 stimulation in RPE are not blocked by SOCS1 overexpression.

Conflict of Interest

The authors declare no financial conflicts of interests.

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Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis

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RESEARCH ARTICLE

Clinical Utility of ^{18}F-FDG PET/CT in the Work-up of Children with Uveitis

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ABSTRACT

Purpose: To evaluate ^{18}F-fluorodeoxyglucose Positron Emission Tomography/ultra low dose Computed Tomography (^{18}F-FDG PET/ ULD CT) in the work-up of pediatric uveitis.

Methods: Retrospective study of 12 children followed for uveitis who underwent whole body ^{18}F-FDG PET/ULD CT between 2011 and 2019.

Results: The average age of the patients was 11 years. A total of 100% of patients presented with bilateral uveitis, 50% had panuveitis and 92% had various choroidal involvement. Relevant information for diagnosis was provided in four patients. 5/12 had an abnormal 18F-FDG uptake. Of these, three patients had pathognomonic images of active granulomatous diseases. Three patients underwent PET CT-guided biopsies of which two were positive for sarcoidosis.

Conclusion: ^{18}F-FDG PET/CT provided important information for final diagnosis in approximately 30% (4/12) of pediatric patients with bilateral uveitis. Whole body FDG PET/ULD CT can contribute to the final diagnosis thanks to pathognomonic image of active granulomatous disease and/or by indicating metabolically active site of biopsy that would not be visualized in thorax CT.

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Although children and adolescents develop uveitis more rarely than adults,[1–5] they are more likely to have severe, chronic inflammation leading to ocular complications and permanent vision loss[2,3]

As in adults, pediatric uveitis can be of various infectious or non-infectious etiologies with geographical and ethnic variations. However, in children idiopathic cause of uveitis is commonly reported and varies from 35% to 59% among studies.[3,5,6] Still, establishing a more precise diagnosis than idiopathic uveitis is worth the effort as it can unveil a systemic disease and help in adjusting treatment.

Some etiologies of childhood uveitis, such as juvenile chronic arthritis, can be diagnosed on characteristic clinical presentation[7,8] and basic systemic work-up, while others, such as sarcoidosis[9] and tuberculosis may need more elaborate testing.[10] As in adults, childhood sarcoidosis definitive diagnosis requires a biopsy. However, no clear diagnostic criteria have been proposed, in the pediatric population, to define non biopsy proven cases. Similarly, there is a lack of agreement on the diagnostic investigation in pediatric tuberculosis uveitis.[11]

Several imaging modalities are used to detect systemic lesions of sarcoidosis and tuberculosis including chest X-rays and high-resolution computed tomography.[12,13]

Recently, 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT (^{18}F-FDG PET/CT) is getting wider clinical acceptance in diagnosis and management of inflammatory/infectious diseases including granulomatous diseases such as sarcoidosis and tuberculosis.[14,15] Several reports have suggested a role for ^{18}F-FDG PET/CT in adult patient with uveitis due to more extensive and potentially more sensitive imaging to detect active systemic disease and to determine an accessible site for a biopsy.[16–19] FDG PET/CT allows to evaluate whether the distribution of metabolism shows typical metabolic patterns of sarcoidosis-type granulomatosis, such as bilateral inflammatory involvement of the parotid and lacrimal glands (panda sign) and bilateral hilar and mediastinal lymphadenopathy (lambda sign). It also allows detecting pulmonary lesions, lymph nodes or other possible locations that may suggest active tuberculosis and guide possible biopsy punctures with diagnostic objectives.

However, to our knowledge, there is no published data concerning the benefit of ^{18}F-FDG PET/CT in children with uveitis.

The aim of this retrospective study is to determine if ^{18}F-FDG PET/CT can be beneficial in determining uveitis etiology in children.

Material and methods

This is a multicenter, retrospective study of 12 children followed for uveitis who underwent 18F-fluorodeoxyglucose positron emission tomography/ ultra low dose computed tomography (^{18}F-FDG PET/ ULD CT) between 2011 and

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2019. The inclusion criteria were: age 0–18 years and sight-threatening uveitis without proven etiology after a preliminary negative uveitis work-up described below. Children with classical JIA were excluded. The patients were followed in the ophthalmology department of tertiary uveitis center in CHU St-Pierre, CHU Brugmann or CHU HUDERF in Brussels, Belgium. The study obtained local ethical committees' permissions. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

The collected patient data includes age at the moment of ^{18}F-FDG PET/ ULD CT, sex, the clinical presentation of uveitis based on clinical examination, multimodal imaging, and results of other examinations performed in uveitis work-up. All patients had a complete ophthalmological exam including: visual acuity, slit lamp examination with dilated fundus examination and imaging with color fundus photography, optical coherence tomography (OCT) of retina and fluorescein angiography of the posterior pole and the peripheral retina. Indocyanine green (ICG) angiography of the posterior pole and the peripheral retina was also routinely done except for one patient. In addition, all patients had a preliminary uveitis work-up including: tuberculin skin test and/or QuantiFERON, chest radiography and/or chest CT, blood testing including hepatic and renal function, angiotensin-converting enzyme (ACE) and serology of syphilis.[20] Most of the patients had also serology for Lyme, Bartonella and cytomegalovirus (CMV) as well as serum lysozyme assessment and ANA by immunofluorescence. All patients underwent pediatric examination, which included palpation of lymph nodes.

Anterior granulomatous uveitis is defined as a presence of granulomatous keratitic precipitates and/or iris granuloma. Choroidal involvement was assessed by fundus examination/ color fundus photography and fluorescein and indocyanine angiography. Five choroidal inflammatory lesions' type were recorded: Dalen-Fuchs nodules (DF), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multifocal choroiditis (MFC), serpiginous like choroiditis (SLC), and ICG-revealed hypocyanescent spots (IRHS). Dalen-Fuchs nodules were defined as small, discrete, yellowish elevated infiltrates at the level of RPE usually observed in the retinal periphery[21] corresponding to clusters of epithelioid cells containing pigment lying between the RPE and Bruchs membrane.[22] APMPPE lesions were described as multiple, flat, yellow-white clearly defined plaques of varying sizes, at the level of the RPE. After the resolution, lesions lose their creamy appearance leaving RPE stippling, mottling and depigmentation.[23] The term multifocal choroiditis (MFC) was used when the choroidal lesions were smaller with a punched-out appearance at the level of the RPE or inner choroid.[23] Serpiginous like choroiditis (SLC) as single/multiple discreet yellowish-white fuzzy choroidal lesions and slightly raised edges that show wave-like progression with an active serpiginous-like edge at the border of healed lesions with central healing.[24] We further used the term ICG-revealed hypocyanescent spots (IRHS) when hypocyanescent lesions were identified during ICG without corresponding visible fundus lesions. Clinical presentation of uveitis is described following SUN classification.[25] Diagnosis of ocular sarcoidosis (definite, presumed, probable), ocular tuberculosis, and TINU follow international adults' criteria.[9,24–27] All ^{18}F-FDG PET/CT were performed at the Bordet Institute in Brussels, with an exception for only one patient, who performed this test in another institution.

^{18}F-FDG PET/ ULD CT were performed using a PET-CT Discovery 690 (GE Medical Systems, Milwaukee, Wisconsin, USA). Prior to ^{18}F-FDG injections, patients fasted for at least 6 hours. Blood glucose level was systematically measured before injection, and the patient was not injected if glucose was greater than 150 mg/dL. Strict intravenous injection of FDG following EANM pediatrics recommendations[28] was adjusted for age and weight. Time-of-flight acquisition was performed with the patient lying in supine position, at least from the midthigh to the cranial vertex. No oral and no iodine-based contrast medium was administered. Typically the CT portion of the hybrid PET/CT was a low/ultra low dose CT using helical 64-row scan with the following parameters: 80 kVp, 5 mAs, and a pitch of 1.5[29]:. The PET element was operated in 3-dimensional mode, for 1.5 minutes per bed position and overlap of 23.4%. Attenuation correction was based on the CT data. PET reconstruction parameters were as follows: slice thickness 3.27 mm, pixel size 2.73 mm, matrix size 192 × 192. PET images were reconstructed with the built-in GE Healthcare Advance software, using the ordered subset expectation maximization algorithm with 2 iterations and 18 subsets, and were postfiltered with a 6.4-mm full-width at half-maximum Gaussian function.

^{18}F-FDG PET/CT Analysis

A senior nuclear medicine specialist reviewed each examination to detect abnormal ^{18}F-FDG systemic uptake and classified it as suggestive or not for active systemic granulomatosis. Three main characteristics of the ^{18}F-FDG PET/ULD CT were previously defined, established, and used to characterize each patient: pathognomonic hypermetabolic lymph node distribution, the high intensity of metabolism for the majority of the lesions, and visceral hypermetabolic lesions frequently observed in active granulomatosis diseases.

As there is no widely recognized SUV (standardized uptake values) threshold to identify a hypermetabolic lesion as suspicious for infectious, inflammatory and/or oncologic origin, in this study we use a classical approach where the FDG PET/CT presumptive diagnosis of sarcoidosis disease or active tuberculosis is based on the distribution of hypermetabolic lesions.

Results

Patients' Characteristics

The average age at the first ophthalmologic consultation where uveitis was detected was 11 years and 11 years at the moment of ^{18}F-FDG PET/ULD CT. The median period between the first uveitis observation and ^{18}F-FDG PET/ULD CT was 45 days. Patients were followed on average for 1088 days (median 828 days) from the first visit, where uveitis was detected, to the date of data collection. Among 12 patients there were 7 females and 5 males (Table 1). The patients did not have typical

Table 1. Uveitis SUN[25] classification and treatment in pediatric patients with ^{18}F-FDG PET/ULD CT. 1 – present 0 – absent and verified; ^{18}F-FDG PET/CT – whole body ^{18}F-fluorodeoxyglucose positron emission tomography imaging; MPS – methylprednisolone; MTX – methotrexate.

			Uveitis						
Patient nr	Age	Sex	Anterior	Intermediate	Posterior	Panuveitis	Bilateral	Granulamatous AU	Systemic treatment
1	9	F	0	0	1	0	1	0	MPS
2	13	F	0	0	0	1	1	1	MPS, MTX, Adalimumab, Infliximab
3	12	F	0	0	1	0	1	0	Isoniazide, Rifampicine, Pyrazinamide
4	9	M	0	0	0	1	1	0	MPS, MTX
5	9	F	1	0	0	0	1	1	Acyclovir, MPS, MTX, Adalimumab
6	14	M	0	0	1	0	1	0	MPS, MTX, Infliximab
7	9	F	0	0	0	1	1	1	0
8	15	M	0	0	1	0	1	0	0
9	9	M	0	0	0	1	1	1	MPS, MTX, Infliximab, Adalimumab
10	9	F	0	0	1	0	1	0	MPS, Mycophenolate mofetil
11	9	M	0	0	0	1	1	0	MPS, MTX, Adalimumab
12	14	F	0	0	0	1	1	1	MPS, Mycophenolate mofetil, Infliximab
TOTAL		7 F /5 M	1	0	5	6	12	5	

clinical characteristics of JIA-associated uveitis (arthritis with predominant anterior uveitis, non-granulomatous) and 8/11 had always negative ANA results. Two further patients had normal ANA results when repeated (patient 1 and 8).

Uveitis Characteristics

Out of 100% of the patients presented bilateral uveitis, 50% (6 out of 12) had panuveitis, 41.6% (5/12) posterior uveitis and 8.3% (1/12) solely anterior granulomatous uveitis. Granulomatous keratic precipitates were observed in 41,.6% (5/12) (Table 1). Choroidal involvement was present in 92% (11/12) of the patients, including two patients with APMPPE (patients 1 and 4), one with SLC (patient 3), one with MFC (patient 6) and seven patients with 'ICG revealed hypocyanescent spots (IRHS),' among whom four had additionally Dalen-Fuchs nodules visible in the fundus examination (Table 2). Among seven patients presenting IRHS, five had bilateral idiopathic panuveitis and two bilateral panuveitits due to TINU. Only one patient (8,3%) presented solitary choroidal nodule visualized in ICG, which was accompanied by vasculitis and vitritis.

Other observed parameters were: posterior synechiae in 50% (6/12) patients, snowballs in 8% (1/12), papillary oedema in 50% (6/12) in slit lamp examination, and hot disc in 67% (8/12) in fluorescein angiography, macular oedema in 25% (4/12), retinal or choroidal scar in 25% (4/12), vitritis 67% (8/12) and vasculitis 25% (4/12). Epiretinal membrane, retinitis, or macroaneurysm were not present in any patient.

^{18}F-FDG PET/CT, Chest CT, and Chest Radiography Results

None of the patients had received oral methylprednisolone or antituberculosis treatment at the moment of or before ^{18}F-FDG PET/ULD CT. The exception was patient number 6, who received a short course of oral methylprednisolone 3 years prior to ^{18}F-FDG PET/ULD CT (Case report of patient 6).

Abnormal ^{18}F-FDG uptake was detected in 41.6% (5/12) of patients (Table 2). In 25% of the cases (3/12), ^{18}F-FDG PET/ULD CT images were pathognomonic of active granulomatous disease (patients number 1, 3, and 4). In one of these cases (Case report of patient 4), a cervical lymphadenopathy biopsy was performed based on ^{18}F-FDG PET/ULD CT, leading to the final diagnosis of sarcoidosis. Biopsies were also performed in

Table 2. Results and the utility of the whole body ^{18}F-FDG PET/ULD CT in pediatric patients with uveitis. 0 – normal; 1 – abnormal ^{18}F-FDG uptake; APMPPE – Acute posterior multifocal placoid pigment epitheliopathy; IRHS – ICG revealed hypofluorescent spots; DF – Dalen-Fuchs nodules; SCL – Serpiginous like choroiditis; MFC – Multifocal choroiditis.

Patient nr	Abnormal 18F-FDG uptake	Abnormal 18F-FDG uptake characteristic of active granulomatous disease	18F-FDG PET/CT utility	Choroidal involvment	Final diagnosis
1	1	1	1	APMPPE	Bilateral idiopathic * posterior uveitis
2	0	0	0	IRHS +DF	Bilatateral granulomatous idiopathic panuveitis
3	1	1	1	SLC	Bilateral tubercular posterior uveitis with tubercular serpignous-like choroiditis phenotype
4	1	1	1	APMPPE	Bilateral panuveitis due to definite ocular sarcoidosis
5	0	0	0	none	Bilateral granulomatous idiopathic anterior uveitis
6	1	0	1	MFC	Bilateral posterior uveitis due to definite ocular sarcoidosis
7	0	0	0	IRHS	Bilateral granulomatous idiopathic panuveitis
8	1	0	0	IRHS+DF	Bilateral idiopathic panuveitis
9	0	0	0	IRHS	Bilateral granulomatous idiopathic panuveitis
10	0	0	0	IRHS+DF	Bilateral panuveitis due to definite TINU
11	0	0	0	IRHS+DF	Bilateral panuveitis due to probable TINU
12	0	0	0	IRHS	Bilateral granulomatous idiopathic panuveitis
TOTAL	5	3	4		

*Diagnosis of uveitis stayed idiopathic as ocular sarcoidosis criteria[9] were not fulfilled.

two other patients (patient 6 and 8) who had abnormal ^{18}F-FDG uptake but without pathognomonic images of granulomatous disease. One patient (Case report of patient 6) presented small bilateral discretely hypermetabolic axillary and inguinal lymph nodes, without other metabolic abnormalities. The other patient (patient 8) had a nasopharyngeal and tonsils hypermetabolism with bilateral cervical adenopathy suggesting an inflammatory/infectious disease centered in the ENT sphere. In patient 6, the performed biopsy guided by the hot spot objectivated on the FDG images, led to the final diagnosis of definite ocular sarcoidosis, however, in patient 8 biopsy failed to reveal the etiology of uveitis and the final diagnosis remained idiopathic. ^{18}F-FDG PET/ULD CT images of 11 out of 12 patients could be compared with the corresponding chest radiography or the chest CT as they were done relatively closely with median of 15.5 days between the examinations.

^{18}F-FDG PET/ULD CT Led to Establishing Final Diagnosis in 33% of Patients (4/12)

^{18}F-FDG PET/ULD CT provided important information for final diagnosis in 33% of patients (4/12) (Table 2). ^{18}F-FDG PET/ULD CT contributed to definite uveitis diagnosis by leading to positive biopsies in 17% of patients (2/12) (patients 4 and 6). Two others contributed to establishing diagnosis showing ^{18}F-FDG uptake pathognomonic for active granulomatous diseases but without biopsy confirmation (patients 1 and 3).

The total uveitis work-up enabled to find etiology of uveitis in 42% (5/12) of the patients. The final diagnosis were: ocular sarcoidosis in 17% (2/12) of the patients, TINU in 17% (2/12) and tubercular uveitis in one patient, 8% (1/12) (Tables 1 and 2). However, the majority of the patients remains with a diagnosis of idiopathic uveitis, 58%.

Patient 3 diagnosed with tubercular uveitis (Table 2) had a positive tuberculin skin test and ^{18}F-FDG PET/ULD CT showed bilateral mediastinal and hilar adenopathy as well as retroperitoneal adenopathy. Biopsy was not performed in this patient. Two patients were diagnosed with TINU[27]: patient 10 (bilateral panuveitis due to definite TINU) and patient 11 (bilateral panuveitis due to probable TINU) (Table 2). In both patients ^{18}F-FDG PET/ULD CT did not show any abnormalities. Both patients presented typical uveitis characteristics[27] and, respectively, complete and incomplete clinical criteria of acute interstitial nephritis.[27] Laboratory findings showed increased beta-2 microglobulin and elevated serum creatinine.

^{18}F-FDG PET/CT contributed to final uveitis diagnosis only in patients with bilateral choroidal involvement characterized as such as APMPPE (2/12), SLC (1/12), and MFC (1/12). Among four patients (patients 1, 3, 4, and 6) (Table 2), for whom ^{18}F-FDG PET/CT was helpful for final diagnosis, all had fluorescent ANA negative result by the date of PET CT.

One patient received a specific antitubercular systemic therapy, 9/12 received systemic steroids, including 8 patients who were also treated by conventional Disease-Modifying Anti-Rheumatic Drugs (DMARDS) as methotrexate or mycophenolate mofetil. Due to incomplete response, 6 of them needed additional treatment with biological DMARDs (Adalimumab - Humira®, Infliximab - Remicade®) (Table 1).

The following two case reports illustrate that both general inflammation and active granulomatous disease abnormalities in ^{18}F-FDG PET/ULD CT can help in establishing the final uveitis diagnosis.

Case report of patient 4

An 11-year-old boy, presented for emergency ophthalmology consultation in children's hospital because of a red and painful right eye accompanied by calf myalgia of unknown origin, lasting for 4 days. Slit lamp examination revealed nongranulomatous anterior uveitis without synechiae and the patient was given prednisolone eye drops hourly and tropicamide once in the evening. After a 7-day-treatment, visual acuity with correction was 10/10 in both eyes but in the right eye anterior uveitis persisted and discrete keratic precipitates were observed. The patient reported increased pain in the lower limbs, which disappeared after a week of NSAIDs treatment prescribed by a pediatrician specialized in rheumatology. ANA/ANCA, RF, and HLA-B27 were negative. Although anterior uveitis seemed to resolve with the disappearance of the keratic precipitates, fundus examination revealed mild vitritis and white dots infiltration, characterized as APMPPE in the posterior pole (Figure 1a–d). OCT, fluorescein angiography, and ICG additionally showed bilateral multiple choroidal lesions associated with outer retinal inflammation at the posterior pole and mid-periphery. An extended uveitis work-up was planned, including ^{18}F-FDG PET/ULD CT, which showed pathognomonic image of active granulomatous disease, suggestive of sarcoidosis (Figure 1e). Cervical adenopathy biopsy confirmed the diagnosis of sarcoidosis. As choroidal lesions persisted and tuberculosis was excluded (negative tuberculin skin test and QuantiFERON), oral methylprednisolone (MPS 16 mg/day) was started accompanied by brinzolamide/timolol eye drops to control intraocular pressure. Oral MPS was gradually decreased over a period of three months without recurrence of active lesions. However, after 10 months without treatment, a relapse of posterior uveitis occurred with 3 active choroidal lesions in the posterior pole of the right eye. Methotrexate (MTX) and 8 mg MPS were started with a good clinical response. Oral MPS and MTX were then slowly decreased and discontinued (Figure 2). After a follow up of 11 months, the patient is still in remission with final acuity of 10/10 in both eyes.

Case report of patient 6

An 11-year-old male patient was addressed to our ophthalmology department because of worsening of visual acuity in the right eye observed in the last 6 months. Visual acuity of the right eye (RE) was 1/20 and of the left eye (LE) 10/10 without correction. Slit lamp examination did not reveal any inflammatory sign in the anterior chamber of both eyes but dilated fundus examination, OCT, and fluorescein angiography showed a subretinal fibrotic neovascularization with a central retinal scar in the right eye and subtle alterations of retinal pigment epithelium in the left eye. A uveitis work- up was done and infectious etiology, including tuberculosis, was excluded based on the negative result of tuberculin skin test, negative QuantiFERON and normal chest X-ray. A short course of oral

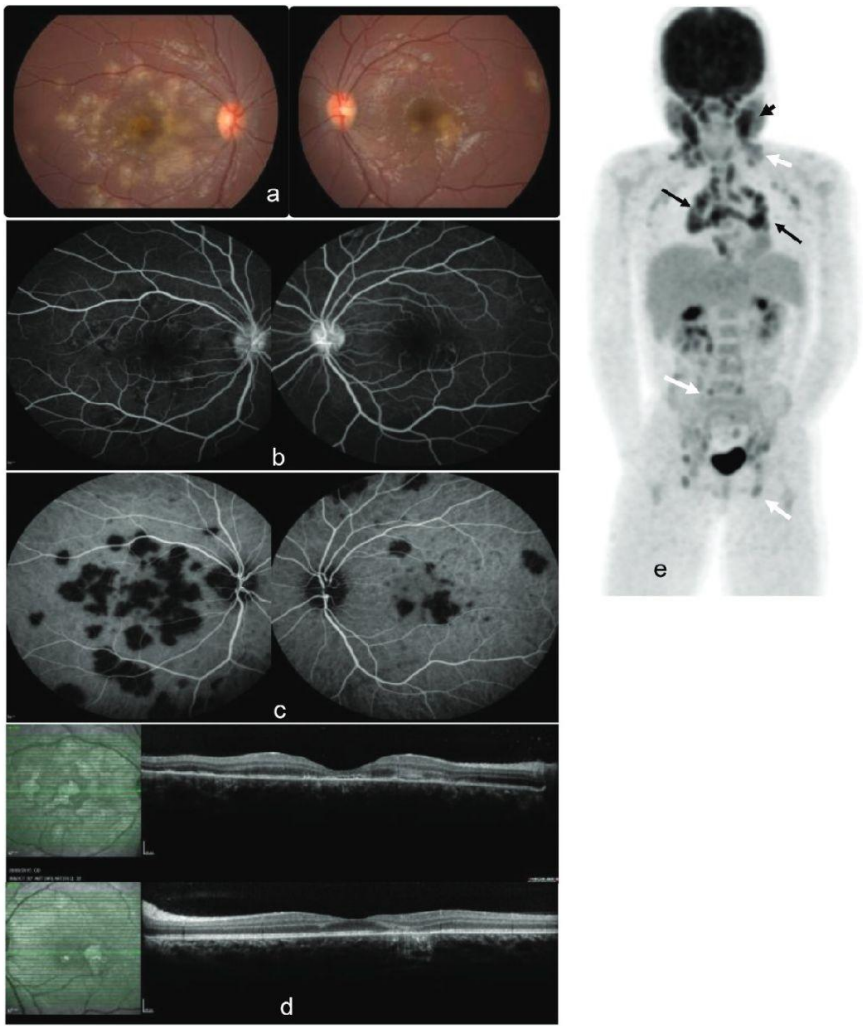

Figure 1. Pretreatment imaging of the right eye and left eye in a pediatric uveitis patient (patient number 4) with biopsy-confirmed diagnosis of sarcoidosis. (a) Color fundus photography revealed mild vitritis associated to the optic disc hyperemia and deep multifocal white dots infiltration characterized as APMPPE lesions at the posterior pole. Late phase fluorescein angiography (b) demonstrated bilateral hot disc and multiple hypo- and hyperfluorescent lesions with irregular staining and focal vasculitis at the posterior pole. Intermediate phase ICG revealed multifocal irregular hypocyanescent spots corresponding to the fundus lesions at the posterior pole and midperiphery (c). OCT (d) showed irregularity in the Bruch membrane and pigmented epithelium complex with the possible alteration of the photoreceptors also associated to hyperreflectivity of the outer nuclear level. (e) Whole body ^{18}F-FDG PET/ultra low dose CT (FDG PET Maximum Image Projection -MIP) revealed pathognomonic image of active granulomatous disease, suggestive of sarcoidosis. **Black long arrows**: high hypermetabolic symmetrical mediastinal and hilar lymph nodes. **White arrows**: moderate hypermetabolic symmetrical cervical, axillary, iliac, and inguinal lymph nodes. **Black short arrow**: high hypermetabolic symmetrical lacrimal and salivary glands. The biopsy of cervical lymph nodes confirmed the diagnosis of sarcoidosis.

methylprednisolone was prescribed as an inflammatory component of the CNVM could not be excluded. As no active inflammation was present and the neovascular lesion was inactive, the patient was regularly followed with no worrying symptoms or active inflammatory signs. After 3 years, however, the patient observed a fluctuating purple spot in the left eye with no visual acuity change (1/10 RE and 10/10 LE). Anterior segment examination was normal but fundus examination, fluorescein angiography, ICG, and OCT highlighted pathologic changes (Figure 3a–d). Fundus examination revealed a large macular scar partially pigmented in the right eye and multiple deep spots in both eyes were observed. Subtle staining in the temporal macular region was visualized on the fluorescein angiography of the left eye. ICG (Figure 3c) confirmed macular scar in the right eye and hypocyanescent spots in both eyes in the posterior pole and midperiphery.

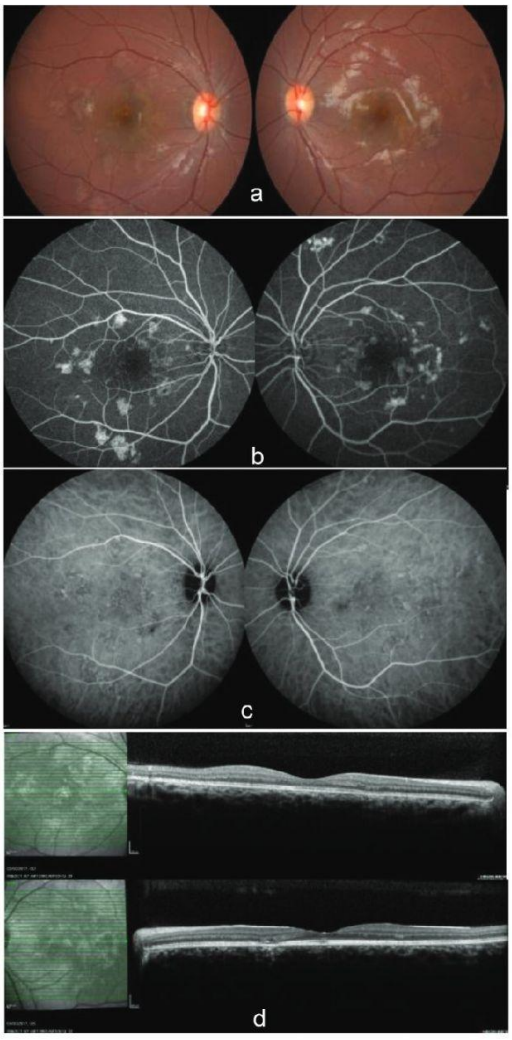

Figure 2. Imaging of the right eye and left eye in patient number 4 after treatment with oral methylprednisolone (MPS) and methotrexate (MTX). (a) Color fundus photography revealed a decrease of the number and size of white dots. However, some deep scars remained at the posterior pole. Late phase fluorescein angiography (b) showed the resolution of vasculitis and hot disc with the appearance of hyperfluorescent lesions (window defect) corresponding to the scars seen on the eye fundus. Intermediate phase ICG (c) confirmed the treatment response by the decrease of choroidal lesions in size and number. OCT (d) showed a more regular Bruch membrane and pigmented epithelium complex with normalization of the outer nuclear cells layer and atrophic scars.

The uveitis workup was repeated and completed by ^{18}F-FDG PET/ULD CT (Figure 3d), which showed bilateral discretely hypermetabolic axillary and inguinal lymph nodes, without classical hypermetabolic symmetric mediastinal adenopathy nor lung hypermetabolic infiltrates, classified as not specific for an active granulomatous disease. A left axillary lymph node biopsy confirmed however sarcoidosis. Methylprednisolone 24 mg was started and slowly decreased. After one month of steroids treatment, clinical examination revealed persistence of active choroidal lesions and methotrexate was added. Steroid dose was slowly decreased but a relapse was observed at the dose of 5 mg. Methotrexate was thus replaced by Infliximab (Remicade®) which led to disease control (Figure 4) and permitted methylprednisolone discontinuation. Final visual acuity is RE 1/10 and LE 10/10 with best correction.

Discussion

Idiopathic cause of uveitis in the pediatric population is reported in up to 59% of patients[3,6] Treatment of pediatric idiopathic uveitis is challenging. As in adults with non-infectious uveitis, sight-threatening pediatric idiopathic uveitis needs systemic immunosuppressive treatment. However, in the case of unfavorable evolution, the possibility of an infectious cause remains. Moreover, non-infectious uveitis can be treated by drugs targeting different pathways of inflammation, and response to different immunosuppressive drugs varies among entities eg. sarcoidosis, Behcet disease. Anti-TNF and anti-IL6 agents can even induce some of these entities. Therefore, treatment optimization requires a more precise diagnosis than idiopathic uveitis.

One of the issues is to detect hidden infectious and non-infectious causes of pediatric uveitis. In this context, ^{18}F-FDG PET/ ULD CT, which can detect metabolically active lymph nodes, is an interesting option as it has been shown to be efficient in detecting isolated extrapulmonary sarcoidosis and tuberculosis in adults.[30] Chauvelot et al have actually shown that ^{18}F-FDG PET/CT can be useful in establishing diagnosis in adult patients with uveitis even in patients with a normal CT scan.[31] However, to the best of our knowledge, there is no data on its role in pediatric uveitis. ^{18}F-FDG PET/ULD CT is classically used in pediatric oncology where it has an established role in staging several pediatric malignancies.[32,33] Its role in evaluating pediatric tuberculosis is also expanding.[34,35]

In this study, ^{18}F-FDG PET/ULD CT provided important information for final diagnosis in approximately 30% (4/12) of patients. In one patient ^{18}F-FDG PET/ULD CT helped to diagnose ocular tuberculosis and in 2 others to ocular sarcoidosis, which was further definitively proved by biopsy. One more patient (patient 1) with posterior uveitis with APMPPE had abnormal ^{18}F-FDG uptake characteristic of active granulomatous disease, which indicates pulmonary sarcoidosis. However, for this patient the strict criteria[9] of ocular sarcoidosis, which have only been defined in adults, were not met.

Our data suggest that in some cases, ^{18}F-FDG PET/ULD CT, might be useful in establishing the etiology of uveitis. This is in accordance with the work of Chauvelot et al., who showed that, in adult uveitis, this examination enabled the diagnosis of intraocular sarcoidosis even in patients with a normal CT scan.[31] Similarly, the usefulness of ^{18}F-FDG PET/CT in the diagnosis of tubercular uveitis has also been suggested,[16,36–39] again also in some cases with normal CT. However, in their study, Burger C et al concluded that PET/

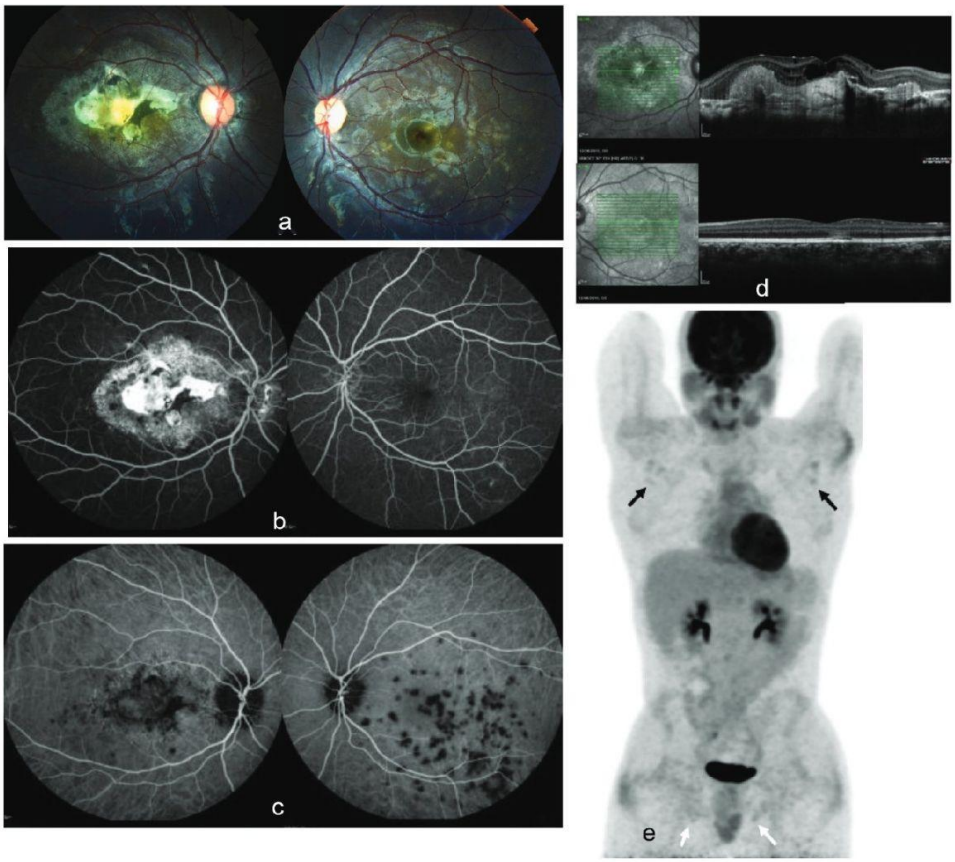

Figure 3. Pretreatment imaging of a pediatric uveitis patient (patient number 6) with biopsy- confirmed diagnosis of sarcoidosis. Color fundus photography (a) showed in the right eye a large macular scar partially pigmented and deep multifocal white dots at the posterior pole and midperiphery of the left eye. The early phase fluorescein angiography (b) showed a large macular area of staining in the right eye and subtle staining in the temporal macular region of the left eye. ICG (c) revealed a large macular hypocyanescent lesion corresponding to the scar in the right eye and highlighted multiple hypocyanescent dots in both eyes in the posterior pole and midperiphery. OCT (d) showed a subretinal fibrotic membrane with cystoid macular oedema in the right eye and subtle alteration of photoreceptors in the left eye associated to hyperreflectivity of the outer nuclear level. (e): Whole body ^{18}F-FDG PET/ultra low dose CT (FDG PET Maximum Image Projection – MIP) revealed abnormal ^{18}F-FDG uptake not specific for an active granulomatous disease. A left axillary lymph node biopsy confirmed however sarcoidosis. **Black arrows:** Low hypermetabolic axillary bilateral lymph nodes. **White arrows**: Low hypermetabolic inguinal bilateral lymph nodes. Left axillary lymph node was biopsied.

CT added no significant additional benefit over chest CT in patients with suspected ocular sarcoidosis or ocular tuberculosis.[40] The exact place of ^{18}F-FDG PET/CT is thus still a subject of debate.

Furthermore, as in our small study ^{18}F-FDG PET/ULD CT contributed to final uveitis diagnosis only in patients with bilateral choroidal involvement characterized as APMPPE, SLC and MFC, therefore maybe ^{18}F-FDG PET/ULD CT should be limited to such cases.

Interestingly, sarcoidosis in children has significantly more frequent extrapulmonary and lacrimal gland involvement when compared to adults.[41] Therefore, the whole body 18F-FDG PET/ULD CT could be of benefit over thoracic CT in search of a biopsy site, especially in the pediatric population.

The two major drawbacks of ^{18}F-FDG PET/ULD CT are the cost and the issue of radiation. The latter being especially true in the pediatric population. Importantly, in the more recent protocol, as in our study, ultra low dose CT is used, strongly minimalizing the radiation exposure.[42] In the ultra low dose CT protocol, the ionizing radiation of CT portion in ^{18}F-FDG PET is decreased at least 30 times in comparison to standard diagnostic CT.

The advantage of 18F-FDG PET/CT is that it is a whole body examination, which can detect metabolically active lesions, such as lymph nodes localized beyond the anatomical scope of CT thorax. Moreover, using ULD CT, instead of CT component, combined with 18F-FDG metabolic images significantly reduces the patient's radiation dose without altering the metabolic

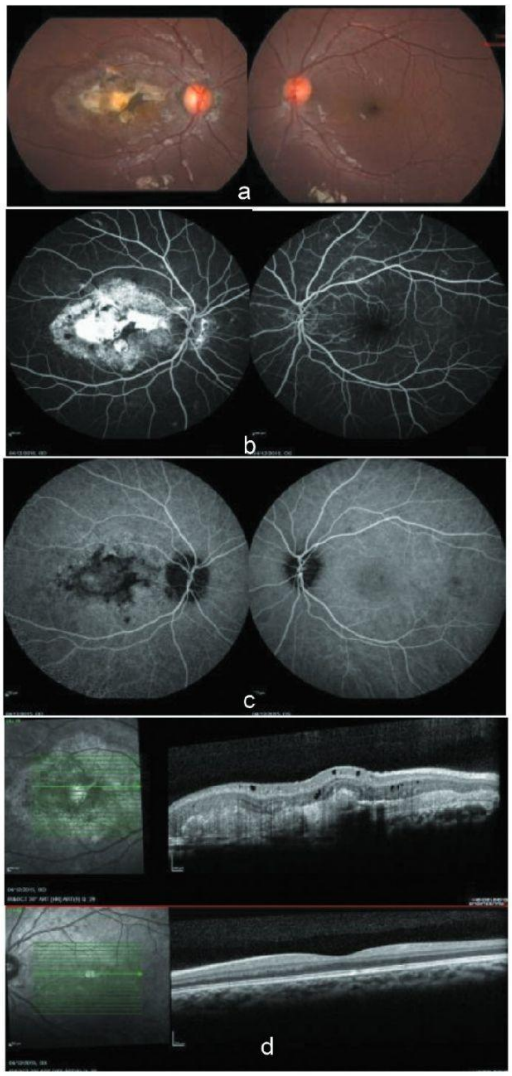

Figure 4. Multimodal imaging of patient number 6 after treatment with oral methylprednisolone (MPS) associated to methotrexate (MTX) and later replaced by Infliximab (Remicade®) i.v. Right and left eye color fundus photography (a), fluorescein angiography (b), ICG (c), and OCT (d) showed persistence of subretinal fibrotic neovascularization with a central retinal scar in the right eye and resolution of multifocal choroiditis in both eyes.

information. Combined radiation load of the whole body 18F-FDG PET/ ULD CT is similar to radiation of diagnostic CT thorax but for some patients, especially the obese ones, can be higher. Furthermore, radiation of the whole body 18F-FDG PET/ ULD CT is for sure lower than radiation of a combined diagnostic thorax CT and abdominal CT.

The limitation of this study is its retrospective character based on medical files. The lack of regular gonioscopy examination searching for trabecular meshwork nodules and predefined granulomatous keratic precipitates description pointing out mutton-fat keratic precipitates, could have led to underestimating intraocular signs of sarcoidosis in some patients. In the absence of pediatric international ophthalmologic criteria for various uveitis etiologies, the adults' disease criteria for ocular sarcoidosis[9] and ocular tuberculosis[24] were used.

In conclusion, ^{18}F-FDG PET/ultra low dose CT provided important information for final uveitis diagnosis in approximately 30% (4/12) of pediatric patients with bilateral uveitis. ^{18}F-FDG PET/ULD CT can contribute to the final diagnosis by either/both pathognomonic image of active granulomatous disease or/and by indicating the site of biopsy. In this small study, 17% (2/12) of ^{18}F-FDG PET/ULD CT led to positive biopsies and 25% (3/12) presented pathognomonic image of active granulomatous disease.

^{18}F-FDG PET/ULD CT contributed to final uveitis diagnosis only in patients with uveitis including bilateral choroidal involvement characterized as APMPPE, SLC, and MFC.

Further studies are needed to precise indications of whole body ^{18}F-FDG PET/ultra low dose CT in children patients with idiopathic uveitis and to define its exact place versus chest CT in the work-up of pediatric uveitis.

Disclosure statement

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Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis

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ORIGINAL ARTICLE

Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis

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ABSTRACT

Purpose: To evaluate neurosyphilis cerebrospinal fluid (CSF) findings and initial ophthalmic manifestations in patients with syphilitic uveitis.

Methods: We retrospectively reviewed the records of CSF analysis of 14 patients with syphilitic uveitis with treponemal analysis - chemiluminescent immunoassay and TPHA- and non-treponemal analysis - Rapid Plasma Reagin test – RPR.

Results: 86% were males and 43% HIV+. Ocular signs of syphilis lead to the diagnosis of syphilis in 78% of patients. Typical syphilitic uveitis presentations included: acute syphilitic posterior placoid chorioretinitis (50% of patients), retinitis (21% of patients) and punctate inner retinitis (7% of patients). 57% of patients had definite neurosyphilis by the CDC criteria, while 71% had CSF abnormalities suggestive of central nervous system involvement.

Conclusion: Based on international guidelines, the frequent CSF abnormalities found in syphilitic uveitis patient supports the diagnosis of neurosyphilis in a majority of patients.

Keywords: Cerebrospinal fluid, lumbar puncture, neurosyphilis, ocular syphilis, uveitis

Syphilis is a sexually transmitted disease caused by a spirochete *Treponema pallidum*, which can affect many organs including the central nervous system and eyes. Ocular manifestations can mimic other ocular diseases and this leads to considering syphilis as "the great masquerader" in ophthalmology.

The interest in syphilis has augmented with its increased frequency since several years.[1] The annual epidemiological report of the European Center for Disease Prevention and Control (ECDC) informs that overall syphilis rates have been increasing between 2010 and. 2014[2] In 2014, 24541 syphilis cases were reported in 29 EU/EEA Member States with an overall rate of 5.1 per 100 000 population.[2] Moreover, a recent French study has also reported a 10-fold increase in ocular syphilis in the uveitis clinic in a tertiary uveitis center in France between 2012 and 2015.[3]

Although ocular manifestations of syphilis are rare, with occurrence estimated in less than one in 1 million persons in the United Kingdom[4], their correct and quick diagnosis can be crucial to reveal a systemic disease. Ocular manifestations can be the first manifestations of syphilis.[5]

Ocular syphilis diagnosis is established on clinical symptoms supported by positive treponemal and non-treponemal serological tests. It is recommended that all patients with clinical signs of neurosyphilis such as ophthalmic abnormalities undergo lumbar puncture with syphilis oriented analysis.[6] In contrast to these guidelines, the data estimating changes in cerebrospinal fluid (CSF) compatible with neurosyphilis in

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patients with ocular syphilis are sparse. Indeed, most of the data about ocular syphilis and CSF neurosyphilis findings come from observations of patients with neurosyphilis.

The goal of this study was to describe lumbar puncture findings in patients with ocular syphilis and verify the frequency of CSF findings indicating neurosyphilis in this population. Also, an analysis of the variety of ophthalmic manifestations in syphilitic uveitis has been performed.

MATERIALS AND METHODS

This is a retrospective study of 14 patients with syphilitic uveitis seen in the tertiary uveitis center of the ophthalmology department of CHU St-Pierre in Brussels between 2004 – 2017.

The collected patients' data include demographics, clinical presentation of uveitis and serological characteristics of serum and cerebrospinal liquid as described below. The data were recorded at the first ophthalmological visit of each patient and therefore before initiating intravenous penicillin treatment, with the exception of patient nr 12 which is the record of the uveitis presentation at the second ophthalmological visit, however always before intra-venous penicillin administration.

The diagnosis of syphilitic uveitis was based on clinical evidence of intraocular inflammation not attributable to other causes and a positive serology for syphilis (treponemal and non-treponemal tests).All patients, except patient 3, had also an HIV test.

The intraocular lesions were registered by color fundus photography, Optical Coherence Tomography (OCT), fluorescein angiography of the posterior pole and the peripheral retina and in some cases, indocyanine green (ICG) angiography.

Routine syphilis serum serology testing included a treponemal test (IgG:IgM, electrochemiluminescence immunoassay, Cobas® (ECL) or chemiluminescent microparticle immunoassay, Architect de Abbott® (CMIA) or chemiluminescent immunoassay, Liaison de Diasorin® (CIA or CLIA)) and a non-treponemal test: Rapid Plasma Reagin test (RPR). All the patients had a positive treponemal test. Data was missing for patient nr 6.

The further exploration of syphilis infection included a neurological examination by a neurologist or infectious diseases specialist and a lumbar puncture of every patient. The CSF analysis included the number of nuclear elements, glucose, proteins, lactates and CSF syphilis serology testing by treponemal (CSF chemiluminescence and CSF TPHA) and non-treponemal tests (CSF RPR) The normal CSF values referred to by the hospital's laboratory are cell count <5,1/µL, glucose 45–80 mg/dL, proteins 0,15–0,45 g/L, lactates 10–22 mg/dL.

Neurosyphilis classification was based on the STD CDC 2015 criteria[6] completed by the laboratory cutoff values of CSF white blood count in HIV- (>5 cells/µl) and HIV+ (>20 cells/µl) patients[6-8] as well as CSF proteins level (>0.45 mg/L) in HIV- patients (Table 1). Following CDC 2015 criteria, syphilitic uveitis is considered as a clinical sign of neurosyphilis. Positive clinical signs of neurosyphilis, including ocular findings, and positive laboratory CSF findings of neurosyphilis lead to the diagnosis of neurosyphilis. In this study, laboratory CSF findings (CSF treponemal and non-treponemal tests, CSF white blood count and CSF protein level) of neurosyphilis were examined. CSF-RPR was performed as a substitute for CSF-VDRL, and CSF-chemiluminescence assay and CSF-TPHA as a substitute for CSF FTA-ABS. At least one positive treponemal test (CSF-chemiluminescence assay or CSF-TPHA) was needed to consider treponemal result as positive. Classification of neurosyphilis was made following CDC 2015 criteria: "In a person with neurologic signs or symptoms, a reactive CSF-VDRL (in

TABLE 1. Neurosyphilis diagnosis: CDC, STD 2015 criteria completed by the laboratory cutoff values for HIV+ and HIV- patients.

	HIV negative patients		HIV positive patients	
reactive serologic test for syphilis (in serum)	+	+	+	+
neurologic signs and symptoms*	+	+	+	+
	and	and	and	and
CSF FINDINGS:				
CSF VDRL (in the absence of blood contamination)	+	-	+	-
CSF white blood cells/µl		>5		>20
CSF Proteins mg/L		and/or 0.45		Unreliable
CSF FTA-ABS		+		+
	NS	NS	NS	NS

* clinical signs of neurosyphilis (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense).

CSF- cerebrospinal fluid; NS - neurosyphilis

the absence of blood contamination) is considered diagnostic of neurosyphilis. When CSF-VDRL is negative despite the presence of clinical signs of neurosyphilis, reactive serologic test results, and abnormal CSF cell count and/or protein, neurosyphilis should be considered. In this instance, additional evaluation using FTA-ABS testing on CSF may be warranted. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Neurosyphilis is highly unlikely with a negative CSF FTA-ABS test, especially among persons with nonspecific neurologic signs and symptoms.[6,7]

RESULTS

Epidemiological Characteristics of Patients with Syphilitic Uveitis. Demographic Data, Serological Status and Uveitis Anatomical Location (Table 2)

Among 14 patients included in the study, there was a majority of males (86%, 12 out of 14) and 6 patients (43%) were HIV positive. The average patient's age for the first ophthalmological visit for signs and symptoms of uveitis was 39 years. For the majority of patients (78%, 11 out of 14) the syphilitic uveitis was the first diagnosed syphilis manifestation. In all the patients, syphilitic uveitis was located in the posterior pole of the eye, which was either a predominant uveitis location in 86% (12 out of 14) of patients or equal to anterior uveitis presentation and thus classified as a panuveitis in 14% (2 out of 14) of patients.[9] 43% (6 out of 14) of patients had a bilateral uveitis. All patients had positive serum treponemal (chemiluminescence immunoassay) and a non-treponemal (RPR) tests with RPR higher or equal 32. Serum RPR ranged from 32 to 512.

TABLE 2. Epidemiological chacteristics of patients with syphilitic uveitis. Demografic data, serological status and uveitis predominant anatomical location.

CASE	SEX	AGE	HIV	serum IgG:IgM	serum RPR	uveitis predominant location
1	M	33	+	+	256	PU
2	M	36	+	+	256	PU
3	M	43	NA	+	64	PU
4	F	51	-	+	256	Panuveitis bilateral
5	M	38	-	+	32	PU bilateral
6	M	37	+	NA	128	PU bilateral
7	M	41	-	+	128	Panuveits bilateral
8	M	30	+	+	128	PU
9	M	48	-	+	126	PU
10	M	30	+	+	32	PU bilateral
11	F	43	-	+	64	PU
12	M	48	-	+	512	PU bilateral
13	M	26	-	+	64	PU
14	M	41	+	+	128	PU

M - male; F -female; NA- not available; PU - unilateral posterior uveitis

Characteristics of Uveitis Presentation in Patients with Syphilis (Table 3)

In this patient series, posterior uveitis was present in all patients. Most frequently posterior uveitis or panuveitis had a non specific presentation as papillitis in 86% (12 out of 14) of patients or vasculitis and vitritis each in 71% (10 out of 14) of patients. The typical syphilitic uveitis presentations, such as acute syphilitic posterior placoid chorioretinitis (ASPPC), retinal necrosis, or punctate inner retinitis were less frequently observed. Among them ASPPC was the most frequent and was objectified in 50% of patients (7 out of 14). Retinal necrosis and punctate inner retinitis were present in 21% and 7% of patients respectively. Neuroretinitis was not observed at the first ophthalmological visit in any of the patients but has developed in one patient during the treatment. Two patients with severe bilateral panuveitis, were HIV negative and also had CSF neurosyphilis findings.

Anterior inflammation was observed in 64% (9 out of 14) of patients but none had a predominant uveitis location in the anterior chamber. Two patients had a severe anterior inflammation associated with a posterior inflammation and were considered as panuveitis according to the SUN classification.[9] Keratic precipitates (KP) were present in 36% (5 out of 14) of patients and posterior synechiae in 7% (1 out of 14) of patients.

Neurosyphilis CSF Findings in Patients with Syphilitic Uveitis (Table 4)

Neurosyphilis classification was made following CDC 2015 criteria, which can be interpreted in two ways as it states that 'neurosyphilis is highly unlikely with a negative CSF FTA-ABS test' (in case of negative CSF VDRL but with abnormal CSF cell count and/or CSF protein).[6] If 'highly unlikely', should be interpreted as a negative result, then in our study 8 out of 14 patients (57%) with ocular syphilis had neurosyphilis. However, 'highly unlikely' does not exclude neurosyphilis and can be interpreted as a positive result. In this case in 2 patients of the study, neurosyphilis could not be excluded. According to this interpretation, neurosyphilis can be present in 10 out of 14 patients (71%) with ocular syphilis. This concerned patients number 2 and 8, who despite negative CSF RPR and negative CSF TPHA, had elevated CSF

TABLE 3. Characteristics of uveitis presentation in patients with ocular syphilis.

		anterior uveitis characteristics						posterior uveitis characteristics													
		Tyndall in anterior chamber		KP		posterior synechiae		papillitis		ASPPC		retinitis (= necrosis)		punctate inner retinitis		neuroretinitis		vasculitis		vitritis	
case	uveitis predominant location	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	PU	+	-	-	-	-	-	+		-	-	+	-	-	-	-	-	+	-	+	-
2	PU	-	+	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	+
3	PU	+	-	-	-	-	-	+	-	-	-	+	-	-	-	-	-	+	-	+	-
4	Panuveitis bilateral	+	+	+	+	-	-	+	+	-	-	-	-	+	+	-	-	+	+	+	+
5	PU bilateral	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	+	+	+	+
6	PU bilateral	+	+	+	+	-	-	+	+	+	+	-	-	-	-	-	-	+	+	+	+
7	Panuveits bilateral	+	+	+	+	+	+	-	-	-	-	-	+	-	-	-	-	-	+	+	+
8	PU	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
9	PU	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	+	-	-	-
10	PU bilateral	+	+	-	-	-	-	+	+	-	-	-	-	-	-	-	-	+	-	-	+
11	PU	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	+	-	+	-
12	PU bilateral	+	+	-	-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-
13	PU	-	-	+	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	+	-
14	PU	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-
TOTLAL NR OF PATIENTS		**8**		**5**		**1**		**12**		**7**		**3**		**1**		**0**		**10**		**10**	

R- right eye, L-left eye, PU - posterior uveitis, KP - keratic precipitates ASPPC - acute syphilitic posterior placoid chorioretinitis

TABLE 4. CSF analysis and neurosyphilis CSF changes in patients with ocular syphilis.

		CSF analysis						
CASE	HIV	cell count (nl<5,1)	RPR	proteins (nl 0,15–0,45)	Treponema IgG: IgM	TPHA	neurological signs other than ocular	neurosyphilis CSF changes
1	+	65	NA	0.36	+	<80	-	+
2	+	41	<1	0.39	doubtful	<80	-	-/+
3	NA	39	2	0.51	+	640	-	+
4	-	23	<1	0.34	+	<80	-	+
5	-	15	<1	0.31	+	80	-	+
6	+	18	1	0.51	NA	3+	-	+
7	-	102	1	0.68	+	160	-	+
8	+	36	<1	0.578	doubtful	<80	+	-/+
9	-	10	<1	0.538	+	NA	-	+
10	+	3	<1	0.388	doubtful	<80	+	-
11	-	3	<1	0.237	doubtful	<80	-	-
12	-	3	<1	0.55	+	80	-	+
13	-	5	<1	0.25	+	80	-	-
14	+	2	<1	0.28	+	80	-	-

NA - not available

WBC, normal or elevated CSF proteins and doubtful CSF chemiluminescence.

All 14 patients had elevated non treponemal serologic tests (RPR ≥1/32), which argues for untreated or recent syphilis infection, and had ophthalmic abnormalities. Only two patients in addition to ophthalmic abnormalities had other neurological signs such as auditory abnormalities (patient 8) and right pyramidal syndrome (patient 10). Patient 10 had negative CSF results for neurosyphilis.

CSF RPR was reactive only in 3 patients out of 14. The CSF RPR titer ranged from <1 to 2. All patients with CSF RPR ≤1, had positive CSF chemiluminescence immunoassay result. . The other analyzed parameters like CSF glucose and lactate, were normal in all tested patients. The CSF protein level ranged from 0,237 to 0,68 g/L, with a median of 0,389 g/L (normal ≤ 0,15–-0,45 g/L). CSF proteins were elevated only in 3 HIV negative patients and were considered as unreliable in HIV positive patients. CSF cells count was elevated in 57% of patients (8 out of 14) with normal cutoff values which are different for HIV- patients (>5 cells/µl) and HIV+ patients (>20 cells/µl). The CSF cell count (white blood cells) ranged from 2 to 102, with a median of 16, 5 cells/µl (normal <5,1 cells/µl).

Of 6 HIV-positive patients, 2 or 4 (depending on interpretation of CDC 2015 criteria) were found to have CSF findings of neurosyphilis.

DISCUSSION

Neurosyphilis CSF Findings

The uniqueness of this study is that it combines both CSF findings in ocular syphilis and detailed clinical syphilis uveitis characterization. Furthermore, all patients in the series underwent lumbar puncture with CSF syphilis analysis which allows estimation of the frequency of CSF changes. However, only 14 patients could be included and this might not be sufficient to draw statistically relevant conclusions.

In this study 57% of patients had definite neurosyphilis by the CDC criteria, while 71% had CSF abnormalities suggestive of central nervous system involvement. Interestingly, a recent study in South Africa, which reported a low frequency of neurosyphilis (26%) among patients with ocular syphilis, has probably underestimated the neurosyphilis frequency as lumbar puncture was done only in 46% of patients with ocular syphilis.[10] On the contrary, Dai Ting et al[11] showed a high CSF abnormal rate in HIV negative patients strongly supporting CSF examination for all patients with ocular syphilis, which is actually the CDC 2015 recommendation.

All the patients of the presented study had serological testing prior to CSF evaluation for neurosyphilis, as it was shown that biological false-positive VDRL-CSF is common in a setting where patients are tested without first establishing a serological diagnosis of syphilis.[12] Furthermore, all 14 patients had serum Rapid Plasma Reagin (RPR) titer of ≥1/32, which in HIV-infected patients with syphilis was shown to be helpful in selecting patients for lumbar puncture.[7]

RPR titer of ≥1/32 was also shown to be helpful in predicting the likelihood of laboratory findings of neurosyphilis. Serum RPR titer of ≥1/32 increased the odds of laboratory findings of neurosyphilis 10.85-fold in human immunodeficiency virus (HIV)-uninfected subjects and 5.98-fold in HIV-infected subjects.[8] This data is in agreement with the fact that in our study all 14 patients had clinical signs of neurosyphilis (ocular abnormalities).However,

only 57% or 71%of them had CSF findings of neurosyphilis

In this study, the CSF WBC in patients with neurosyphilis(ocular syphilis and CSF neurosyphilis findings) were higher (median of 20.5 or 29.5 cells/µl, depending on interpretation of CDC 2015 criteria) than in patients without neurosyphilis (ocular syphilis without CSF neurosyphilis findings) (median of 3 cells/µl). This is a logical consequence of neurosyphilis classification, which includes higher WBC values for patients with negative CSF VDRL. Also CSF protein levels were higher in patients with neurosyphilis (median of 0,51 g/L for both interpretations of CDC 2015) in comparison to patients without neurosyphilis (median of 0,265 g/L). An interesting observation was made in a recent study, which showed that HIV-infected patients with neurosyphilis and ocular syphilis were more likely to have CSF WBC elevation than HIV-infected neurosyphilis patients without ocular syphilis.[13]

For neurosyphilis diagnosis, CDC STD 2015 criteria recommends CSF VDRL analysis and if negative CSF FTA-ABS. At CHU St-Pierre in Brussels, the available analysis for CSF are CSF-RPR and CSF- chemiluminescence immunoassay. The former is a non-treponemal test, an equivalent of CSF-VDRL. The latter is a treponemal chemiluminescence immunoassay test, which is an equivalent of CSF FTA-ABS. The CSF-VDRL is generally considered to be the "gold standard" test. However, there are studies which suggested that the CSF-RPR or CSF toluidine red unheated serum test (CSF-TRUST) could be suitable alternatives to the CSF-VDRL.[14–16]

However, Marra and coauthors conclude otherwise.[17] They also show that independently of the definitions of neurosyphilis, the CSF-RPR had a high false-negative rate of 35.6%, providing no improvement on this known limitation of the CSF-VDRL. To exclude this high false-negative rate, a treponemal chemiluminescence immunoassay test on CSF was performed. Electrochemiluminescence immunoassay specificity tested on serum samples ranges from 99,81 to 99.88% and sensitivity from 99.57 to 100%.[18–20] The utility of immunoassay tests on CSF in patients with neurosyphilis was proven.[21]

CDC 2015 criteria for neurosyphilis are somehow debated as they are considered strict. Using another criteria for neurosyphilis[8]: CSF white blood cells elevated >20 cells/µl (for HIV+ and HIV- patients) or reactive VDRL, would have classified 7 out of 14 (50%) patients of the presented study as suffering from neurosyphilis.

Ocular Syphilis as Initial Clinical Presentation

In this study, uveitis was the first diagnosed syphilis presentation for the majority of patients (78%). Syphilis can often be diagnosed by an ophthalmologist first which can be of high importance for prompt detection of systemic disease. The correct diagnosis and immediate treatment of ocular syphilis is crucial as a treatment delay of >12 weeks[22], or 28 days in HIV positive patients[23] is associated with low visual acuity outcome

Characteristics of Uveitis in Patients with Syphilis

The most frequent predominant ocular syphilis presentation in this study was posterior uveitis (86%; 12 out of 14), of which 4 were bilateral, followed by bilateral panuveitis (14%; 2 out of 14). The same frequency of panuveitis was recently observed in France.[3] Among posterior uveitis manifestations characteristic for syphilis, ASPPC is described as an uncommon but clinically and angiographically distinct manifestation of ocular syphilis.[24] In this small cohort it was the most frequent presentation among the typical syphilitic uveitis manifestations (50% of patients). Other known presentations such as retinal necrosis or punctate inner retinitis[25] were less common and no neuroretinitis was observed.[26] However, the most frequently observed changes in the posterior pole were not specific: papillitis (86%), vitritis (71%) and vasculitis isolated to the posterior pole, periphery, or diffuse (71%). Anterior inflammation in this series was present in 69% of patients but was always accompanied by more severe posterior inflammation. There was no observation of a predominant or solitary anterior uveitis presentation.

Interestingly, two most severe cases - bilateral panuveitis, were HIV negative and were classified as neurosyphilis positive. This finding is in contrast somehow to a study that shows that panuveitis in HIV positive patients is more frequent than in HIV negative patients.[27] However, a systematic review[28] did not determine whether panuveitis were more common in HIV positive patients.

Conclusions

In conclusion, in this study all patients with ocular syphilis underwent lumbar puncture with a treponemal and a non-treponemal analysis. 57% of patients had definite neurosyphilis by the CDC criteria, while 71% had CSF abnormalities suggestive of central nervous system involvement, which supports treating ocular syphilis with the neurosyphilis treatment protocol. In 78% of the patients, ocular syphilis was the first diagnosed syphilis presentation. ASPPC (acute syphilitic posterior placoid chorioretinitis) was observed in 50% of the patients with syphilitic uveitis and was the most frequently seen amongst the typical syphilis presentations. Those data are only

representative of our small cohort and should be confirmed by larger studies.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis

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Abstract

Sarcoidosis-associated uveitis, is the predominant ocular sarcoidosis presentation, which affects both adults and children. For adults, international ocular sarcoidosis criteria (IWOS) and sarcoidosis-associated uveitis criteria (SUN) are defined. However, for children they are not yet established internationally. Due to the specificity of pediatric manifestations of sarcoidosis, this task is even more challenging. In children, sarcoidosis is subdivided into Blau syndrome and early-onset sarcoidosis (BS/EOS) affecting younger children (< 5 years) and the one affecting older children with clinical presentation resembling adults. Differential diagnosis, clinical work-up as well as diagnostic criteria should be adapted to each age group. In this article, we review the clinical manifestation of sarcoidosis-associated uveitis in adults and children and the sensitivity and specificity of various ocular sarcoidosis diagnostic modalities, including chest X-ray and CT, FDG PET-CT, gallium-67 scintigraphy, bronchoalveolar lavage fluid, genetic testing for NOD2 mutations and serum biomarkers, such as ACE, lysozyme and IL2R.

Keywords Uveitis, Sarcoidosis, Diagnosis, Criteria, Biomarkers, Children

Introduction

Sarcoidosis is a rare inflammatory condition of unknown cause that affects both adults and children. Its prevalence in adults ranges from 8.1/100 000 in Caucasians to 17.8/100 000 in African Americans. Notably, the disease is less common in children with a prevalence of 0.22–0.27/100000 (Danish study) [1].

The hallmark of the disease is the presence of non-caseating granulomas in affected tissues. Nevertheless, systemic presentation varies among age groups, which often leads to delayed diagnosis in younger patients. It is of note that sarcoidosis in children < 5 years old does not typically involve lungs but skin, joints, and eyes [2, 3].

Ophthalmic manifestations of sarcoidosis can involve any part of the eye and its adnexa in the inflammatory process [4]. The prevalence of ocular involvement in patients diagnosed with systemic sarcoidosis ranges from 13 to 79% [4]. Furthermore, ocular involvement remains the presenting symptom in 30–40% of patients diagnosed with systemic sarcoidosis [5, 6]. The most common ocular manifestation of sarcoidosis is uveitis and is reported

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in up to 70% of cases [4]. International Workshop on Ocular Sarcoidosis (IWOS) clinical criteria for ocular sarcoidosis are referring only to uveitis and not to other ophthalmic manifestations. Following nomenclature used by IWOS and many other authors, in this review 'ocular sarcoidosis' refers only to sarcoidosis-associated uveitis.

Considering the above, certain patients diagnosed with uveitis e.g. patients with granulomatous or posterior uveitis should undergo sarcoidosis screening as a routine workup. However, a definite diagnosis is often difficult to obtain as according to the revised IWOS Criteria for diagnosis of ocular sarcoidosis a biopsy of the lesion is required [7]. It is feasible for the skin and lymph node involvement but is often avoided in the case of vital organs i.e. lungs, heart, or liver [7]. Therefore, a high-level of clinical suspicion and a thorough slit-lamp examination are essential for setting a presumed or probable diagnosis [7].

This clinical scenario is even more complex in children. The lack of a typical pattern of systemic presentation and the absence of standardized guidelines on ocular sarcoidosis in children makes a clinical diagnosis of ocular sarcoidosis difficult [3].

Here, we present overlapping as well as distinguishing features of ocular sarcoidosis in children and adults followed by a differential diagnosis and novel diagnostic approach. The contrast between features of the disease across various age groups aims to increase clinicians' awareness regarding this diagnosis and ensure a timely diagnosis for more patients, particularly those under 5 years of age.

Methods

We utilized the Pubmed database to search for relevant publications. Manuscripts published between 2013 and 2022 were utilized as the primary source of data. Ocular sarcoidosis, sarcoidosis, early onset sarcoidosis, Blau syndrome, and uveitis served as primary search terms.

Systemic sarcoidosis

Adults

There are no firmly established guidelines dedicated to the diagnosis of sarcoidosis. However, it is agreed that the disease is deemed highly probable in an individual with typical clinical features, non-caseating granulomas in the histopathological examination, and in whom other granulomatous diseases have been ruled out [8].

The 2014 guidelines issued by the World Association of Sarcoidosis and other Granulomatous Diseases point out that certain clinical manifestations and imaging or laboratory findings are suggestive of the disease and these patients should undergo sarcoidosis screening [9]. Clinical manifestations include: Lofgren syndrome (bilateral hilar adenopathy, erythema nodosum, and/or arthritis), Heerfordt-Waldenström syndrome (rare subacute variant of sarcoidosis, characterized by enlargement of the parotid or salivary glands, facial nerve paralysis and anterior uveitis) [10], lupus pernio, uveitis, optic neuritis, erythema nodosum. Nonspecific benign lymphoepithelial lesion or Mikulicz's disease or syndrome is a type of benign enlargement of the parotid and/or lacrimal glands, which has been described also in sarcoidosis. Virtually any organ and system can be involved in the process including the central nervous system, liver, kidneys, spleen, or muscles [9]. Imaging features include: bilateral hilar adenopathy, perilymphatic nodules, gadolinium enhancement on MRI, osteolysis, trabecular bone pattern, bone cysts and contrast uptake by the parotid; laboratory findings include hypercalcemia or hypercalciuria [9]. It is of note that the conditions listed above do not exhaust all possible sites involved in sarcoidosis.

Considering that the clinical picture of the disease is non-specific, a biopsy of the lesion is usually endorsed by sarcoidosis experts [11]. However, as sarcoid granulomas do not have any specific features that would allow them to distinguish them from other non-necrotizing granulomas, the exclusion of other diseases with similar histopathology is usually required to confirm the diagnosis of sarcoidosis [12]. The differential diagnoses of systemic sarcoidosis should include infectious and non-infectious causes [13]. The detailed differential of systemic sarcoidosis remains beyond the scope of this review, however, the most common mimickers include tuberculosis and other mycobacteria, fungal infections, and a range of non-infectious diseases including vasculitis or lymphoma [14]. For a more thorough list of differential diagnoses of systemic sarcoidosis, the reader is referred to dedicated sources [13–17].

Children > 5 years

The course of systemic sarcoidosis in children older than 5 years is similar to the adult disease described above [3, 18]. Clinical symptoms include fever of unknown origin and malaise accompanied by hilar adenopathy and lung changes [18]. Interestingly, peripheral lymph nodes involvement is more common in children (40–70%) than in adults (4.8%) [1, 2].

Systemic sarcoidosis usually affects teenagers with a mean age of 13–15 years. Notably, its prevalence is much lower than in adults and a recent Danish study showed that it equals 0.22–0.27/100 000 [1]. Sarcoidosis

in children older than 5 years has usually a less severe course than in adults. It is estimated that approximately 25% of adults and 12% of children develop chronic or progressive disease [19, 20].

Children < 5 years

Sarcoidosis in children younger than 5 years is usually considered separately and is labeled as Blau Syndrome when there is a family history proving an autosomal dominant trait or Early Onset Sarcoidosis (EOS) when no family history is evident [21]. Children under 5 typically present with a triad of a rash, polyarthritis, and uveitis [22]. Although any organ can be involved in the inflammatory process, lungs are typically spared [23]. BS and EOS are respectively defined as the familial and sporadic forms of the same pediatric noncaseating granulomatous autoinflammatory disease [24] and are shown to share a common genetic etiology [25]. Although, traditionally, Blau syndrome is recognized if there is a family history of the disease, and EOS if the mutation is sporadic [21], this traditional naming is not always followed, as authors of some recent publications [26–29] use the name Blau Syndrome for both familial and sporadic mutations.

Notably, Blau syndrome and EOS are a result of Nucleotide-binding oligomerization domain-containing protein 2 (NOD2), previously known as CARD15 gene mutation [30]. NOD2 serves as an intracellular pattern recognition receptor that activates the immune system in response to muramyl dipeptide, a constituent of the cell wall of certain bacteria. Therefore, the gain mutation of this gene leads to the overactivation of the immune system [30].

Data from the Blau syndrome registry shows that patients with Blau syndrome develop rash, arthritis, and uveitis with a median age of 1.1 years, 2 years, and 4.4 years respectively [31]. Furthermore, 30 out of 31 patients included in a published report required systemic medication to control the disease [26, 31]. Other expanded manifestations of BS/EOS are fever, pneumonitis, bronchial granulomas, hepatosplenomegaly, hepatic granulomas, sialadenitis, erythema nodosum, leukocytoclastic vasculitis, transient neuropathies, arterial hypertension, pericarditis, pulmonary embolism, granulomatous glomerular and interstitial nephritis, and chronic renal failure [21]. Expanded manifestations beyond the classical triad were observed in 52% patients [31]. Neurologic involvement is infrequent in BS/EOS. Typical central nervous system manifestations seen in adult sarcoidosis, namely meningeal and white matter disease have not been described in Blau until 2021 [21, 32].

Ophthalmic manifestations of sarcoidosis and ocular sarcoidosis

Ophthalmic manifestations of sarcoidosis affect virtually any part of the eye and its adnexa. The most common form includes uveitis (anterior, intermediate, posterior) and conjunctival granuloma. The former may lead to significant visual disability, whereas the latter is usually asymptomatic. Other ophthalmic manifestations of sarcoidosis consist of dacryoadenitis, orbital inflammation, eyelid granuloma, madarosis, poliosis, keratitis, and optic neuritis [33].

Coulon et al. reported that among 194 adult patients with biopsy-proven and presumed uveitis only 9% had additionally other ocular involvement, including conjunctival node (2%), scleritis (1%), episcleritis (1%), optic neuropathy (5%), dacryoadenitis (0,5%) [34].

Ocular sarcoidosis might thus globally refer to any inflammation of the eye and its adnexa [4] and can be divided in ocular surface, intraocular (uveitis), adnexal, orbital and neuro-ophthalmological manifestation. However, as mentioned above, in this review, 'ocular sarcoidosis' follows nomenclature used in the cited studies and practically refers to sarcoidosis-associated uveitis.

Ocular sarcoidosis as well as systemic sarcoidosis show some differences among the ethnic groups. Systemic involvement of sarcoidosis is more frequent in North Africans than in White Europeans, who show a higher frequency of isolated ocular involvement at onset and during follow-up [34]. Anterior uveitis is more frequent in Afro-Caribbeans (59.1%) [34]. Caucasian sarcoid uveitis patients are older at presentation (48 vs 41 years; $P=0.009$) and have less granulomatous anterior uveitis (26.4% vs 51.7%; $P<0.001$) [35]. Afro-Caribbeans and North Africans have first ocular manifestation of the disease earlier than White Europeans ($p<0.001$), respectively 34.3, 43.1 and 57.8 years [35].

Uveitis

Adults

Features of sarcoidosis-associated uveitis are included in numerous cohort studies [7, 36, 37] as well as in the international diagnostic criteria such as revised diagnostic criteria of ocular sarcoidosis by IWOS (Table 1) [7] and criteria for sarcoidosis-associated uveitis by Standardization of Uveitis Nomenclature (SUN) Working Group [38] (Table 2). Characteristics and common features of sarcoid uveitis in adults are presented in Table 3 which include the biggest recent ophthalmologic studies in adult patients with sarcoidosis.

Uveitis in adults presents typically as a bilateral and chronic disease. It is predominantly either panuveitis (8–67%) or anterior uveitis (20–52%) and it varies among

Table 1 Revised International Workshop on ocular sarcoidosis (IWOS) criteria for the diagnosis of ocular sarcoidosis (OS)[7], published in 2019

I. Other causes of granulomatous uveitis must be ruled out
II. Intraocular clinical signs suggestive of OS
1. Mutton-fat keratic precipitates (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Busacca)
2. Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechia
3. Snowballs/string of pearls vitreous opacities
4. Multiple chorioretinal peripheral lesions (active and atrophic)
5. Nodular and/or segmental periphlebitis (± candle wax drippings) and/or macroaneurysm in an inflamed eye
6. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
7. Bilaterality (assessed by ophthalmological examination including ocular imaging showing subclinical inflammation)
III. Systemic investigation results in suspected OS
1. Bilateral hilar lymphadenopathy (BHL) by chest X-ray and/or chest computed CT scan
2. Negative tuberculin test or interferon-gamma releasing assays
3. Elevated serum ACE
4. Elevated serum lysozyme
5. Elevated CD4/CD8 ratio (> 3.5) in bronchoalveolar lavage fluid
6. Abnormal accumulation of gallium-67 scintigraphy or 18F-fluorodeoxyglucose positron emission tomography imaging
7. Lymphopenia
8. Parenchymal lung changes consistent with sarcoidosis, as determined by pulmonologists or radiologists
IV. Diagnostic criteria
Definite OS: diagnosis supported by biopsy with compatible uveitis
Presumed OS: diagnosis not supported by biopsy, but BHL present with two intraocular signs Probable OS: diagnosis not supported by biopsy and BHL absent,but three intraocular signs and two systemic investigations selected from two to eight are present

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Table 2 The criteria for sarcoidosis-associated uveitis by Standardization of Uveitis Nomenclature (SUN) Working Group[33], published in 2021

1. Compatible uveitic picture, either
a. Anterior uveitis OR
b. Intermediate or anterior/intermediate uveitis OR
c. Posterior uveitis with either choroiditis (paucifocal choroidal nodule(s) or multifocal choroiditis) OR
d. Panuveitis with choroiditis or retinal vascular sheathing or retinal vascular occlusion
AND
2. Evidence of sarcoidosis, either
a. Tissue biopsy demonstrating non-caseating granulomata OR
b. Bilateral hilar adenopathy on chest imaging
Exclusions
1. Positive serology for syphilis using a treponemal test
2. Evidence of infection with Mycobacterium tuberculosis[a] either
a. Histologically- or microbiologically-confirmed infection with M. tuberculosis[b]OR
b. Positive interferon-γ release assay (IGRA)[c] OR
c. Positive tuberculin skin test[d]

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[a] Routine exclusion of tuberculosis is not required in areas where tuberculosis is non-endemic but should be performed in areas where tuberculosis is endemic or in tuberculosis-exposed patients. With evidence of latent tuberculosis in a patient with a uveitic syndrome compatible with either sarcoidosis or tubercular uveitis and bilateral hilar adenopathy, the classification as sarcoid uveitis can be made only with biopsy confirmation of sarcoidosis (and therefore exclusion of tuberculosis)

[b] E.g. biopsy, fluorochrome stain, culture, or polymerase chain reaction based assay

[c] E.g. Quantiferon-gold or T-spot

[d] E.g. Purified protein derivative (PPD) skin test; a positive result should be > 10 mm induration

Table 3 Characteristics and common features of sarcoid uveitis in adults, children and Blau Syndrome/ Early Onset Sarcoidosis (BS/EOS)

	Study	nbr of patients in the study with ocular manifestation of sarcoidosis or BS/EOS	Number of all patients in the study	Age, years, median of patients' age with ocular manifestations of sarcoidosis or BS/EOS; for BS/EOS median age at ocular onset and age at study baseline	Bilateral	Granulomatous	Mutton-fat keratic precipitates	Mutton-fat KPs, iris nodules, or both	Non granulomatous
Adults	SUN, 2021	278[b]	2684	49 (IQR 39–61)	82%	-	23%	35%	-
	Acharya,2018	167[c]	884	49 (IQR 39—60)	86%	-	35%	46%	-
	Coulon, 2019	194[d]	194	52.1 ± 17.8	77.8%	60%	-	-	-
	Niederer, 2021	362[e]	362	46 (IQR 35–57)	87%	48%	-	-	-
	Allegri, 2022	235	235	mean age 52	85%	52%	-	-	-
Children > 5 years	Choi, 2011	13[f]	460	12 (range: 5 to 16)	-	31%	-	-	62%
	Morelle, 2019	9[b]	147	-, mean age 10.5 (range: 7–14)	100%	23%	-	-	-
	Waduthantri S, 2021	8[g]	73	mean age 12 (range: 5–15)	-	-	-	-	-
Blau Syndrome / Early Onset Sarcoidosis	Sarens, 2018	38	50	5 (range 0,5- 48); at study baseline: 17 (range 2–56)	97%	-	-	-	-
	Kumrah, 2022	9	11	4 (range: 2–26); median age at diagnosis: 9 (range: 2–26)	100%	44%	-	11% only iris nodules specified	11%
	Matsuda, 2020	38	50	-, -; all patients in the study: mean 26.7 (range 0–61)	-	-	-	-	-
	Wu,2019	7	7	5,5 (range 2-24y), at study baseline: 10,5 (range: 4–34)	-	-	-	-	-
	Babu, 2020	7	7	-, at study baseline: 9 (range 2,5–25)	71%[i]	71%[j]	14%	-	-
	Rosé, 2015	25	31	4.4 (range 0,5–22); at study baseline 16.5 (range: 1.9–58)	96%	-	-	-	-

Table 3 (continued)

	No keratic precipitates	Anterior[a] uveitis	Intermediate[a] uveitis	Posterior[a] uveitis	Panuveitis [a]	Multifocal choroiditis	Retinal vascular inflammation[h]	Solitary choroidal nodule (optic disc nodules or granulomas)
Adults	52%	40%	19%	4%	37%	30%	18%	2% (-)
	-	20%	3%	9%	67%	45%	36%	3% (4%)
	-	34%	10%	7%	49%	40%	30%	-
	-	-	-	-	-	43%	21%	11% isolated choroidal or optic nerve granuloma
	-	52%	10%	29%	8%	-	-	-
Children > 5 years	8%	-	-	-	-	54%	31%	-
	-	77%	-	-	23%	-	-	-
	-	12.50%	-	25%	62.50%	-	-	-
Blau Syndrome / Early Onset Sarcoidosis	-	29%	-	-	51%	39%	0%	- (12%) peripapillary nodules
	-	33%	-	-	67%	67%	11%	-
	-	-	-	-	-	-	-	-
	-	14%	-	-	85%	-	-	-
	-	29%	-	-	43%	-	-	14% (-)
	-	-	-	-	-	-	-	-

IQR interquartile range; data not available

[a] anatomic class (SUN)/ type by anatomic location (Acharya, 2018)

[b] sarcoidosis-associated uveitis

[c] including 98 patients with definite ocular sarcoidosis and 69 patients with presumed ocular sarcoidosis according to IWOS 2009 criteria

[d] including 145 with biopsy-proven and 49 with presumed sarcoid uveitis following the WASOG/ATS/ERS criteria

[e] including definite or presumed ocular sarcoidosis according to IWOS 2009 criteria

[f] including 4 definite, 3 presumed, or 6 probable sarcoidosis according to selfestblished scoring system

[g] 8 patients with presumed ocular sarcoidosis and 2 patients with sarcoid scleritis

[h] refered to as: retinal vascular sheathing or periphebitis or vasculitis

[i] at least 71%, no data available on bilaterality for 2 other patients with only conjunctival granulomas

[j] and additionally 29% with only conjunctival granulomas

- no data available

the studies. Intermediate uveitis is less frequent (3–19%) and isolated posterior uveitis is rare (4–29%) [34, 38–40].

Anterior segment inflammation is granulomatous in 48–60% [34, 35, 40]. The presence of mutton-fat keratic precipitates (Fig. 1A) and/or iris stromal nodules is observed in up to 46% of patients [39, 40]. 27% of patients with sarcoid uveitis present also with posterior synechiae [38]. Additional features of anterior sarcoid uveitis include trabecular meshwork nodules and tent-like anterior synechiae, which can be observed in 18% and 35% of patients respectively [39].

Although intermediate uveitis is not frequent, vitreous involvement is often observed with snowballs or string of pearls in 17–50% of patients [38, 39].

The most common manifestation of sarcoid-associated uveitis in the posterior segment is multifocal choroiditis (Fig. 1B) followed by retinal vascular sheathing/periphlebitis (Figs. 1C and 2A, B) and rarely choroidal or optic disc granuloma (Fig. 1D) (Table 3).

Children > 5 years

The available data concerning children is very limited. In Table 3 most recent and largest studies were included. Among the published data, in the last 12 years only three studies present each more than 5 pediatric patients with detailed description of ocular involvement in sarcoidosis.

The paucity of data allows only for preliminary conclusions. Granulomatous anterior uveitis is present in 23–31% of pediatric patients above 5 years old. One study indicates non-granulomatous anterior uveitis as more prevalent in children than granulomatous anterior uveitis [41]. Inflammation in the anterior segment is the most frequent manifestation (77%), followed by panuveitis [42] in the European population (France). However, in a multi-ethnic Asian population (Singapore) sarcoidosis-associated panuveitis is the most frequent (63%), followed by posterior uveitis [43]. As in adults, multifocal choroiditis and periphlebitis are the most prevalent forms of posterior segment involvement [41].

Children < 5 years

Multicenter studies on patients with Blau syndrome reported a 76–81% prevalence of ocular involvement (with bilateral disease in 96–97% of patients) [26, 31].

The typical ocular presentation in Blau syndrome is bilateral panuveitis observed in 43–85% of patients [26] (Table 3) (Fig. 3). Anterior uveitis occurred in 14–33% of patients. Intermediate and posterior uveitis, as predominant sites of inflammation, were not noticed. Some patients present with mutton-fat keratic precipitates [44] and some with nummular corneal infiltrates, white when new and active, almost transparent when inactive (Fig. 3A and B). Sarens et al. reported that chorioretinal disease, optic disc involvement and macular edema were observed at baseline in 39%, 29%, and 11% of patients respectively [26].

Available studies show that uveitis in Blau syndrome is resistant to anti-inflammatory treatment [26]. Despite treatment with local steroids and systemic immunosuppressive agents, Sarens et al. did not observe any statistically significant decrease in inflammation over a 3-year follow-up period [26]. Furthermore, in addition to posterior segment inflammation, complications related to anterior segment involvement led to significant ocular morbidity [26]. The authors of the study reported the prevalence of band keratopathy, posterior synechiae, and cataracts as 21%, 45% (Fig. 3C), and 55% respectively [26].

Differential diagnosis

Adults

Differential diagnosis depends largely on the uveitis presentation, especially the main site involved.

For the most typical presentation of sarcoidosis, bilateral granulomatous posterior/panuveitis (Table 3), the main differential diagnosis includes tuberculosis and syphilis.

Some posterior presentations of sarcoidosis can resemble Birdshot, APMPPE, recurrent VKH, sympathetic ophthalmia, intraocular lymphoma or tubulointerstitial nephritis and uveitis (TINU) syndrome [45].

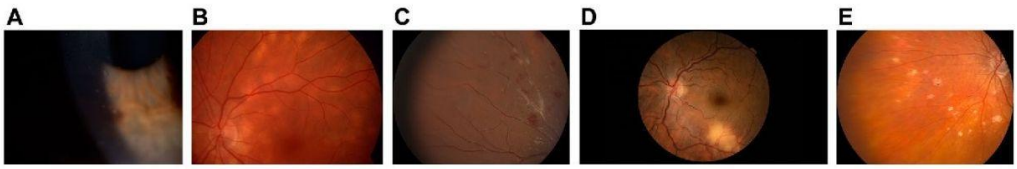

Fig. 1 Anterior and posterior uveitis findings in adult patients with definite or presumed ocular sarcoidosis. **A** Color photography of granulomatous keratic precipitates type mutton-fat in patient with definite ocular sarcoidosis proven by biopsy from lacrimal gland. **B** Color fundus photography of multifocal choroiditis in the left eye of a patient with definite ocular sarcoidosis proven by biopsy of cervical lymph nodes. **C** Fundus color photography showing periphlebitis with perivenous sheating and retinal hemorrages in a patient with presumed sarcoidosis. **D** Color fundus photography of choroidal granuloma in the left eye of a patient with definite ocular sarcoidosis proven by biopsy of intrathoracic lymph nodes and lung. **E** Fundus color photography showing peripheral chorioretinal lesions in a patient with presumed sarcoidosis

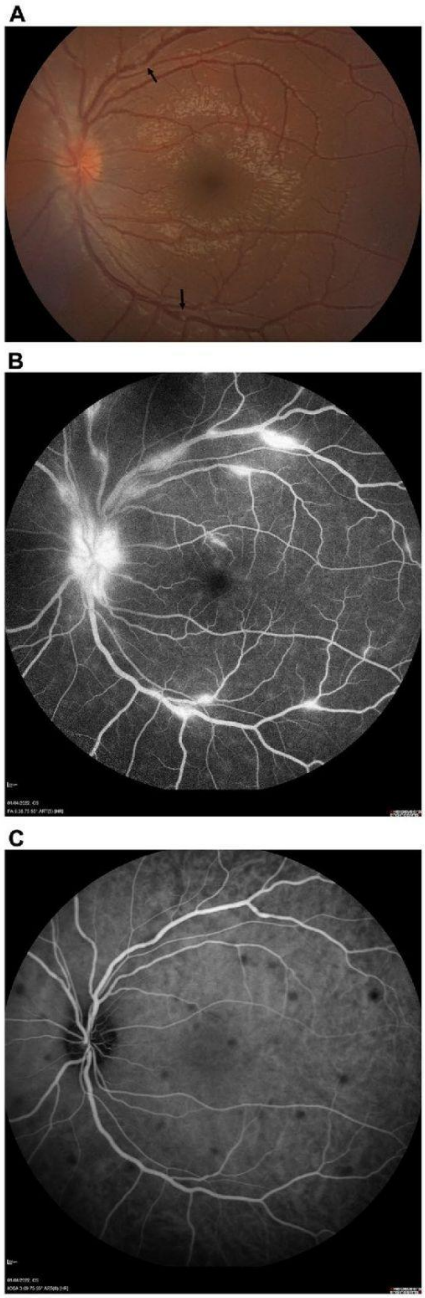

Fig. 2 Multimodal imaging of posterior uveitis in a patient with presumed ocular sarcoidosis. The vasculitis might normally barely be seen in that particular case and is strongly highlighted by the fluorescein angiogram. **A** Color fundus photography of the left eye showing hyperemic optic disc and barely visible vasculitis. Black arrows: barely visible vasculitis. **B** Fundus fluorescein angiography of the left eye showing hot disc and active vasculitis (**C**) Indocyanine green angiography of the left eye showing hypocyanescent spots

Other causes of granulomatous uveitis may also be included especially in cases of atypical presentations or in immunocompromised patients: toxoplasmosis, lyme, cat scratch disease, cryptococcosis (in immunocompromised patients) or even endophthalmitis [46].

Rarely sarcoid uveitis can have less typical presentations eg. unilateral (16%) [39] or non-granulomatous, which will then open up the differential diagnosis to include other conditions such as viral uveitis in case of unilateral granulomatous anterior uveitis.

Non-caseating granuloma remains a histopathological hallmark for sarcoidosis and is included in diagnostic criteria of definite ocular sarcoidosis [7] and sarcoidosis-associated uveitis [38]. However, caseation in the granulomas in sarcoidosis can also occur, which may complicate differential diagnosis with tuberculosis [47, 48],

Children > 5 years

The typical presentation of ocular sarcoidosis in this age group is bilateral anterior uveitis, which can be either granulomatous or non-granulomatous (Table 3.)

In case of anterior granulomatous as well as non-granulomatous uveitis, juvenile idiopathic arthritis (JIA) should be considered in the differential diagnosis. Indeed, although granulomatous uveitis in JIA really makes you wonder about the diagnosis, at least two papers mention that JIA-associated uveitis can be granulomatous [49, 50]. Furthermore, uveitis in sarcoidosis can also present as non-granulomatous anterior uveitis [41].

Also, TINU, although known mainly as anterior non-granulomatous uveitis, can present as granulomatous uveitis with subclinical choroidal involvement [45].

In case of bilateral granulomatous panuveitis/posterior uveitis, the main differential diagnosis is ocular tuberculosis.

In adolescents, as in adults, syphilis can be considered in differential diagnosis, although pure choroidal disease will not be syphilis.

Children < 5y

In Blau syndrome, a typical association of uveitis with arthritis and skin rash can guide the diagnosis. It is worth noticing that skin involvement and arthritis in EOS differ from the ones in JIA (previously called JRA) [3]. However, an BS/EOS patient without joint involvement has

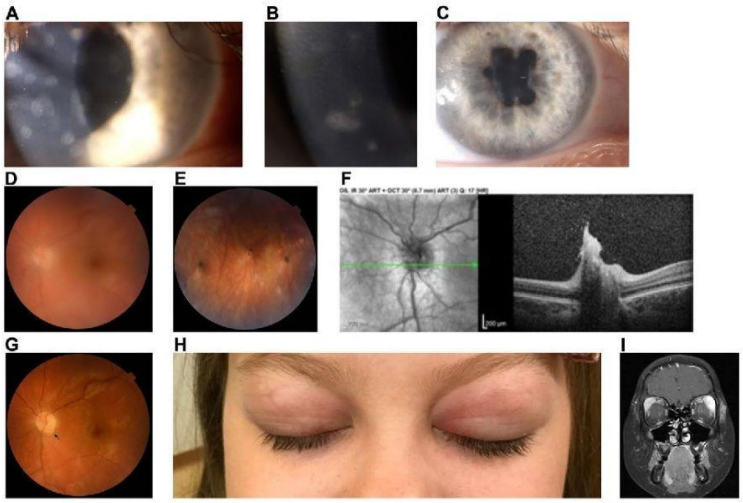

Fig. 3 A pediatric female patient with suspected Blau Syndrome with de novo NOD2 mutation was followed for 10 years (2–12 y.o.). During the course of the disease, bilateral corneal old and new active subepithelial nummular infiltrates were noted and visualized here on color photographs of the right eye (**A**) and (**B**). The patient also developed bilateral posterior synechiae visualized here on color photograph of the right eye (**C**). Her fundus examination revealed bilateral vitritis and multifocal choroiditis with active and inactive peripheral lesions visualized on the left eye fundus color photography (**D**, **E**). Left eye optic disc granuloma, which appeared during relapse on adalimumab, was documented on the OCT (**F**) and later on the fundus color photography (**G**) after vitritis resolution following treatment with infliximab. Several years later, during another relapse initiated by switching to anakinra treatment, the patient developed Mikulicz's syndrome with enlargement of bilateral lacrimal glands visualized on (**H**) color photography and on (**I**) brain MRI, coronal plane. The disease is now controlled with JAK-1 inhibitor baricitinib. Black arrow: optic disc granuloma

also been reported [51]. In Blau syndrome, differential diagnosis with JIA, Behçet's disease, ocular tuberculosis and ocular sarcoidosis was proposed [27, 28].

Diagnostic modalities

Diagnosis of ocular sarcoidosis recommended by IWOS, unless biopsy-proven, relies on various clinical and investigational criteria (Table 1). Most of the studies supporting these criteria or other potential sarcoidosis biomarkers included only adults. In clinical practice, in the absence of guidelines dedicated for children, the ocular sarcoidosis adults' criteria are used also for the pediatric population. However, literature on ocular sarcoidosis biomarkers in children is very scarce or missing. Here, we resume the available data on systemic imaging modalities and biomarkers for ocular sarcoidosis relating to adults as well as to children.

Chest X-ray and chest computed tomography (CT) scan

Adults

Chest X-ray and/or chest computed CT scan are the mainstay imaging examinations in the diagnosis of granulomatous uveitis. Their role is to detect pulmonary changes characteristic for pulmonary sarcoidosis or tuberculosis. The findings that can support sarcoidosis diagnosis are bilateral hilar lymphadenopathy (BHL) and/or parenchymal lung changes. High resolution CT or CT with contrast were also described in patients with ocular sarcoidosis [52, 53].

In diagnosing presumed or probable ocular sarcoidosis, BHL and parenchymal lung changes are the criteria recognized by IWOS 2019. Chest X-ray and CT differ not only in their sensitivity and specificity in detecting this sarcoidosis related pulmonary features but also in availability and cost of the examination.

Chest X-ray still plays a role and its biggest advantage is low cost and availability. Chest X-ray was shown to be the second, after tuberculin skin test, most contributory investigation among the first step's systematic tests in patients with uveitis. Chest CT was placed among the second step's systematic tests in patients with uveitis, and among these it was a second most often contributory investigation, after HLA-B27 [54].

Chest CT was shown in many studies to have higher sensitivity (with similar specificity) in detecting BHL than chest X-ray. Nevertheless, for diagnosis of ocular sarcoidosis, even chest radiograph with its sensitivity 68%

accompanied by specificity 96%, had high enough sensitivity to be considered as sufficient evidence of sarcoidosis among patients with uveitis [39]. In the same study, sensitivity of BHL on chest CT scan in patients with negative chest radiography results was 73% with high specificity 95%. Other recent studies showed lower chest X-ray BHL sensitivities in OS (57,1 -57,6%) (Burger 2021 57,1%, Niederer RL 2019, 57.6%) with 100% specificity. For comparison the chest CT scans BHL sensitivity for OS was higher and ranged from 85.7% [55] to 98.0% [35] with a specificity of 95.5%-100% [35, 55].

BHL, either by chest CT scans or chest X-ray, was found to be the most sensitive investigational finding in a study evaluating first IWOS ocular sarcoidosis criteria from 2009 [39].

Interestingly, BHL frequency is shown to significantly differ in an age-related manner in patients with uveitis associated with sarcoidosis. In Japan, older patients (> 65 years) with OS had BHL detectable in 52% and younger patients (≤ 65 years) in 78% of cases [56].

CT is also more sensitive in detecting parenchymal lung changes, another typical manifestation of pulmonary sarcoidosis [57]. Parenchymal lung changes consistent with sarcoidosis, as determined by pulmonologists or radiologists, is one of the revised IWOS criteria for suspected OS.

Parenchymal lung changes seen in chest CT scans can be seen both in sarcoidosis and tuberculosis. In one study, parenchymal involvement among patients with uveitis was observed more frequently in patients with tuberculosis than with presumed sarcoidosis [58]. Allegri et al. reported that among adult patients with definite and presumed ocular sarcoidosis, HRCT showed purely parenchymal involvement in 40% of patients and in 13,2% parenchymal involvement was combined with hilar and/or mediastinal lymphadenomegaly [40].

Children > 5 years and < 5 years

The sensitivity and specificity of various findings in chest imaging modalities in diagnosis of ocular sarcoidosis in children or in Blau syndrome is unknown.

However, in children of mean age 13 years with all types of sarcoidosis, bilateral hilar lymphadenopathy was shown to be the most frequent chest X-ray manifestation (78%) [1] Parenchymal involvement with or without BHL was less frequent (16%) [1]. Also, in contrast, enhanced chest CT in children with pulmonary sarcoidosis hilar/mediastinal lymphadenopathy was the most common finding [59].

In one study, among 13 children (median age 12 years old) with sarcoidosis-associated uveitis, none of the 3 patients with definite, biopsy-proven sarcoidosis in whom chest X-ray was performed, had chest X-ray consistent with sarcoidosis [41]. In the same study, 5 patients (39%) had X-ray consistent with sarcoidosis, and were classified as presumed or probable sarcoidosis following criteria established by authors [41].

In Blau syndrome, pulmonary involvement with interstitial lung disease (ILD) is rare but can occur [31, 60]. The studies do not specify presence of BHL in Blau syndrome, although generalized lymphadenopathy was observed in 52% of patients with Blau syndrome in one study [31].

Conclusion chest X-ray and chest computed tomography (CT) scan

Both chest X-ray and chest CT scan play an important role in detecting BHL and parenchymal lung changes that can support diagnosis of suspected ocular sarcoidosis in adults. They were proven to be the most sensitive investigations supporting diagnosis of OS in adults. In children, who have more often extrapulmonary sarcoidosis, there is no comparative data on chest X-ray and chest CT scan contribution to diagnosis of ocular sarcoidosis.

18F-fluorodeoxyglucose positron emission tomography imaging (FDG PET CT) and gallium-67 scintigraphy

Adults

18F-fluorodeoxyglucose positron emission tomography (FDG PET CT) and Gallium-67 scintigraphy are nuclear medicine imaging methods that use radiopharmaceuticals (FDG) or radioactive isotopes to detect increased inflammatory activity. 18F-fluorodeoxyglucose positron emission tomography indicates increased glucose uptake by macrophages and lymphocytes which indicates active sites of inflammation [61].

Although FDG PET CT has gained much more attention in the research in the last decade it is still not easily accessible everywhere, where Gallium-67 scintigraphy can still have its place. FDG PET CT advantages over Gallium-67 scintigraphy are increased contrast and resolution [62]. FDG PET CT was also shown to detect more pulmonary than non-pulmonary [63] or extra thoracic [64] sarcoidosis lesions than 67 Ga citrate scintigraphy.

Neither FDG PET CT nor Gallium-67 scintigraphy is recommended in standard systemic sarcoidosis workup. However, in cardiac sarcoidosis FDG PET CT is a second choice in a lack of cardiac MRI [61, 65].

Both Gallium-67 scintigraphy and 18F-fluorodeoxyglucose positron emission tomography are included in revised criteria for ocular sarcoidosis IWOS.

FDG PET CT's main advantage is that it is a single whole-body examination that can detect various extrapulmonary sites of sarcoidosis [66]. In FDG PET CT and in Gallium-67 scintigraphy lambda sign and panda signs are used as characteristic signs [67, 68] for diagnosis

of sarcoidosis. Moreover, other sites of FDG intake can also be helpful for diagnosis by indicating locations for accessible biopsies [66, 69] (Fig. 4A, B).

Opinions vary concerning the utility of FDG PET CT in ocular sarcoidosis in adults. Chauvelot et al., showed that FDG PET CT enabled the diagnosis of intraocular sarcoidosis even in patients with a normal CT scan [70]. However, Burger et al., did not observe additional benefit of FDG PET CT over chest CT in diagnosing suspected OS [55].

FDG PET CT's sensitivity and specificity for ocular sarcoidosis are respectively 85.7% and 95.5%. Positive and negative predictive values for FDG PET CT for ocular sarcoidosis were also calculated to be 85.7% and 95.5% [55].

As far as gallium-67 scintigraphy is concerned, there is considerably less data related to ocular sarcoidosis. The combination of elevated ACE and a positive 67GA scan increased the diagnostic specificity to 100% without affecting sensitivity (73%) in patients with suspected ocular sarcoidosis and normal chest radiographs [71].

Children > 5 years

FDG PET CT in pediatrics is a valuable diagnostic tool for fever of unknown origin (FUO) [72] leading to final diagnosis mostly of inflammatory (43%) or infectious (23%) origins, followed by malignancies (11%) [73]. FDG PET CT can also detect other granulomatous diseases such as intrathoracic and extra thoracic tuberculosis in children [74].

In children, a variety of strategies are possible to reduce the radiation dose while ensuring image quality [75]. These include CT attenuation correction and patient preparation.

Using ultra-low dose protocols in total body FDG PET CT is possible in children and should have special attention. Recently an ultra-low dose infection imaging using FDG PET CT was reported to be performed without sedation even in a newborn [76].

In diagnosing bilateral uveitis of undetermined origin in children, FDG PET/ ultra-low dose CT provided important information for final diagnosis in 30% patients [69]. In this study, for three pediatric patients the extra thoracic FDG intake showed biopsy accessible sites (cervical, axillary or inguinal lymph nodes) and led in 2 patients to biopsy proven, PET-CT guided ocular sarcoidosis (Fig. 4).

Children < 5 years

No studies were found on FDG PET CT in patients with Blau syndrome.

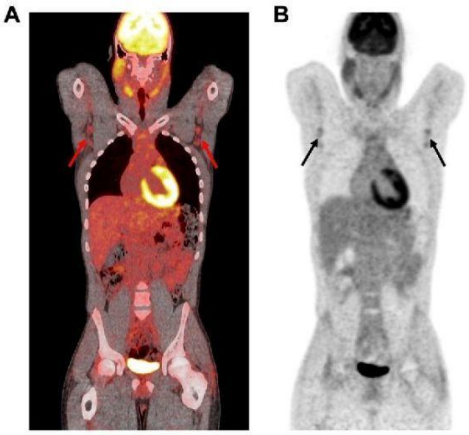

Fig. 4 Whole body 18F-FDG PET/ ultra low dose CT in a 11 year-old patient revealed abnormal 18F-FDG uptake not specific for an active granulomatous disease. A left axillary lymph node was biopsied and definite ocular sarcoidosis was diagnosed. **A** FDG PET/CT Fusion Coronal View. **B** FDG PET coronal view. Red and black arrows: Low hypermetabolic axillary bilateral lymph nodes

Conclusion 18F-fluorodeoxyglucose positron emission tomography imaging (FDG PET CT) and gallium-67 scintigraphy

FDG PET CT and Gallium-67 scintigraphy have their place in diagnosing OS and abnormal intake and these imaging modalities are among the revised 2019 IWOS criteria in adults. In children, who have more often extra thoracic sarcoidosis presentations, a single whole body FDG PET/ ultra-low CT could be useful for final diagnosis in indeterminate uveitis as it can indicate places accessible for biopsy that are out of scope of thoracic CT. Nowadays, many strategies can be used to reduce the radiation dose, including PET/CT with ultra-low dose CT protocol which should be of special consideration in children.

CD4/CD8 ratio (> 3.5) in bronchoalveolar lavage fluid

Adults

Systemic sarcoidosis diagnosis is supported by a CD4/CD8 ratio > 3.5 and lymphocytosis > 15% in bronchoalveolar lavage (BAL) fluid. However, BAL lymphocytosis alone is not specific for sarcoidosis as it is present in many other disorders, including hypersensitivity pneumonitis, nonspecific interstitial pneumonitis, or organizing pneumonia [77, 78]. Using CD4/CD8 ratio > 3.5 increases specificity for sarcoidosis to 93–96% but still does not have high sensitivity (53 to 59%).

Other authors cited by Kraaijvanger et al. showed a wider range of BAL CD4/CD8 ratio sensitivity (54—80%) with lower specificity (59—80%) [62].

In revised IWOS criteria, elevated CD4/CD8 ratio (> 3.5) in bronchoalveolar lavage fluid (BAL) was recognised as one of systemic investigations for diagnosing suspected ocular sarcoidosis. The sensitivity and specificity of CD4/CD8 ratio (> 3.5) in BAL in diagnosing ocular sarcoidosis was not reported in the literature. However, there are studies showing its importance in diagnosing ocular sarcoidosis even in patients with normal chest imaging [79] including high-resolution computed tomography (HRCT) [80]. Another study showed that positive BAL findings were present in 67.3% of adult patients with definite and presumed ocular sarcoidosis [40].

Children > 5 years and < 5 years

In children as well as in adults, BAL can be performed under sedation and topical anesthesia and using flexible bronchoscopy [81]. However, serial BAL is not routinely recommended in pulmonary sarcoidosis in children in whom BAL lymphocytosis does not correlate with disease activity and treatment response [3].

There is no data on the utility of CD4/CD8 ratio (> 3.5) in BAL in ocular sarcoidosis in children or in Blau Syndrome.

Conclusion CD4/CD8 ratio (> 3.5) in bronchoalveolar lavage fluid

In adults, testing CD4/CD8 ratio (> 3.5) in bronchoalveolar lavage fluid (BAL) can be considered in diagnosing suspected ocular sarcoidosis, as stated in revised IWOS criteria. However, its character needing at least sedation and topic anesthesia do not place it as a first-choice diagnostic examination. Furthermore, in children, it can be even less recommended due to lack of data regarding its utility in ocular sarcoidosis.

Serum Angiotensin Converting Enzyme (sACE)

Adults

ACE, studied in sarcoidosis since 1975, is the best-known serum biomarker in this disease. Serum ACE is an acid glycoprotein converting angiotensin I into angiotensin II. In the context of sarcoidosis ACE is produced by activated alveolar macrophages and correlates with granulomas burden [62]. Elevated sACE is also observed in ocular sarcoidosis, although no correlation was found between activity of sarcoidosis-associated uveitis and ACE [82].

Elevated sACE is one of the eight IWOS systemic investigations recommended as criteria for probable ocular sarcoidosis. However, it is not needed for definite or presumed ocular sarcoidosis (IWOS criteria 2019) nor for SUN Criteria for Sarcoidosis-Associated Uveitis) [7, 38]. sACE, as a sarcoidosis biomarker, is also mentioned among recent criteria of probable systemic sarcoidosis recommended by American Thoracic Society [65].

Elevated levels of sACE can be found not only in sarcoidosis but also in several other diseases, among which some can also have ocular manifestations eg. tuberculosis, leprosy, diabetes mellitus and histoplasmosis. sACE levels can be influenced by ACE inhibitors, corticosteroids use and cigarette smoking [33, 62, 83].

Notably, it was recently shown that genotype influences the sACE levels and some researchers advise to take ACE gene polymorphism into account while interpreting normal sACE levels for individuals. Taking into account the insertion (I)/deletion (D) polymorphism in the ACE gene can influence interpretation of 8,5% of measurements by either elevating or normalizing ACE values in patients with confirmed or suspected systemic sarcoidosis [84].

Sensitivity and specificity of sACE in ocular sarcoidosis varies among the studies. However, all recent studies are compatible with the fact that sACE has lower sensitivity than specificity, with sensitivity 48% and specificity 96% [50, 53, 83, 85, 86]. sACE had positive predictive value (PPV) of 44.9% and negative predictive value (NPV) 89.2% in diagnosing sarcoid uveitis [85].

To increase the sensitivity of sACE as a biomarker in ocular sarcoidosis, the combination with other biomarkers was tested leading to better sensitivity while keeping high specificity. The combinations of sACE and chest radiography, lymphopenia or sIL2R were studied and showed the following changes in sensitivity of combined examinations vs sensitivity of sACE alone. Combination of sACE and chest radiography showed increase of sensitivity (70% vs 30%) [82] as well as combination of sACE and sIL2R (75.0% vs 44.2%) [87]. Combination of sACE and lymphopenia showed an increase of sensitivity to 18.9% when compared with sensitivity of lymphopenia alone (15.3%) but showed a decrease in sensitivity when compared with sensitivity of sACE alone (45.8%) [85].

The standard cut off value of sACE for adults is 68 U/L. However, the optimal cutoff point for sACE levels in the population with uveitis was calculated to be 51 U/L [82]. The normal standard values may vary among the regions eg. in Japan standard sACE normal range is 7.0–25.0 IU/L [88] with recent proposition to change the cut-off value to 17.7 IU/L which would increase sensitivity of detecting sarcoidosis to 67.0% in Japan [88].

In a recent study of ocular sarcoidosis patients, the mean serum levels of ACE were 49.17 ± 29 IU/L versus 27.4 ± 15.34 IU/L in the control group of non-granulomatous (i.e., non-sarcoidosis) uveitis patients [50].

Children > 5 years and < 5 years

Although, there is no study that determines sensitivity or specificity of sACE in children with ocular sarcoidosis, this biomarker is used in pediatric clinical practice. From a study in Louisiana on childhood sarcoidosis ($n = 27$) we

know that ACE was elevated in 74% of sarcoidosis pediatric patients and among all patients in the study 77% children had uveitis [20]. Another study showed that among 13 children with probable, presumed, or definite sarcoidosis, 6 patients had elevated ACE levels [41].

In the 1980s, Baarsma and co found that ACE were age dependent [89]. In accordance with this finding, nowadays pediatric sACE normal values are (29–112 U/I) and they differ from those used for adults (20–70 U/I) [50].

In one study, all ($n=9$) pediatric patients diagnosed with sarcoidosis-associated uveitis had elevated ACE levels [42].

Conclusion serum Angiotensin Converting Enzyme (sACE)

sACE is a biomarker used in ocular and systemic sarcoidosis in adults and children. It is among the revised IWOS criteria for diagnosing suspected sarcoidosis. Its sensitivity in ocular sarcoidosis is not very high but it can be increased if combined with other diagnostic tests. The recent studies show that ACE gene polymorphism can affect the interpretation of sACE normal values. In children ACE normal values are higher than for adults. There are few studies reporting ACE in pediatric systemic or ocular sarcoidosis.

Serum lysozyme

Adults

Lysozyme is a bacteriolytic enzyme, a part of innate immunity. It degrades peptidoglycans that are mostly present in the walls of gram positive bacteria. In sarcoidosis, lysozyme is produced by monocyte macrophage systems and epithelioid cells, and is involved in granuloma formation [62].

In ocular sarcoidosis, elevated serum lysozyme has been among the diagnostic criteria indicated by IWOS since 2006 and in the reviewed 2019 IWOS criteria it is even stated as a criterion separate from ACE. However, in the systemic sarcoidosis criteria of American Thoracic Society from 2020 [65] lysozyme is not mentioned among the criteria.

The frequency of elevated lysozyme in sarcoidosis patients varies among the studies, 18,8% [90]—79,1% [91] and its level correlates with the number of organs involved [91]. In ocular sarcoidosis (biopsy-proven or BHL positive or suspected) lysozyme levels were shown to be elevated in 59,4% of patients [50]. Both lysozyme and ACE were elevated in 24,3% patients and ACE alone was elevated in only 5,4% of patients [50]. Another study showed that 61% of patients with ocular sarcoidosis (biopsy-proven or BHL positive) had elevated sACE or lysozyme or both [39].

Moreover, similarly to systemic sarcoidosis [91] in ocular sarcoidosis there is a correlation between serum lysozyme levels and disease burden [92]. In ocular sarcoidosis, lower lysozyme levels were observed in patients with biopsied sub-centimetric mediastinal lymph nodes in comparison to patients that had bigger (≥ 1 cm) lymph nodes [93].

Rarely lysozyme can be elevated in ocular infections but it was not elevated in autoimmune ocular disorders other than presumed ocular sarcoidosis. Serum lysozyme was found to be rarely elevated in presumed latent ocular tuberculosis or presumed latent syphilis [94]. However, it was not elevated in patients with ocular involvement of other autoimmune diseases such Behçet's disease and ankylosing spondylitis [94].

In ocular sarcoidosis, lysozyme has a sensitivity of 83.7% and a specificity of 90% [50], which contrasts with sACE's low specificity. The authors of this recent study concluded that lysozyme was found to be more useful than ACE as a laboratory test to support the diagnosis of ocular sarcoidosis [50].

Normal lysozyme values are 9.6–17.1 mg/L for all ages and mean serum lysozyme levels was 39.92 ± 55.5 mg/L in the ocular sarcoidosis group versus 10.5 ± 5.8 mg/L ($p \leq 0.0013$) in the control group ($n=30$) [50].

Children > 5 years and < 5 years

There are no studies stating lysozyme sensitivity and specificity in ocular sarcoidosis in children. In one study, among 13 children with probable, presumed, or definite sarcoidosis 5 patients had elevated lysozyme levels [41].

Serum lysozyme normal values in children are the same as for adults (9.6–17.1 mg/L) [50], although initially reported in the 80 s to be age dependent in ocular sarcoidosis [89].

Conclusion serum lysozyme

Serum lysozyme is among systemic investigations criteria for diagnosing probable OS according to revised IWOS. It has high sensitivity in diagnosing OS and some studies find it even more useful than sACE. It was shown to be elevated in some pediatric patients with OS.

Lymphopenia

Lymphopenia or lymphocytopenia is the blood lymphocyte count below an age-appropriate reference.

Lymphopenia can occur in many conditions and among them are: steroid therapy, autoimmune disorders like lupus erythematosus, infectious diseases like tuberculosis, AIDS and viral hepatitis. Significant lymphopenia (below 1000 cells/μL) was shown to be an independent predictor of sarcoidosis in new patients presenting with uveitis [95].

In IWOS 2019 criteria lymphopenia (< 1000 cells/μL) was added among the diagnostic criteria of ocular sarcoidosis, as the peripheral blood lymphocyte count is a simple, non-invasive test that is readily performed in patients with uveitis (IWOS 2019).

Lymphopenia was observed in 35.1% patients with ocular sarcoidosis in a German study [86] as well as in 26.8% patients with sarcoidosis-associated uveitis in the UK [95].

Although, different laboratories may have slightly different normal values, in many publications the normal lymphocyte count in adults is 1000 to 4800/mcL (1 to 4.8×10^9/L) and in children younger than 2 years 3000 to 9500/mcL (3 to 9.5×10^9/L) [96]. For children aged 6 years, lymphopenia is recognized if lymphocyte count is less than 1500/mcL (1.5×10^9/L). The range of normal lymphocyte values in teenagers (12-18y) approach adults' norms (1,1—4.5×10^9/L) [97] but should be verified with local laboratory values. Notably, some authors distinguish severe lymphopenia < 1000/mcL (< $1,0\times10^9$/L) and relative lymphopenia < 1500/mcL (< $1,5\times10^9$/L) [98].

Sensitivity of lymphopenia as a biomarker in diagnosing uveitis can vary and can depend on the choice of lymphocyte cut-off value. There are two recent studies that calculated sensitivity and specificity of lymphopenia in diagnosing sarcoid uveitis but the results differ. When considering the cut-off value of severe lymphopenia (< $1,0\times10^9$/L), the lymphopenia sensitivity in diagnosing sarcoid uveitis was low (15.3%) with high specificity (96.7%) [85]. However, in another study a cut-off value close to relative lymphopenia (< 1.47×10^9/L) gave higher sensitivity (75%) with lower specificity (77%) [82]. In the latter study, authors justify the choice of lymphocyte cut-off < 1.47×10^9/L with the highest Youden index, a marker of the performance of a diagnostic test, for diagnosing sarcoidosis-associated uveitis.

In children > 5 years and < 5 years

There is no study showing the frequency of lymphopenia in children with ocular sarcoidosis or with patients with Blau syndrome.

Conclusion lymphopenia

Lymphopenia is of importance in diagnosing suspected ocular sarcoidosis and can be detected by a simple and routinely done blood test. It is one of the criteria in revised IWOS for probable OS in adults. There is no data concerning the role of lymphopenia in diagnosing OS in children or in Blau syndrome.

Serum Soluble Interleukin 2 Receptor (sIL2R)

sIL2R is a circulating form of membrane receptor for IL2 which is shed from the surface of activated Th1 cells. Activated Th1 cells are involved in formation and perpetuation of granuloma [62] including those sarcoidosis-associated. Elevated sIL2R is not specific for sarcoidosis and can also be present in other granulomatous diseases, hematological malignancies, and various autoimmune disorders [62].

sIL2R has been studied as a potential biomarker in systemic sarcoidosis. However, its role is not yet well established and is not mentioned in the diagnostic guidelines for lung sarcoidosis [65]. sIL2R was neither included in the reviewed IWOS ocular sarcoidosis criteria as it was not used widely enough at the time [7]. However, there is accumulating data supporting the diagnostic value of sIL2R in ocular sarcoidosis.

sIL2R was found to be elevated in 69,2% [87]- 76.2% [86] patients with ocular sarcoidosis. sIL2R can be elevated also in 5.4% patients without sarcoid uveitis and in 16.7% of patients with primary intraocular lymphoma (PIOL) [87]. Another study found that serum sIL-2R levels can be elevated in patients with HLA-B27–associated and varicella-zoster virus–associated uveitis, however, with serum sIL2R levels lower than in sarcoidosis-associated uveitis [82].

Recently, several studies evaluating sensitivity and/or specificity of sIL2R in ocular sarcoidosis diagnosis have been published. Two of them showed high specificity of sIL2R in ocular sarcoidosis in the Japanese population [53, 87]. sIL2R sensitivity in ocular sarcoidosis diagnosis ranged from 69.2% [87] to 76.4% [53] and specificity from 93.0% [87] to 93.8% [53]. The third study showed sIL2R sensitivity of 70.6% in definite and presumed ocular sarcoidosis in the German population [86]. Interestingly, an earlier German study, considering not only definite, presumed, but also probable and possible OS, showed sIL2R sensitivity of 98% and specificity of 94% [99]. All these data suggest that sIL2R shows higher sensitivity and specificity in ocular sarcoidosis diagnosis than sACE.

Measurements of Youden index were performed in some recent studies in ocular sarcoidosis. Youden index of sIL2R (0.70) in Japanese population was higher than for other biomarkers in ocular sarcoidosis eg. ACE (0.35), KL-6 (0.26), and calcemia (0.07). The authors suggested that it can indicate superior utility of sIL2R among serum biomarkers in diagnosing ocular sarcoidosis [53]. Although the highest Youden index for sIL2R (0.45) found by the Dutch group was lower than by the Japanese group, the researchers conclusion was similar underlying the usefulness of sIL2R for diagnosing sarcoidosis in patients with uveitis [82]. Another earlier European German study, including not only definite, presumed but also probable and possible OS, calculated the Youden index of sIL2R to be 0,92 [99].

The optimal sIL2R cutoff value in detecting ocular sarcoidosis found by Dutch researchers was 4000 pg/mL [82]

and a Japanese group used sIL2R cutoff values > 543 U/mL [87]. Mean serum sIL-2R levels were 834.5 ± 486.7 U/mL in patients with sarcoid uveitis, which was higher than in patients with non-sarcoid uveitis 313.0 ± 127.7 U/mL [87]. Another group measured average serum sIL-2R levels in the presumed disease group to be 1325.2 U/mL [86].

Children > 5 years and < 5 years

There are no studies on sIL2 in sarcoidosis nor in ocular sarcoidosis in the pediatric population.

Conclusion Serum Soluble Interleukin 2 Receptor (sIL2R)

In conclusion, serum sIL2R is a promising biomarker in ocular sarcoidosis with many recent studies carried out in adult patients. Several independent groups showed that the sensitivity of serum sIL2R in diagnosing ocular sarcoidosis is higher than the sensitivity of sACE. However, there are no related studies in the pediatric population.

Other potential biomarkers tested in ocular sarcoidosis

Krebs von den Lungen-6 (KL-6)

Krebs von den Lungen-6 (KL-6), which is a mucin-like glycoprotein produced by pneumocytes or bronchiolar epithelial cells, was proposed as a marker of pulmonary cells injury or inflammation. Its elevated serum levels were found in sarcoidosis but also in idiopathic pulmonary fibrosis and other interstitial lung diseases [62]. KL-6 was tested in the Japanese population as a biomarker for ocular sarcoidosis in adults. It showed sensitivity of 26.3% with good specificity (96.2%)[53]. In the same study it showed lower sensitivity than sIL2R (76,4%) and ACE (37,7%) but higher than Ca (11,8%).

KL-6 was not tested in children with sarcoidosis nor with ocular sarcoidosis. There are several studies testing KL-6 in pediatric pulmonary diseases. One study showed KL-6 as a useful biomarker for pediatric patients with connective tissue disease accompanied by interstitial lung disease [100].

Hypercalcemia

Hypercalcemia occurs in up to 4% of the population in many health conditions, including sarcoidosis, tuberculosis and lymphomas. In systemic sarcoidosis it is present in 7–18% patients [77, 101], although in Japan it was observed even in 35% patients [90]. Hypercalcemia in sarcoidosis is a result of ectopic production of calcitriol 1,25(OH)2D3 by activated macrophages within granulomas [77].

For diagnosing ocular sarcoidosis in adults in Japan, elevated calcium (Ca) levels had rather low sensitivity (11.8%) with good specificity (95.1%)[53].

There are no studies concerning hypercalcemia in children with ocular sarcoidosis. One case report found hypercalcemia useful in diagnosing uncommon onset sarcoidosis in a 14-year-old child without ocular involvement [102].

Polyclonal antibody

Polyclonal antibody activity testing bases on an observation that there is a compensatory increase of immunoglobulins as a result of decrease of T cell activity in sarcoidosis. The serologies of four herpesviruses (EBV, CMV, HSV, VZV) were used to calculate the polyclonal activation ratio [50].

One study showed that polyclonal antibody testing has high sensitivity (70%) and specificity (90.4%) in ocular sarcoidosis [50].

There is no data concerning children with ocular sarcoidosis and polyclonal antibody activity.

CXCL9 and CXCL10

Several chemokines produced by monocyte-macrophage cell lineage were shown to be elevated in sarcoidosis and to play many different roles including T-cell attraction and promotion of Th1/Th17 differentiation [62].

In diagnosed or suspected ocular sarcoidosis, serum levels of both CXCL9 and CXCL10 were markedly elevated and correlated with ocular disease activity and ACE level [103]. Chemokines were also tested in aqueous humor in patients with uveitis and it was found that CXCL13 were significantly higher in granulomatous uveitis, including sarcoidosis [104].

There are no further studies concerning sensitivity or specificity of chemokines in ocular sarcoidosis neither in children nor in adults.

Liver enzymes

Liver enzymes are not included in the revised IWOS criteria for diagnosing ocular sarcoidosis, in contrast to previous criteria from 2009. In sarcoidosis liver involvement was shown to be present in 2.5–11.5% patients [66] or even up to 35% of patients [77]. However, in ocular sarcoidosis elevated hepatic enzymes were rarely present, only in 5% of patients [39].

B-cell activating factor (BAFF)

B-cell activating factor (BAFF) is a cytokine of the TNF family that plays a vital role in the growth and function of B cells [62]. Elevated BAFF levels are not specific for sarcoidosis and have also been found in other immunomodulatory diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [62].

One study has shown that in sarcoidosis patients elevated serum BAFF show no significant difference between patients with anterior uveitis and those without ocular involvement [105].

There are no further studies concerning sensitivity or specificity of serum BAFF in ocular sarcoidosis neither in children nor in adults.

Serum microRNA (miRNA)

MiRNAs are small noncoding RNAs that regulate gene expression at the post-transcriptional level and are among the circulating cell-free nucleic acids released into the serum/plasma by various tissues and cells [106]. MiRNAs were proposed as biomarkers for the diagnosis of non-infectious uveitis [107].

Very recently miRNA microarrays (GeneChip®) were used to investigate serum miRNA profiles in patients with ocular sarcoidosis and patients with intraocular inflammation that appears typical for patients diagnosed with ocular sarcoidosis, but in whom the results of laboratory testing do not fulfill the IWOS diagnostic criteria (suspected ocular sarcoidosis). The study demonstrated a high overlap of the differential expression of serum miRNAs in these two groups of patients [106].

Although it is only one, small and preliminary study that does not indicate sensitivity and specificity for ocular sarcoidosis diagnosis, it can open a way to establish diagnoses in idiopathic uveitis patients. There are no studies on serum miRNA in children with ocular sarcoidosis or BS.

Conclusion other potential biomarkers tested in ocular sarcoidosis

Among other biomarkers tested in ocular sarcoidosis such as KL-6, hypercalcemia, polyclonal antibody activity, chemokines,serum BAFF, and serum microRNA. The latter.

seems most promising, although further studies are needed. There is no data related to these biomarkers in pediatric patients with ocular sarcoidosis.

Chitotriosidase and other biomarkers tested in systemic sarcoidosis but not yet in ocular sarcoidosis

Biomarkers tested in pulmonary sarcoidosis and not yet in ocular sarcoidosis are: chitotriosidase, serum neuron-specific enolase (NSE), Serum Amyloid A (SAA), neopterin, YKL40, sCD16 and CCL18 [62, 108, 109]. Among them chitotriosidase is very promising and in some specialties now often used as a biomarker.

Chitotriosidase is a chitinase involved in defense against chitin-containing pathogens [110]. The enzyme has been found elevated in serum and bronchoalveolar lavage (BAL) of patients with sarcoidosis in comparison to patients with other interstitial lung diseases, pulmonary tuberculosis and healthy controls [111, 112]. In sarcoidosis patients, chitotriosidase showed higher sensitivity and specificity than other biomarkers, including angiotensin converting enzyme (ACE), lysozyme and soluble IL-2 receptor. It has been found increased in active sarcoidosis patients [108, 113–116].

Ocular biopsies

Adults

Ocular biopsies can be divided into intraocular biopsies including vitreous fluid and ocular adnexa biopsies such as conjunctival biopsy.

Intraocular biopsies are really performed because of its invasive character. However, it is worth noticing that the CD4/CD8 ratio in the vitreous fluid showed high sensitivity (100%) and specificity (96.3%) for the diagnosis of ocular sarcoidosis in one study [117]. Another multicenter, prospective study confirmed that vitreous CD4/CD8 or CD4+measurements are higher in ocular sarcoidosis than in other uveitis etiologies [118].

In very rare cases, choroidal or subretinal biopsies in 27-Gauge pars plana vitrectomies are performed [119]. This is limited to atypical, progressing and sight-threatening lesions where other diagnostic methods were inconclusive [120]. A new alternative to histological biopsy of the uvea for diagnosing ocular sarcoidosis is histological detection of epithelioid granuloma and epithelioid cells in liquid-based cytology from vitreous body specimens and in the cell block procedure from vitreous cell components in an intraocular irrigating solution [121].

Conjunctival biopsy is less invasive, however, not commonly used. Conjunctival biopsy may be positive in approximately 50% of patients with sarcoidosis [122]. The direct data on its sensitivity and specificity in patients with uveitis were not found. However, there is some data concerning conjunctival biopsies in patients with uveitis. One study on a group of 10 patients with ocular findings like those of multifocal choroiditis with panuveitis showed that non-directed conjunctival biopsy disclosed non-caseating granulomata in seven of them [123]. In another study, in patients with uveitis suspected to be secondary to sarcoidosis, directed biopsy of conjunctival follicles was found to be positive for sarcoidosis in up to 63% of patients [124].

Furthermore, several studies mention conditions for increased positive conjunctival biopsy yield in diagnosis of sarcoidosis. Spaide et al. reported that the conjunctival biopsy was more likely to be positive in patients with conjunctival follicles, ocular abnormalities consistent with sarcoidosis, and in patients with pulmonary infiltrates on chest X-ray [125]. To increase the positive yield of conjunctival biopsies it was also recommended to perform bilateral conjunctival biopsies from multiple levels of the tissue [122] or to use a multi-plane technique instead of standard sectioning technique [124].

Conjunctival biopsy is very interesting from a cost-effectiveness point of view. While positive results of

conjunctival biopsy were like mediastinoscopy, the cost of conjunctival biopsy was ten times lower.

Children > 5 and < 5 years

The data on conjunctival biopsies in children in sarcoidosis is limited to case reports. One case report presented a 10-year-old female patient with conjunctival deposits but with no other ocular or systemic complaints, in whom conjunctival biopsies proved systemic sarcoidosis [126]. Another case report showed noncaseating lipogranulomatous subconjunctival nodules as a novel presenting finding in Blau syndrome in the absence of uveitis [127].

In Blau syndrome, conjunctival biopsies proved conjunctival granulomas in 2 adults and one 10-year-old child [44].

Conclusion ocular biopsies

Although highly sensitive and specific for sarcoidosis, the CD4/CD8 ratio in the vitreous fluid, can rarely be performed in everyday clinics. Conjunctival biopsy is a minimal invasive and cost-effective examen that should not be forgotten especially in patients with suspected ocular sarcoidosis and conjunctival follicles.

Genetic testing

In case of the typical triad of Blau Syndrome (arthritis, rash, uveitis) genetic testing can be performed not only in children below 5 years of age but also in older patients. Although the median age at onset of eye involvement in Blau Syndrome is 5 years (range 0,5–48 years) [26] in studies the final diagnosis of Blau Syndrome was made even in the adults, sometimes proving a long diagnostic delay.

To diagnose Blau syndrome or EOS, confirmation of mutation in NOD2 gene is needed and genetic counseling for patients is recommended. Traditionally, Blau syndrome is recognised if there is a family history of the disease and EOS if the mutation is sporadic [21]. However, authors of some recent publications [26–29] use the name of Blau Syndrome for both familial and sporadic mutations.

Mutations that are most frequently present in Blau Syndrome are R334W and R334Q [21, 26] and several more mutations have been identified in recent years [26, 29, 51, 128, 129]. Mutations in Blau Syndrome are autosomal dominant, gain of function mutations.

Diagnosing ocular sarcoidosis with onset in adulthood does not need genetic testing and is based on international criteria (Tables 1 and 2) [7, 38].

The diagnostic criteria for ocular sarcoidosis in children are not yet clearly stated.

Of interest, single nucleotide polymorphisms (SNPs) in HLA and non-HLA genes are known to be associated with ocular sarcoidosis. HLA-DRB1*04:01 is known to be associated with OS in European-Americans [130]. Variants of several non-HLA genes were also shown to be associated with increased risk of sarcoidosis-associated uveitis or OS: RAB23, ANXA11 [131] and MAGI1 [130], CHF [132], HSP-70/Hom [133], IL23R gene [134].

Conclusions

In this article, we review the clinical manifestations, differential diagnosis and diagnostic modalities of sarcoidosis-associated uveitis/ocular sarcoidosis in adults and children. We also refer to Blau Syndrome and Early Onset Sarcoidosis, in which uveitis typically starts in children under 5 years of age.

Clinical features of sarcoidosis-associated uveitis (SUN criteria) or ocular sarcoidosis (revised IWOS criteria) are well studied in adults but data concerning children older than 5 years is sparse.

In adults and children over 5 years of age ocular sarcoidosis is typically bilateral with panuveitis or anterior uveitis as a predominant site of inflammation depending on the study. Panuveitis is more frequent in Asian populations and most common in BS/EOS. In adults, granulomatous uveitis was observed in about half of the patients, often with mutton-fat keratic precipitates. In children over 5 years old it is possible that non-granulomatous uveitis is more frequent. In all age groups, multifocal choroiditis is the most frequent posterior presentation, followed by periphlebitis. In BS/EOS posterior synechiae and peripapillary nodules are more common than in other forms of sarcoidosis.

Differential diagnosis should exclude especially ocular tuberculosis and syphilis. In children ocular sarcoidosis should be differentiated with JIA-associated uveitis and TINU.

There are many diagnostic modalities supporting the diagnosis of ocular sarcoidosis but none of them is ideal or self-sufficient. Definite ocular sarcoidosis diagnosis can be stated only in case of biopsy proven lesions with compatible ocular involvement. For presumed and probable ocular sarcoidosis diagnosis performing systemic imaging or checking for serum biomarkers is needed.

If biopsy is not possible, bilateral hilar lymphadenopathy (BHL) is the next most important test. CT has higher sensitivity than chest X-ray in detecting BHL in adults. Serum ACE and lysozyme are well documented as ocular sarcoidosis biomarkers. Availability of lymphopenia is its major advantage although its sensitivity is not high. There are several very promising studies on sIL2R as an ocular sarcoidosis biomarker showing its higher sensitivity even

than ACE. In some patients, conjunctival biopsies or vitreous biopsies can be considered.

There is very little data concerning the utility of diagnostic tests in ocular sarcoidosis in children, therefore a detailed comparison with adults is not possible. In contrast to adults, in children, extrapulmonary sarcoidosis is more frequent. Therefore, searching for biopsy accessible peripheral lymph nodes by the means of FDG PET/CT (with ultra-low CT protocol) could be an interesting option especially in children with bilateral uveitis with negative chest imaging. Blau Syndrome and EOS are, respectively, the familial and sporadic forms of the same monogenic autoinflammatory disease that needs genetic testing to be confirmed. A search for NOD2 gene mutation should be considered if a typical triad of arthritis, rash, uveitis is present.

Abbreviations

IWOS	International Workshop on Ocular Sarcoidosis
SUN	Standardization of Uveitis Nomenclature
BS	Blau syndrome
EOS	Early-onset sarcoidosis
CT	Computed tomography
FDG PET-CT	18F-fluorodeoxyglucose positron emission tomography - computed tomography
NOD2	Nucleotide-binding oligomerization domain-containing protein 2
ACE	Angiotensin converting enzyme
IL2R	Soluble interleukin 2 receptor
CARD15	Caspase recruitment domain-containing protein 15
APMPPE	Acute posterior multifocal placoid pigment epitheliopathy
VKH	Vogt-Koyanagi-Harada
TINU	Tubulointerstitial nephritis and uveitis
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
BHL	Bilateral hilar lymphadenopathy
HLA-B27	Human leukocyte antigen
OS	Ocular sarcoidosis
ILD	Interstitial lung disease
MRI	Magnetic resonance imaging
CD4/CD8	Clusters of differentiation 4/ clusters of differentiation 8
BAL	Bronchoalveolar lavage
HRCT	High-resolution computed tomography
sACE	Serum angiotensin converting enzyme
PPV	Positive predictive value
NPV	Negative predictive value
PIOL	Primary intraocular lymphoma
KL-6	Krebs von den Lungen-6
CXCL9	C-X-C motif chemokine ligand 9
BAFF	B-cell activating factor
TNF	Tumor necrosis factor
miRNA	MicroRNA

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M.B. and J.S. wrote the manuscript with support from F.W., J.H. and C.P.. F.W., J.S. and M.B conceived the original idea. F.W. supervised the project. M.B. gathered, analyzed the data for text and tables. F.W. and J.H. provided photographs. M.B. and J.H. provided figure descriptions. All authors provided critical feedback and helped shape the research, analysis and manuscript. F.W. and J.S. contributed equally to this work.

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Publisher's Note

Podsumowanie i wnioski

Podsumowując, niniejsza rozprawa doktorska dotyczy współczesnych metod diagnostycznych w zapaleniach błony naczyniowej. Zaprezentowane badania eksperymentalne pokazują mechanizmy związane z zapaleniem błony naczyniowej, które mogą zostać potencjalnie wykorzystane w diagnostyce autoimmunologicznego zapalenia błony naczyniowej. Wyniki badań klinicznych wykazały z kolei przydatność FDG PET CT w diagnostyce pediatrycznych zapaleń błony naczyniowej, które wstępnie zostały zaklasyfikowane jako idiopatyczne. Ponadto, badania płynu-mózgowo rdzeniowego u pacjentów z kiłą oczną pokazały częste zajęcie ośrodkowego układu nerwowego i wskazują na konieczność leczenia według schematów opracowanych dla kiły ośrodkowego układu nerwowego. Ostatnia publikacja wskazuje, że metody diagnostyczne w sarkoidozie ocznej dynamicznie się rozwijają i dają nadzieję na coraz precyzyjniejsze znajdowanie etiologii zapaleń błony naczyniowej.

Najważniejsze wnioski:

- badanie eksperymentalne in vitro wykazało, że nadekspresja SOCS1 w komórkach RPE hamuje niektóre prozapalne szlaki związane ze stymulacją IFNy, które prowadzą do rozwoju zapalenia błony naczyniowej oka. Badanie ukazuje rolę SOCS1 w molekularnych mechanizmach autoimmunologicznego zapalenia błony naczyniowej i daje nadzieję, że nadekspresja SOCS1 może być nowym celem w leczeniu lub diagnostyce autoimmunologicznego zapalenia błony naczyniowej oka.

- diagnostyka obuocznego zapalenia błony naczyniowej u dzieci może być udoskonalona poprzez użycie FDG PET/ ultra low dose CT. Użycie FDG PET/ ultra low dose CT dostarczyło informacji umożliwiających rozpoznanie zapaleń błony naczyniowej w przebiegu sarkoidozy lub gruźlicy u ok. 30% pacjentów pediatrycznych ze wstępnym rozpoznaniem idiopatycznego, obuocznego zapalenia błony naczyniowej. FDG PET/ultra low dose CT może pomóc w postawieniu ostatecznej diagnozy poprzez patognomoniczny obraz aktywnej choroby ziarniniakowej i/lub wskazanie miejsca biopsji.

- pogłębiona diagnostyka wykorzystująca badanie płynu-mózgowo rdzeniowego u dorosłych pacjentów z kiłą oczną wykazała częste zajęcie ośrodkowego układu nerwowego (71%) i wskazuje na konieczność leczenia według schematów opracowanych dla kiły ośrodkowego układu nerwowego.
- W przeprowadzonym badaniu, objawy oczne były pierwszym zdiagnozowanym objawem kiły u 78% pacjentów. Ukazuje to wagę jaką może mieć badanie okulistyczne w diagnozowaniu kiły.

- zastosowanie nowoczesnych metod diagnostycznych poprawia skuteczność w diagnozowaniu zapalenia błony naczyniowej w przebiegu sarkoidozy.
- Badania obrazowe, takie jak CT czy HRCT mają większą czułość diagnostyczną w porównaniu z tradycyjną radiografią klatki piersiowej. FDG PET/ CT całego ciała pozwala na wykrycie aktywnej choroby ziarniniakowej oraz na zlokalizowanie powiększonych węzłów chłonnych dostępnych dla biopsji. Obok dobrze

przebadanych biomarkerów ACE i lizozymu, liczne badania ukazują kolejne potencjalne biomarkery na czele z sIL2R, który ma wyższą czułość niż ACE.

- U dzieci, młodzieży oraz dorosłych pacjentów, u których zapalenie błony naczyniowej rozpoczęło się w dzieciństwie z charakterystyczną triadą objawów (arthritis, rash, uveitis) wykonanie testów genetycznych może potwierdzić diagnozę BS/EOS.

Opinia Komisji Etycznej

Hôpital Universitaire
des Enfants Reine Fabiola

Universitair Kinderziekenhuis
Koningin Fabiola

www.huderf.be

ULB

Docteur M. BAZEWICZ
Unité d'Ophtalmologie

CHU SAINT-PIERRE

Bruxelles, le 3 avril 2020

Comité d'Ethique de l'Hôpital Universitaire des Enfants Reine Fabiola
Monsieur F. DEVAUX.
Président
Contact : Mme C. CLAPUYT
Secrétariat
Tél 02 477 22 66 (vendredi matin)
comite-ethique@huderf.be

C.C. : Au Président du Comité d'Ethique – CHU SAINT-PIERRE.
Docteur L. POSTOLACHE – Unité d'Ophtalmologie ; HUDERF

Chère Collègue,

Le Comité d'Ethique a, en sa séance du 31 mars 2020, examiné votre étude «L'utilité du FDG PET/CT dans le diagnostic d'uvéite granulomateuse chez les enfants ». Dossier CEH n° 37/20.

Liste des documents étudiés :
- Formulaire de soumission au CEH.
- Accord du responsable pour la conduite d'un projet au sein de l'HUDERF..
- Engagement relatif à l'accès aux données de santé des patients via le logiciel bDoc, MedView et tout autre système informatique de l'HUDERF.
- Dérogation à l'information et consentement ou assentiment éclairés
- Demande d'accès aux données d'un service/unité médicale, données des patients par un médecin ou assimilé.
- Protocole _CE_Brugmann_ corrected ; 1.
- CV.
- Table_empty.
- Accord Comité d'Ethique Principal – CHU Saint-Pierre

Accord du Comité d'Ethique.

Recevez, Chère Collègue, l'expression de mes salutations distinguées.

Monsieur F. DEVAUX
Président du CEH

Docteur J. GROSWASSER
Vice-Président

Avenue J. J. Crocqlaan 15
Bruxelles 1020 Brussel

Tłumaczenie

Uniwersytecki Szpital Pediatryczny Reine Fabiola

Doktor M.Bazewicz
Oddział Okulistyki
Uniwersyteckie Centrum Kliniczne Świętego Piotra (CHU Saint-Pierre)

Komisja Etyczna Uniwersyteckiego Szpitala Pediatrycznego Reine Fabiola
Monsieur F. DEVAUX.
Président
Contact : Mme C. CLAPUYT
Secrétariat
Tél 02477 22 66 (piątki rano)
com ite-ethiq ue@ huderf . be

Bruksela 03.04.2020

Szanowna Pani Doktor,

Komisja Etyczna na posiedzeniu w dniu 3 marca 2020 r. zapoznała się z Państwa badaniem „«Przydatność badania FDG PET/CT w diagnostyce ziarniniakowego zapalenia błony naczyniowej oka u dzieci» sygn. CEH 37120.

Lista zbadanych dokumentów.
- Formularz zgłoszeniowy do Komisji Etycznej.
- Zgoda menadżera na prowadzenie projektu w ramach HUDERF.
- Zobowiązanie do dostępu do danych dotyczących zdrowia pacjenta za pośrednictwem oprogramowania bDoc, MedView i dowolnym innym systemie komputerowym HUDERF.
- Zrzeczenie się informacji i świadomej zgody lub zgoda pacjenta
- Wniosek o udostępnienie danych oddziału/oddziału medycznego, danych pacjenta przez lekarza lub zasymilowane
- Protokół badania Protocole _CE_Brugmann_ corrected ; L
- CV (Curriculum vitae)
- Table_empty.
- Zgoda Głównej Komisji Etycznej - CHU Saint-Pierre

Komisja wyraża zgodę na przeprowadzenie badania.

Z wyrazami szacunku,

Pan F. Devaux
Przewodniczący Komisji Etycznej

Doktor J. Groswasser
Wiceprzewodniczący

CHU Saint-Pierre
UMC Sint-Pieter

COMITE LOCAL D'ETHIQUE HOSPITALIER
N° d'agréation : O.M. 007

AK/11-10-79/4075
P.4

CHU St. Pierre
Dr François WILLERMAIN
Ophtalmologie

Bruxelles, le 5 décembre 2019

Cher Confrère,

Le Comité d'Ethique du C.H.U. Saint-Pierre a examiné l'amendement au protocole de l'étude intitulée:

Etude rétrospective de patients atteints d'uvéites et kératites.

Cet amendement prolonge la durée de l'étude jusqu'au 6/09/2020 pour analyse des données récoltées au plus tard le 6/09/2019.

Le Comité d'Ethique rend un avis favorable sur cet amendement.

Nous vous prions d'agréer, Cher Confrère, l'expression de nos sentiments les meilleurs.

Dr E. STEVENS
Président du Comité d'Ethique

Tłumaczenie

Uniwersyteckie Centrum Kliniczne Świętego Piotra (CHU St Pierre)

LOKALNA SZPITALNA KOMISJA ETYCZNA
Numer: OM 007

Uniwersyteckie Centrum Kliniczne Świętego Piotra (CHU St Pierre)
Dr François Willermain
Okulistyka

Bruksela, 05.12.2019

Szanowny Panie Doktorze,

Komisja Etyczna w CHU Saint-Pierre rozpatrzyła poprawkę do protokołu badania pt.:

Retrospektywne badanie pacjentów z zapaleniem błony naczyniowej oka i zapaleniem rogówki.

Niniejsza nowelizacja wydłuża czas trwania badania do 6.09.2020 r. na analizę danych zebranych nie później niż w dniu 6.09.2019 r.

Komisja etyczna zatwierdza przedłużenie zgody.

W wyrazami szacunku,

Dr E. Stevens
Przewodniczący Komisji etycznej

C H U | U V C
B R U G M A N N

Réf. : CE 2023/52

Dr Bazewicz

cc : ct.ec@afmps.be

COMITE D'ETHIQUE HOSPITALIER
OM 026
Secrétariat
☎ *02 / 477.39.16*
🖷 *02 / 477.39.20*

E-mail comite.ethique@chu-brugmann.be

14/03/2023

Cher Dr Bazewicz,

Concerne:
Case report: Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis.

Le Comité d'Ethique Hospitalier du C.H.U. BRUGMANN a pris connaissance des documents relatifs à l'étude dont l'intitulé est repris sous rubrique.

Documents examinés :

Manuscrit
Document d'information et de consentement
Figures

Le comité d'éthique marque son accord.

Nous vous prions de croire en l'assurance de nos sentiments les meilleurs.

Docteur P. VERBANCK,
Secrétaire

Docteur J. VALSAMIS,
Président

Le Comité d'Ethique rappelle que les amendements substantiels et les notifications de sécurité, comme décrites dans la loi du 7 mai 2004, doivent lui être soumis

ULB - VUB
Association Hospitalière de Bruxelles et de Schaerbeek
Association dotée d'une personnalité juridique régie par la loi du 8 août 1926

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Centre Hospitalier Universitaire - Partenaire de la VUB et de l'ULB - Membre du réseau IRIS
Universitair Ziekenhuis - Partner van de VUB en ULB - Lid van IRIS

réseau iris

Tłumaczenie

Uniwersyteckie Centrum Kliniczne im. Brugmanna (CHU Brugmann)
Nr Ref. CE 2023/52

Szpitalna Komisja Etyczna
Nr: OM 026

Doktor Bazewicz
cc: ct.ec@afmps.be
14/03/2023

Szanowna Pani Doktor,

Dotyczy:
Opis przypadków klinicznych w ramach artykułu: Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis.

Szpitalna Komisja ds. Etyki C.H.U. BRUGMANN zapoznała się z dokumentami dotyczącymi badania, którego tytuł podano pod nagłówkiem.
Zbadane dokumenty:
- manuskrypt artykułu
- Dokument informacyjny i zgoda pacjentów
- Figury

Komisja wyraża zgodę.

Doctor P. Verbanck
Sekretarz

Doctor J. Valsamis
Przewodniczący

Oświadczenia wszystkich współautorów publikacji

PUBLIKACJA nr 1

Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines

Magdalena Bazewicz

Dafina Draganova

Maya Makhoul

Abdel Chtarto

Valerie Elmaleh

Liliane Tenenbaum

Laure Caspers

Catherine Bruyns

François Willermain

Bruksela, 22/10/2023
Brussels, 22/10/2023

Dafina Draganova

OŚWIADCZENIE

STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines.."

As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines..'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji i metodologii badań, przeprowadzeniu eksperymentów, przygotowaniu niektórych figur zawartych w pracy, analizie danych i formułowaniu wniosków.

I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in the development of the concept and research methodology, conducting experiments, preparation of some figures included in the work, analysing data and formulating conclusions.

Mój udział procentowy w przygotowaniu publikacji określam jako 25%.

I define my percentage share in the preparation of the publication as 25%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.

Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%,

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.

it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.

At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Dafina Draganova (podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Maya Makhoul

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines"
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w przeprowadzeniu części eksperymentów.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in conducting some experiments.

Mój udział procentowy w przygotowaniu publikacji określam jako 7%.
I define my percentage share in the preparation of the publication as 7%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%.

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

First name and the last name

Maya Makhoul

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Abdel Chtarto

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines"
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu metodologii badań i konstrukcji plazmidu SOCS1.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in the development of research methodology and SOCS1 plasmid construction.

Mój udział procentowy w przygotowaniu publikacji określam jako 6%.
I define my percentage share in the preparation of the publication as 6%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%,

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Abdel Chtarto

(podpis oświadczającego)
(signature of the declarant)

Nicea, 23/10/2023
Nice, 23/10/2023

Valérie Elmaleh

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines"
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w przeprowadzeniu części eksperymentów.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in conducting some experiments.

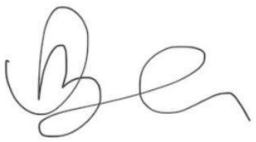
Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%,

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Valérie Elmaleh



(podpis oświadczającego)
(signature of the declarant)

Lozanna, 23/10/2023
Lausanne, 23/10/2023

Liliane Tenenbaum

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines"
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowywaniu metodologii badań i analizie danych.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in the development of the research methodology and analysing data.

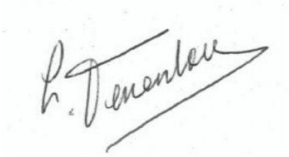
Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%,

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Liliane Tenenbaum



(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Laure Caspers

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines.."
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%,

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

L. Caspers **Laure Caspers**

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Catherine Bruyns

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines"
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji i metodologii badań, analizie danych i formułowaniu wniosków.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in the development of the concept and research methodology, analysing data and formulating conclusions..

Mój udział procentowy w przygotowaniu publikacji określam jako 10%.
I define my percentage share in the preparation of the publication as 10%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%,

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie figur zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Catherine Bruyns

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 22/10/2023
Brussels, 22/10/2023

François Willermain

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines.."
As a co-author of the work entitled 'Effect of SOCS1 overexpression on RPE cell activation by proinflammatory cytokines..'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji i metodologii badań, analizie danych, formułowaniu wniosków i przygotowaniu manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in development of the concept and research methodology, analysing data and formulating conclusions, manuscript preparation.

Mój udział procentowy w przygotowaniu publikacji określam jako 15%.
I define my percentage share in the preparation of the publication as 15%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 25%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 25%.

obejmował on: opracowanie koncepcji i metodologii badań, przeprowadzenie eksperymentów, przygotowanie rycin zawartych w pracy, analiza statystyczna wyników badań, analiza danych i sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, conducting experiments, preparation of figures included in the work, the statistical analysis of research results, analysing data and formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

(podpis oświadczającego)
(signature of the declarant)

PUBLIKACJA nr 2

Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis

Magdalena Bazewicz

Dorine Makhoul

Laurence Goffin

Jamella El Mouden

Lia Judice M Relvas

Laure Caspers

Dafina Draganova

Laurence Postelmans

Garcia Camilo & François Willermain

Bruksela, 23/10/2023
Brussels, 23/10/2023

Dorine Makhoul

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w analizie danych i rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in data analysing and manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Dorine Makhoul

(podpis oświadczającego)
(signature of the declarant)

Paryż, 23/10/2023
Paris, 23/10/2023

Jamella El Mouden

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w gromadzeniu i analizowaniu danych.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in data gathering and analysing.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%,
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Jamella El Mouden

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Laurence Goffin

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w analizie danych i rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in data analysing and manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Laurence Goffin

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Lia Judice M. Relvas

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w akceptacji całości manuskryptu (critical feedback).
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in critical feedback.

Mój udział procentowy w przygotowaniu publikacji określam jako 4 %.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%,
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Lia Judice M. Relvas

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Laure Caspers

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %.

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Laure Caspers

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 22/10/2023
Brussels, 22/10/2023

Dafina Draganova

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis,'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w akceptacji całości manuskryptu (critical feedback).
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in critical feedback.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %.

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

(podpis oświadczającego)
(signature of the declarant)

Dafina Draganova

Bruksela, 23/10/2023
Brussels, 23/10/2023

Laurence Postelmans

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 4 %.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %.

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Laurence Postelmans

Postelmans

(podpis oświadczającego)
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Bruksela, 22/10/2023
Brussels, 22/10/2023

Camilo Garcia

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled 'Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji, przygotowaniu figur PET-CT i przygotowaniu manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in the development of the concept, preparation of PET-CT figures and manuscript preparation.

Mój udział procentowy w przygotowaniu publikacji określam jako 11 %.
I define my percentage share in the preparation of the publication as 11%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Camilo Garcia MD
(podpis oświadczającego)
(signature of the declarant)

Bruksela, 22/10/2023
Brussels, 22/10/2023

François Willermain

OŚWIADCZENIE

STATEMENT

Jako współautor pracy pt. "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."
As a co-author of the work entitled "Clinical Utility of 18F-FDG PET/CT in the Work-up of Children with Uveitis."

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji i metodologii badań, formułowaniu wniosków i poprawianiu manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in development of the concept and research methodology, formulating conclusions, manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 11%.
I define my percentage share in the preparation of the publication as 11%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 50%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 50 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

(podpis oświadczającego)
(signature of the declarant)

PUBLIKACJA nr 3

Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis

Magdalena Bazewicz

Sophie Lhoir

Dorine Makhoul

Agnès Libois

Sigi Van den Wijngaert

Laure Caspers & François Willermain

Bruksela, 23/10/2023
Brussels, 23/10/2023

Sophie Lhoir

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis."
As a co-author of the work entitled 'Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w gromadzeniu danych.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participating in data gathering.

Mój udział procentowy w przygotowaniu publikacji określam jako 7 %.
I define my percentage share in the preparation of the publication as 7%.

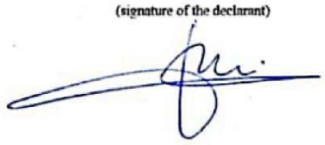
Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55 %.

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analyzing, preparation of tables, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Sophie Lhoir

(podpis oświadczającego)
(signature of the declarant)



Bruksela, 23/10/2023
Brussels, 23/10/2023

Dorine Makhoul

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis."
As a co-author of the work entitled 'Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w analizie danych i rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participating in data analyzing and manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.
I define my percentage share in the preparation of the publication as 5%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55 %.

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analyzing, preparation of tables, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Dorine Makhoul

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Agnes Libois

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis."
As a co-author of the work entitled 'Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w analizie danych.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participating in data analyzing.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
I define my percentage share in the preparation of the publication as 5%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analyzing, preparation of tables, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Agnes Libois

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 23/10/2023
Brussels, 23/10/2023

Sigi Van Den Wijngaert

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis."
As a co-author of the work entitled 'Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participating in manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 4%.
I define my percentage share in the preparation of the publication as 4%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%,
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel, sformułowanie wniosków, przygotowanie manuskryptu,
it included: development of the concept and research methodology, data gathering and analyzing, preparation of tables, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

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Bruksela, 23/10/2023
Brussels, 23/10/2023

Laure Caspers

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis."
As a co-author of the work entitled 'Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji, formułowaniu wniosków i rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participating in the development of the concept, formulating conclusions and manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 12%.
I define my percentage share in the preparation of the publication as 12%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55 %.

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analyzing, preparation of tables, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

L Caspers

Laure Caspers

(podpis oświadczającego)
(signature of the declarant)

Brukscla, 22/10/2023
Brussels, 22/10/2023

François Willermain

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis."
As a co-author of the work entitled 'Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis.'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji, formułowaniu wniosków i przygotowaniu manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participating in development of the concept, formulating conclusions and manuscript preparation.

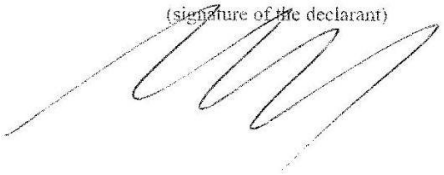
Mój udział procentowy w przygotowaniu publikacji określam jako 12 %.
I define my percentage share in the preparation of the publication as 12%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%,
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55 %,

obejmował on: opracowanie koncepcji i metodologii badań, zebranie i analiza danych, przygotowanie tabel, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and research methodology, data gathering and analyzing, preparation of tables, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

(podpis oświadczającego)
(signature of the declarant)



PUBLIKACJA nr 4

Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis

Magdalena Bazewicz

Jarmila Heissigerova

Carlos Pavesio

François Willermain & Janusz Skrzypecki

Praga, 23/10/2023
Prague, 23/10/2023

Jarmila Heissigerova

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis"
As a co-author of the work entitled 'Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w przygotowaniu figur i manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in figures and manuscript preparation.

Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.
I define my percentage share in the preparation of the publication as 10%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%,
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55%,

obejmował on: opracowanie koncepcji i metodologii, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Jarmila Heissigerova

(podpis oświadczającego)
(signature of the declarant)

Londyn, 23/10/2023
London, 23/10/2023

Carlos Pavesio

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis"
As a co-author of the work entitled 'Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
udział w rewizji manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 5%.
I define my percentage share in the preparation of the publication as 5%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55%.

obejmował on: opracowanie koncepcji i metodologii, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

Carlos Pavesio

(podpis oświadczającego)
(signature of the declarant)

Bruksela, 22/10/2023
Brussels, 22/10/2023

François Willermain

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis"
As a co-author of the work entitled 'Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji, formułowaniu wniosków i poprawianiu manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in development of the concept, formulating conclusions and manuscript corrections.

Mój udział procentowy w przygotowaniu publikacji określam jako 15%.
I define my percentage share in the preparation of the publication as 15%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55%.

obejmował on: opracowanie koncepcji i metodologii, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
it included: development of the concept and methodology, data gathering and analysing, preparation of tables and figures, formulating conclusions, manuscript preparation.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Bazewicz.
At the same time, I consent to the use of the above-mentioned work as part of the doctoral dissertation of doctor Magdalena Bazewicz.

(podpis oświadczającego)
(signature of the declarant)

Warszawa, 24/10/2023
Warsaw, 24/10/2023

Janusz Skrzypecki

OŚWIADCZENIE
STATEMENT

Jako współautor pracy pt. "Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis"
As a co-author of the work entitled 'Ocular sarcoidosis in adults and children: update on clinical manifestation and diagnosis'

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
współudział w opracowaniu koncepcji i przygotowaniu manuskryptu.
I declare that my own substantive contribution in the preparation, conduct and development of research and the presentation of the work in the form of a publication is:
participation in the development of the concept, manuscript preparation.

Mój udział procentowy w przygotowaniu publikacji określam jako 15%.
I define my percentage share in the preparation of the publication as 15%.

Wkład lek. Magdaleny Bazewicz w powstawanie publikacji określam jako 55%.
Contribution of doctor Magdalena Bazewicz in the creation of the publication I define as 55%,

obejmował on: opracowanie koncepcji i metodologii, zebranie i analiza danych, przygotowanie tabel i figur, sformułowanie wniosków, przygotowanie manuskryptu.
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