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IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Klinika i Katedra Okulistyki

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Zmiany w narządzie wzroku w przebiegu układowych zapaleń naczyń

ROZPRAWA DOKTORSKA

Cykl publikacji powiązanych tematycznie

PROMOTOR:

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SPIS TREŚCI

1. WYKAZ PRAC STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

Publikacja 1 (P1)

Szydełko-Paśko Urszula, Przeździecka-Dołyk Joanna, Kręcicka Julia, Małecki Rafał, Misiuk-Hojło Marta, Turno-Kręcicka Anna. Arteritic anterior ischemic optic neuropathy in the course of giant cell arteritis after COVID-19, American Journal of Case Reports, The, 2022, vol. 23, art.e933471 [5 s.], DOI:10.12659/AJCR.933471

Współczynnik wpływu (IF): 1,2

Punktacja MEiN: 70

Publikacja 2 (P2)

Szydełko-Paśko Urszula, Przeździecka-Dołyk Joanna, Małecki Rafał, Szuba Andrzej, Misiuk-Hojło Marta. Ocular manifestations of Buerger's disease - a review of current knowledge, Clinical Ophthalmology, 2022, vol. 16, s. 851-860, DOI:10.2147/OPTH.S352608

Współczynnik wpływu (IF): 2,2

Punktacja MEiN: 100

Publikacja 3 (P3)

Szydełko-Paśko Urszula, Przeździecka-Dołyk Joanna, Nowak Łukasz, Małyszczak Artur, Misiuk-Hojło Marta. Ocular manifestations of Takayasu's arteritis - a case-based systematic review and meta-analysis, Journal of Clinical Medicine, 2023, vol. 12, nr 11, art.3745 [14 s.], DOI:10.3390/jcm12113745

Współczynnik wpływu (IF): 3,9

Punktacja MEiN: 140

Publikacja 4 (P4)

Szydełko-Paśko Urszula, Przeździecka-Dołyk Joanna, Dołyk Andrzej, Małyszczak Artur, Misiuk-Hojło Marta. Evaluation of choroidal and retinal features in patients with primary vasculitis—an original optical coherence tomography and optical coherence tomography angiography study, Journal of Clinical Medicine, 2023, vol. 12, nr 21, art.6827 [13 s.], DOI:10.3390/jcm12216827

Współczynnik wpływu (IF): 3,9

Punktacja MEiN: 140

Sumaryczny współczynnik wpływu (IF): 11,2

Sumaryczna punktacja MEiN: 450

2. WYKAZ SKRÓTÓW

AAION	przednia niedokrwienna neuropatia nerwu wzrokowego z zapaleniem tętnic (ang. arteritic anterior ischemic optic neuropathy)
ACR	Amerykańskie Kolegium Reumatologiczne (ang. American College of Rheumatology)
AION	przednia niedokrwienna neuropatia nerwu wzrokowego (ang. anterior ischemic optic neuropathy)
ANCA	przeciwciała przeciwko cytoplazmie neutrofilów (ang. antineutrophil cytoplasmic antibodies)
BCVA	najlepsza skorygowana ostrość wzroku (ang. best corrected visual acuity)
BRAO	zamknięcie gałęzi tętnicy środkowej siatkówki (ang. branch retinal artery occlusion)
cc	w korekcji (ang. with correction, łac. cum correctione)
CDR	współczynnik zagłębienie – tarcza (ang. cup to disk ratio)
cf	liczenie palców (ang. counting fingers)
CI	wskaźnik kolistości (ang. circularity index)
CRAO	zamknięcie tętnicy środkowej siatkówki (ang. central retinal artery occlusion)
CT	grubość naczyniówki (ang. choroidal thickness)
CVI	naczyniowy indeks naczyniówkowy (ang. choroidal vascularity index)
DM	cukrzyca (ang. diabetes mellitus)
ERG	elektroretinografia (ang. electroretinography)
EULAR	Europejski Sojusz Stowarzyszeń na rzecz Reumatologii (ang. The European Alliance of Associations for Rheumatology)
FA	angiografia fluoresceinowa (ang. fluorescein angiography)
FAZ	dołeczkowa strefa beznaczyniowa (np. foveal avascular zone)
GCA	olbrzymiokomórkowe zapalenie tętnic (ang. giant cell arteritis)
GPA	ziarniniakowatość z zapaleniem naczyń (ang. granulomatosis with polyangiitis)
HLAs	ludzkie antygeny leukocytarne (ang. human leukocyte antigens)

ICG	zieleń indocyjaninowa
ICGA	angiografia indocyjaninowa (ang. indocyanine green angiography)
IOP	ciśnienie wewnątrzgałkowe (ang. intraocular pressure)
LA	powierzchnia światła naczyń (ang. luminal area)
NAION	przednia niedokrwienna neuropatia nerwu wzrokowego bez zapalenia tętnic (ang. non-arteritic ischemic optic neuropathy)
NORD	Krajowa Organizacja ds. Rzadkich Chorób (ang. National Organization for Rare Diseases)
NTG	jaskra normalnego ciśnienia (normal tension glaucoma)
OCT	optyczna koherentna tomografia (ang. optical coherence tomography)
OCTA	angiografia optycznej koherentnej tomografii (angio-OCT, ang. optical coherence tomography angiography)
OD	prawe oko (ang. right eye, łac. oculus dexter)
OP	potencjały oscylacyjne (ang. oscillatory potentials)
OS	lewo oko (ang. left eye, łac. oculus sinister)
OU	oboje oczu (ang. both eyes, łac. oculi uterque)
PN	guzkowe zapalenie tętnic (ang. polyarteritis nodosa)
RAPD	względne uszkodzenie drogi dośrodkowej odruchu źrenicznego (ang. relative afference pupillary defect)
RT-PCR	reakcja łańcuchowa polimerazy z odwrotną transkrypcją (ang. reverse transcription polymerase chain reaction)
SD-OCT	spektralna optyczna koherentna tomografia (ang. spectral domain optical coherence tomography)
TA	choroba Takayasu (ang. Takayasu's arteritis)
VA	ostrość wzroku (ang. visual acuity)
VZV	wirus ospy wietrznej i półpaśca (ang. varicella zoster virus)

3. STRESZCZENIE W JĘZYKU POLSKIM

Rozprawa doktorska składa się z cyklu 4 artykułów opublikowanych w międzynarodowych czasopismach naukowych. Są to opis przypadku, przegląd literatury, przegląd systematyczny z metaanalizą i praca badawcza. Łączna punktacja prac wynosi: 11,2 IF oraz 450 punktów MEiN.

Wstęp

Układowe zapalenia naczyń stanowią heterogenną grupę chorób, których istotą jest proces zapalny skutkujący pogrubieniem ściany naczyń krwionośnych oraz ich zwężeniem. W rezultacie dochodzi do zmniejszenia ukrwienia tkanek dotkniętych chorobą. Proces zapalny może obejmować zarówno strefę wokół zmiany pierwotnej jak i obwodowe obszary i narządy. Układowe zapalenia naczyń można podzielić na podstawie wielkości zajętych naczyń (małe, średnie i duże), a także przyczyny stanu zapalnego (pierwotne – bez uchwytnej przyczyny i wtórne). Patogeneza postaci pierwotnej nie jest w pełni znana. Istotne wydają się czynniki genetyczne i autoimmunologiczne. Postawienie rozpoznania często stanowi wyzwanie i obejmuje przeprowadzenie licznych badań laboratoryjnych oraz obrazowych w celu wykluczenia innych chorób ogólnoustrojowych. Leczenie obejmuje stosowanie leków steroidowych i immunosupresyjnych, a także przeciwciał monoklonalnych. Zajęcie narządu wzroku w przebiegu pierwotnych układowych zapaleń naczyń zostało obszernie opisane. Pacjenci z wyżej wymienionymi chorobami nie są jednak objęci przesiewowymi badaniami okulistycznymi, mimo ryzyka wystąpienia poważnych powikłań okulistycznych wywołanych uogólnionym procesem zapalnym i niedokrwiennym.

Cel badań

Celem projektu było przeanalizowanie zarówno poprzez przegląd literatury jak i badanie obserwacyjne zajęcia narządu wzroku w przebiegu pierwotnych układowych zapaleń naczyń. Przeprowadzanie badań przesiewowych u pacjentów z tymi chorobami mogłoby ułatwić wykrycie wczesnych zmian patologicznych, tym samym przyspieszając proces diagnostyczny oraz wdrożenie odpowiedniego leczenia. Dodatkowo celem badania obserwacyjnego było opracowanie nieinwazyjnych badań, które dzięki niższym kosztom i krótszemu czasowi wykonywania w porównaniu do badań inwazyjnych, mogłyby zostać wykorzystane jako badania przesiewowe.

Materiały i metody

P1: Opis przypadku 69-letniej pacjentki z przednią niedokrwienną neuropatią nerwu wzrokowego z zapaleniem tętnic w przebiegu olbrzymiokomórkowego zapalenia tętnic po infekcji COVID-19

P2: Przegląd dostępnej literatury dotyczącej zajęcia narządu wzroku w przebiegu choroby Buergera

P3: Przegląd systematyczny i metaanaliza na temat zajęcia narządu wzroku w przebiegu choroby Takayasu

P4: Prospektywne, obserwacyjne badanie, do którego zakwalifikowano 41 pacjentów chorujących na następujące pierwotne układowe zapalenia naczyń: chorobę Takayasu, olbrzymiokomórkowe zapalenie tętnic, chorobę Buergera, ziarniniakowatość z zapaleniem naczyń i guzkowe zapalenie tętnic. Analizie poddano wyniki badań 78 oczu z grupy badanej oraz 88 oczu z grupy kontrolnej (44 zdrowych uczestników). Za pomocą OCT i angio-OCT oceniano parametry związane z siatkówką (powierzchnię i obwód FAZ, wskaźnik kolistości) oraz naczyniówką (grubość naczyniówki, naczyniowy indeks naczyniówkowy).

Wyniki

P1: Po analizie przypadku klinicznego stwierdzono, że infekcja COVID-19 może stanowić czynnik wyzwalający olbrzymiokomórkowe zapalenie tętnic wraz z powikłaniem w postaci przedniej niedokrwiennej neuropatii nerwu wzrokowego z zapaleniem tętnic.

P2: Przedstawiono wyniki przeglądu literatury w oparciu o 13 prac naukowych. Zajęcie narządu wzroku w przebiegu choroby Buergera opisano u 44 pacjentów. Do możliwych powikłań okulistycznych należą: przednia niedokrwienna neuropatia nerwu wzrokowego bez zapalenia tętnic, okluzyjne zapalenie naczyń siatkówki i zapalenie okołożylne, zapalenie żył tarczy nerwu wzrokowego, zamknięcie tętnicy środkowej siatkówki, zamknięcie gałęzi tętnicy środkowej siatkówki, jaskra normalnego ciśnienia, zapalenie błony naczyniowej, zanik naczyniówkowo-siatkówkowy, zapalenie siatkówki, zapalenie tarczy nerwu wzrokowego, zanik nerwu wzrokowego, zmiany

charakterystyczne dla retinopatii nadciśnieniowej. Mogą także występować nieprawidłowości w elektroretinografii.

P3: Przedstawiono wyniki analizy 106 prac naukowych. Zajęcie narządu wzroku w przebiegu choroby Takayasu dotyczyło 122 pacjentów. Średnia wieku pacjentów wynosiła 31,4, a stosunek kobiet do mężczyzn – 4,8:1. Zdecydowana większość była w wieku od 11 do 40 lat, ze szczytem w trzeciej dekadzie życia. Dominowały przypadki pochodzące z Azji. W ponad 74% przypadków zajęcie narządu wzroku wystąpiło przed rozpoznaniem choroby Takayasu. Do najczęściej występujących powikłań okulistycznych należały: niedokrwienie siatkówki, neuropatia nerwu wzrokowego, zaćma i zamknięcie naczyń tętniczych siatkówki. Glikokortykosteroidy w postaci doustnej, procedury naczyniowe oraz metotreksat stosowane były jako leczenie pierwszego rzutu. Pacjenci skarżyli się najczęściej na stopniowe pogorszenie widzenia, nagłe pogorszenie widzenia, ból oka, a także przemijające zaniewidzenie (łac. amaurosis fugax). Dominującą postacią zajęcia narządu wzroku u dzieci było niedokrwienie siatkówki i zapalenie błony naczyniowej.

P4: Zaprezentowano wyniki badań oceniających siatkówkę i naczyniówkę u pacjentów z 5 chorobami z kręgu układowych zapaleń naczyń. Średnia grubość naczyniówki w grupie badanej wynosiła 341 μm, a w grupie kontrolnej 262 μm. Średnia wartość naczyniowego indeksu naczyniówkowego wynosiła 49,6% w grupie badanej oraz 64,5% w grupie kontrolnej. W grupie badanej średnia powierzchnia FAZ wynosiła 0,34 mm^2 natomiast w grupie kontrolnej 0,26 mm^2. Średnia wartość obwodu FAZ również była wyższa w grupie badanej (2,18 mm vs. 1,89 mm). Średnia wartość wskaźnika kolistości wynosiła 0,86 dla grupy badanej i 0,87 w grupie kontrolnej.

Wnioski

1. W przebiegu układowych zapaleń naczyń może dojść do zajęcia wielu struktur narządu wzroku.
2. Konieczna jest współpraca między okulistami, angiologami i reumatologami ze względu na możliwość wystąpienia powikłań okulistycznych przed postawieniem rozpoznania choroby podstawowej.
3. Wprowadzenie przesiewowych badań okulistycznych oceniających naczyniówkę i siatkówkę u pacjentów z układowymi zapaleniami naczyń może

skutkować wykryciem patologicznych zmian zanim zostaną one zauważone przez pacjentów.

4. Naczyniowy indeks naczyniówkowy zdaje się szczególnie przydatny w ocenie naczyniówki ze względu na mniejszą podatność na wpływ innych czynników w porównaniu do grubości naczyniówki.
5. Konieczne jest szybkie rozpoznanie olbrzymiokomórkowego zapalenia tętnic aby uniknąć wystąpienia poważnych powikłań takich jak obuoczna utrata widzenia.
6. Choroba Buergera może nie mieć charakteru miejscowej waskulopatii, lecz być zaburzeniem ogólnoustrojowym i – podobnie jak inne układowe zapalenia naczyń – obejmować wiele narządów.
7. W przypadku młodych pacjentów z zaburzeniami w obrębie narządu wzroku, bez współistniejących chorób należy rozważyć chorobę Takayasu.

4. STRESZCZENIE W JĘZYKU ANGIELSKIM

The PhD dissertation consists of four publications: a case-report, a review of the literature, a systematic review with meta-analysis and an original study. The total impact factor and the MEiN score of the 4 articles equals 11.2 and 450 points respectively.

Introduction

Vasculitis is a term for a group of rare diseases in which an inflammation of the blood vessels develops. This results in thickening of the blood vessel wall, stenosis, and eventually reduction of blood flow to various tissues and organs. The pathological process may affect the area surrounding the lesion as well as peripheral areas and visceral organs. Vasculitis can be classified according to the size of the blood vessels affected by the inflammation (large, medium, or small vessel vasculitis) or the underlying cause of the disease — primary (with no certain cause) and secondary (to other diseases or drug-induced). The pathogenesis of primary vasculitis is not fully known. A combination of genetic and autoimmune factors is usually taken into account. The diagnostic process is often challenging and involves comprehensive examinations, including laboratory and imaging tests, to rule out other systemic diseases. The treatment of vasculitis typically involves the use of steroids and immunosuppressive drugs, with monoclonal antibodies also reported as beneficial. Ocular manifestations have been documented in various types of vasculitis. Although the association between primary vasculitis and ocular manifestations is well-known, routine ophthalmological examinations for patients with these diseases seem to be lacking, despite the potential for systemic inflammation and ischemia to lead to severe ophthalmic complications. To ensure holistic care together with the co-authors we aimed to investigate the involvement of the eye in the course of primary vasculitis.

Aim:

The aim of the research project was to emphasize the involvement of various structures of the eye in the course of vasculitis. Conducting screenings for patients with those diseases may be beneficial in detecting early abnormalities and accelerating the administration of appropriate treatment. The objective of the original study was to use non-invasive methods, which would not be time- and cost-consuming, yet would be

helpful in routine tests. The goal of conducting such examinations is to detect ocular complications of the disease, even before the patients notice any symptoms.

Materials and methods:

P1: Case report of arteritic anterior ischemic optic neuropathy in the course of giant cell arteritis after COVID-19 in a 69-year old woman

P2: Review of available literature data on the topic of ocular manifestations of Buerger's disease.

P3: Systematic review and metaanalysis of available literature on ocular manifestations of Takayasu's arteritis.

P4: A prospective and observational study was conducted in 41 patients with 5 types of primary vasculitis: TA, GCA, Buerger's disease, GPA and PN. A total of 78 eyes were included in the study group. In addition, 44 healthy individuals were enrolled in the control group for comparison (88 eyes). The retina and the choroid were assessed with the use of OCT and OCTA. The following parameters were measured: choroidal thickness, choroidal vascularity index, area and perimeter of FAZ as well as circularity index.

Results:

P1: The case analysis led us to conclude that SARS-CoV-2 infection might be a possible risk factor for the onset of giant cell arteritis and its ocular manifestation, such as arteritic anterior ischemic optic neuropathy.

P2: 13 articles concerning 44 patients with ocular manifestations of Buerger's disease were analyzed. Those patients may develop: non-arteritic anterior ischemic optic neuropathy, occlusive retinal vasculitis and periphlebitis, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, normal tension glaucoma, uveitis, chorioretinal atrophy, retinitis, papillitis, optic atrophy, changes typical for hypertensive retinopathy. Additionally, the abnormalities in electroretinography might be present.

P3: 106 articles concerning 122 patients with ocular manifestations of Takayasu's arteritis were analyzed. The mean age of those patients was 31.4 years, with a female-

to-male ratio of 4.8:1. The vast majority were aged between 11 and 40 with the peak in the third decade. Most patients were from Asia. In over 74% of cases, the ocular manifestations preceded the diagnosis of TA. The most common eye disorder accompanying the disease was retinal ischemia, followed by optic neuropathy, cataract and retinal artery occlusion. Systemic steroid therapy, vascular procedures, and methotrexate were predominantly used as primary treatments for TA. Patients mostly complained of gradual vision acuity loss, sudden vision acuity loss, ocular pain and amaurosis fugax. Children (under the age of 18) presented mainly with retinal ischemia and uveitis.

P4: The findings of examinations evaluating the choroid and retina in patients with 5 diseases representing primary vasculitis were presented. The mean choroidal thickness in the study group equaled 341 μm, whereas in the control group, it measured 262 μm. Regarding central choroidal vascularity index, the mean value in our study group was 49.6%, compared to 64.5% in the control group. In the study group, the mean FAZ area equaled 0.34 mm^2, while in the control group it measured 0.26 mm^2. Similarly, the mean FAZ perimeter was higher in the study group (2.18 mm vs. 1.89 mm). Regarding the circularity index, the mean values were 0.86 for the study group and 0.87 for the control group.

Conclusions:

1. Vasculitis is a group of diseases affecting various structures of the eyes.
2. The multidisciplinary cooperation between ophthalmologists, angiologists, and rheumatologists is crucial, as eye disorders may be the first sign of vasculitis.
3. Conducting routine ophthalmological examinations in patients diagnosed with vasculitis with the assessment of the retina and choroid could be beneficial, as they may detect pathological changes before any ocular symptoms alarm the patients.
4. Choroidal vascularity index seems to be especially promising for choroidal evaluation, as it appears to be less influenced by various factors compared to choroidal thickness.
5. The diagnosis of giant cell arteritis should be made as soon as possible to avoid serious complications of the disease, such as bilateral vision loss.
6. Buerger's disease may not be localized vasculopathy but a systemic disease and

- like other vasculitis – it may affect various organs and systems.

7. In the case of young patients presenting with ocular disorders and without any known comorbidities Takayasu's arteritis should be considered as a possible diagnosis.

5. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

Rozprawa doktorska składa się z cyklu 4 artykułów opublikowanych w międzynarodowych czasopismach naukowych. Są to opis przypadku, przegląd literatury, przegląd systematyczny z metaanalizą i praca badawcza. Łączna punktacja prac wynosi: 11,2 IF oraz 450 punktów MEiN.

5.1 Wstęp

Układowe zapalenia naczyń stanowią heterogenną grupę chorób, których istotą jest proces zapalny skutkujący pogrubieniem ściany naczyń krwionośnych oraz ich zwężeniem. W rezultacie dochodzi do zmniejszenia ukrwienia tkanek dotkniętych chorobą [1, 2]. Proces zapalny może obejmować zarówno strefę wokół zmiany pierwotnej jak i obwodowe obszary i narządy [3]. Układowe zapalenia naczyń można podzielić na podstawie wielkości zajętych naczyń na małe, średnie i duże. Można także dokonać podziału ze względu na przyczynę stanu zapalnego na pierwotne (bez uchwytnej przyczyny) i wtórne [3]. Patogeneza postaci pierwotnej nie jest w pełni znana. Istotne wydają się czynniki genetyczne i autoimmunologiczne [1, 2]. Postawienie rozpoznania często stanowi wyzwanie i obejmuje przeprowadzenie licznych badań laboratoryjnych oraz obrazowych w celu wykluczenia innych chorób ogólnoustrojowych [4]. Leczenie obejmuje stosowanie leków steroidowych i immunosupresyjnych, a także przeciwciał monoklonalnych [3, 4]. Zajęcie narządu wzroku w przebiegu układowych zapaleń naczyń zostało opisane w licznych pracach naukowych. Turk i współautorzy opublikowali obszerny przegląd systematyczny z metaanalizą dotyczący rodzaju i częstości powikłań okulistycznych u pacjentów z reumatoidalnym zapaleniem stawów, chorobami tkanki łącznej i układowymi zapaleniami naczyń [5]. Autorzy podają, że w przypadku olbrzymiokomórkowego zapalenia tętnic do zajęcia narządu wzroku dochodzi w 27% przypadków, zaś w ziarniniakowatości z zapaleniem naczyń w 26%. Częstość powikłań okulistycznych lub neuro-okulistycznych w guzkowym zapaleniu tętnic oscyluje między 10% a 20%, natomiast w przypadku choroby Kawasaki sięga aż 90% [6, 7]. Pacjenci z układowymi zapaleniami naczyń nie są jednak objęci przesiewowymi badaniami okulistycznymi, mimo ryzyka wystąpienia poważnych powikłań okulistycznych wywołanych uogólnionym procesem zapalnym i niedokrwiennym. W przypadku cukrzycy przeprowadzanie kontrolnych badań okulistycznych stało się standardem postępowania

[8]. Celem badań przesiewowych byłoby wykrycie wczesnych powikłań choroby ogólnoustrojowej i wdrożenie odpowiedniego leczenia. W ostatnich latach angio-OCT stało się powszechnie wykonywanym badaniem ze względu na większy profil bezpieczeństwa w porównaniu z klasycznymi badaniami angiograficznymi, możliwość uzyskania danych jakościowych i ilościowych oraz krótki czas przeprowadzania badania [9]. Cechy te są szczególnie istotne w przypadku badań przesiewowych. Jednym z przydatnych parametrów w ocenie naczyniówki może być naczyniowy indeks naczyniówkowy, którego wartość można obliczyć na podstawie wyników angio-OCT. Everekliogłu ze współautorami oznaczyli wyżej wspomniany indeks u pacjentów z pierwotnym układowym zapaleniem naczyń w postaci choroby Behceta [10]. Stwierdzono, że niższe wartości występowały zarówno w przypadkach aktywnej jak i nieaktywnej formy choroby z zajęciem narządu wzroku w porównaniu z grupą kontrolną. Nie stwierdzono jednak różnic pomiędzy chorymi bez zajęcia oczu a grupą kontrolną. Wstępny przegląd dostępnej literatury pozwolił na zaplanowanie projektu dotyczącego zajęcia narządu wzroku w przebiegu układowych zapaleń naczyń.

5.2 Cel badań

Celem projektu było przeanalizowanie zarówno poprzez przegląd literatury jak i badanie obserwacyjne zajęcia narządu wzroku w przebiegu pierwotnych układowych zapaleń naczyń. Przeprowadzanie badań przesiewowych u pacjentów z tymi chorobami mogłoby ułatwić wykrycie wczesnych zmian patologicznych, tym samym przyspieszając proces diagnostyczny oraz wdrożenie odpowiedniego leczenia. Dodatkowo celem badania obserwacyjnego było opracowanie nieinwazyjnych badań, które dzięki niższym kosztom i krótszemu czasowi wykonywania w porównaniu do badań inwazyjnych, mogłyby zostać wykorzystane jako badania przesiewowe.

Cele szczegółowe:

1. Zwrócenie uwagi na COVID-19 jako potencjalny czynnik ryzyka wystąpienia przedniej niedokrwiennej neuropatii nerwu wzrokowego z zapaleniem tętnic w przebiegu olbrzymiokomórkowego zapalenia tętnic.
2. Przedstawienie aktualnego stanu wiedzy dotyczącego zajęcia narządu wzroku w przebiegu choroby Buergera.
3. Przedstawienie aktualnego stanu wiedzy na temat zajęcia narządu wzroku w chorobie Takayasu.

4. Ocena zajęcia siatkówki i naczyniówki w przebiegu następujących układowych zapaleń naczyń: choroby Takayasu, olbrzymiokomórkowego zapalenia tętnic, choroby Buergera, ziarniniakowatości z zapaleniem naczyń i guzkowego zapalenia tętnic.
5. Analiza przydatności badania OCT i angio-OCT w ocenie powikłań siatkówkowych i naczyniówkowych u pacjentów z układowymi zapaleniami naczyń.

5.3 Materiały i metody

W publikacji numer 1 zaprezentowano opis przypadku 69-letniej pacjentki z przednią niedokrwienną neuropatią nerwu wzrokowego z zapaleniem tętnic w przebiegu olbrzymiokomórkowego zapalenia tętnic po infekcji COVID-19. Opisano proces diagnostyczny, leczenie a także wynik leczenia.

W publikacji numer 2 dokonano przeglądu dostępnej literatury dotyczącej zajęcia narządu wzroku w przebiegu choroby Buergera. Wykorzystano dwie elektroniczne bazy danych: Medline i Web of Science. Użyto następującej kombinacji słów i wyrażeń kluczowych: (“Buerger’s disease” OR “thrombangitiis obliterans”) AND („ocular” OR “ocular manifestation” OR “eye” OR “ophthalmology”).

Publikacja numer 3 przedstawia wyniki przeglądu systematycznego i metaanalizy na temat zajęcia narządu wzroku w chorobie Takayasu. Przegląd przeprowadzono zgodnie z zaleceniami PRISMA. Przeszukano 3 elektroniczne bazy danych (PubMed, Scopus i Web of Science) z wykorzystaniem następujących słów i wyrażeń kluczowych: (“Takayasu’s arteritis” OR “pulseless disease” OR “aortoarteritis”) AND (“ocular” OR “ophthalmology” OR “eye” OR “ocular manifestations”). W pracy zaprezentowano częstość występowania poszczególnych powikłań okulistycznych, objawów zgłaszanych przez pacjentów, stosowanych terapii, a także podsumowano dane demograficzne.

W publikacji numer 4 przedstawiono wyniki prospektywnego, obserwacyjnego badania, do którego zakwalifikowano 41 pacjentów chorujących na następujące pierwotne układowe zapalenia naczyń: chorobę Takayasu (8 pacjentów), olbrzymiokomórkowe zapalenie tętnic (5 pacjentów), chorobę Buergera (11 pacjentów), ziarniniakowatość z zapaleniem naczyń (12 pacjentów) i guzkowe

zapalenie tętnic (5 pacjentów). Analizie poddano wyniki badań 78 oczu z grupy badanej oraz 88 oczu z grupy kontrolnej (44 zdrowych uczestników). U wszystkich pacjentów w grupie badanej występowała aktywna postać choroby wymagająca hospitalizacji i włączenia leczenia. Badania okulistyczne wykonywano przed włączeniem leczenia. Za pomocą OCT i angio-OCT oceniano parametry związane z siatkówką (powierzchnię i obwód FAZ, wskaźnik kolistości) oraz naczyniówką (grubość naczyniówki, naczyniowy indeks naczyniówkowy). Do przeprowadzenia analizy posłużył program MATLAB. Początkowo oznaczono powierzchnię i obwód FAZ za pomocą modelu aktywnego konturu (ang. active contour model), a następnie obliczono wskaźnik kolistości korzystając ze wzoru: $4\pi \times$ powierzchnia FAZ / obwód FAZ^2. Do obliczenia wartości grubości naczyniówki oraz powierzchni światła naczyń użyto metody progowania w celu uzyskania obrazu binarnego. Naczyniowy indeks naczyniówkowy obliczono na podstawie wzoru: powierzchnia światła naczyń / grubość naczyniówki. Analizę statystyczną przeprowadzono z użyciem oprogramowania MedCalc. Wyniki uznano za istotne statystycznie w przypadku wartości $p \leq 0{,}05$. W celu oceny różnić pomiędzy grupą badaną i grupą kontrolną zastosowano test Kruskala-Wallisa. Przeprowadzono również analizę post-hoc, by ocenić różnice pomiędzy poszczególnymi podgrupami grupy badanej.

5.4 Wyniki

Po analizie przypadku klinicznego zaprezentowanego w publikacji numer 1 stwierdzono, że infekcja COVID-19 może stanowić czynnik wyzwalający olbrzymiokomórkowe zapalenie tętnic wraz z powikłaniem w postaci przedniej niedokrwiennej neuropatii nerwu wzrokowego z zapaleniem tętnic. Włączenie leczenia nie poskutkowało poprawą ostrości widzenia w zajętym oku, zapobiegło jednak wystąpieniu powikłania w drugim oku.

W publikacji numer 2 przedstawiono wyniki przeglądu literatury w oparciu o 13 prac naukowych. Zajęcie narządu wzroku w przebiegu choroby Buergera opisano u 44 pacjentów. Do możliwych powikłań okulistycznych należą: przednia niedokrwienna neuropatia nerwu wzrokowego bez zapalenia tętnic, okluzyjne zapalenie naczyń siatkówki i zapalenie okołożylne, zapalenie żył tarczy nerwu wzrokowego, zamknięcie tętnicy środkowej siatkówki, zamknięcie gałęzi tętnicy środkowej siatkówki, jaskra normalnego ciśnienia, zapalenie błony naczyniowej, zanik siatkówki i naczyniówki,

zapalenie siatkówki, zapalenie tarczy nerwu wzrokowego, zanik nerwu wzrokowego, zmiany charakterystyczne dla retinopatii nadciśnieniowej. Mogą także występować nieprawidłowości w elektroretinografii. Do najczęstszych powikłań przedstawionych w pracach o charakterze opisu przypadku należały: zamknięcie naczyń tętniczych siatkówki (3 przypadki), jaskra normalnego ciśnienia (2 przypadki) oraz zapalenie błony naczyniowej (2 przypadki).

W publikacji numer 3 przedstawiono wyniki analizy 106 prac naukowych. Zajęcie narządu wzroku w przebiegu choroby Takayasu dotyczyło 122 pacjentów. Średnia wieku pacjentów wynosiła 31,4, a stosunek kobiet do mężczyzn – 4,8:1. Zdecydowana większość była w wieku od 11 do 40 lat (76,3%), ze szczytem w trzeciej dekadzie życia (33,6%). Dominowały przypadki pochodzące z Azji. W ponad 74% przypadków zajęcie narządu wzroku wystąpiło przed rozpoznaniem choroby Takayasu. Do najczęściej występujących powikłań okulistycznych należały: niedokrwienie siatkówki (57,4% przypadków), neuropatia nerwu wzrokowego (18%), zaćma (14,8%) i zamknięcie naczyń tętniczych siatkówki (12,3%). Glikokortykosteroidy w postaci doustnej, procedury naczyniowe oraz metotreksat stosowane były jako leczenie pierwszego rzutu (odpowiednio 68,9%, 32% i 27%). Pacjenci skarżyli się najczęściej na stopniowe pogorszenie widzenia (52,5%), nagłe pogorszenie widzenia (23%), ból oka (17,2%), a także przemijające zaniewidzenie (łac. amaurosis fugax, 25,4%) – opisywane jako rozmazanie, zamglenie, przyciemnienie, zbielenie (ang. white out) lub widzenie cieni/kurtyny. Dominującą postacią zajęcia narządu wzroku u dzieci było niedokrwienie siatkówki (57,1%) i zapalenie błony naczyniowej (28,5%). Spośród 5 przypadków zapalenia błony naczyniowej u pacjentów z chorobą Takayasu, 4 dotyczyły dzieci.

Publikacja numer 4 przedstawia wyniki badań oceniających siatkówkę i naczyniówkę u pacjentów z 5 chorobami z kręgu układowych zapaleń naczyń. Średnia grubość naczyniówki w grupie badanej wynosiła 341 μm, a w grupie kontrolnej 262 μm. Stwierdzono statystycznie istotną różnicę między grupami. Najwyższą średnią wartość odnotowano w podgrupie pacjentów chorujących na guzkowe zapalenie tętnic, natomiast najniższą u pacjentów z chorobą Buergera. Nie stwierdzono statystycznie istotnej różnicy pomiędzy podgrupami grupy badanej. Średnia wartość naczyniowego indeksu naczyniówkowego wynosiła 49,6% w grupie badanej oraz 64,5% w grupie

kontrolnej. Różnica była istotna statystycznie. Najniższa średnia wartość występowała w olbrzymiokomórkowym zapaleniu tętnic, najwyższa zaś w chorobie Takayasu. W grupie badanej średnia powierzchnia FAZ wynosiła 0,34 mm^2 natomiast w grupie kontrolnej 0,26 mm^2. Średnia wartość obwodu FAZ również była wyższa w grupie badanej (2,18 mm vs. 1,89 mm). Pacjentów z olbrzymiokomórkowym zapaleniem tętnic cechowały najwyższe średnie wartości powierzchni i obwodu FAZ, najniższe zaś dotyczyły podgrupy z guzkowym zapaleniem tętnic. W odniesieniu do powierzchni i obwodu FAZ stwierdzono statystycznie istotne różnice pomiędzy grupą badana i kontrolną oraz statystycznie nieistotne różnice pomiędzy podgrupami grupy badanej. Średnia wartość wskaźnika kolistości wynosiła 0,86 dla grupy badanej i 0,87 w grupie kontrolnej, bez istotnej różnicy między grupami.

5.5 Etyka badań

Badania opisane w publikacjach numer 1 i 4 przeprowadzono zgodnie z Deklaracją Helsińską, za zgodą Komisji Bioetycznej (377/2020, data uzyskania zgody: 10.06.2020). Artykuły numer 2 i 3 stanowią przegląd literatury.

5.6 Wnioski

1. W przebiegu układowych zapaleń naczyń może dojść do zajęcia wielu struktur narządu wzroku.
2. Konieczna jest współpraca między okulistami, angiologami i reumatologami ze względu na możliwość wystąpienia powikłań okulistycznych przed postawieniem rozpoznania choroby podstawowej.
3. Wprowadzenie przesiewowych badań okulistycznych oceniających naczyniówkę i siatkówkę u pacjentów z układowymi zapaleniami naczyń może skutkować wykryciem patologicznych zmian zanim zostaną one zauważone przez pacjentów.
4. Naczyniowy indeks naczyniówkowy zdaje się szczególnie przydatny w ocenie naczyniówki ze względu na mniejszą podatność na wpływ innych czynników w porównaniu do grubości naczyniówki.
5. Konieczne jest szybkie rozpoznanie olbrzymiokomórkowego zapalenia tętnic aby uniknąć wystąpienia poważnych powikłań takich jak obuoczna utrata widzenia.
6. Choroba Buergera może nie mieć charakteru miejscowej waskulopatii, lecz być

zaburzeniem ogólnoustrojowym i – podobnie jak inne układowe zapalenia naczyń – obejmować wiele narządów.

7. W przypadku młodych pacjentów z zaburzeniami w obrębie narządu wzroku, bez współistniejących chorób należy rozważyć chorobę Takayasu.

6. ARTYKUŁ PIERWSZY

Arteritic Anterior Ischemic Optic Neuropathy in the Course of Giant Cell Arteritis After COVID-19.

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Arteritic Anterior Ischemic Optic Neuropathy in the Course of Giant Cell Arteritis After COVID-19

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 69-year-old
Final Diagnosis: Anterior ischemic neuropathy • giant cell arteritis
Symptoms: Headache • tenderness • vision loss
Medication: —
Clinical Procedure: —
Specialty: Ophthalmology

Objective: Rare disease

Background: Giant cell arteritis (GCA) is an inflammation of large vessels that affects the lining of the arteries and leads to vessel swelling and the eventual reduction of blood flow. This can result in ischemia of the optic nerve, which is known as arteritic anterior ischemic optic neuropathy (AAION). The present case seems noteworthy because the patient developed GCA with the ocular manifestation of AAION shortly after having COVID-19.

Case Report: A 69-year-old woman was admitted to the Clinic of Ophthalmology after having COVID-19. She reported vision loss in the left eye, which appeared 2.5 weeks after a positive SARS-CoV-2 test. While in the hospital, she was diagnosed with AAION and GCA. The patient was treated with enoxaparin sodium, prednisone, and methotrexate. Three months after the hospitalization, the visual acuity of the left eye was limited to light perception, and optic nerve atrophy was reported.

Conclusions: We would like to emphasize the role of SARS-CoV-2 infection as a possible risk factor for the onset of GCA and its ocular manifestations, such as AAION. However, further research is needed to determine the relationship between SARS-CoV-2 infection and GCA. Because some symptoms of the 2 diseases are similar, the diagnosing process might be long and challenging. The diagnosis of GCA should be made as soon as possible to avoid serious complications, such as bilateral vision loss.

Keywords: COVID-19 • Giant Cell Arteritis • Optic Neuropathy, Ischemic • Vision Disorders

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933471

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Giant cell arteritis (GCA) is an inflammation of the large vessels. Most commonly, it affects the temporal arteries; hence, it is also called temporal arteritis. The exact causes of the disease have not yet been discovered; however, an autoimmune and infectious background is considered relevant. Patients with GCA develop an inflammatory reaction which affects the lining of the arteries, leading to vessel swelling and the eventual reduction of blood flow [1]. This can result in ischemia of the optic nerve, a condition known as arteritic anterior ischemic optic neuropathy (AAION), which accounts for 5% to 10% of anterior ischemic optic neuropathies (AION). The disease results in unilateral or bilateral blindness if left untreated. In about 20% of patients with AAION, there are no other symptoms of GCA, and the ocular manifestations might be the only symptoms present [2].

The case we are presenting seems noteworthy because the patient developed GCA with the ocular manifestations of AAION shortly after having COVID-19. It is not unlikely that SARS-CoV-2 infection may have triggered the onset of GCA.

Case Report

A 69-year-old woman was admitted to the Clinic of Ophthalmology at the beginning of January 2021 after having COVID-19, which started at the beginning of December 2020. While having the SARS-CoV-2 infection, which was confirmed by a RT-PCR test (performed in an authorized laboratory in Wrocław, Poland), the patient had fever, fatigue, and cough. The patient did not receive any treatment before hospitalization. She reported vision loss in the left eye (OS), which initially covered only the superior half of the visual field (described by the patient as a falling curtain) and proceeded into complete vision loss. The vision loss appeared 2.5 weeks after the positive SARS-CoV-2 test. Additionally, the patient had severe headaches, which were near the eyeballs and the occiput, and scalp tenderness. Unfortunately, the patient did not remember the exact time when the symptoms appeared. She claimed that all of them began around 2.5 weeks after the onset of COVID-19. On admission, the patient provided documentation concerning arterial hypertension and type II diabetes. Both conditions were controlled with appropriate oral treatment. Her glycosylated hemoglobin levels were unremarkable, and her blood pressure was within normal limits.

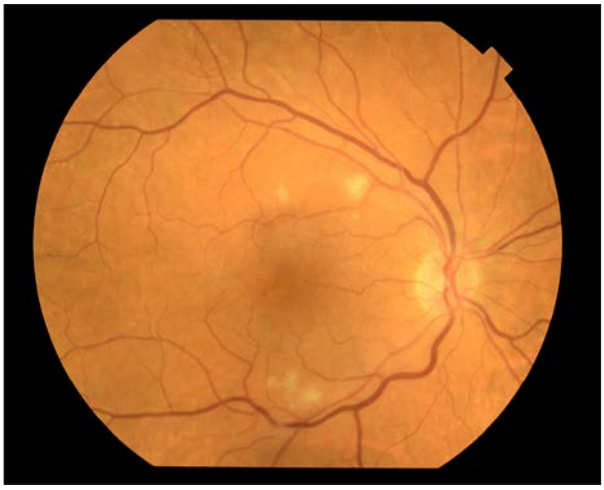

Figure 1. Fundus of right eye: cotton wool spots in the area of watershed zones seen in fluorescein angiography.

The patient's ocular examination on admission showed the following: The visual acuity of the right eye (OD) was 0.9 cc, and in the OS, the patient had light perception from the nasal and superior side. The intraocular pressure was 10 mm Hg in the OD and 9 mm Hg in the OS. The pupil of the OD showed no abnormalities. The pupil of the OS was wider than that of the OD and showed no direct response and a slow indirect response to light. In both eyes, cortical cataracts were present. The dilated fundus examination of the OD revealed cotton wool spots near the major superior artery and vein (**Figure 1**). In the OS, the blurring of the optic margins with flame hemorrhages

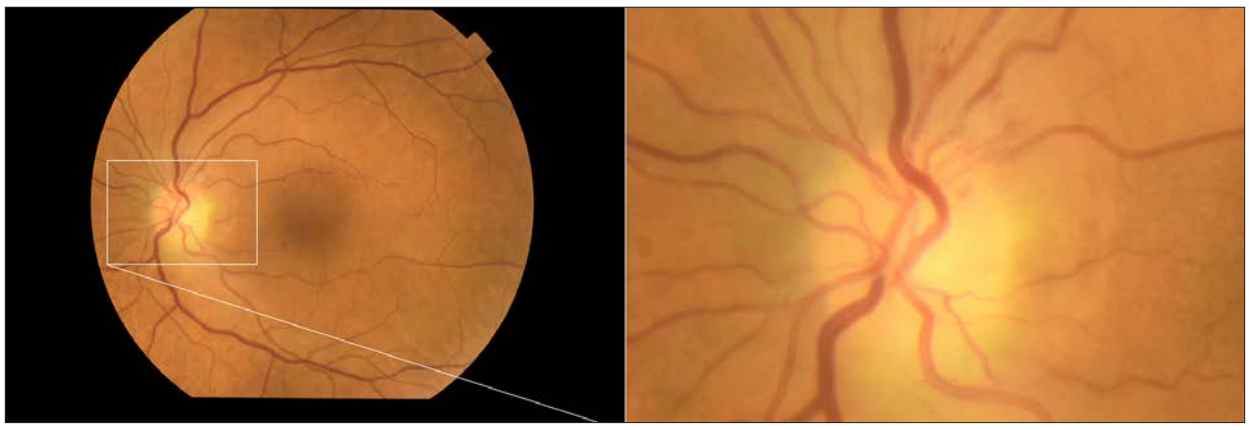

Figure 2. Fundus of left eye: blurring of the optic margins with flame hemorrhages.

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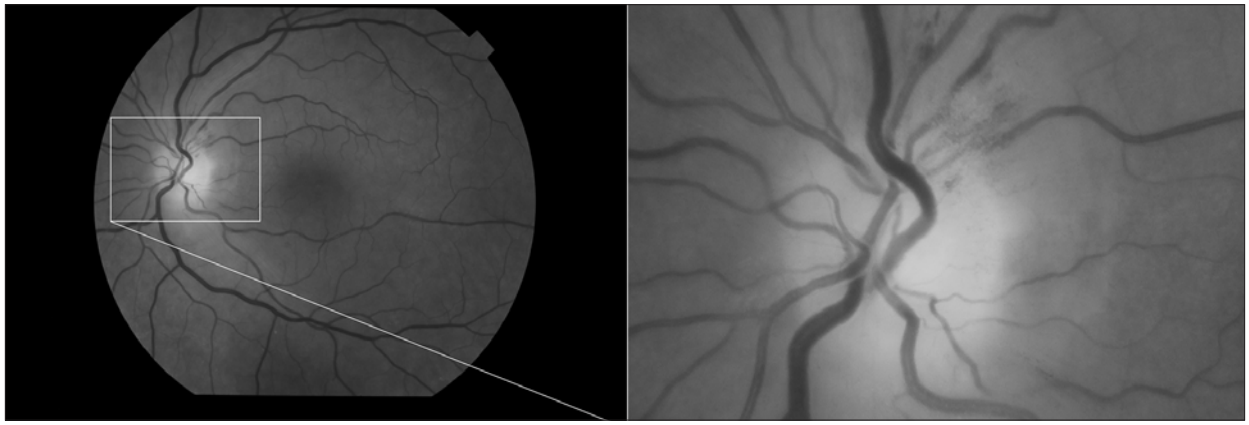

Figure 3. Fundus of left eye (red-free): blurring of the optic margins with flame hemorrhages.

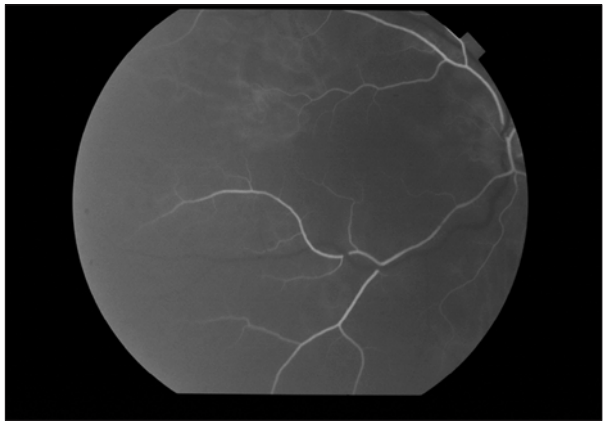

Figure 4. Fluorescein angiography of right eye, with time frame of 15.6 s: delayed choroidal filling.

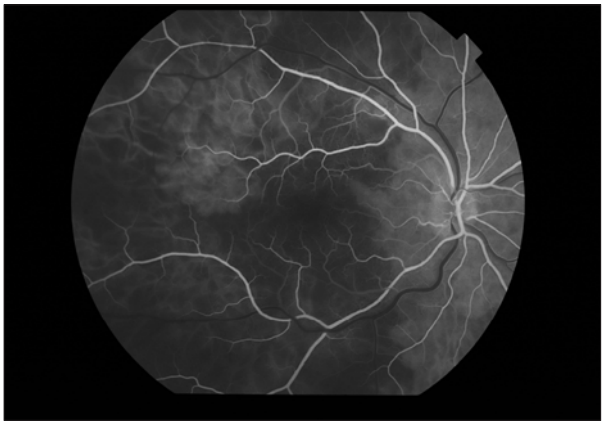

Figure 5. Fluorescein angiography of right eye, with time frame of 17.7 s: watershed zones.

were found (**Figures 2, 3**). Fluorescein angiography indicated the following abnormalities: delayed choroidal filling (**Figure 4**) and watershed zones (**Figures 5, 6**). The result of the C-reactive protein test was unremarkable, and the erythrocyte sedimentation rate (ESR) was elevated (63 mm/h; range, 3-15 mm/h). The results of the complete blood count (including platelet count), renal and liver function, activated partial thromboplastin time, prothrombin time, and antithrombin tests were unremarkable. The result of the D-dimer test was only slightly elevated (0.511 ug/mL; range, <0.5 ug/mL). The patient was also tested for the presence of anti-neutrophil cytoplasmic antibodies, anti-cyclic citrullinated peptide antibodies, and rheumatoid factor. The results of these tests were unremarkable. The electrocardiogram was within the normal range.

Additionally, the patient reported some typical symptoms of GCA on admission, including tenderness of the scalp and headaches near the occiput. The patient's overall image suggested the onset of GCA; therefore, an ultrasound of the temporal arteries was performed. The result revealed the signs of an inflammation: wall thickening and a "halo". The patient also underwent ultrasound of the retrobulbar arteries, which

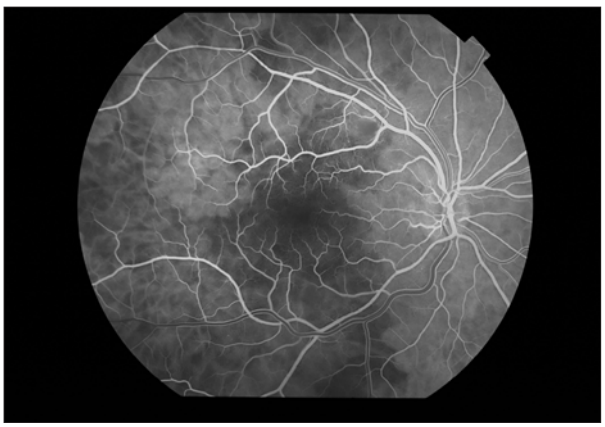

Figure 6. Fluorescein angiography of right eye, with time frame of 21.3 s: watershed zones.

suggested thrombosis in the ciliary arteries, as no flow was detected in them. Flow was detected in the ophthalmic artery and in the central retinal artery. The American College of Rheumatology does not require biopsy for the diagnosis of GCA. Our patient satisfied the required minimum of 3 out of 5 criteria with the following 4 satisfied criteria: patient age

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>50 years, new-onset headache, temporal artery abnormality, and elevated ESR > 50 mm/h [3]. We therefore diagnosed the patient with GCA and AAION.

The patient was treated with enoxaparin sodium 0.4 mL/day for 10 days and prednisone 80 mg/day for 4 days. At the end of the hospital stay, she was prescribed methotrexate 15 mg/week and prednisone, with a reduction of doses until reaching 60 mg.

At the follow-up visit at the end March 2021, the visual acuity of the OD was 0.8 cc, and there was light perception in OS. The intraocular pressure was 12 mm Hg in the OD and 10 mm Hg in the OS. Optical coherence tomography demonstrated macular traction in both eyes, and retinal nerve fiber layer analysis of the OS revealed optic nerve atrophy.

After treatment, the condition of the OS showed no improvement. Fortunately, the OD was not affected by the disease. The visual acuity of the OS was limited to light perception, and optical coherence tomography and retinal nerve fiber layer analysis revealed optic nerve atrophy.

Discussion

In our case, the clinical presentation (scalp tenderness, headaches), laboratory tests (elevated ESD) and imaging exam ("halo" and thickening of the wall in the ultrasound of the temporal arteries) suggested AAION caused by GCA. The comorbidities of the patient included diabetes type II and hypertension, which were both controlled with appropriate oral treatment. As the overall image pointed to the inflammatory character of the disease, and the patient's past medical history had not suggested any other pathological background, we did not conduct additional tests for thrombophilia or arteriosclerosis.

Reports on the coexistence of GCA and COVID-19 seem scarce. Lecler et al observed an increased incidence of GCA by 70% during the pandemic, compared with 2019 [4]. Luther et al stated that while 28 patients were diagnosed with GCA in 2019, between April 2020 and June 2020, the number of new GCA cases was 24, suggesting that viral etiopathogenesis of GCA might exist. Higher rates of ocular manifestations of GCA were also observed during the pandemic; however, none of the patients diagnosed with GCA had any symptoms suggesting COVID-19 [5]. Mulhearn et al observed the excess of 33 cases of GCA in 2020 in comparison with 2019, which they reported might have been caused by the damage to the endothelium and activation of T-helper cell type 1 cellular immunity and the monocyte-macrophage system [6]. Monti et al, on the other hand, noticed fewer cases of GCA during the past year, which might have been caused by the reluctance of patients to visit hospitals and more complicated access to medical care during the pandemic [7]. There are some reports concerning non-arteritic anterior ischemic optic neuropathy (NAION) during or after a course of COVID-19. Rho et al described a case of a 43-year-old man who developed NAION in the setting of COVID-19 [8]. Garcia Briones et al presented a case of a 55-year-old man who developed bilateral simultaneous NAION and concluded that COVID-19 significantly contributed to the disease [9]. However, AAION during the course of COVID-19 has not yet been described.

Unfortunately, we failed to find pathogenetic similarities between COVID-19 and AAION. However, we did find more references relevant to the topic of our case report. Riera-Marti et al described a case of a 50-year-old man who had had GCA with spontaneous resolution, most likely triggered by SARS-CoV-2, as the virus was claimed to have affinity for vascular endothelium [10]. According to Ostrowski et al, the hypothesis that the pathogenesis of GCA might include viral infection (VZV infection) should be treated with caution but not dismissed [11]. Therefore, it does not seem unlikely that other viruses may also trigger the disease. Xu et al suggested a link between SARS-CoV-2 infection and Kawasaki disease in children [12]. Kawasaki disease, just like GCA, is a type of vasculitis. Hanafi et al reported a case of a central nervous system-vasculitis-like pattern as a complication of SARS-CoV-2 infection and hypothesized about the presence of endothelitis in the course of the viral infection [13].

What also needs to be emphasized is that some symptoms of COVID-19 and GCA overlap, including headache, fatigue, elevated inflammatory markers, and fever, which can make diagnosing GCA challenging [14]. In both conditions, the vascular endothelium is affected, which can lead to thrombosis of the blood vessels [10,15]. Having analyzed our case, we suspect that COVID-19 might have triggered the sudden onset of GCA and the following AAION.

Conclusions

We would like to emphasize the role of SARS-CoV-2 infection as a possible risk factor for the onset of GCA and its ocular manifestation, such as AAION. However, further research is needed to determine the relation between COVID-19 and GCA. Because a few symptoms of the 2 diseases are similar, the diagnosing process might be long and challenging. The diagnosis of GCA should be made as soon as possible to avoid serious complications of the disease, such as bilateral vision loss.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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7. ARTYKUŁ DRUGI

Ocular Manifestations of Buerger's Disease – A Review of Current Knowledge

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REVIEW

Ocular Manifestations of Buerger's Disease – A Review of Current Knowledge

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Abstract: Buerger's disease, also known as thromboangiitis obliterans, is a disorder of primarily small and medium arteries and veins of the arms and legs. We have failed to find a comprehensive review discussing a possible link between the disease and the eyes. The aim of this study is to review current knowledge on the topic of ocular manifestations in the course of Buerger's disease. The Medline and Web of Science databases were searched without a time or language limit. We have managed to review 13 articles, describing the involvement of the eyes in thromboangiitis obliterans. It appears that patients suffering from Buerger's disease may develop non-arteritic anterior ischemic optic neuropathy (NAION), occlusive retinal vasculitis and periphlebitis, papillophlebitis, central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), normal tension glaucoma (NTG), uveitis, chorioretinal atrophy, retinitis, papillitis, optic atrophy, changes typical for hypertensive retinopathy. Additionally the abnormalities in electroretinography might be present. The treatment options and the possible outcome depend on the type of ocular manifestations, so it seems impossible to propose a universal therapy. We would like to raise awareness of the possible ocular manifestations in the course of Buerger's disease.

Keywords: Buerger's disease, anterior ischemic optic neuropathy, central retinal artery occlusion, normal tension glaucoma, uveitis

Introduction

The involvement of the eye in the course of systemic diseases has been the topic of extensive research. In some disorders ocular manifestations have been found to be one of the first signs and symptoms. In others, however, they develop as complications secondary to the initial health problem. The connection between the eye and diseases such as diabetes mellitus, hypertension, sarcoidosis or multiple sclerosis has been studied for many years. In recent years some interesting links between rare diseases and ocular findings have been observed. Kreuzpointner et al described ophthalmological complications of Lemierre syndrome.[1] The ocular involvement and the role of optical coherence tomography in Fabry disease was studied by Wiest et al.[2] Multimodal imaging was shown by Böni et al to be effective in disclosing choroidal lesions in patients with disseminated Mycobacterium chimaera infection.[3] Carneval et al demonstrated how useful optical coherence tomography angiography was in revealing ocular vascular changes in patients with systemic sclerosis.[4] Even though extensive research has been conducted in the field of systemic diseases and their impact on the eye, we have failed to find a review discussing a possible link between Buerger's disease and some ocular findings.

Buerger's disease, also known as thromboangiitis obliterans, is a disease of primarily small and medium arteries and veins of the arms and legs.[5] It was first reported by an Austrian physician Felix von Winiwarter in 1879, however, it was named after an Austrian American physician Leo Buerger, whose description of the pathological basis was very accurate (1908).[6,7] The highest prevalence of the disease is in the Middle and Far East. It constitutes 45% to 63% of all patients with peripheral arterial disease in India as opposed to Western Europe, where it accounts for 0.5 to 5.6%.[5] The annual incidence in the United States is equal to 12.6 per 100,000.[8] The disease usually affects tobacco smoking men under 45

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years of age. The ratio of men to women suffering from thromboangiitis obliterans equals 10:1 respectively.[9] Smoking tobacco has been proven to be one of the main risk factors. However, it was discovered that the disease might also affect smokeless tobacco users (eg tobacco chewers).[9] Another risk factor is chronic gum disease, although the reasons for it are still unknown.[10] When left untreated, Buerger's disease may lead to the development of gangrene because of insufficient blood supply. The most important form of prevention is quitting smoking.[10]

The symptoms of Buerger's disease are caused by stenosis and occlusion of small blood vessels, which leads to ischemia typically of the upper and lower extremities.[8] The patients suffer from intermittent claudication of the upper and lower extremities, rest pain, ulcers and gangrene, Raynaud's phenomenon, change of skin colour, tingling and numbness of fingers and toes. Although the typical signs and symptoms connected with the extremities are well known, other manifestations of the disease seem understated. Fakour and Fazeli conducted a systematic review, in which they presented 78 case reports, 2 case series and 3 original papers concerning the involvement of the following organs in patients with thromboangiitis obliterans: the gastrointestinal tract, the heart, the central nervous system, the eye, the kidneys, the urogenital system, the mucocutaneous zones, the joints, the lymphohematopoietic system and the ear.[11] In some patients the involvement of other organs had been noted long before the diagnosis of thromboangiitis obliterans whereas in others the first signs and symptoms later linked to Buerger's disease began after the diagnosis. The results of Fakour and Fazeli's study seem to be consistent with the findings of Leo Burger, who observed visceral arterial involvement in the patients with thromboangiitis obliterans he had examined.[11] According to Fakour and Fazeli, neglecting a possible systemic character of the disease might be unfavourable for the patients. Olin et al also stated that some larger blood vessels (eg cerebral, coronary, pulmonary, mesenteric, renal) might be affected by the disease.[12] Cabezas-Moya and Dragstedt described intestinal involvement of thromboangiitis obliterans in a patient, and Harten et al observed cerebral, splenic, pulmonary and myocardial signs of the disease.[13,14]

What also seems noteworthy is the involvement of the eye in other types of vasculitis. The prevalence of ocular symptoms is significant in granulomatosis with polyangiitis (50%), Behçet's disease (60%-80) and giant cell arteritis (12%-70%).[15–17] One third of patients with systemic lupus erythematosus develop ocular signs and symptoms, too.[18] This made us raise the question whether thromboangiitis obliterans is localized vasculopathy or a systemic disorder like the diseases mentioned above.

The aim of this study was to review current knowledge on the topic of ocular manifestations in Buerger's disease and raise awareness on the possible systemic character of the disease.

Materials and Methods

The search strategy consisted in searching the Medline and Web of Science databases without a time or language limit by entering the following key words or phrases: "Buerger's disease", "thromboangiitis obliterans" in conjunction with "ocular", "ocular manifestations", "eye" and "ophthalmology". The last search was conducted on the 28th of May 2021. The inclusion criterion regarding Buerger's disease we adopted was the diagnosis of the condition provided by the authors of the reviewed articles. The inclusion criterion for the ophthalmological involvement was any type of ocular manifestation with no restrictions. Buerger's disease is known as a very rare disorder. Ophthalmological complications in its course are even rarer. We were keen on reviewing any type of article. The exclusion criterion was when there was no reference to the eye involvement in the course of Buerger's disease. The references of the reviewed articles were also screened so as not to omit any eligible papers. The search was conducted independently by two authors (USzP and JPD). The total number of records identified from both databases equaled 142. After removing duplicates with the use of Zotero we considered 42 articles. After reading abstracts or full texts 29 articles were excluded from the study as not relevant to the topic. The final number of articles, on which our study is based equals 13. We reviewed 10 cases of ophthalmological manifestations of Buerger's disease (each case was a separate publication) and 3 studies describing the involvement of the eye in Buerger's disease in 43 patients (Homma et al. – 9 patients, Arslan et al. – 24 patients, Valdes et al. – 10 patients.[19–21]

The form of the presentation was mainly inspired by Fakour and Fazeli's article entitled "Visceral bed involvement in thromboangiitis obliterans: a systemic review".[11] However, we decided to resign from some features included in the original work and replace them with what we believed to be more relevant to the topic. In the systematic review the

tables included more categories connected to internal medicine, whereas we wanted our article to be mostly about the ophthalmological aspects. We decided not to write about the duration of Buerger's disease and the smoking status. Instead, we wanted to describe in detail all the performed imaging tests and ophthalmological findings. We also included some information on the course of Buerger's disease in each case.

Results

We present 9 articles in the form of a table summing up the findings (Table 1). The other 4 publications will be discussed in a narrative form. We would have liked to include all the information coming from our research in one table Yet, not from all the analyzed works could we obtain enough information to fill in the appropriate categories in the table For example for Copeto and Adamczyk or Homma et al only abstracts were available.[19,22] Arslan et al's. work or Valdes et al's. paper, on the other hand, are not case reports.[20,21] The structure of these studies is different, which means that they are incomparable to the case reports presented in the table To avoid numerous empty slots in the table, we decided to discuss all the incomplete data separately.

As mentioned above, we have found 4 articles which we would like to discuss in a narrative form. Coppeto and Adamczyk reported anterior ischemic optic neuropathy in a 77-year-old patient suffering from Buerger's disease.[22] Arslan et al examined 26 men suffering from Buerger's disease and compared them to 26 healthy men in a similar range of age.[20] The only risk factors in both groups were male gender and smoking. The patients suffering from thromboangiitis obliterans were diagnosed based on the criteria proposed by Shinoaya.[23] The extra-ophthalmological signs and symptoms of some patients included: segmental occlusions in extremities, foot wounds (12), rest pain and hyperemia (14), wounds on the fingers (3), positive Allen's test (6). Nineteen patients had undergone unilateral lumbar sympathectomy, 2 patients had bilateral lumbar sympathectomy performed and in 4 cases finger amputation was carried out. All patients were treated with acetylsalicylic acid (150 mg). In the experimental group only 2 patients had no pathology in the fundus of their eyes. The other patients presented with optic atrophy (2 patients) and atherosclerotic hypertensive retinopathy (10 patients - grade I, 12 patients - grade II). In the control group only 4 patients were diagnosed with grade I retinopathy and the results of the other patients were unremarkable.[20] Homma et al observed severe narrowing of the bulbar conjunctival arteries in patients with thromboangiitis obliterans.[19] Valdes et al performed electroretinography in 10 patients previously diagnosed with Buerger's disease on the basis of clinical, angiographical and anatomopathological criteria.[21] They observed changes in the latency, amplitude and number of oscillatory potentials as well as changes in the a and b waves in the electroretinogram (eg elongated latency of OP, absence of subcomplex b, decreased amplitude of OP, decreased number of OP).[21]

The number of patients with ocular manifestations of Buerger's disease described in the reviewed articles equaled 44. We did not take into account the study published by Homma et al, as the exact number of patients with ocular involvement had not been given. The percentage of different types of ophthalmological involvement is given in Table 2.

Discussion

The first reports concerning ocular manifestations of Buerger's disease date back to the 1930s and 1940s. The following presentations were described: narrowing and obliteration of a vascular lumen in the vessels of the retina, iris and ciliary body in retinal periphlebitis, iritis, iridocyclitis, complicated cataract, phthisis bulbi, choroiditis, vitreous opacities, choroid atrophy, white colouring of the retinal artery, white sheath on the retinal arteries, embolism of the central retinal arteries, hemorrhages in the retina and the vitreous body, retinitis proliferans, retinal atrophy, optic atrophy and Eale's disease.[33] Except for the case report published in the 1980s, the topic was not further researched until the next millennium. We managed to review 13 articles describing the involvement of the eyes in the course of thromboangiitis obliterans. We presented 10 isolated cases and 3 studies (conducted by Homma et al, Arslan et al, Valdes et al and Homma et al) showing ophthalmological changes in more than one patient. There seems to be no more studies on a larger group.

The criteria for the diagnosis of Buerger's disease differ depending on the author. Ollin et al have included the following aspects in the diagnosis: "an age of less than 45 years and current (or recent) history of tobacco use; the presence of distal-extremity ischemia (indicated by claudication, pain at rest, ischemic ulcers, or gangrene) documented

Table 1 Review of 9 Articles Concerning Ocular Manifestations of Buerger's Disease

Authors, Year of Publication	Sex and Age of the Patient on Admission, the Affected eye	Extra-Ophthalmologic Signs and Symptoms and Past History	Symptoms, Signs and Basic Examination on Admission	Results of the Ophthalmic Examination of the Affected eye	Final Diagnosis	Treatment	Outcome
Boeke W. and Duncker G, 1983[24]	Male, 30, right and left eye	Thrombophlebitis of the deep leg and pelvic veins (recurrences of the thrombophlebitis in the lower extremities were accompanied by deterioration in the eye condition)	-	Slit lamp of OU: features of anterior uveitis, opacification of the vitreous body, complicated cataract Fundoscopy of OU: white retinal foci, retinal hemorrhages, retinal edema, constriction of the retinal vessels	Bilateral uveitis, retinitis and papillitis (recurrent)	Azathioprine (150 mg/d) Fluocortolone (15 mg every other day) Phenprocumarol	Visual loss Optic atrophy VA OD = 1/15 VA OS = 0.1 Concentric constrictions in the visual field
Dimopoulos I.S. et al., 2020[25]	Male, 48, right eye	Recurrent ulcers at the tip of the fingers (duration: 3 years) Macrocytosis (probably secondary to the alcohol intake) Protein C and antithrombin III deficiency Abnormal photoplethysmography in the upper limb arterial duplex scan - small vessel occlusive disease in the upper extremity and a mild degree of reverse flow in the left ulnar artery Digital pitting, finger nail bed changes	Sudden onset of vision loss VA OD = 20/500 VA OS = 20/20	Fundoscopy of OD: ischemic retina, cotton wool spots Fundoscopy of OS: normal	Occlusive retinal vasculitis and periphlebitis	Aspirin 81 mg/day po	-
	One year later - left eye	-	Sudden onset of severe vision loss VA OD = 20/600 VA OS = cf at 1m	Slit lamp of OU: mild nuclear sclerotic cataract Fundoscopy of OU: retinal thinning in the macular region, vascular loops with collateralization, dot-blot and flame-shaped hemorrhages, arteriolar narrowing with venular dilation and sheathing Additionally in the fundus of OD: a few nerve fiber layer infarcts FA: early phase vessel wall staining involving veins and collateral arteries and mid/ late phase leakage, the arm-retinal and arteriovenous transit times for the left eye was equal to 16.8 s and 11.3 s respectively, the foveal avascular zone (FAZ) was enlarged more in the right eye compared to left OCT of OU: areas of inner retinal atrophy with paracentral cystoid degeneration and edema		Apixaban 5 mg/day po	-

Eris E. et al., 2017[26]	Male, 64, left eye	After left leg amputation	Sudden vision loss VA OD = 16/20 VA OS = hand motion RAPD+	Fundoscopy: area of interpapillomacular retinal ischemia with whitish edges and a red spot in the macula OCT: increased reflectivity of the inner retinal layers, central macular thickness = 650 uM FA: no perfusion in the macular area with late staining of small veins and arterioles and leakage	Central retinal artery occlusion (CRAO)	Hyperbaric oxygen therapy (20 sessions)	VA OS = 10/200 OCT: macular atrophy
Koban Y. et al., 2014[27]	Male, 48, right and left eye	After bilateral below-the-knee amputations for ischemic ulcers of the lower limbs Diabetes mellitus (controlled by oral antidiabetics) Left carotid artery stenosis in bilateral carotid artery color doppler ultrasound	Vision loss of OS BCVA OD = 20/20 BCVA OS = 20/32 Ishihara plates OD = 10/10 Ishihara plates OS = 6/10 RAPD+ in OS IOP OD (applanation) = 18 mm Hg IOP OS (applanation) = 16 mm Hg	Gonioscopy OU: open iridocorneal angles to the ciliary body bands for 360 degrees Slit lamp OU: mild posterior subcapsular cataract Fundoscopy OD: arteriolar constriction, minimal pallor of the temporal rim, c/d = 0.5 Fundoscopy OS: relatively superior entrance to the central retinal artery, temporal peripapillary atrophy, arteriolar constriction, retinal edema in the inferopapillary area, splinter hemorrhages, soft exudate, c/d = 0.8 Visual field test: peripheral constriction, decreased retinal sensitivity in the Bjerrum area of the right eye, and a small temporal island FA: delay in inferonasal branch retinal artery filling in the left eye	Acute inferonasal branch retinal artery occlusion in the left eye and bilateral normal tension glaucoma (NTG)	-	-
Korkmaz A et. al, 2018[28]	Male, 43, left eye	Infrapopliteal artery occlusive disease Occlusion in the right posterior tibial artery Phlebitis migrans	Sudden decrease of VA of OS (duration: 5 days) BCVA OD = 10/10 BCVA OS = 2/10 Ishihara plates OD = 21/21 Ishihara plates OS = 8/21 RAPD+	Fundoscopy: blurring, hemorrhagic swelling of optic disc Humphrey visual field: inferior altitudinal defect FA: late phase - leakage of optic disc	Non-arteritic anterior ischemic optic neuropathy (NAION)	Acetyl salicylic acid (330 mg/d) + Prednisone 1mg/kg/d for 14 days)	After 4 days of treatment: BCVA: 4/10 Ishihara plates: 14/21 Fundoscopy: partially improved disc edema

(*Continued*)

Table 1 (Continued).

Authors, Year of Publication	Sex and Age of the Patient on Admission, the Affected eye	Extra-Ophthalmologic Signs and Symptoms and Past History	Symptoms, Signs and Basic Examination on Admission	Results of the Ophthalmic Examination of the Affected eye	Final Diagnosis	Treatment	Outcome
Marques A. et al., 2015[29]	Male, 64, right and left eye	After amputation of some of the fingers and toes	Progressive bilateral visual acuity decrease and nyctalopia BCVA OD = cf BCVA OS = 0.7	Slit lamp OU: phacosclerosis Fundoscopy OU: extensive confluent areas of chorioretinal atrophy with involvement of the posterior pole (except in the perifoveal area of OS), diffuse arteriolar narrowing FA: delay in the arm-to-retina time (27 seconds), areas of staining; OD – evident exposure of the sclera in the foveal area SD-OCT: reduction in the thickness of the internal and external layers of the retina (except in the fovea of OS) Visual field test: bilateral generalized retinal sensitivity reduction, small central island of vision in OS Flash ERG, scotopic ERG and photopic ERG: extremely diminished amplitudes of both a and b waves	Chorioretinal atrophy	Acetylsalicylic acid 150mg/d	After a year: Maintenance of the VA of OU
Ohguro I. et al, 2006[30]	Male, 66, left eye	After lumbar sympathectomy After an acute myocardial infarction (1995) Ankle-brachial pressure index: 0.69 (norm: 0.9–1,3)	Progressive visual field disturbance in the left eye VA OD = 1.2 VA OS = 1.5 IOP OU = 13 mm Hg	Slit lamp OU: slight nuclear sclerosis Fundoscopy of OU: retinal vessel tortuosity, arteriosclerosis and glaucomatous cupping c/d of OD = 0.8 c/d of OS = 0.6 Additionally in the fundoscopy of OS: plaques and occlusion in the inferotemporal retinal artery, retinal edema in the inferotemporal area of the macula Humphrey Field Analyzer: decreased retinal sensitivities in the Bjerrum area of OU, retinal artery occlusion area of OS FA: retardation of arm-to-retina circulation time and filling defect of the inferotemporal retinal artery in the left eye	Branch retinal artery occlusion and normal tension glaucoma	-	-

Reche Sainz JA et al., 2018[31]	Male, 27, right eye	Chronic distal ischemia of the left lower limb (durations: years)	Sudden visual loss VA OD = 0.9 VA OS = no information	Fundoscopy: congestive papilla, cotton wool spots, venous tortuosity, scattered retinal hemorrhages	Papillophlebitis	Acetylic acid (100 mg/d)	VA OD = 1.0 The papilledema and most of retinal hemorrhages have resolved
Zaoui K. et al., 2020[32]	Male, 30, right eye	Paresthesia of the lower right extremity with intermittent coldness of the feet Necrosis of the right little toe during hospitalization which lead to the amputation	Rapidly progressing visual acuity drop of the right eye and blurred vision of the left eye VA OD = 5/10 VA OS = 10/10	Slit lamp: mixed bilateral granulomatous keratic precipitates with "mutton fat" at the bottom Fundoscopy of OU: multiple, yellow-white spots, greyish pigmented lesions (choroidal lesions) FA: delay in filling the choriocapillary, progressive impregnation of the lesions with slight diffusion per area	Bilateral panuveitis	–	–

Abbreviations: OD, oculus dexter; OS, oculus sinister; OU, oculus uterque (both eyes); VA, visual acuity; BCVA, best corrected visual acuity; FA, fluorescein angiography; OCT, optical coherence tomography; ERG, electroretinogram; SD-OCT, spectral domain optical coherence tomography; IOP, intraocular pressure; CDR, cup to disc ratio; RAPD, relative afferent pupillary defect; cf, counting fingers.

Table 2 The Percentage of Different Types of Ophthalmological Involvement in Patients with Buerger's Disease

Diagnosis	Number	Percentage (Out of 44)
Non-arteritic ischemic optic neuropathy	2	4.55%
Occlusive retinal vasculitis and periphlebitis	1	2.27%
Papillophlebitis	1	2.27%
Central retinal artery occlusion	1	2.27%
Branch retinal artery occlusion	2	4.55%
Normal tension glaucoma	2	4.55%
Uveitis	2	4.55%
Chorioretinal atrophy	1	2.27%
Retinitis	1	2.27%
Papillitis	1	2.27%
Optic atrophy	2	4.55%
Changes typical for atherosclerotic hypertensive retinopathy	22	50.00%
Abnormalities in electroretinography	10	22.73%

by noninvasive vascular testing; exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus by laboratory tests; exclusion of a proximal source of emboli by echocardiography and arteriography; and consistent arteriographic findings in the clinically involved and noninvolved limbs".[12] The slightly different criteria were proposed by Papa et al, Mills and Porter or Shionoya.[23,34,35] The reviewed articles were written from the ophthalmological perspective and in many cases the patients had been diagnosed with Buerger's disease prior to the eye problems. That is why the information on the exact criteria on the basis of which Buerger's disease was actually diagnosed is frequently missing.

What needs to be emphasized is that diagnosing thromboangiitis obliterans is based mainly on excluding some other systemic diseases (eg autoimmune diseases). In almost each reviewed article the process of diagnosing was explained in details. Laboratory tests, imaging tests (eg color duplex ultrasound, extremities angiography, photoplethysmographic waveform analysis) and clinical presentation were taken into account. This also explains how the ophthalmological manifestations were attributed to Buerger's disease, as patients suffering from thromboangiitis obliterans are usually thoroughly examined in search for any other comorbidity. That is why the chance of some other disorder causing the involvement of the eye in Buerger's disease is low.

We understand the necessity of providing strict inclusion criteria for Buerger's disease, uniform for all articles and based on the acknowledged classifications. Yet, we could not follow such rigorous methodology because of all articles reviewed in our analysis only two referred to a specific classification of criteria for diagnosing Buerger's disease (Dimopoulos et al and Arslan et al.). In the remaining works the diagnosis was taken for granted as the starting point for further investigation of ocular problems. Some researchers stated that other causes, risk factors or systemic diseases had been excluded (Eris et al, Korkmaz et al, Re-Sainz et al, Zaoui et al, Marques et al.). Ohguro et al mentioned the patient's past medical history. We assumed that the diagnoses of Buerger's disease in the reviewed papers were accurate.

It appears that patients suffering from Buerger's disease may develop non-arteritic anterior ischemic optic neuropathy (NAION), occlusive retinal vasculitis and periphlebitis, papillophlebitis, central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), normal tension glaucoma (NTG), uveitis, chorioretinal atrophy, retinitis, papillitis, optic atrophy, changes typical for hypertensive retinopathy. Additionally, the abnormalities in electroretinography might be present. In the presented cases the occlusion of retinal vessels was the most common ocular manifestation of thromboangiitis obliterans (3 cases: 1 patient with central retinal artery occlusion and 2 patients with branch retinal artery occlusion), followed by normal tension glaucoma (2 cases) and uveitis (2 cases). The first condition mentioned above could be explained by vasospasm and thrombotic occlusion in the course of Buerger's disease.[26,30] Vasospasm may also be responsible for the development of normal tension glaucoma and non-arteritic anterior ischemic optic neuropathy, as it may lead to disturbances in the blood flow within the optic nerve head.[27,28,30] There are studies suggesting an

autoimmune background in thromboangiitis obliterans, which might be connected with the development of uveitis (also an autoimmune disease) in two cases.[32,36,37]

The types of tests which may be useful when examining patients suffering from Buerger's disease mainly depend on the symptoms. However, in many cases fluorescein angiography was conducted and delivered important information. The treatment options and the possible outcome also depend on the type of ocular manifestations, so it seems impossible to propose a universal therapy.

To our knowledge, there seems to be no publication which would discuss all the articles we have managed to find. The most comprehensive review published by Fakour and Fazeli summed up 5 positions.[11] The limitation of our review might be that we did not restrict the time span within which the publications for the analysis were to be found. Only 5 articles were published in the past 5 years. Finally, our inclusion criterion regarding the diagnosis of Buerger's disease in the reviewed works was not based on any specific classification.

Conclusion

Although the number of publications we have found might not be impressive (13), we need to remember that Buerger's disease is rare and the ocular manifestations in its course are extremely rare. Furthermore, there seems to be no specific features that would make it possible to predict which patient with Buerger's disease is likely to develop ophthalmological complications. The patients described in the review articles did not differ from a typical patient suffering from thromboangiitis obliterans. That is why all patients with this disorder should be treated with caution as potentially at risk for eye problems. Introducing routine eye examination for all patients with Buerger's disease might be helpful. Some of the ocular manifestations of the disorder could be detected during a basic ophthalmic examination comprised of visual acuity and intraocular pressure tests as well as a slight lamp examination. Having analyzed the findings we suspect that Buerger's disease may not be localized vasculopathy but a systemic disease and - like other vasculitis – it may affect various organs and systems. We hope our review may help to raise awareness of possible ocular manifestations in the course of Buerger's disease and encourage physicians taking care of patient with thromboangiitis obliterans to perform ophthalmological examinations.

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Disclosure

The authors report no conflicts of interest in this work.

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8. ARTYKUŁ TRZECI

Ocular Manifestations of Takayasu's Arteritis – A Case-Based Systematic Review and Meta-Analysis

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Systematic Review

Ocular Manifestations of Takayasu's Arteritis—A Case-Based Systematic Review and Meta-Analysis

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Abstract: Takayasu's arteritis (TA) is a type of vasculitis in which inflammation develops in large vessels, especially in the aorta and its branches. Our study aims to determine the prevalence and type of ocular manifestations in TA. A systematic literature search was conducted in December 2022 using three electronic databases (PubMed, Scopus, and Web of Science). The following data were extracted from each article: the name of the first author; the patient's age, sex, and origin (continent); circumstances connected with the diagnosis of TA; symptoms given by the patients; reported ocular manifestations; and administered treatment. The final analysis was based on data collected from 122 cases. Retinal ischemia, followed by optic neuropathy, cataract, and retinal artery occlusion, were the most prevalent eye conditions associated with the disease. Systemic steroid therapy, vascular procedures, and methotrexate were mainly used to treat pulseless disease. Patients mostly complained of gradual vision acuity loss, sudden vision acuity loss, ocular pain, and amaurosis fugax. The diagnosis of Takayasu's arteritis should be considered in patients presenting symptoms of visual decline/loss, ocular pain, or signs of retinal ischemia, optic neuropathy, or early cataract formation. A proper diagnosis is crucial to ensure the patient receives treatment without significant delay.

Keywords: Takayasu's arteritis; pulseless disease; ocular manifestations; retinal ischemia; retinal artery occlusion; retinal vein occlusion; uveitis; optic neuropathy

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1. Introduction

Numerous systematic reviews have been devoted to ocular manifestations of various systemic diseases. Not many of them, however, have been concerned with the involvement of the eye in Takayasu's arteritis (TA). In 2021, Turk et al. published a systematic review and meta-analysis concerning ocular findings in diseases such as rheumatoid arthritis, connective tissue diseases, and vasculitis, including giant cell arteritis and granulomatosis polyangiitis [1]. Subsequently, in another systematic review and meta-analysis, Turk et al. described the ocular manifestations of Behcet's disease [2]. Even though the association between the eye and TA has been pointed out in some previous review articles, a systematic review summarising the current evidence has not been published to date. Therefore, we sought to perform a systematic review and meta-analysis to determine the prevalence and type of ocular manifestations in TA.

TA is a type of vasculitis in which inflammation develops in large vessels, especially in the aorta and its branches [3]. A chronic inflammatory process eventually leads to the obliteration and narrowing of the blood vessels [4]. The prevalence of the disease varies from 0.9 to 40 cases per million; however, according to epidemiological data, the number is estimated to be between 4 and 15 cases per million [5]. Geographical and ethnic differences

might explain this wide range. TA is more common in Asian, Central, and South American populations. In addition, women are more frequently affected by the disease, with the women-to-men ratio being 1.6–12:1 in adults [5]. The highest incidence occurs in the third decade, although the disease may develop even in infancy [5]. The pathogenesis of TA is not fully known; however, autoimmune processes and genetic factors are believed to be significant [6,7].

2. Methods

2.1. Search Strategy

The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [8]. A systematic literature search was conducted independently by two authors (USP and JPD) using three electronic databases (PubMed, Scopus, and Web of Science). Any disagreements were discussed with a third author (MMH). The combination of the following Medical Subject Headings (MeSH), keywords, and phrases was used: ("Takayasu's arteritis" OR "pulseless disease" OR "aortoarteritis") AND ("ocular" OR "ophthalmology" OR "eye" OR "ocular manifestations"). No language and publication time restrictions were applied. The last search was conducted on 15 December 2022. The references of the included articles were also examined in order to expand the eligible sources.

2.2. Inclusion and Exclusion Criteria

In the present study, we included studies reporting data from patients with previously or newly diagnosed TA who presented any ocular manifestation. Data from case reports, case series, clinical images and letters to the editors were found to be eligible. The coexistence of TA with any other vasculitis or autoimmune disease was the first exclusion criterion. Another exclusion criterion was no description of an ophthalmological examination. Studies in which only subjective visual disturbances were reported by the patients, as well as reports of ocular manifestations secondary to the administered treatment, were additionally excluded. Reviews, conference abstracts and animal studies were also rejected, as well as studies on a large number of patients as they were sparse and incomplete.

2.3. Data Extraction

The following data were extracted from each article: the name of the first author, patient's age, sex, and origin (continent), circumstances connected with the diagnosis of TA, symptoms given by the patients, reported ocular manifestation, and administered treatment. The disease diagnosis was either new for the patient or made before the diagnostic period described in a specific article. Only the systemic treatment for TA was taken into account. Specific treatments connected with various ocular manifestations of the disease were not presented.

2.4. Statistical Analysis

Data were analysed using Statistica 13.3 software (Tibco Software Inc., Palo Alto, CA, USA). We gathered individual patient data from each study. Categorical variables (patient characteristics, ocular manifestations, treatment and symptoms) were summarized descriptively and presented as counts and percentages. A subset of analyses was performed to determine the potential differences in the occurrence of ocular manifestations of Takayasu's arteritis concerning gender (male vs. female) and age (children vs. adults). In a subgroup analysis, categorical variables were assessed by the Chi-squared test or Fisher's exact test. A p-value ≤ 0.05 was considered statistically significant.

3. Results

The detailed flow diagram of the study selection process (with subsequent exclusions) is presented in Figure 1. The literature search identified 932 references. All citations were exported to the citation manager EndNote 20 (Clarivate Analytics), and duplicate references

(n = 322) were removed. After screening the titles and abstracts, 169 studies were excluded due to their irrelevance to the current topic. The full text of 153 articles was read in detail to determine their eligibility. Subsequently, 47 articles were excluded for the following reasons: overlapping diseases (17), ocular manifestations secondary to treatment (5), no ophthalmological examination (20), and no ophthalmological manifestations (5). Eventually, 106 records were included in the analysis. The included records consisted of five case series, seven letters to editors, one photo essay, one clinical image, and 92 case reports. Selected articles provided data on 122 patients, as summarised in Tables 1–4 (Supplementary Tables S1–S3). The age distribution of patients with ocular manifestations of TA is presented in Table 5.

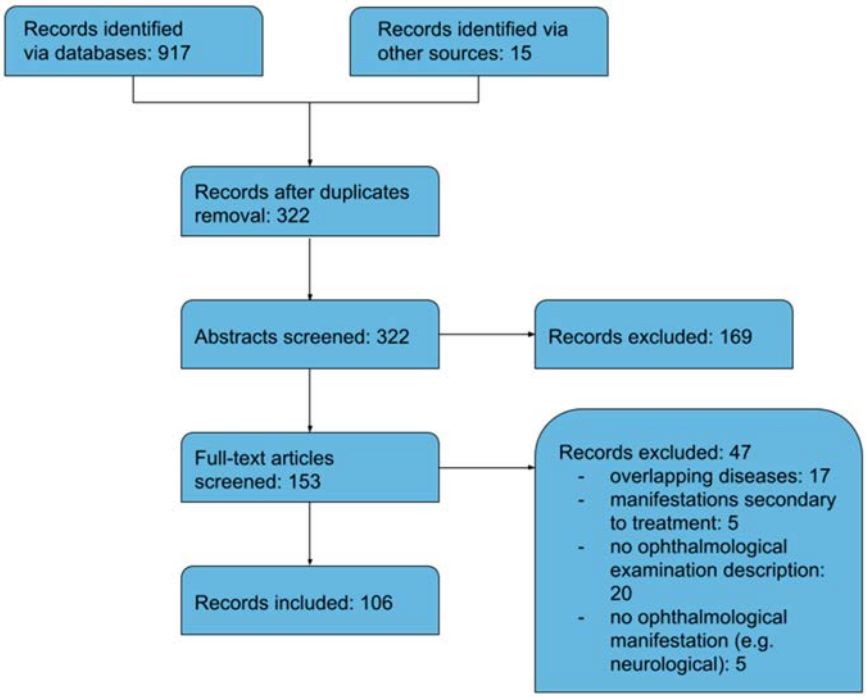

Figure 1. Flow diagram of meta-analysis.

Table 1. Characteristics of patients with TA's ocular manifestations.

First Author	Age	Sex	Patient's Origin (Continent)	New Diagnosis of TA
Akhtar [9]	35	M	-	No
Amer [10]	26	M	-	No
Anguita [11]	12	F	South America	Yes
Arya [12]	45	F	-	No
Austen [13]	28	F	Asia	Yes
Babu [14]	31	F	-	Yes
Bajgai [15]	25	F	-	Yes
Balaskas [16]	35	F	Europe	No
Bapat [17]	24	M	-	Yes
Batliwala [18]	18	F	Europe	No
Becker [19]	5	F	-	Yes
Bodker [20]	22	F	South America	Yes
Bouzas [21]	45	F	Europe	No

Table 1. *Cont.*

First Author	Age	Sex	Patient's Origin (Continent)	New Diagnosis of TA
Caccamise [22]	19	F	-	Yes
Chaudhary [23]	44	F	South America	Yes
Chawla [24]	28	M	Asia	Yes
Christiansen [25]	19	F	Asia	Yes
Conrath [26]	28	F	Africa	Yes
Das [27]	37	F	-	Yes
Demir [28]	14	F	-	Yes
Do Vale [29]	46	F	-	Yes
Dowling [30]	54	-	-	Yes
Elizalde [31]	63	F	-	No
Escano [32]	34	M	-	No
Font [33]	35	F	Asia	Yes
Gaur [34]	27	F	-	Yes
Genc [35]	52	M	-	Yes
Gong [36]	18	F	Asia	Yes
Guclu [37]	48	F	-	Yes
Gupta [38]	18	M	-	Yes
Harada [39]	34	F	Asia	Yes
Hayasaka [40]	33	F	Asia	No
Hayasaka [40]	19	F	Asia	Yes
Herath [41]	38	F	Asia	Yes
Ibrahim [42]	39	F	-	No
Jain [43]	40	F	Asia	Yes
Jain [44]	39	F	Asia	Yes
Jain [45]	15	F	-	No
Kaliaperumal [46]	35	F	-	Yes
Kancherla [47]	27	F	-	Yes
Kannan [48]	13	M	Asia	Yes
Kapran [49]	29	M	-	Yes
Karam [50]	28	F	-	Yes
Karam [50]	24	F	-	Yes
Karam [50]	27	F	-	Yes
Karam [50]	24	F	-	Yes
Karam [50]	21	F	-	Yes
Karam [50]	8	F	-	Yes
Karam [50]	30	F	-	Yes
Karwatowski [51]	66	F	Asia	No
Kaushik [52]	40	F	-	Yes
Kausman [53]	12	M	Asia	Yes
Kavitha [54]	40	F	-	Yes
Kim [55]	25	F	Asia	Yes

Table 1. *Cont.*

First Author	Age	Sex	Patient's Origin (Continent)	New Diagnosis of TA
Kimura [56]	41	M	-	No
Kinoshita [57]	28	F	-	No
Koz [58]	45	M	-	Yes
Kumar [59]	65	M	-	Yes
Kuwahara [60]	57	F	Asia	No
Larrazabal [61]	26	F	-	Yes
Lee [62]	23	F	-	Yes
Lee [63]	28	F	Asia	Yes
Leonard [64]	37	F	-	Yes
Lewis [65]	59	F	-	Yes
Lim [66]	53	F	-	No
Mahajan [67]	36	F	-	Yes
Mahajan [67]	14	F	-	Yes
Mahajan [67]	34	F	-	Yes
Mahajan [67]	25	F	-	Yes
Mahajan [67]	30	F	-	Yes
Mahendradas [68]	18	F	-	No
Mashru [69]	31	F	-	Yes
Matalia [70]	16	F	-	Yes
Matsumoto-Otake [71]	31	F	-	Yes
McDonald [72]	12	M	Asia	Yes
Milea [73]	32	F	Africa	No
Moncada [74]	32	F	Asia	Yes
Nithyanandam [75]	30	F	-	No
Noel [76]	58	F	-	Yes
Noel [76]	48	M	-	No
Noel [76]	58	F	-	No
Ostler [77]	47	M	-	Yes
Padhy [78]	35	M	-	No
Pahwa [79]	27	F	Asia	No
Pallangyo [80]	24	F	Africa	Yes
Paterson [81]	25	F	-	Yes
Paul [82]	30	F	Asia	No
Pelegrin [83]	42	M	Asia	Yes
Peter [84]	37	F	-	Yes
Peter [85]	25	F	-	No
Peter [85]	29	F	-	Yes
Peter [85]	13	F	-	Yes
Peter [85]	28	M	-	No
Rainer [86]	30	F	-	Yes
Rahman [87]	22	F	Asia	No

Table 1. *Cont.*

First Author	Age	Sex	Patient's Origin (Continent)	New Diagnosis of TA
Rajshri [88]	50's	M	-	Yes
Ramteke [89]	48	F	-	Yes
Reddy [90]	27	F	-	No
Rodriguez [91]	26	F	-	Yes
Sakthiswary [92]	20	F	-	Yes
Santhanam [93]	19	F	-	Yes
Setty [94]	23	F	-	Yes
Setty [94]	23	F	-	Yes
Shailaja [95]	22	F	-	Yes
Shrestha [96]	20	F	-	Yes
Shukla [97]	44	F	Asia	Yes
Smith [98]	36	F	Asia	Yes
Stone [99]	13	F	North America	Yes
Strauss [100]	25	F	Asia	Yes
Subira [101]	32	F	-	Yes
Suematsu [102]	34	F	-	Yes
Suh [103]	52	F	-	Yes
Sureja [104]	48	F	-	Yes
Tani [105]	42	M	-	Yes
Taylan [106]	40	F	-	Yes
Tian [107]	23	F	Asia	Yes
Topcuoglu [108]	42	F	-	Yes
Torun [109]	20	F	-	No
Ueno [110]	17	F	Asia	No
Wu [111]	13	F	-	Yes
Zahaf [112]	20	F	-	Yes
Zeng [113]	29	F	Asia	No

Table 2. Ophthalmological symptoms reported by patients with TA.

Ophthalmological Symptoms	Number of Cases	% of Cases
Amaurosis fugax	31	25.4
Diplopia	2	1.6
Orbital pain	4	3.3
Ocular pain	21	17.2
Gradual visual acuity decrease	64	52.5
Sudden visual acuity decrease/loss	28	23.0
Ocular redness	16	13.1
Photophobia	10	8.2
Metamophopsia	1	0.8
Xanthopsia	1	0.8
No eye movement	1	0.8

Table 3. Ocular manifestations of TA.

Ocular Manifestation	Number of Cases	% of Cases
Retinal ischemia	70	57.4
Hypertensive retinopathy	7	5.7
Scleritis	9	7.4
Keratitis	3	2.5
Atypical Tolosa Hunt syndrome	1	0.8
Retinal artery occlusion	15	12.3
Cataract	18	14.8
Uveitis	5	4.1
Epiretinal membrane	1	0.8
Episcleritis	1	0.8
Optic neuropathy	22	18.0
Facial nerve palsy	2	1.6
Acquired ocular motor apraxia	1	0.8
Retinal vein occlusion	4	3.3
Ptosis	2	1.6
Ophthalmoplegia	1	0.8
Retinal vasculitis	5	4.1
Sterile corneal melt	1	0.8
Multiple evanescent white dot syndrome	1	0.8
Orbital pseudotumor	1	0.8
Exudative retinal detachment	1	0.8

Table 4. Systemic treatment used in patients with ocular manifestations of TA.

Systemic Treatment	Number of Cases	% of Cases
Systemic steroids	84	68.9
Vascular procedure	39	32.0
Mycophenolate mofetil	6	4.9
Azathioprine	8	6.6
Cyclophosphamide	7	5.7
Methotrexate	33	27.0
Leflunomide	1	0.8
Acetylsalicylic acid	22	18.0
Monoclonal antibody	9	7.4
Antiplatelet drugs	9	7.4
Anticoagulants	9	7.4
Antihypertensives	12	9.8

Table 5. Age distribution of patients with TA's ocular manifestations.

Age Range	Number of Patients	% of Patients
0–10	2	1.6
11–20	24	19.7
21–30	41	33.6
31–40	28	23.0
41–50	15	12.3
51–60	9	7.4
61–70	3	2.5

The mean age of patients with ocular manifestations of Takayasu's arteritis was 31.4 years, with a female-to-male ratio of 4.8:1. The vast majority were aged between 11 and 40 (76.3%) with the peak in the third decade (33.6%). Most patients were from Asia (23.8%). In over 74% of cases, the ocular manifestations preceded the diagnosis of TA. The most common eye disorder accompanying the disease was retinal ischemia (present in 57.4% of patients), followed by optic neuropathy (18%), cataract (14.8%), and retinal artery occlusion (12.3%). Systemic steroid therapy, vascular procedures, and methotrexate were predominantly used as primary treatments for TA (68.9%, 32%, and 27%, respectively). Patients mostly complained of gradual vision acuity loss (52.5%), sudden vision acuity loss (23%), ocular pain (17.2%), and amaurosis fugax (25.4%), with the last one described as transient blurring, fogging, dimming, seeing shades/curtains or "white out". Children (under the age of 18) presented mainly with retinal ischemia (57.1%) and uveitis (28.5%). Out of five cases of uveitis reported in the course of TA, four concerned children. The difference in the prevalence of uveitis in children and adults was statistically significant ($p < 0.05$). The occurrence of other ocular manifestations and symptoms of TA was similar in children and adults. No statistically significant difference in the prevalence of any ocular manifestation of TA was found in the gender subgroup analysis (men vs. women).

4. Discussion

The first description of a patient suffering from TA dates back to 1908 and is attributed to Mikito Takayasu [114]. The Japanese ophthalmologist had observed malformations of the retinal blood vessels and shared his findings with fellow physicians, who ascribed similar findings to patients with an impalpable pulse. A classification of specific retinal disorders was introduced in 1976 by Uyama and Asayama [115]. In 1990, the American College of Rheumatology published criteria for the classification of TA to facilitate the diagnostic process [116]. However, none of the criteria refers to changes in the eye. So even though the eyes of patients with pulseless disease are known to be affected by the systemic condition, no ophthalmological examination is required when establishing a diagnosis. Therefore, some severe ocular manifestations may go unnoticed for an extended time.

Based on the results of our study, the characteristics of patients with ocular manifestations were consistent with the profile of a patient with TA without any eye disorders. Most cases described young women diagnosed and treated in Asia. The majority of patients were in the third decade of their lives, followed by those in their 30 s and teenagers. Although the age range between 20 and 40 is typical for the disease, TA may also affect children. The youngest reported case was 5 years old. Ocular disorders present in relatively young patients should be particularly concerning, as they usually cannot be attributed to other comorbidities that are commonly associated with advanced age.

What seems particularly interesting is that in 91 cases (74.6%), the diagnosis of TA was made after the patients had noticed some ocular problems. The first symptoms of TA might be non-specific (e.g., malaise, fever, fainting) and attributed to many conditions. For this reason, the diagnosis of the disease is challenging and may leave the patient unalarmed for a long time. However, visual decline/loss, ocular pain, or redness of the eyes can prompt

the patient to seek professional medical consultation. That is why ophthalmologists should be aware of the ocular manifestations of pulseless disease, especially in relatively young people without an obvious underlying cause. They should run detailed diagnostics and reach out to angiologists or rheumatologists to ensure comprehensive medical care.

Most patients presented with features of retinal ischemia caused by insufficient blood supply due to the narrowing and fibrosis of the aorta and its branches. In 15 cases, the ocular ischemic syndrome was described as a result of carotid artery stenosis. Even though hypoperfusion retinopathy seems typical of the disease, one must not forget that hypertensive retinopathy may also develop as a result of renal artery stenosis. Therefore, while analysing the results of imaging studies, it may be possible to predict what type of ocular disorder a patient can develop based on the branch of the aorta affected by the disease.

The changes in the blood flow in the course of the disease are secondary to an inflammatory process. Our research has shown that some patients with TA developed ocular manifestations such as scleritis, episcleritis, uveitis, keratitis, which are typically associated with autoimmune diseases. A systemic inflammatory response may lead to a local manifestation of the disease. Bolek et al. reported that in children with TA, inflammation was more severe than in adults [117]. This may partially explain why four out of five cases of uveitis concerned children.

The diagnosis of TA in children is challenging indeed. In Clemente et al.'s material, 26.8% of pediatric TA cases were initially misdiagnosed [118]. As time is of the essence, the sooner the accurate diagnosis is made and the appropriate treatment administered, the smaller the chances of irreversible damage. Ueno et al. described a complete resolution of retinal ischemic features in the fundus in a 17-year-old girl thanks to a proper diagnosis and successful vascular procedure [110].

In most cases analysed in our study (68.9%), systemic steroids were used to induce remission. Additionally, some patients were prescribed immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and leflunomide). This combination is consistent with the 2018 EULAR recommendations for the management of large vessel vasculitis [119]. Zeng et al. also proposed a similar algorithm to cope with ocular ischemia in the course of TA [113]. Moreover, their systematic review suggested surgical intervention in conjunction with medications in order to achieve the best results. According to our results, vascular procedures were performed in only 32% of cases. However, it should be noted that some cases date back to the second half of the previous century, and not all of the operative techniques were commonly used then. Furthermore, several patients refused to undergo surgery.

The main limitation of this paper is the inclusion of only case reports and case series. However, we are mainly interested in diseases of low prevalence, for which there are only a few incomplete original studies on a large number of patients ("incomplete" in the sense that some crucial information is missing such as patients' comorbidities, the diagnostics and administered treatment). Clinical knowledge of rare diseases often relies on case reports, which can have significant implications for healthcare decision-making. Conducting future multicenter research involving a large number of patients could provide clinicians with guidelines on managing ocular manifestations of TA.

5. Conclusions

Ophthalmologists must be aware of the possible ocular symptoms of TA to ensure the patient gets a correct diagnosis and treatment without significant delay. Young people presenting with ocular disorders and without any known comorbidities should be particularly alert. The multidisciplinary cooperation between ophthalmologists, angiologists, and rheumatologists is crucial, as eye disorders may be the first sign of TA. Raising awareness among patients with TA about possible ocular complications is also crucial to accelerating the administration of appropriate treatment. Conducting screenings for patients with pulseless disease may be beneficial in detecting early abnormalities.

Supplementary Materials: The following supplementary material can be downloaded at https://www.mdpi.com/article/10.3390/jcm12113745/s1, Table S1. Ophthalmological symptoms reported by TA patients. Table S2. Ocular manifestations of TA. Table S3. Systemic treatment in patients with ocular manifestations of TA.

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9. ARTYKUŁ CZWARTY

Evaluation of Choroidal and Retinal Features in Patients with Primary Vasculitis – An Original Optical Coherence Tomography and Optical Coherence Tomography Angiography Study.

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Evaluation of Choroidal and Retinal Features in Patients with Primary Vasculitis—An Original Optical Coherence Tomography and Optical Coherence Tomography Angiography Study

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Abstract: Ocular manifestations have been described in the course of various types of vasculitis. However, there seems to be no routine ophthalmological examinations for patients suffering from those diseases. To ensure holistic care we aimed to investigate any retinal and choroidal abnormalities in patients suffering from primary vasculitis. The objective was to use non-invasive methods, which would not be time- and cost-consuming, yet would be helpful in routine tests. We conducted a prospective and observational study in 41 patients (78 eyes) with 5 types of primary vasculitis, including: Takayasu's arteritis; giant cell arteritis; Buerger's disease; granulomatosis with polyangiitis; and polyarteritis nodosa. A total of 44 healthy individuals were enrolled in the control group for comparison (88 eyes). With the use of optical coherence tomography, optical coherence tomography angiography, and MATLAB, the following parameters were assessed: choroidal thickness; vascularity index; area and perimeter of foveal avascular zone; and circularity index. The following parameters were lower in the study group compared to the control group: mean nasal and temporal CTs; mean central, temporal, and nasal CVI; and mean CI. In contrast, the results of mean central CT as well as the area and perimeter of FAZ were higher in the study group. The differences were statistically significant in the case of all parameters except for CI. Conducting routine ophthalmological examinations in patients diagnosed with vasculitis by assessment of the retina and choroid by measuring parameters like CT, CVI, area and perimeter of FAZ, and CI could be beneficial, as it may detect pathological changes before any ocular symptoms alarm the patients. CVI seems to be especially promising for choroidal evaluation, as it appears to be less influenced by various factors compared to CT.

Keywords: vasculitis; choroidal vascularity index; FAZ; circularity index; OCT; OCTA

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1. Introduction

Vasculitis is a term for a group of rare diseases in which an inflammation of the blood vessels develops. This results in thickening of the blood vessel wall, stenosis, and eventually reduction of blood flow to various tissues and organs [1,2]. The pathological process may affect the area surrounding the lesion as well as peripheral areas and visceral organs [3]. Vasculitis can be classified according to the size of the blood vessels affected by the inflammation (large, medium, or small vessel vasculitis) or the underlying cause of the disease—primary (with no certain cause) and secondary (to other diseases or drug-induced) [3]. The pathogenesis of primary vasculitis is not fully known. A combination of genetic and autoimmune factors is usually taken into account [1,2]. In the cases of Takayasu's arteritis (TA), giant cell arteritis (GCA), and Buerger's disease, the involvement of various types of human leukocyte antigens (HLAs) has been documented [4,5].

Polyarteritis nodosa (PN) has been associated with immune complex deposition, while granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) have been linked to the presence of antineutrophil cytoplasmic antibodies (ANCA) [4,6]. The diagnostic process is often challenging and involves comprehensive examinations, including laboratory and imaging tests, to rule out other systemic diseases [4]. The treatment of vasculitis typically involves the use of steroids and immunosuppressive drugs, with monoclonal antibodies also reported as beneficial [3,4].

Ocular manifestations have been documented in various types of vasculitis. Turk et al. conducted a systematic review and meta-analysis examining the involvement of the eye in systemic diseases, including GCA and GPA [7]. The prevalence of ocular disorders present in those two types of primary vasculitis was established to be 27% and 26%, respectively. Between 10% and 20% of patients diagnosed with PN develop ophthalmic or neuro-ophthalmic signs and symptoms, whereas in the case of Kawasaki disease (KD), the presence of eye disorders reaches 90% [8,9]. Our findings, described in a systematic review and meta-analysis focusing on ocular manifestations of TA, revealed that in over 74% of the analyzed cases (122 patients), ophthalmic pathologies preceded the diagnosis of TA [10]. Although the association between primary vasculitis and ocular manifestations is well-known, routine ophthalmological examinations for patients with these diseases seem to be lacking, despite the potential for systemic inflammation and ischemia to lead to severe ophthalmic complications.

To ensure holistic care we aimed to investigate any retinal and choroidal abnormalities in patients suffering from primary vasculitis. The objective was to use non-invasive methods, which would not be time- and cost-consuming, yet would be helpful in routine tests. In the case of diabetes mellitus, a systemic disease (DM), routine ophthalmological examinations have become a standard practice [11]. The goal is to detect ocular complications of the disease, even before the patients notice any symptoms. It might be worth considering such examinations for patients diagnosed with vasculitis as well. In recent years, optical coherence tomography angiography (OCTA) has gained widespread use, as an examination method. It offers increased safety compared to conventional angiography techniques, both qualitative and quantitative analysis of the retina and the choroid, as well as shorter examination time [12]. These attributes can be particularly beneficial when conducting screening or routine tests. Lately, a parameter called choroidal vascularity index (CVI), which can be calculated on the basis of OCTA results, has gained more attention. It is defined as a ratio of vascular area to the total choroidal area [13]. Evereklioglu et al. examined patients with Behcet's disease, another type of primary vasculitis, and concluded that lower CVI values were present in patients with both active and inactive forms of ocular Behcet's disease compared to the control group, whereas there were no differences between patients with non-ocular Behcet's disease and the control group [14]. In our study, we decided to assess the choroid by calculating the choroidal thickness (CT) and CVI and the retina with the use of the following parameters: area and perimeter of foveal avascular zone (FAZ); and circularity index (CI).

2. Materials and Methods

We conducted a prospective and observational study in 41 patients with 5 types of primary vasculitis: TA (n = 8); GCA (n = 5); Buerger's disease (n = 11); GPA (n = 12); and PN (n = 5). A total of 78 eyes were included in the study group. A total of 4 eyes were excluded because of reduced quality of the obtained images. The diagnoses of GCA, TA, GPA, and PN were based on ACR criteria. For Buerger's disease, Shinoaya's criteria were used. An approval from the local Ethical Committee was granted. In addition to the diagnosis of the five selected diseases, another inclusion criterion was the presence of active disease. All patients in the study group were hospitalized due to the necessity of initiating treatment. In some cases, the diagnosis of vasculitis was newly established, while others experienced a relapse of the disease. All patients received the appropriate treatment. Ophthalmological examinations were conducted immediately before the initiation of treatment. The ages of

the patients ranged from 24 to 71, with the mean value being equal to 50.9. In addition, 44 healthy individuals were enrolled in the control group for comparison (88 eyes; mean age 36.3).

The patients underwent complete ophthalmological diagnostics, in which the following examinations were performed: best-corrected visual acuity; intraocular pressure (air puff measurement); slit-lamp examination with dilated fundus examination; optical coherence tomography (OCT; Heidelberg Engineering, Heidelberg, Germany); and OCTA (RTVue XR 100 Avanti Edition, Optovue Inc., Fremont, CA, USA).

OCTA examination involved taking 6 × 6 mm scans of the retina with the fovea being in the center. The built-in software enabled the extraction of superficial and deep retinal capillary plexus images. Numerical values of the area and perimeter of FAZ as well as CI were obtained with the use of the MATLAB software (R2018a, MathsWorks, Inc., Natick, MA, USA). A low-pass filter and an active contour method were employed to determine the perimeter pixels and center of the FAZ. The following pattern was used to calculate CI: $CI = 4\pi \times (area/perimeter^2)$. A more detailed description of this part of the methodology was presented by one of our co-authors in a study concerning glaucomatous macular vasculature [15].

The OCT examination enabled acquisition of 21 volume B-scans using the enhanced depth imaging (EDI) mode, with the scans centered on the fovea. Subsequently, images were exported for further analysis, focusing on the subfoveal choroidal area with a width of 1.0 mm. The first step involved calculating CT, which measures the vertical distance between the outer border of the retinal pigment epithelium (outside the hyperreflective line) to the border of the inner sclera (hyporeflective line). CT was determined using a previously described binarization method, which allows the conversion of a grayscale image into a binary image (comprising dark and light pixels) [16]. Following the CT calculations, the luminal area (LA) was determined, and CVI was calculated using the following formula: CVI = LA/CT. Details of this methodology are comprehensively described by Agrawal et al. [16].

For statistical analysis, MedCalc Statistical Software was used (version 22.007). The analysis was performed to determine potential differences between the study group and the control group as well as within the study group (between the subgroups consisting of patients with different types of vasculitis). The variables were assessed by the Kruskal–Wallis test and, additionally, a post-hoc analysis was conducted. The results were considered statistically significant when the value of p was ≤ 0.05.

3. Results

The raw data for choroidal and retinal measured variables can be found in the Supplementary Materials. Table 1 presents mean values for the following choroidal parameters: central, nasal, and temporal CTs; as well as central, nasal, and temporal CVIs. Both parameters were measured at the foveal center and at 500 µm nasally and temporally from the center. The results below are provided for the entire study group and are also presented separately for each type of vasculitis, as well as for the control group.

The mean CT in the study group equaled 341 µm, whereas in the control group, it measured 262 µm. The highest mean value was observed in PN patients, while the lowest was observed in the Buerger's disease subgroup. While a statistically significant difference was found between the study and control groups, no significance was observed among the subgroups. Regarding central CVI, the mean value in our study group was 49.6%, compared to 64.5% in the control group, and this difference was statistically significant. The lowest mean central CVI value was found in GCA patients, while the highest value was seen in the TA subgroup. Post-hoc analysis revealed no statistically significant differences among the subgroups.

Table 1. Mean values of choroidal parameters in the study and control groups.

Group	Mean Central Choroidal Thickness (μm)	Mean Nasal Choroidal Thickness (μm)	Mean Temporal Choroidal Thickness (μm)	Mean Central Vascularity Index (%)	Mean Nasal Vascularity Index (%)	Mean Temporal Vascularity Index (%)
Takayasu's arteritis	355	333	334	52.0	51.5	51.5
Giant cell arteritis	336	319	314	47.4	46.2	46.4
Buerger's disease	333	323	324	49.1	49.0	48.5
Granulomatosis with polyangiitis	334	327	327	48.7	47.7	48.9
Polyarteritis nodosa	356	347	360	51.2	49.3	49.0
Vasculitis (all types)	341	329	330	49.6	48.8	49.0
Control group	262	368	387	64.5	62.0	63.6

Table 2 contains data related to mean values of retinal parameters, including the area and perimeter of FAZ, as well as CI. As in Table 1, these data are provided for the entire group, each subgroup separately, and for the control group.

Table 2. Mean values of retinal parameters in the study and control groups.

Group	FAZ—Area [mm^2]	FAZ—Perimeter [mm]	CI
Takayasu's arteritis	0.36	2.26	0.88
Giant cell arteritis	0.38	2.38	0.85
Buerger's disease	0.34	2.16	0.89
Granulomatosis with polyangiitis	0.33	2.18	0.83
Polyarteritis nodosa	0.26	1.93	0.82
Vasculitis (all types)	0.34	2.18	0.86
Control group	0.26	1.89	0.87

Abbreviations: FAZ—foveal avascular zone.

In the study group, the mean FAZ area equaled 0.34, while in the control group it measured 0.26. Similarly, the mean FAZ perimeter was higher in the study group (2.18 mm vs. 1.89 mm). GCA patients exhibited the highest values for both FAZ area and perimeter, while the PN subgroup had the lowest values. Statistically significant differences were found between the study and control groups for both FAZ area and perimeter, but no significance was observed among the subgroups. Regarding the CI, the mean values were 0.86 for the study group and 0.87 for the control group, with no significant differences between the groups.

A graphical presentation of the data from Tables 1 and 2 can be found in Figures 1–8. In these figures, the median values of the measured parameters for each disease and the control group are indicated by a blue square, while brackets represent the 95% confidence interval. Subgroups are considered separately in each figure.

Figures 1–3 depict central, nasal, and temporal CTs in both the study and control groups.

The values of central, nasal, and temporal CVIs in the study and control groups are presented in Figures 4–6.

Figures 7 and 8 show the FAZ area and perimeter in the study and control groups.

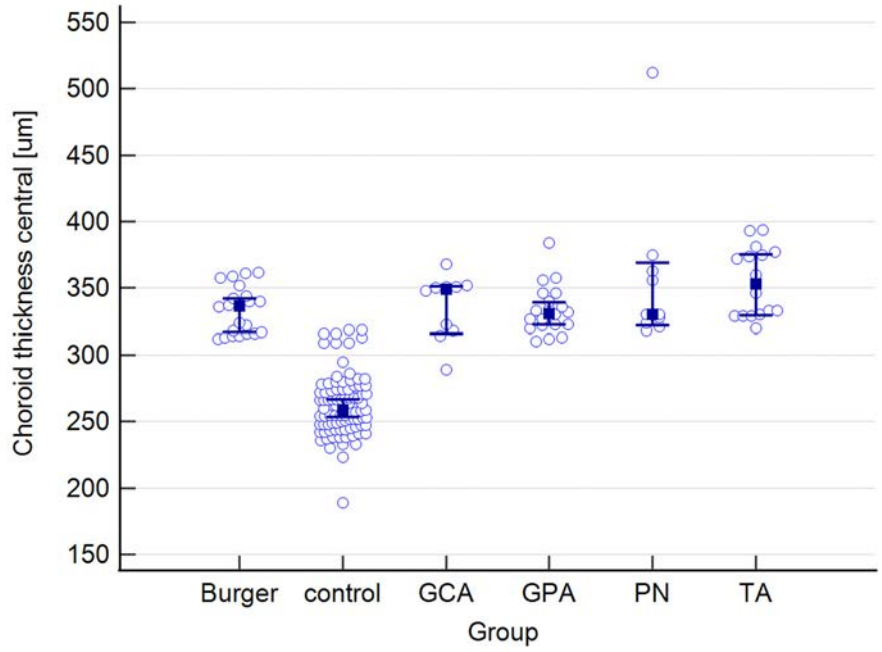

Figure 1. Central choroidal thickness in the study and control groups. Abbreviations: TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

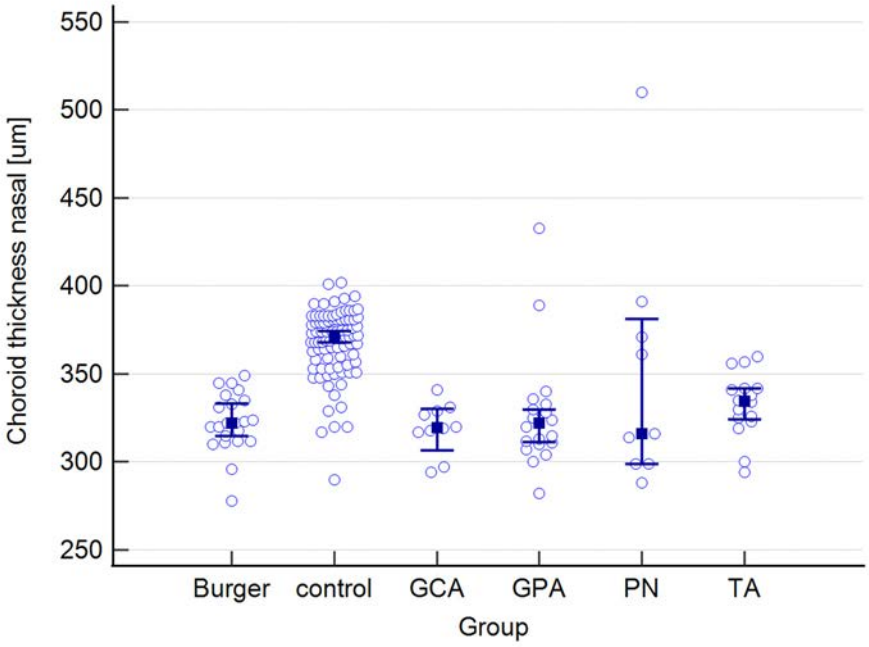

Figure 2. Nasal choroidal thickness in the study and control groups. Abbreviations: TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

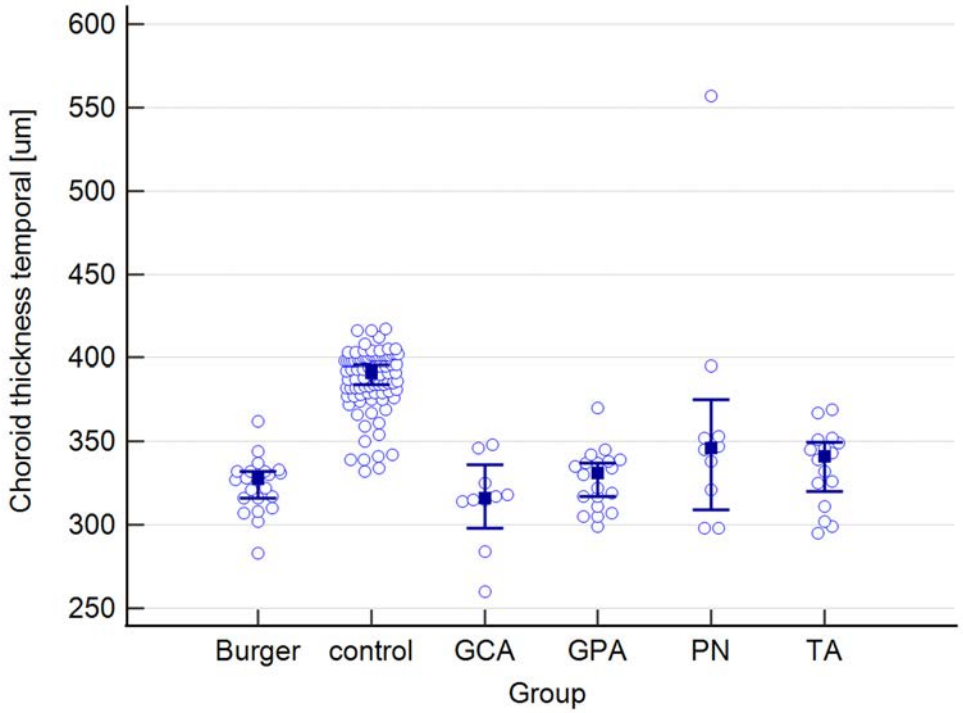

Figure 3. Temporal choroidal thickness in the study and control groups. Abbreviations: TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

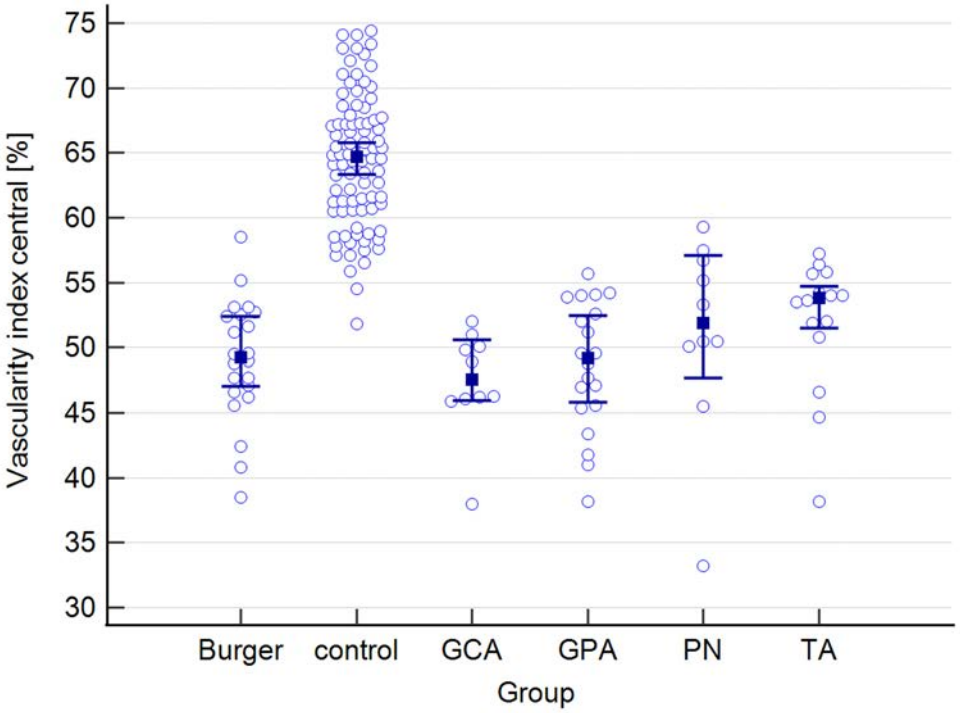

Figure 4. Central vascularity index in the study and control groups. Abbreviations: TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

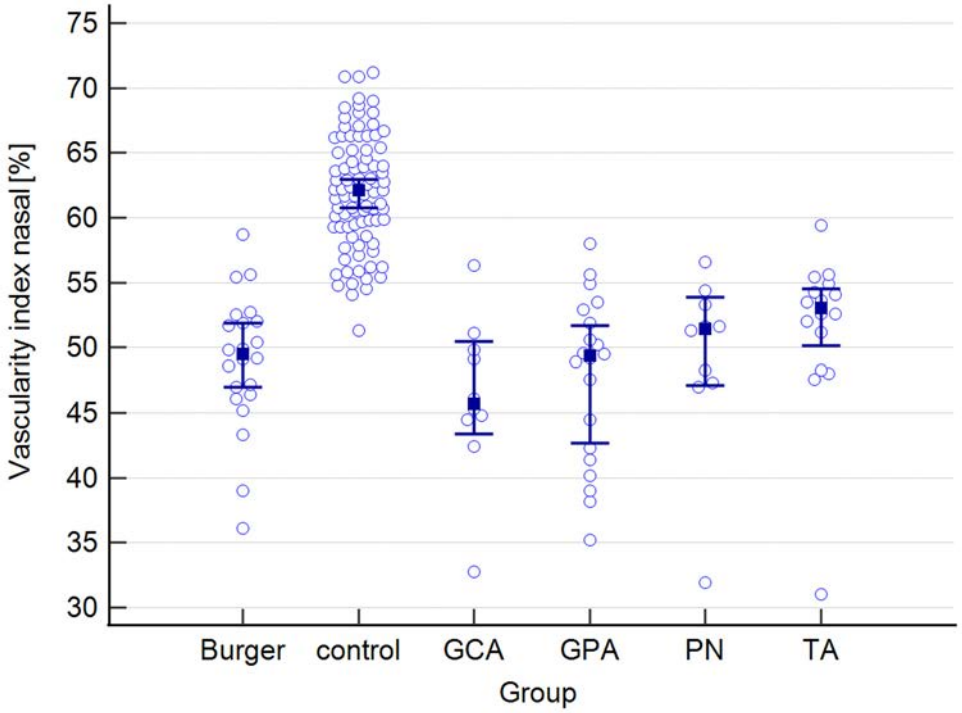

Figure 5. Nasal vascularity index in the study and control groups. Abbreviations: TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

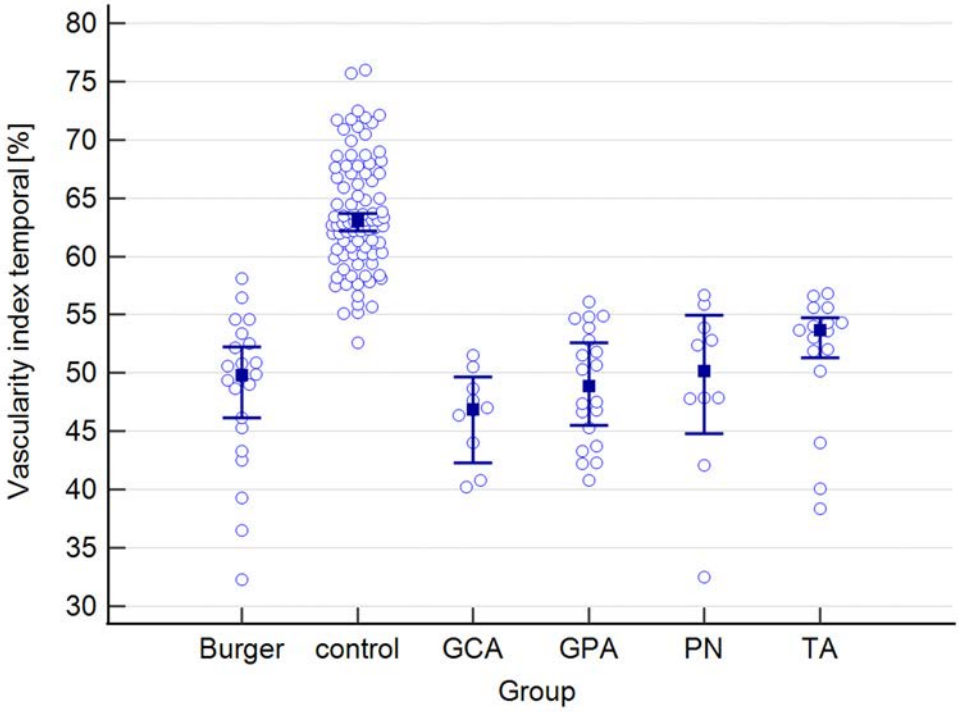

Figure 6. Temporal vascularity index in the study and control groups. Abbreviations: TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

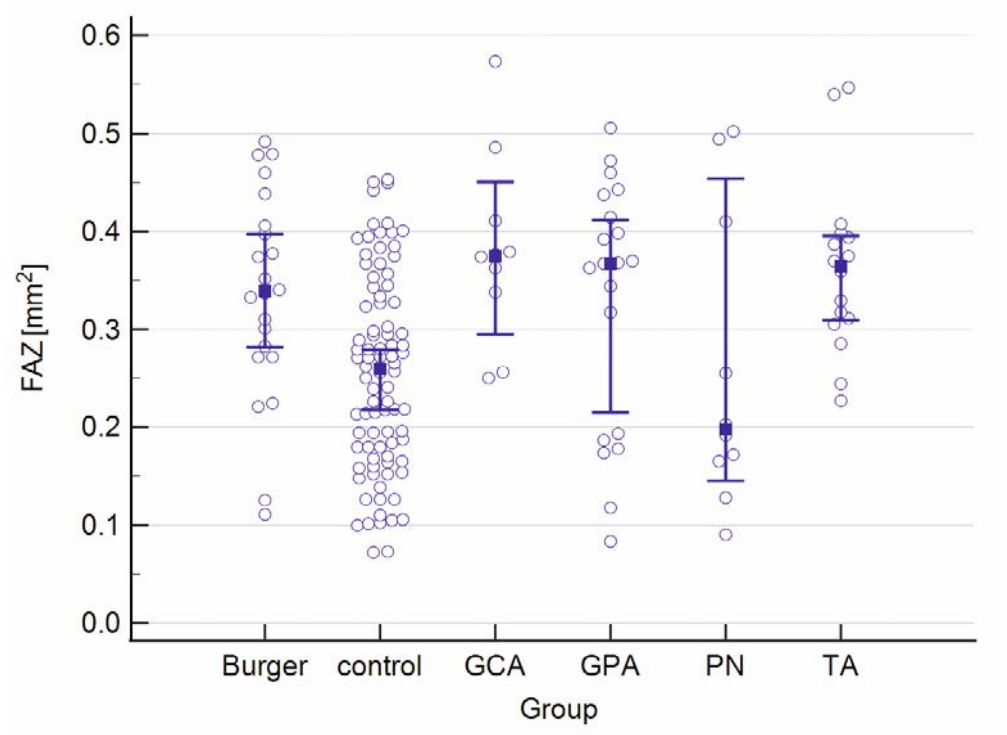

Figure 7. The FAZ area in the study and control groups. Abbreviations: FAZ—foveal avascular zone, TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

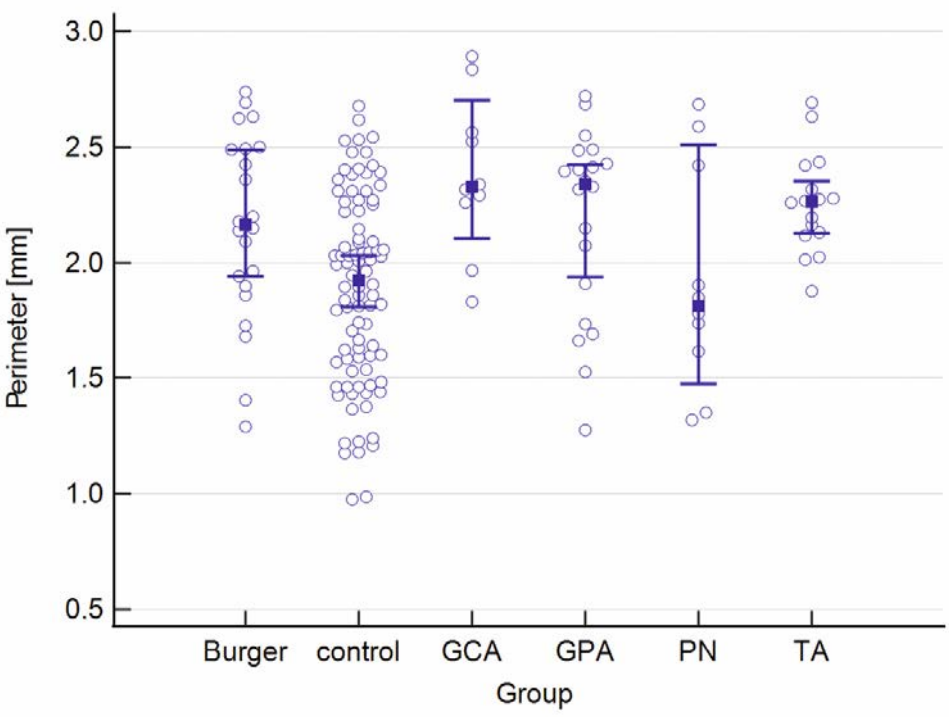

Figure 8. The FAZ perimeter in the study and control groups. Abbreviations: FAZ—foveal avascular zone, TA—Takayasu's arteritis, GCA—giant cell arteritis, GPA—granulomatosis with polyangiitis, PN—polyarteritis nodosa.

4. Discussion

We have decided to measure two parameters when evaluating the choroid: CT and CVI. The first one is considered to be influenced by many factors–refractive error, gender, and age for example [17–19]. That is why a need for a more versatile parameter emerged. In recent years, CVI has become promising in determining the risk of a possible visual impairment. Its decrease has been associated with many ophthalmological conditions (e.g., age-related macular degeneration) as well as systemic diseases with ocular manifestations (e.g., diabetic retinopathy). CVI appears to be less influenced by the same factors as CT, making it a potentially more valuable parameter for choroidal evaluation [20]. For many years, indocyanine green angiography (ICG) has been regarded as an examination dedicated to the assessment of the choroid. Its huge advantage is a much wider field of imaging compared to non-invasive techniques and the ability to characterize the presence of granulomatous lesions in the difficult-to-access peripheral areas [21]. However, its invasive character raises some serious issues as to the safety of the procedure. While OCTA cannot fully replace ICG, especially when diagnosing inflammatory processes, it can be highly beneficial for screening and routine tests and in cases where contrast administration is contraindicated.

The mean central CT value was higher in the study group compared to the control group. While statistical analysis revealed a significant difference, it is worth noting that the results in both groups appear to be within the normal range reported by other authors [22–26]. Higher values of CT in the study group, in comparison to the control group, could be attributed to a subclinical inflammatory process, as proposed by Baytaroğlu et al., in their study on childhood PN [27].

Agrawal et al. measured a mean value of CVI in a group of 345 healthy eyes and the result was equal to 65.61 $\pm$ 2.33% [16]. In a study on healthy subjects conducted by Xuan et al., the CVI was established to be 69.7% [28]. In all our groups, the values of CVI were lower than the results given by previously mentioned authors and were significantly different from the results of our control group. Decreased CVI values have been documented in diabetic retinopathy [29,30]. Chronic inflammation in vasculitis patients can result in vascular stenosis and subsequent ischemic changes. This observation suggests potential similarities between vasculitis and diabetic retinopathy, possibly accounting for decreased CVI values in both conditions.

Even though the CT values in our study were similar to the norms in healthy subjects, the CVI values were lower. This shows that, when evaluating the choroid, one should not solely rely on CT but also incorporate CVI measurements.

The first measured retinal parameter was the area of FAZ. The results of other authors show significant variability when it comes to determining the values of FAZ area among healthy individuals and what is considered a norm. However, the values usually oscillate around 0.2–0.3 [31–35]. Even though the mean FAZ area values in the study and control groups seem to be similar to the previously mentioned norms, a statistically significant difference emerged between these groups, with higher FAZ area values observed in the study group. Information regarding perimeter values in healthy individuals seems scarce. Nevertheless, our findings align with the reported range of 1.7 to 4.3 [35–38]. As with the FAZ area, the mean FAZ perimeter values were higher in the study group compared to the control group, and these differences were statistically significant. It is important to note that, similarly to the FAZ area, perimeter values may be influenced by individual characteristics such as age [38]. The enlargement of the FAZ area is often described in the course of various retinovascular diseases such as diabetic retinopathy [39,40]. Soules et al. compared healthy individuals with patients suffering from diabetic retinopathy, and the results of FAZ area were, respectively, 0.28 and 0.35 [41]. It is not unlikely that the ischemic systemic changes in patients with vasculitis may cause microcirculatory deficiencies similar to diabetic retinopathy and hence the enlargement of the FAZ area and perimeter in our study group. However, what needs to be remembered is that many factors are believed to have an impact on FAZ area, for example age and gender (though the impact of these

factors is debatable) [42,43]. The mean age of our control group was lower than in the study group. The female-to-male ratio also differed (study group—22:19; control group—29:15).

The final assessed parameter was CI. The difference between the study and control groups appeared to be statistically insignificant. This parameter is supposed to provide information about the resemblance of the FAZ shape to a circle. Values closer to 1.0 indicate a more circular FAZ shape [44]. Although this parameter has not been extensively examined so far, we have managed to find mean values in healthy individuals oscillating around 0.7–0.8 [35,37,44–46]. Considerably lower values have been described in the course of glaucoma or diabetic retinopathy [45,47]. It seems that vasculitis does not affect CI in the same way as other conditions that compromise perfusion.

The main limitation of the study is the heterogeneity of the patient group. Primary vasculitis, with which all patients were diagnosed, encompasses a broad group of diseases. This heterogeneity is a common challenge when researching rare diseases. All of the studied types of vasculitis are part of the registry of rare diseases published by organizations such as the National Organization for Rare Diseases (NORD), Genetic and Rare Diseases Information Center (GARD) or European Rare Disease Organisation. Gathering a larger sample is extremely difficult, especially in the areas of low prevalence. Scientific data must be obtained on the bases of case reports, case series, and small sample studies. The mean age of our control group was also lower than that of the study group, and the female-to-male ratio was different in both groups. Some parameters are believed to be influenced by age and gender. Unfortunately, the examinations were conducted during the pandemic, making it exceptionally challenging to recruit healthy volunteers, as the fear of contracting COVID-19 deterred individuals from visiting hospitals and outpatient clinics unless absolutely necessary.

It is also important to look for similar studies conducted on individuals of the same ethnicity, as the results may vary [48]. Unfortunately, we encountered challenges in finding many studies that measure the parameters we examined in a Caucasian population.

5. Conclusions

Vasculitis is a group of diseases affecting various structures of the eyes, including the retina and the choroid. Conducting routine ophthalmological examinations in patients diagnosed with vasculitis with the assessment of the retina and choroid by measuring parameters like CT, CVI, area and perimeter of FAZ, and CI could be beneficial, as it may detect pathological changes before any ocular symptoms alarm the patients. CVI seems to be especially promising for choroidal evaluation, as it appears to be less influenced by various factors compared to CT. However, due to the limited number of ophthalmologically oriented studies on patients with vasculitis, comprehensive analyses are needed for both vasculitis patients as well as healthy individuals in order to establish normative values for many parameters related to retinal and choroidal condition.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12216827/s1, Table S1: Choroidal thickness and vascularity index of patients with vasculitis; Table S2: The area and perimeter of FAZ and circularity index of patients with vasculitis; Table S3: Choroidal thickness and vascularity index of individuals in the control group; Table S4: The area and perimeter of FAZ and circularity index of individuals in the control group.

Author Contributions: Conceptualization, U.S.-P., J.P.-D., A.D. and M.M.-H.; methodology, U.S.-P., J.P.-D., A.D., A.M. and M.M.-H.; formal analysis, U.S.-P., J.P.-D. and A.M.; investigation, U.S.-P.; resources, U.S.-P. and J.P.-D.; data curation, U.S.-P. and J.P.-D.; writing—original draft preparation, U.S.-P.; writing—review and editing, U.S.-P., J.P.-D. and A.M.; visualization, U.S.-P. and J.P.-D.; supervision, M.M.-H. and J.P.-D.; project administration, U.S.-P.; funding acquisition, U.S.-P., J.P.-D. and M.M.-H. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Wrocław Medical University (374/2020, date of approval 22 June 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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11. CURRICULUM VITAE

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- Szkoła Doktorska Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu, Katedra Okulistyki (2019 – 2024)

Praca zawodowa

- Uniwersytecki Szpital Kliniczny im. Jana Mikulicza-Radeckiego we Wrocławiu – staż podyplomowy (2019 – 2020)
- Uniwersytecki Szpital Kliniczny im. Jana Mikulicza-Radeckiego we Wrocławiu, Klinika Okulistyki – specjalizacja (2021 –)

Znajomość języków obcych: język angielski, język niemiecki

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- Grant dla Młodych Naukowców Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu: na badania dotyczące pacjentów chorujących na układowe zapalenia naczyń

12. DOROBEK NAUKOWY (z wyłączeniem prac stanowiących część rozprawy doktorskiej)

12.1 Lista publikacji

1. Janczak Dawid, **Szydełko Urszula**, Apoznański Wojciech, Panek Wojciech, Szydełko Tomasz. W-type suture in Anderson-Hynes laparoscopic pyeloplasty: a novel approach to an old technique, Wideochirurgia i Inne Techniki Maloinwazyjne, 2018, vol. 13, nr 4, s. 512-517, DOI:10.5114/wiitm.2018.76087
2. Panek Wojciech, Janczak Dawid, Panek Marta, **Szydełko Urszula**, Chrzan Rafał, Chabowski Mariusz, Szydełko Tomasz. Quality of life of patients after laparoscopic pyeloplasty due to ureteropelvic junction obstruction: a long-term observation, Advances in Experimental Medicine and Biology, 2021, vol. 1335, s. 45-51, [Publikacja w serii wydawnictwa Springer], DOI:10.1007/5584_2020_616
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12.2 Doniesienia zjazdowe

1. **Szydełko Urszula**, Pytrus Wiktoria. Zajęcie narządu wzroku w przebiegu kiły. IX Międzynarodowa Konferencja OKULISTYKA– KONTROWERSJE. Wrocław. 2019
2. **Szydełko Urszula**, Pytrus Wiktoria, Bulek Magdalena, Juszkiewicz Sara. The Resurgence of Syphilis – Ocular Manifestations of the Disease (Case Study). World Ophthalmology Congress. Capetown. 2020
3. Szmigiel Marta, Dołyk Irena, Geniusz Malwina, **Szydełko Urszula**, Przeździecka-Dołyk Joanna. Soczewki kontaktowe w dobie COVID-19 – przegląd aktualnych wytycznych i wskazówek klinicznych. e-Okulistyka. Wrocław. 2020.
4. **Szydełko-Paśko Urszula**, Turno-Kręcicka Anna. Obustronne herpetyczne zapalenie siatkówki. XI Międzynarodowa Konferencja OKULISTYKA – KONTROWERSJE. Karpacz. 2021

5. Misiuk-Hojło Marta, **Szydełko-Paśko Urszula**. Zmiany w wytycznych Polskiego Towarzystwa Diabetologicznego 2021 w leczeniu retinopatii cukrzycowej – wpływ na działania okulisty. Konferencja Okulistyczna Młode Talenty. Wrocław. 2021
6. Misiuk-Hojło Marta, **Szydełko-Paśko Urszula.** Ozurdex – nie tylko w leczeniu DME**.** XII Międzynarodowa Konferencja OKULISTYKA – KONTROWERSJE. Wrocław. 2022.

13. OŚWIADCZENIA WSPÓŁAUTORÓW

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Wydział Lekarski

Katedra i Klinika Okulistyki

Wrocław, 12.12.2023

DEKLARACJA WSPÓŁAUTORA
Prof. dr hab. Marta Misiuk-Hojło

Wyrażam zgodę na włączenie poniższych prac naukowych, których jestem współautorką, do cyklu publikacji składających się na rozprawę doktorską Urszuli Szydełko-Paśko.

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Dr n.med. Joanna Przeździecka-Dołyk

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13.12.2023 Joanna Przeździecka-Dołyk
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DEKLARACJA WSPÓŁAUTORA
Dr hab. n. med. Anna Turno-Kręcicka, prof. UMW

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Wrocław, 03.01.2024

DEKLARACJA WSPÓŁAUTORA
Prof. dr hab. Andrzej Szuba

Wyrażam zgodę na włączenie poniższej pracy naukowej, której jestem współautorem, do cyklu publikacji składających się na rozprawę doktorską Urszuli Szydełko-Paśko.

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Wrocław, 15.12.2023

DEKLARACJA WSPÓŁAUTORA
Dr hab. n.med. Rafał Małecki

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15.12.23 Rafał Małecki

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Dr n. med. Andrzej Dołyk

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DEKLARACJA WSPÓŁAUTORA
Lek. Julia Kręcicka

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Wrocław, 03.01.2024

DEKLARACJA WSPÓŁAUTORA
Dr n.med. Łukasz Nowak

Wyrażam zgodę na włączenie poniższej pracy naukowej, której jestem współautorem, do cyklu publikacji składających się na rozprawę doktorską Urszuli Szydełko-Paśko.

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