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Aspekty diagnostyczne atypowych parkinsonizmów

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

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Key words

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Spis treści

Wykaz używanych skrótów

- AD- choroba Alzheimera
- APS- atypowy parkinsonizm
- BBB- bariera krew-mózg
- CBD- zwyrodnienie korowo-podstawne
- CBS- zespół korowo-podstawny
- FAB- Frontal Assessment Battery
- FTD- otępienie czołowo-skroniowe
- HDL- lipoproteina wysokiej gęstości
- IFNα2- interferon α2
- IFNγ- interferon γ
- IL-1β- interleukina 1β
- IL-2- interleukina 2
- IL-4- interleukina 4
- IL-6- interleukina 6
- LDL- lipoproteina o niskiej gęstości
- MHC II- główny układ zgodności tkankowej klasy II
- MoCA- Montrealska Skala Oceny Funkcji Poznawczych
- MRI- rezonans magnetyczny
- MSA- zanik wieloukładowy
- NHR- stosunek neutrofili do lipoproteiny o wysokiej gęstości
- NLR- stosunek neutrofili do limfocytów
- OUN- ośrodkowy układ nerwowy
- PD- choroba Parkinsona
- PET- pozytonowa tomografia emisyjna
- PLR- stosunek płytek krwi do limfocytów
- PMR- płyn mózgowo-rdzeniowy
- PSP- postępujące porażenie nadjądrowe
- PSP-P- postępujące porażenie nadjądrowe typu parkinsonowskiego
- PSP-RS- postępujące porażenie nadjądrowe–zespół Richardsona
- PSP-CBS- postępujące porażenie nadjądrowe–zespół korowo-podstawny
- SPECT- tomografia emisyjna pojedynczego fotonu
- TCS- przezczaszkowe badanie ultrasonograficzne
- TDP-43- trans-activation response DNA-binding protein of 43 kDa
- TNFβ- czynnik martwicy nowotworu β

Streszczenie w języku polskim

Wstęp:

Zespół parkinsonowski występuje głównie w chorobie Parkinsona (PD). Rzadziej można go obserwować w grupie atypowych parkinsonizmów (APS), która składa się między innymi z postępującego porażenia nadjądrowego (PSP), zespołu korowo-podstawnego (CBS) i zaniku wieloukładowego (MSA). Fenotypy tych zaburzeń nakładają się na siebie, co stanowi trudność w odpowiednim zaklasyfikowaniu schorzenia. Pewna diagnoza jedynie może być postawiona na podstawie pośmiertnego badania neuropatologicznego. Przyżyciowo, możliwe jest tylko prawdopodobne rozpoznanie APS, które obarczone jest stosunkowo wysokim ryzykiem popełnienia błędu. Celem niniejszego cyklu publikacji jest przedstawienie trudności diagnostycznych APS oraz dodatkowych narzędzi, które mogą być potencjalnie użyteczne w różnicowaniu chorób, a także analiza czynników potencjalnie związanych z ich patofizjologią.

Metodologia:

Do realizacji pracy przeglądowej wykonano szczegółowy przegląd literatury, korzystając z medycznych źródeł dostępnych w bazie PubMed. Wybrane badania poddano ocenie i analizie w kontekście możliwej asymetrii w badaniach klinicznych i obrazowych występującej w atypowych parkinsonizmach. W publikacji porównującej 2 tauopatie - PSP i CBS, podzielono badanych na 3 grupy, odpowiednio z rozpoznaniem PSP, CBS oraz grupę z rozpoznaniem PD. Zbadano perfuzję wybranych struktur mózgu przy pomocy tomografii emisyjnej pojedynczego fotonu (SPECT), a następnie pobrano od każdego uczestnika próbkę krwi obwodowej. Wyliczono na podstawie otrzymanych parametrów obwodowe czynniki zapalne, które mogą wykazywać zależność z neurodegeneracją. W drugiej pracy badającej 2 najczęstsze typy PSP jakimi są postępujące porażenie nadjądrowe–zespół Richardsona (PSP-RS) i postępujące porażenie nadjądrowe typu parkinsonowskiego (PSP-P) wykonano analizę z wykorzystaniem czynników zapalnych i badań neuropsychologicznych. Do oceny funkcji poznawczych każdego uczestnika użyto Montrealskiej Skali Oceny Funkcji Poznawczych (MoCA) i testu Frontal Assessment Battery (FAB). Następnie analogicznie względem poprzedniej publikacji zbadano surowicę uczestników badania oraz obliczono na jej podstawie wartości obwodowych czynników zapalnych. Analizę poszerzono o ocenę stężeń interleukin otrzymanych zarówno z surowicy jak i płynu mózgowo-rdzeniowego (PMR).

Wyniki:

W pracy oceniającej związek perfuzji badanych rejonów mózgu, a obwodowymi markerami zapalnymi, przedstawiono negatywną korelację między stosunkiem neutrofili do lipoproteiny

wysokiej gęstości (NHR) a obustronną perfuzją wysp i wzgórz wśród chorych z rozpoznaniem CBS. W badaniu analizującym zaburzenia funkcji poznawczych względem obwodowych czynników zapalnych stwierdzono negatywną zależność pomiędzy punktacją w MoCA, a wskaźnikami takimi jak stosunek płytek krwi do limfocytów (PLR) i stosunek neutrofili do limfocytów (NLR). Ostatni wskaźnik wykazuje także ujemną korelację z wynikami uzyskanymi w teście FAB. Dodatkowo uzyskano pozytywną zależność stężenia interleukiny 1β (IL-1β) w surowicy w odniesieniu do funkcji poznawczych mierzonych z pomocą MoCA. Nie stwierdzono korelacji parametrów neuropsychologicznych z innymi zapalnymi parametrami obwodowymi we krwi oraz badanymi interleukinami w PMR.

Wnioski:

Cykl przedstawia zasadność oceny obwodowych markerów zapalnych w ramach rutynowych badań u pacjentów z podejrzeniem APS. Pomimo relatywnie niskiej czułości i swoistości, narastanie wyżej wymienionych czynników wydaje się zaburzać funkcjonowanie poznawcze w tych jednostkach chorobowych. Natomiast dane wskazują, że interleukina 1β ma potencjalnie powiązanie z protekcyjnym efektem dotyczącym funkcji poznawczych, jednak z uwagi na brak powiązania MoCA z parametrem w płynie mózgowo-rdzeniowym, wskazana jest dalsza analiza tego parametru oparta na większej liczbie pacjentów. Na podstawie analizy wykonanej w ramach pracy poglądowej wskazane na istotne zróżnicowanie występowania symetrii w ocenie klinicznej i obrazowej w konkretnych rodzajach APS.

Podsumowanie:

Przedstawione publikacje wskazują na potencją użyteczność oceny badań czynników zapalnych w powiązaniu z oceną neuropsychologiczną oraz symetrii w manifestacji klinicznej i obrazowaniu jako badania dodatkowego. W ramach niniejszego cyklu wskazano na konieczność dalszych badań na większych grupach pacjentów, w ramach szerszych paneli parametrów stanu zapalnego, co może pomóc w bardziej wnikliwym zrozumieniu mechanizmów chorobowych i identyfikacji potencjalnych celów terapeutycznych w APS w przyszłości.

Streszczenie w języku angielskim

Introduction:

Parkinsonian syndrome occurs primarily in Parkinson's disease (PD). It is less commonly observed in the group of atypical parkinsonisms (APS), which includes progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and multiple system atrophy (MSA). The phenotypic overlap between these conditions complicates accurate diagnosis. The definitive diagnosis can only be established by postmortem neuropathological examination.
In vivo, only a probable diagnosis of APS can be made, which carries a relatively high risk of misclassification. The aim of this publication series is to present the diagnostic challenges of APS and additional tools that may be potentially useful in differentiating these diseases, as well as to analyze factors potentially related to their pathophysiology.

Methodology:

To conduct the review, a detailed literature search was performed using medical sources available in PubMed. Selected studies were evaluated and analyzed in the context of potential asymmetry in clinical and imaging studies observed in atypical parkinsonism. In a publication comparing two tauopathies - PSP and CBS, participants were divided into three groups: those diagnosed with PSP, CBS, and a control group with Parkinson's disease (PD). Perfusion of selected brain structures was assessed using single-photon emission computed tomography (SPECT), followed by the collection of peripheral blood samples from each participant. Based on the obtained parameters, peripheral inflammatory factors were calculated, which may be associated with neurodegeneration. In the second study investigating the two most common PSP subtypes—progressive supranuclear palsy-Richardson syndrome (PSP-RS) and progressive supranuclear palsy-parkinsonism predominant (PSP-P)—an analysis was conducted using inflammatory markers and neuropsychological assessments. Cognitive function was evaluated in each participant using the Montreal Cognitive Assessment (MoCA) and the Frontal Assessment Battery (FAB). Similarly to the previous study, serum samples were analyzed to determine peripheral inflammatory factor levels. Additionally, the analysis was expanded to include interleukin concentrations measured in both serum and cerebrospinal fluid (CSF).

Results:

In the study assessing the relationship between brain perfusion in selected regions and peripheral inflammatory markers, a linear negative correlation was observed between neutrophil-to-high-density lipoprotein ratio (NHR) and bilateral perfusion of the insulae and

thalami in patients diagnosed with CBS. In the study analyzing cognitive function impairments in relation to peripheral inflammatory markers, a negative correlation was found between MoCA scores and platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) levels. Additionally, NLR also showed a negative correlation with FAB test results. Furthermore, a positive association was identified between interleukin-1β (IL-1β) levels in serum and cognitive function as measured by MoCA. No correlation was found between neuropsychological parameters and other inflammatory peripheral parameters evaluated in serum or the interleukins analyzed in CSF.

Conclusion:

The series highlights the relevance of assessing peripheral inflammatory markers as part of routine examinations in patients with suspected APS. Despite relatively low sensitivity and specificity, the increase in these markers might have a negative impact on cognitive function in these disorders. However, the data suggest that interleukin 1β may be potentially associated with a protective effect on cognitive function. Nevertheless, due to the lack of correlation between MoCA scores and this parameter in cerebrospinal fluid, further analysis based on a larger patient cohort is recommended. Based on the review analysis, significant differences in the presence of symmetry in both clinical and imaging assessments were identified across specific types of APS.

Summary:

The presented publications highlight the potential usefulness of assessing inflammatory markers alongside neuropsychological evaluation and symmetry in clinical manifestation and imaging as an additional diagnostic approach. This series emphasizes the need for further studies on larger patient cohorts, including broader panels of inflammatory parameters in order to enhance understanding of disease mechanisms and identify potential therapeutic targets in APS in the future.

Hipoteza badawcza

Potencjalne znaczenie symetrii, czynników zapalnych w diagnostyce atypowych parkinsonizmów i ich potencjalny wpływ na manifestację kliniczną.

Wykaz publikacji stanowiących rozprawę doktorską

Chunowski P [aut. koresp.], Madetko-Alster N, Alster P. Asymmetry in atypical Parkinsonian syndromes - a review. Journal of Clinical Medicine. 2024.
Punkty IF: 3,0, punkty MNiSW: 140,0, kwartyl Q1

Chunowski P [aut. koresp.], Migda B, Madetko-Alster N, Migda A, Kutyłowski M, Królicki L, Alster P. The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study. Frontiers in Neurology. 2024.
Punkty IF: 2,7, punkty MNiSW: 100,0, kwartyl Q2

Chunowski P, Otto- Ślusarczyk D, Duszyńska-Wąs K, Drzewińska A, Załęski A, Madetko-Alster N, Wiercińska-Drapało A, Struga M, Alster P. Possible impact of peripheral inflammatory factors and interleukin-IB (IL-IP) on cognitive functioning in progressive supranuclear palsy-richardson syndrome (PSP-RS) and progressive supranuclear palsy-predominant parkinsonism (PSP-P). International Journal of Molecular Sciences. 2024.
Punkty IF: 4,9, punkty MNiSW: 140,0, kwartyl Q1

Sumaryczna punktacja IF: 10,6

Sumaryczna punktacja MNiSW: 380

Wykaz publikacji stanowiących całokształt dorobku naukowego

Szczyrek M, Bitkowska P, **Chunowski P**, Czuchryta P, Krawczyk P, Milanowski J. Diet, Microbiome, and Cancer Immunotherapy-A Comprehensive Review. Nutrients. 2021.
Punkty IF: 6,706, punkty MNiSW: 140,0, kwartyl Q1

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Punkty IF: 3,0, punkty MNiSW: 140,0, kwartyl Q1

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Punkty IF: 2,7, punkty MNiSW: 100,0, kwartyl Q2

Chunowski P, Otto- Ślusarczyk D, Duszyńska-Wąs K, Drzewińska A, Załęski A, Madetko-Alster N, Wiercińska-Drapało A, Struga M, Alster P. Possible impact of peripheral inflammatory factors and interleukin-Iβ (IL-I) on cognitive functioning in progressive supranuclear palsy-richardson syndrome (PSP-RS) and progressive supranuclear palsy-predominant parkinsonism (PSP-P). International Journal of Molecular Sciences. 2024.
Punkty IF: 4,9, punkty MNiSW: 140,0, kwartyl Q1

Sumaryczna punktacja IF: 17,306

Sumaryczna punktacja MNiSW: 520

Łączna liczba cytowani (bez autocytowań) wszystkich publikacji wg bazy Scopus (05.02.2025): 57

Wprowadzenie

Omawiane w niniejszej pracy postępujące porażenie nadjądrowe (PSP), zespół korowo-podstawny (CBS) i zanik wieloukładowy (MSA) należą do heterogennej grupy chorób zbiorczo nazwanej atypowymi parkinsonizmami (APS). [1] Nazwa ta nieprzypadkowo sugeruje podobieństwo do choroby Parkinsona (PD), gdyż choroby te, szczególnie w początkowych fazach charakteryzują się podobnym obrazem klinicznym do PD. [2] Do typowych objawów wiązanych z atypowymi parkinsonizmami należą m.in.: wczesne wystąpienie zaburzeń poznawczych (w PSP i CBS), słaba odpowiedź na lewodopę, znacząca dysfunkcja autonomiczna (w MSA), dysfagia, dysfonia i dyzartria, wczesne i częste upadki oraz szybsza progresja choroby w porównaniu do PD.

W związku z czym, coraz częściej podnoszoną kwestią staje się konieczność opracowania optymalnych narzędzi diagnostycznych. Współczesne kryteria rozpoznania odpowiednio PSP [3] zwyrodnienie korowo-podstawne (CBD) [4] i MSA [5] zapewniają możliwość pewnego rozpoznania wyłącznie na podstawie badania neuropatologicznego mózgu. Obecnie przyżyciowo, możliwe jest stawianie możliwego lub prawdopodobnego rozpoznania. Pomimo licznych publikacji na temat PSP, MSA i CBD zagadnienie symetrii w tych schorzeniach, zwłaszcza w odniesieniu do MSA, pozostaje słabo poznane. Neuroobrazowanie zastosowane w tych jednostkach chorobowych ujawniło zmniejszenie perfuzji, zmniejszenie metabolizmu i atrofię m.in. pnia mózgu, płatów wyspy, płatów czołowych czy struktur głębokich mózgu. [6-8] Jednak patofizjologia tych zaburzeń jest złożona i niejednoznaczna, co skutkuje występowaniem zróżnicowanych hipotez dotyczących patofizjologii, wśród których można wymienić hipotezę naczyniową [9-11] czy zyskująca coraz większą popularność hipotezę zapalną. [11-13] Hipoteza naczyniowa i zapalna wykazują dwukierunkowe powiązanie z jednej strony przewlekły proces zapalny, obecny zarówno lokalnie, jak i na poziomie ogólnoustrojowym, jest uznawany za kluczowy czynnik sprzyjający progresji zmian miażdżycowych. [14] Z drugiej strony, kluczowy czynnik aterogenny jakim jest lipoproteina o niskiej gęstości (LDL) w środowisku błony wewnętrznej naczyń odizolowanej od antyoksydantów osocza, czynnik jest podatny na modyfikacje oksydacyjne. Utleniona forma LDL gromadzi się w blaszkach miażdżycowych wywołując reakcje sprzyjające tworzeniu się procesowi zapalnemu. [15] Co więcej wykazano, różnice w patofizjologii czynników zapalnych w zależności od nasilenia objawów u chorych ze zdiagnozowanymi chorobami sercowo-naczyniowymi. W blaszkach pacjentów objawowych scharakteryzowano odrębną podgrupę limfocytów T CD4+. Natomiast w blaszkach pacjentów bezobjawowych stwierdzono większą aktywność interleukiny-1β (IL- 1β), wydzielanej przez komórki mikrogleju [16], co jest komplementarne z hipotezą zapalną, zakładającą głównie prozapalną aktywację mikrogleju oraz astrocytów w odpowiedzi na uszkodzenie ośrodkowego układu nerwowego (OUN). [17] Procesy zapalne w mózgu mogą zwiększać pobudliwość neuronów, uszkadzać komórki oraz zwiększać przepuszczalność bariery krew-mózg (BBB). [18] W chorobach neurodegeneracyjnych nie tylko upośledzona jest aktywacja mikrogleju, ale także zaburzone jest rozmieszczenie tych komórek. W fizjologicznych warunkach, występowanie

mikrogleju zaobserwowano głównie w obszarach okołonaczyniowych. [17] Postuluje się, że w MSA akumulacja alfa-synukleiny prowadzi do zwiększonej ekspresji cząsteczek głównego układu zgodności tkankowej klasy II (MHC II) na mikrogleju, co może sprzyjać rekrutacji oraz infiltracji limfocytów T CD4+ i monocytów z krążenia obwodowego do ośrodkowego układu nerwowego. [19] W PSP i CBD obecność komórek zapalnych odnotowano w drogach piramidowych i strukturach pozapiramidowych. W PSP zlokalizowany jest również w strukturach móżdżku. [17] Ponadto, nadmierna aktywacja mikrogleju prowadzi do utraty synaps między komórkami nerwowymi [20] oraz wydzielania szeregu cytokin, które prowadzą do neurodegeneracji. [17] W PSP i MSA są to głównie TNF-α, IL-1β, IL-4 i IL-6, które w porównaniu z osobami z PD oraz grupą kontrolną wykazują wyższe wartości stężeń. [21, 22] Warto dodać, że zwiększone stężenie IL-2 występuje w korze przedczołowej mózgu u osób z PSP. [23] Stężenia innych cytokin prozapalnych takich jak m.in. interferon α2 (IFNα2), interferon γ (IFNγ) czynnik martwicy nowotworu β (TNFβ) interleukina 6 (IL-6) [11] czy interleukina 4 (IL-4) wydają się być zmienne. Aktywność zapalna w przypadku PSP-RS jest najbardziej nasilona we wczesnych stadiach choroby, która szybko inicjuje postępującą neurodegenerację najczęściej prowadząc do większego nasilenia objawów. Natomiast w PSP-P odpowiedź zapalna pozostaje stosunkowo stabilna i mniej intensywna, co prowadzi do wolniejszego tempa neurodegeneracji i stosunkowo bardziej korzystnego przebiegu klinicznego. [22] co może wskazywać, iż zapalenie odgrywa kluczową rolę w patogenezie APS i być może odpowiada za szybszą progresję objawów. Stosunek neutrofili do limfocytów (NLR), stosunek neutrofili do lipoproteiny o wysokiej gęstości (NHR) oraz stosunek płytek krwi do limfocytów (PLR) są uznawane jako obwodowe biomarkery stanu zapalnego między innymi w chorobach neurologicznych [24] w tym APS, ponadto dane wskazują na to, że te markery przyjmują wyższe wartości w PSP, w porównaniu do pacjentów chorujących na PD. [12] oraz do grupy kontrolnej. [25] Ponadto wskaźniki wykorzystujące stosunek 2 czynników są mniej narażone na odchylenia związane z wartościami bezwzględnymi pojedynczych elementów. [26]

Cykl składa się 3 powiązanych tematycznie ze sobą publikacji [27-29] wśród których wymienia się jedną pracę poglądową i dwie prace oryginalne o łącznej punktacji Impact Factor wynoszącej 10,6 oraz łącznej punktacji Ministerstwa Nauki i Szkolnictwa Wyższego stanowiącej wynoszącej 380 punktów. Omawiane zagadnienia dotyczą głównie tauopatycznych parkinsonizmów, w mniejszym stopniu położony został nacisk na MSA. Celem niniejszego cyklu artykułów, stanowiącego podstawę przewodu doktorskiego, jest przedstawienie alternatywnych, pomocniczych metod diagnostycznych APS, opierających się zarówno na badaniu klinicznym jak i na badaniach obrazowych.

Omówienie cyklu

Tematyką pierwszej poglądowej pracy było przedstawienie przydatności oceny symetrii objawów w badaniu klinicznym oceny symetrii zmian w rezonansie magnetycznym (MRI) w przezczaszkowym badaniu ultrasonograficznym (TCS), w pozytonowej tomografii emisyjnej (PET) oraz tomografii emisyjnej pojedynczego fotonu (SPECT). Warto zaznaczyć, że aktualnie obowiązujące kryteria diagnostyczne włączają asymetrię jako główne kryterium tylko w odniesieniu do CBS. [4] W kontekście PSP jest to kryterium dodatkowe w przypadku pewnych podtypów choroby, [3] natomiast kryteria MSA nie odnoszą się do symetrii. [5] W CBD o podłożu genetycznym znacznie częściej wykazano symetrię objawów w porównaniu do sporadycznej postaci tej choroby.

Przegląd ten ilustruje różnice w występowaniu symetrycznych objawów w poszczególnych typach APS. W przypadku badania klinicznego ocena nasilenia symetrii pomiędzy poszczególnymi badaniami była trudna do ustandaryzowania, zatem zdecydowano się przyjąć podział na objawy symetryczne lub asymetryczne bez oceny nasilenia zróżnicowania nasilenia objawów pomiędzy stronami ciała pacjenta. Potwierdzono podobny podział proporcji występowania symetrii typowych objawów z uwzględnieniem występowania ich symetrycznie lub asymetrycznie oraz wydzielając osobną grupę objawów dotyczących nieparzystych struktur anatomicznych w badaniach obrazowych. Temat symetrii w APS nie jest szeroko omawiany ani w kryteriach diagnostycznych ani w literaturze. Istnieje istotna predylekcja w częstości występowania symetrii w poszczególnych APS. Postępujące porażenie nadjądrowe–zespół Richardsona (PSP-RS) jest najbardziej symetryczną patologią [30], natomiast najmniejszy odsetek symetrii obserwowany jest w kontekście CBS [31] Różnice w częstości występowania symetrii w tych jednostkach chorobowych mogą być powiązane z obniżonym wiązaniem receptorów D2 zlokalizowanych w prążkowiu. Ocena tego parametru wydaje pomocniczym narzędziem pozwalającym na zróżnicowanie konkretnego typu APS w przypadkach wątpliwych [32] W drugiej pracy analizę najbardziej asymetrycznego APS jakim jest CBS poszerzono o badanie potencjalnej użyteczności diagnostycznej czynników zapalnych w porównaniu do PSP, wykazującego znacznie większy odsetek symetrii w badaniu klinicznym i obrazowym. W tym celu badaniu zostało poddanych 71 osób podzielonych na 3 grupy: CBS, PSP i ostatnią kohortę PD stanowiąca grupę odniesienia. Rozpoznania kliniczne w każdej grupie stawiane były na podstawie najnowszych wytycznych. Każdy z uczestników, bez wywiadu niewyrównanych chorób współistniejących, wyraził pisemną zgodę na udział w badaniu klinicznym. Wykazano istotnie statystycznie bardziej nasiloną hipoperfuzję wyspy i wzgórza w badanych APS, której nie zaobserwowano w odniesieniu do grupy kontrolnej z rozpoznaniem PD. Co więcej, badanie wykazałoodwrotnie proporcjonalna zależność pomiędzy stosunkiem neutrofili do lipoproteiny wysokiej gęstości (NHR), a perfuzją w zakresie wyspy i wzgórza pośród chorych cierpiących na CBS. Przypuszczalnie może być to spowodowane funkcją lipoproteiny o wysokiej gęstości (HDL) hamującą proliferację i różnicowanie komórek prekursorowych monocytów, co skutkuje obniżeniem ich aktywności i w konsekwencji zmniejszeniem ich różnicowania do formy

makrofagów. [33] Mniejsza aktywność makrofagów przekłada się na mniejszą aktywność zapalną. Zmniejszenie stężenia HDL wiąże się z upośledzeniem BBB, co potęguje transport komórek zapalnych do OUN. [34, 35] Odwrotna korelacja NHR z perfuzją wzgórza i wyspy sugeruje także proporcjonalne nasilenie hipoperfuzji dwóch wyżej wspomnianych struktur w związku z nasileniem stanu zapalnego z możliwym przełożeniem na upośledzenie m.in. funkcji poznawczych. Postulowany jest niewielki udział wyspy w obrębie funkcjonowania poznawczego. [36] Wzgórze tradycyjnie uważane jest za strukturę odpowiedzialną za przetwarzanie bodźców czuciowych, natomiast dzięki swoim licznym połączeniom z korą czołową wydaje się brać pomocniczy udział także w funkcjonowaniu poznawczym. [37, 38] Wydaje się zatem, iż hipoperfuzja wyspy i wzgórza nasila zaburzenia poznawcze opisane w kryteriach diagnostycznych CBS [4] Warto podkreślić, że podobnej zależności nie wykazano w kontekście PSP, co może wynikać z faktu, że CBS jest rozpoznaniem znacznie bardziej heterogennym w porównaniu do PSP. CBS jest niejednorodnym syndromem obejmującym patologie takie jak CBD, chorobę Alzheimera (AD), otępienie czołowo skroniowe (FTD), a także zespół o mieszanym fenotypie postępujące porażenie nadjądrowe-zespół korowo-podstawny (PSP-CBS**)** CBS jest związany z białkiem trans-activation response DNA-binding protein of 43 kDa (TDP-43), które jest głównym składnikiem neuronalnych wtrętów tau-ujemnych i ubikwityna-dodatnich sugerując pośrednio ważną rolę TDP-43 w rozwoju chorób neurodegeneracyjnych. [39] Postuluje się że obecność patologii TDP-43 modyfikuje cechy kliniczno-patologiczne CBS. CBS z ciężką patologią TDP-43 to odrębny podtyp kliniczno-patologiczny, charakteryzujący się objawami PSP i nasilonymi zmianami w układzie oliwkowo-mostowo-móżdżkowym. [40]

W związku z wykazaniem hipoperfuzji w zakresie wzgórza i wyspy przekładającej się między innymi na funkcjonowanie poznawcze i brakiem korelacji z hipoperfuzji z NHR u pacjentów z rozpoznaniem PSP, zdecydowano o poszerzeniu diagnostyki dotyczącej zaburzenia funkcjonowania poznawczego, wymienionego w kryteriach diagnostycznych PSP [3] wśród chorych z rozpoznanymi najczęstszymi podtypami PSP jakimi są PSP-RS oraz postępujące porażenie nadjądrowe typu parkinsonowskiego (PSP-P) w odniesieniu do stanu zapalnego mierzonego za pomocą NLR oraz PLR. Analizę poszerzono o zbadanie wpływu IL-1β oraz IL-6 ze względu na przypisywaną, m.in. tym czynnikom, rolę w mechanizmach zapalnych. Funkcjonowanie poznawcze badanych pacjentów zostało ocenione za pomocą najczęściej stosowanego do oceny łagodnych zaburzeń funkcji poznawczych, przesiewowej Montrealskiej Skali Oceny Funkcji Poznawczych (MoCA). [41] Przy użyciu tego narzędzia ocenianych jest 6 domen poznawczych takich jak uwaga, orientacja język, pamięć, funkcje wzrokowo-przestrzenne oraz funkcje wykonawcze. [42] Z powodu statystycznie istotnego częstego występowania zaburzeń wykonawczych występujących w PSP [43] zdecydowano o dokładniejszej ocenie tych funkcji. Aby to osiągnąć użyto narzędzia Frontal Assessment Battery (FAB), ukierunkowanego w większym stopniu na ocenę domen funkcji wykonawczych. [44] Zbadano łącznie 36 osób, z czego 12 z rozpoznaniem PSP-RS zawierająca 5 kobiet i 7 mężczyzn w średnim wieku 70,3 lat, 12 z rozpoznaniem PSP-P

zawierająca 4 kobiety, 8 mężczyzn w średnim wieku 68,8 lat oraz grupę kontrolną o takiej samej liczebności, co 2 grupy kryterialne w przeciętnym wieku 50 lat składającą się z 7 kobiet orz 5 mężczyzn. Funkcje poznawcze tych osób były oceniane za pomocą wyżej wspomnianych przesiewowych testów MoCA i FAB. Od każdego uczestnika badania pobrano krew, z próbki której oceniono parametry niezbędne do wyliczenia wskaźników obwodowych parametrów zapalnych, stężenie IL-1β oraz IL-6. Oceniono także inne parametry stanu zapalnego, aby wykluczyć obecną w chwili badania infekcję ogólnoustrojową. Dodatkowo pobierano płyn mózgowo-rdzeniowy (PMR) celem oceny stężenia wyżej wspomnianych interleukin. Wszyscy chorzy podpisali pisemną zgodę na udział w badaniu, byli zbadani internistycznie i nie byli leczeni psychiatrycznie. Na podstawie uzyskanych danych, wykazano, że istnieje odwrotnie skorelowany związek między NLR oraz uzyskaną punktacją zarówno w teście MoCA jak i w teście FAB. Pokazano także, iż istnieje również odwrotna zależność między PLR i MoCA. Nie odnotowano związku pomiędzy pozostałymi obwodowymi markerami zapalnymi, a parametrami neuropsychologicznymi mierzonymi za pomocą użytych testów. Co ciekawe uwidoczniono także wprost proporcjonalną korelację między stężeniem IL-1β w surowicy a wysoką punktacją w badaniu MoCA. Nie wykazano związku pomiędzy stężeniem wspomnianej interleukiny w PMR ani poziomem IL-6, analizowanym niezależnie w surowicy i PMR, a funkcjami poznawczymi wśród pacjentów cierpiących na PSP. Należy zaznaczyć, że we wnioskach nie wyróżniano poszczególnych typów choroby podstawowej z uwagi na relatywnie niewielką grupę kryterialną i zaistniałą potrzebę zwiększenia istotności statystycznej badania. Wystąpienie słabej ujemnej korelacji IL-1β wyłącznie w odniesieniu do obwodowego stanu zapalnego, bez współwystępowania podwyższonego poziomu przytoczonej cytokiny w PMR, odzwierciedlającej ogólnoustrojowy stan zapalny jest warte uwagi, natomiast sugeruje to konieczność pogłębienia analizy na rozszerzonej grupie pacjentów nie tylko pod względem zwiększonej liczebności ale także innych parametrów takich jak wiek, płeć, pochodzenie objawów czy stopień symetrii objawów. Wydaje się, że stan zapalny również wpływa na funkcje poznawcze nie tylko chorych z rozpoznanym CBS, ale też z rozpoznaniem jednego z dwóch najczęstszych rodzajów PSP. Natomiast w nawiązaniu do pracy nr 2 omawianego cyklu publikacji mechanizmy tych zaburzeń są inne. Jednak, warto podkreślić, że odchylenia funkcji poznawczych mogą być wtórne do występujących w obu wymienionych schorzeniach, zaników korowych zwłaszcza w obrębie płata czołowego.

Wnioski

Analiza PSP, MSA i CBS wykazała, że ocena symetrii zarówno w badaniu klinicznym jak i ocena obecności symetrii typowych obrazów obecnych w badaniach dodatkowych może być dodatkowym narzędziem diagnostycznym ułatwiającym rozpoznanie różnicowe poszczególnych rodzajów APS. Asymetria neurodegeneracji prowadzącej do zróżnicowanych obrazów APS może mieć przełożenie także na neuropsychologiczne aspekty funkcjonowania

pacjentów w zależności od indywidualnej lateralizacji funkcjonalnej mózgu. Sprawność funkcji poznawczych i czołowych mierzonych za pomocą przesiewowych narzędzi neuropsychologicznych (MoCA i FAB) jest odwrotnie proporcjonalnie skorelowana z NLR i PLR wśród chorych z rozpoznaniem dwóch najczęstszych typów PSP – PSP-RS i PSP-P. Natomiast stężenie IL-1β może mieć ochronny wpływ na zachowanie funkcji poznawczych i tym samym jest wprost proporcjonalnie skorelowane z uzyskaną punktacją w wyżej przytoczonych testach. Pomimo ograniczonej czułości i swoistości użytych testów, warta podkreślenia jest ich szeroka dostępność i łatwość przeprowadzenia w codziennej praktyce lekarskiej. Wydaje się, że w CBS spadek stężenia HDL jest jednym z czynników determinujących upośledzenie funkcjonalności BBB, która może wpływać na perfuzję określonych rejonów w mózgowia. Warto podkreślić, że obwodowe czynniki zapalne cechują się stosunkowo niewielką swoistością w odniesieniu do upośledzenia aspektów kognitywnych, jednak wydają się wskazywać określone tendencje. Dalsze badania dotyczące diagnostyki APS winny opierać się na większych grupach pacjentów. Warto również ocenić korelację czynników zapalnych oraz symetrię obecną w badaniu klinicznym i w badaniach obrazowych w odniesieniu do innych tauopatii. Badania wskazują na zasadność przeprowadzenia badań określających korelację obwodowych czynników zapalnych z bardziej zaawansowanymi aspektami funkcjonowania poznawczo-emocjonalnego. Ewentualne wskazanie istoty konkretnych czynników zapalnych, może w przyszłości przełożyć się na określenie potencjalnych punktów uchwytu umożliwiających modyfikację przebiegu chorób, aktualnie pozbawionych skutecznych metod leczenia.

Uwaga

W ostatniej pracy cyklu doktorskiego zatytułowanej: „*Possible Impact of Peripheral Inflammatory Factors and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P)*” sekcja metodologii znajduje się pod sekcją wyników oraz pod dyskusją z uwagi na decyzję redaktora w czasopiśmie International Journal of Molecular Sciences dotyczącą układu publikacji i nie wynikał z pierwotnych intencji autorów.

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Review

Asymmetry in Atypical Parkinsonian Syndromes—A Review

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Abstract: Background/Objectives: Atypical parkinsonian syndromes (APSs) are a group of neurodegenerative disorders that differ from idiopathic Parkinson's disease (IPD) in their clinical presentation, underlying pathology, and response to treatment. APSs include conditions such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and dementia with Lewy bodies (DLB). These disorders are characterized by a combination of parkinsonian features and additional symptoms, such as autonomic dysfunction, supranuclear gaze palsy, and asymmetric motor symptoms. Many hypotheses attempt to explain the causes of neurodegeneration in APSs, including interactions between environmental toxins, tau or α-synuclein pathology, oxidative stress, microglial activation, and vascular factors. While extensive research has been conducted on APSs, there is a limited understanding of the symmetry in these diseases, particularly in MSA. Neuroimaging studies have revealed metabolic, structural, and functional abnormalities that contribute to the asymmetry in APSs. The asymmetry in CBS is possibly caused by a variable reduction in striatal D2 receptor binding, as demonstrated in single-photon emission computed tomography (SPECT) examinations, which may explain the disease's asymmetric manifestation and poor response to dopaminergic therapy. In PSP, clinical dysfunction correlates with white matter tract degeneration in the superior cerebellar peduncles and corpus callosum. MSA often involves atrophy in the pons, putamen, and cerebellum, with clinical symmetry potentially depending on the symmetry of the atrophy. The aim of this review is to present the study findings on potential symmetry as a tool for determining potential neuropsychological disturbances and properly diagnosing APSs to lessen the misdiagnosis rate. **Methods:** A comprehensive review of the academic literature was conducted using the medical literature available in PubMed. Appropriate studies were evaluated and examined based on patient characteristics and clinical and imaging examination outcomes in the context of potential asymmetry. **Results:** Among over 1000 patients whose data were collected, PSP-RS was symmetrical in approximately 84% ± 3% of cases, with S-CBD showing similar results. PSP-P was symmetrical in about 53–55% of cases, while PSP-CBS was symmetrical in fewer than half of the cases. MSA-C was symmetrical in around 40% of cases. It appears that MSA-P exhibits symmetry in about 15–35% of cases. CBS, according to the criteria, is a disease with an asymmetrical clinical presentation in 90–99% of cases. Similar results were obtained via imaging methods, but transcranial sonography produced different results. **Conclusions:** Determining neurodegeneration symmetry may help identify functional deficits and improve diagnostic accuracy. Patients with significant asymmetry in neurodegeneration may exhibit different neuropsychological symptoms based on their individual brain lateralization, impacting their cognitive functioning and quality of life.

Keywords: atypical parkinsonism; PSP; symmetry; neurodegeneration; parkinsonism; movement disorders

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1. Introduction

Atypical parkinsonian syndromes (APSs) are a group of neurodegenerative diseases featuring the intracellular accumulation of amyloidogenic proteins, such as α-synuclein or tau, based on diverse pathologies [1]. Among the diseases in this group are dementia

with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBS). PSP and CBS are rare disorders; more precisely, the prevalence rates of MSA, PSP, and CBS generally fall below 10 per 10^5 individuals [2], with PSP affecting approximately 3 to 7 individuals per 100,000, CBS having a prevalence of around 5 to 7 cases per 100,000, and MSA having a prevalence ranging from 1.9 to 6.2 per 100,000 [2,3]. APSs are commonly primarily misdiagnosed as Parkinson's disease (PD) due to their symptoms frequently resembling those typical of PD in the initial stages [4]. Common symptoms of PD and APSs are collectively referred to as parkinsonism and include rest tremor, rigidity, bradykinesia, and postural instability [5], which is caused by a decline in muscle strength. A significant number of these symptoms can be traced back to compromised skeletal muscle health [6]. Symptoms typical of APSs that differentiate these two conditions are, among others, early autonomic dysfunction, early falls, early cognitive impairment, early bulbar dysfunction, and poor or absent response to levodopa [7–10]. A positive response to levodopa treatment was confirmed in 44% of PSP cases, 52% of MSA patients, and up to 12.5% of individuals with CBS in comparison to PD subjects, where an efficient levodopa response was observed in 91% of cases [11]. Clinically, patients with MSA present with a variable combination of parkinsonian, cerebellar, autonomic, and pyramidal signs. PSP, on the other hand, is characterized by parkinsonism, supranuclear gaze palsy, postural instability, and early falls, which can appear in different subtypes. In contrast, the typical clinical presentation of CBD is corticobasal syndrome (CBS), characterized by parkinsonism, dystonia, myoclonus, cortical sensory loss, ideomotor apraxia, alien limb phenomena with a predominantly asymmetrical distribution, and additional cognitive and behavioral impairments [12]. However, these clinical signs do not offer complete certainty in establishing an APS diagnosis, and many of the symptoms only become apparent in the later stages of the disease [13]; because of this, inadequate diagnosis can occur in up to 24% of PSP cases [14]. It is estimated that individuals meeting MSA criteria were diagnosed properly in 62% of samples [15]. Among patients who received a clinical diagnosis of CBS, only 50% had a confirmed diagnosis of CBD [16]. These data indicate the need to find an additional diagnostic tool. Symmetry is cited as one of the main diagnostic criteria in the context of CBS [8] but only an additional criterion in PSP [9]. According to the diagnostic criteria, it is assumed that PSP is the most symmetrical disease, and on the other end of the spectrum is CBS [8,9]. The diagnosis of Parkinson's disease is determined by the occurrence of unilateral symptoms, especially at the beginning of the disease [17], and these symptoms are consistent with APSs; therefore, early-stage symmetry can potentially indicate a particular APS subtype, which should prompt further diagnostic evaluation, even at an early stage of the disorder. This is why potential symmetry evaluation seems to be a promising additional diagnostic method for differentiating between APSs and PD. However, the current criteria do not address MSA or particular subtypes of tauopathic illnesses. The aim of this review is to present the study findings on the potential symmetry evaluation as a tool for making proper diagnoses and identifying potential cognitive and emotional dysregulation, such as depression, anxiety, agitation, appetite changes, or increased levels of aggression in APSs.

2. Materials and Methods

A review was conducted in order to select suitable studies evaluating subjects with APSs, especially regarding symmetry, published between 1993 and 2024. The search algorithm used the following search terms in Medical Literature, Analysis, and Retrieval System Online (MEDLINE) and the Cochrane Central Register of Controlled Trials (CENTRAL): "asymmetry in atypical parkinsonian syndromes", "MRI in atypical parkinsonian syndromes", "PET in atypical parkinsonian syndromes", "SPECT in atypical parkinsonian syndromes", "transcranial sonography in atypical parkinsonian syndromes", "progressive supranuclear palsy", "corticobasal syndrome", "corticobasal degeneration", "multisystem atrophy", "asymmetry in progressive supranuclear palsy", "asymmetry in multisystem atrophy", "asymmetry in corticobasal syndrome", "asymmetry in corticobasal degeneration".

The review was limited to studies enrolling at least 3 subjects and to articles published in Polish or English. Studies conducted on fewer than 3 participants, those with duplicate cohorts, and those in languages other than Polish or English were excluded from this review.

3. Atypical Parkinsonism's Clinical Symptom Asymmetry

Differentiating between PD and APSs can be challenging due to overlapping clinical manifestations, especially in the initial stages [18]. Progressive supranuclear palsy-Richardson syndrome (PSP-RS) is considered the most common and symmetrical subtype of PSP. Using the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) criteria [19], 18 patients were classified as having PSP, and 7 of them (38.9%) were further classified into the PSP-RS group [20]. Another study, in which 50 PSP patients were thoroughly examined, concluded that 28 of them (56%) had PSP-RS [21]. In this study, 33 patients were excluded due to incomplete data (n = 7) or because they qualified for other phenotypes, such as probable or possible PSP-RS and progressive supranuclear palsy-parkinsonism (PSP-P) or possible progressive supranuclear palsy–corticobasal syndrome (PSP-CBS) (n = 26). Among 334 patients diagnosed with PSP, the majority (72%) were identified as having the PSP-RS subtype using the Movement Disorder Society (MDS) criteria for PSP from 2017 [22]. In total, over 400 people were examined, revealing a significant numerical predominance of PSP-RS diagnoses over other types of PSP. Motor characteristics such as bradykinesia, rigidity, rest tremor, and dystonia were assessed using specific elements from the NNIPPS scale. Features that showed variations in scoring between the right and left sides were considered asymmetric. PSP patients might display asymmetric limb bradykinesia and rigidity [20]. The research demonstrated that parkinsonian syndrome symptoms, including bradykinesia, rigidity with tremor, and other symptoms, such as dystonia or myoclonus, exhibited asymmetry in a significant proportion of PSP-RS cases (53.6%, 21.4%, and 17.9%, respectively). Additionally, a smaller percentage of patients displayed asymmetry in higher cortical functions, such as limb apraxia (35.7%). The higher cortical function assessment comprised 24 activities split evenly, with 12 focusing on symbolic gestures and 12 on nonsymbolic gestures. In certain instances, PSP may manifest symptoms associated with CBS, such as apraxia, the alien limb phenomenon, and the loss of cortical sensory functions. CBS is often suspected when there are asymmetrical signs and symptoms during an individual's lifetime [23]. Both PSP-P and PSP-CBS are considered to express notable asymmetric clinical features. Regarding motor symptoms, rigidity and bradykinesia exhibited asymmetry in over half of 50 participants with different PSP types, according to the MDS criteria, whereas tremor was asymmetric in only 14.3% of cases of probable PSP-RS [22]. In evaluating the eyes, up- and downward asymmetry in vertical saccade velocity was observed in approximately 34% of 80 patients suffering from PSP [24]. The symmetry in eye movement disorders is most likely correlated with the symmetry of midbrain atrophy. In 18 individuals in a small cohort study (PSP-RS (n = 7), PSP-P (n = 3)), progressive supranuclear palsy-pure akinesia with gait freezing (PSP-PAGF) (n = 2), progressive supranuclear palsy-frontotemporal dementia (PSP-FTD) (n = 4), progressive supranuclear palsy-apraxia of speech syndrome (PSP-AOS), and progressive non-fluent aphasia (PSP-PNFA) (n = 2) exhibited symmetrical symptoms [20]. In a retrospective study that examined 25 patients, 9 were classified as having probable PSP-RS, while 16 were assigned to the possible PSP-CBS group. Both groups exhibited asymmetrical dystonia of the limbs, but they did not present cortical signs. However, it should be noted that focal limb dystonia might be an early feature of CBS when compared to cortical dysfunction. Early asymmetric limb dystonia might indicate evolving PSP-CBS rather than PSP-RS and thus requires longitudinal patient follow-up. However, the MDS-PSP criteria do not consider asymmetric dystonia when classifying potential PSP-CBS [25]. Symmetry in PSP can vary, leading to the identification of two subgroups that highlight the degree of symptom symmetry. A hemi-PSP classification was assigned to PSP patients displaying notable asymmetry in rigidity, dystonia, or bradykinesia, in contrast to those with a symmetric

presentation (symPSP). On the other hand, the least symmetrical representative of APSs is CBS, which involves the presence of apraxia, cortical sensory loss, and/or alien limb phenomena, along with an asymmetric hypokinetic disorder, often accompanied by limb dystonia. According to the diagnostic criteria consensus, 23 individuals were diagnosed with PSP, and 8 patients were diagnosed with CBS. Of those with PSP, 14 presented with a symmetric illness manifestation (symPSP, 60.9%), whereas 9 showed a markedly lateralized manifestation (hemi-PSP, 39.1%). In all PSP-P patients, asymmetric symptoms were observed, two out of two PAGF patients had symmetric symptoms, and all CBD patients expressed symptom asymmetry [26], which is consistent with the CBS diagnostic criteria. PSP might also resemble MSA, as mentioned above for PSP-CBS, especially when they are characterized by early falls and a supranuclear palsy affecting vertical gaze [27]. CBS might mimic PSP in terms of symmetry, especially when CBS has a genetic basis. Based on the symmetry of symptoms, 33 CBS patients were divided into two subgroups: S-CBD (n = 5) and CBS (n = 28). The study compared clinical symptoms and signs between the two groups, regardless of whether the manifestation was symmetric or asymmetric. When categorizing the signs as motor, behavioral, language, cognitive, apraxia, and sleep issues, key differences emerged. Notably, behavioral changes were significant in symmetric CBD but not present in CBS. Conversely, language issues, limb apraxia, and several motor symptoms, such as axial rigidity, bradykinesia, myoclonus, alien limb, and the Babinski sign, were prevalent in CBS but absent in cases of symmetric CBD. Both groups exhibited motor symptoms, like limb rigidity, falls, parkinsonism, rest tremor, gaze palsy, hyper-reflexia, and dysphagia, as well as cognitive symptoms, including memory loss and difficulty with calculations. When motor symptoms appeared in CBD and they manifested symmetrically. This disease is conventionally viewed as a sporadic disorder; however, a positive family history of neurodegenerative disease was more prevalent in cases of symmetric corticobasal degeneration (S-CBD), implying a potential genetic predisposition to the development of symmetric degeneration [23]. This is why distinguishing S-CBD from PSP-RS is very hard. Five patients were reported to initially present with highly asymmetric parkinsonism accompanied by dystonia, initially diagnosed as CBS. However, as the disease progressed (approximately five years after disease onset), the parkinsonism became less asymmetric, and the patients developed autonomic features and respiratory issues, ultimately leading to a revised diagnosis of multiple system atrophy-parkinsonism (MSA-P). In this condition type, clearly distinguishable asymmetry is generally rare; because of asymmetric dystonia of the limbs and myoclonic jerks, individuals were incorrectly diagnosed with CBS [28]. According to Kouri et al.'s study, patients with corticobasal degeneration-corticobasal syndrome (CBD-CBS) commonly show asymmetric limb stiffness (asymmetric in 100%), apraxia (asymmetric in 91%), localized limb dystonia, myoclonus, and cortical sensory impairments, more so than those with corticobasal degeneration-Richardson syndrome (CBD-RS). Rigidity is present in 20% of CBD-RS cases, but in PSP-RS, all cases are symmetric. While limb apraxia is infrequent in both CBD-RS and PSP-RS, it appears symmetrically when it occurs, in contrast to the pronounced asymmetric limb apraxia in CBD-CBS patients. Signs of both pyramidal and extrapyramidal disorders are observed at comparable rates among these groups [29]. This may indicate that the degree of symmetry is not directly proportional to the extent of neurodegeneration. MSA patients, in most cases (but not always), have symmetrical rigidity and bradykinesia [30]. Of 16 MSA patients, only 7 showed symmetrical disease symptoms, such as tremor or rigidity [31]. In another study, 20/23 (87%) MSA-P patients and 8/12 (67%) MSA-C individuals exhibited clinical symptom asymmetry [32], which is consistent with Van Laere and colleagues' research, in which a significant difference in the degree of clinical lateralization between PSP and MSA was observed [33]. The symmetry rate is summarised in the Figures 1 and 2.

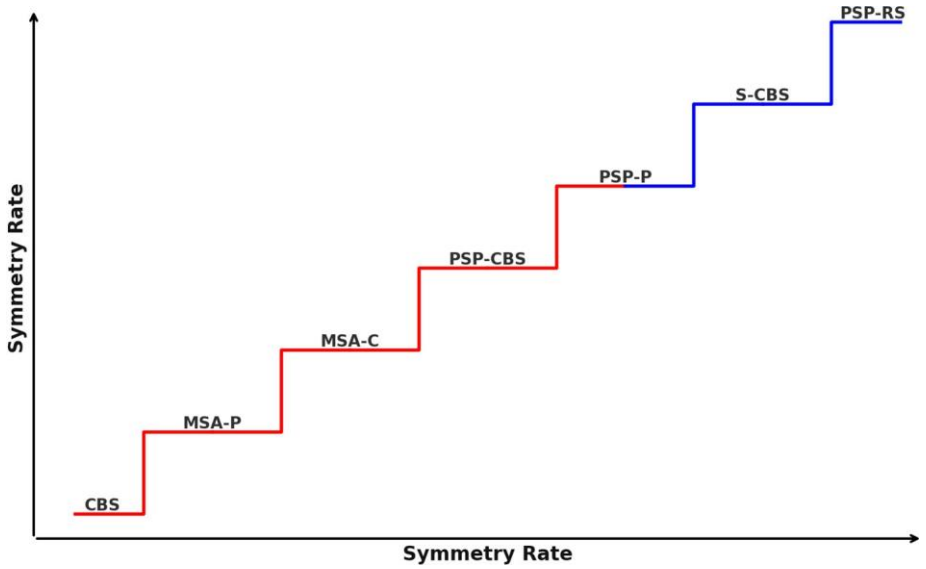

Figure 1. Increase in the percentage of symmetry in different types of APSs. The figure is for illustrative purposes. Red—<50% symmetry rate; Blue—>50% symmetry rate.

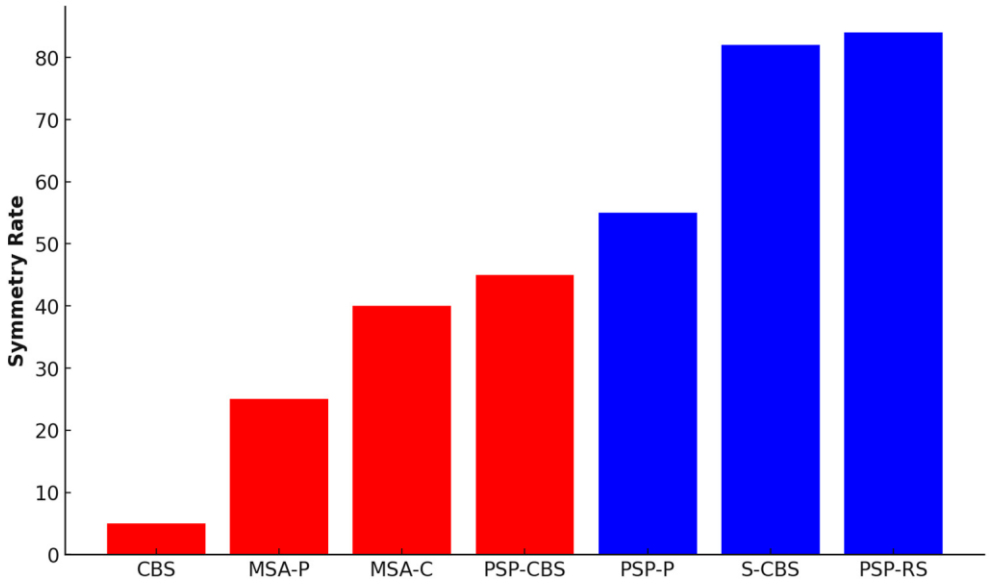

Figure 2. Percentage distribution of the symmetrical occurrence of clinical symptoms in the various types of APSs. CBS is presented collectively (except for S-CBS) due to the very rare occurrence of symmetrical clinical symptoms. Red—<50% symmetry rate; Blue—>50% symmetry rate.

4. Brain Lateralization

Left-handed individuals make up approximately 10% of the population, a rarity that is believed to result from the development of language lateralization in the left hemisphere, which has led to a predominantly right-handed population [34]. The relationship between language lateralization and handedness has been extensively studied. Furthermore, the differences in the brains of left- and right-handed individuals extend beyond language lateralization, encompassing variations in motor and somatosensory networks [35]. There is a belief that hand dominance and skillful learned control are intricately linked. The development and activation of the primary motor cortex show mirror-opposite patterns in right- and left-handers. An analogous shift in dominance to the right hemisphere for different types of praxis might be expected in left-handed persons [36]. Neuroimaging studies have increasingly highlighted these differences through functional activation analyses [35].

5. Imaging Tests

The current diagnostic criteria for PSP and MSA consider imaging of atrophy or hypometabolism using magnetic resonance imaging or PET. CBS criteria do not take into account magnetic resonance imaging (MRI) and positron emission tomography (PET) results [7–9].

6. MRI

Patients with PSP-RS typically present with significant midbrain atrophy. The characteristic imaging features include the "hummingbird" sign, alternatively termed the "penguin" sign, which describes the flat or concave appearance of the midbrain. Additionally, the "morning glory" sign corresponds to the concave aspect of the lateral margin of the midbrain tegmentum on axial slices, and this feature is also observed in PSP-RS. While these imaging characteristics are indicative of PSP-RS, with a specificity of 99.5% for the "hummingbird sign" and 97% for the "morning glory sign", both of them exhibit low sensitivity [4,37–39]. In PSP patients, decreased midbrain [40,41], total brain, and thalamus volumes, along with an increased volume of the ventricles, were observed at both 6 and 12 months when compared to the initial assessment. However, the difference in midbrain volume turned out to be the largest, so the speed of midbrain shrinkage seems to be the most effective measure of PSP progression. It turned out to be a better indicator than the pons-to-midbrain ratio [41]. In each of the mentioned studies, MRI changes did not show clinically significant asymmetry, which is consistent with the fact that PSP-RS is considered the most symmetrical form among atypical parkinsonism syndromes. The volumes of the putamen and globus pallidus within the basal ganglia are observed to be symmetrically smaller compared to those in PD. Additionally, the volume of the thalamus is also symmetrically smaller in PSP-RS. Frontal brain atrophy is observed as well [4]. Atrophy also occurs in cases of CBS. The posterior frontal and parietal lobes consistently exhibited more severe atrophy than other lobes, while atrophy in the occipital lobe was rarely observed. Atrophy in the temporal and anterobasal frontal lobes was frequent but less severe than in the posterior frontal and parietal lobes. Cerebral peduncle atrophy was noted in seven patients, with six of them exhibiting atrophy ipsilateral to the dominant atrophic cerebral hemisphere. Additionally, the dynamics of the atrophy were significant over the course of one year in the patient cohort. Initially, 18 patients presented with asymmetrical parietal cortical atrophy contralateral to the more affected limbs, which increased to 23 patients at follow-up. Initially, 8 patients exhibited both asymmetrical frontal and parietal atrophy, predominantly affecting the posterior frontal areas contralateral to the more affected side, which rose to 12 patients at follow-up. Bilateral parietal atrophy was initially seen in 5 patients, which increased to 10 patients. Subcortical atrophy of the white matter in the corresponding parietal area, initially observed in 7 patients with concurrent lateral ventricle enlargement, was later identified in 15 patients. Lastly, the loss of the putamen signal on high-field T2-weighted MRI was noted in 13 patients initially, which increased to 17 patients after one year. These findings highlight progressive brain atrophy, particularly in the parietal and frontal regions, and increasing signal loss in the putamen over time. It is postulated that CBS subjects exhibit increased levels of depression, anxiety, agitation and aggression, and changes in appetite compared to those with PD, and more than 87% of individuals suffering from CBS developed apathy (in the case of PD, it was 24%) [42], which might be connected with the above-mentioned parietal atrophy, especially when the non-dominant cerebral hemisphere is affected.

Apathy and depression were observed in 13 out of 26 MSA-P patients. Compared to the controls, these patients demonstrated significant cortical thinning in the fronto-temporal-parietal regions, as well as atrophy in the periaqueductal gray matter, left cerebellar hemisphere, left pallidum, and bilateral putamen [43].

Diffusion tensor imaging (DTI) and DTI-based fiber tractography are now commonly used techniques for assessing and illustrating the path, position, and size of significant white matter pathways, including the arcuate fasciculus, corticospinal tract, and optic

radiation [44]. In one study, 27 individuals—9 with CBS and 18 with definite or probable PSP (half of them pathologically confirmed)—were prospectively recruited and underwent 3.0 T DTI. The most prominent areas displaying decreased fractional anisotropy (FA) and heightened mean diffusivity (MD) in subjects with CBS were identified in supratentorial regions, including the body of the white matter regions of the premotor, prefrontal, and motor cortices, as well as the middle cingulate cortex and corpus callosum, in comparison to the control group. The observed abnormalities in both FA and MD exhibited asymmetry, with a more pronounced impact on the hemisphere that was more affected. Additional regions showing reduced FA and increased MD included the parietal lobes and fornix, along with the splenium of the corpus callosum in the more affected hemisphere. Furthermore, diminished FA was noted in the pons and cerebellum in both the more and less affected hemispheres, as well as in the superior cerebellar peduncle of the less affected hemisphere. Elevated MD was also evident in the thalamus and posterior temporal white matter in the more affected hemisphere. In contrast to CBS, the most notable areas displaying diminished FA and heightened MD in individuals with PSP were identified in infratentorial brain regions, including both the bilateral superior cerebellar peduncles and midbrain, as compared to the control group. Additionally, reduced FA was observed bilaterally in the body of the corpus callosum, middle cingulate bundle, pons, fornix, and white matter of the premotor and prefrontal cortices [45]. DTI research on patients with PSP-RS shows higher MD in the putamen, caudate nucleus, and globus pallidus when compared to individuals with PD and healthy participants. On the other hand, in CBS, specific degeneration patterns above the tentorium cerebelli, characterized by asymmetric shrinkage in areas like the superior parietal lobe, posterior frontal lobe, and basal ganglia, can be observed. Atrophy may be asymmetrical, but the absence of pronounced asymmetry does not exclude the possibility of CBS [46]. Additionally, there is deterioration in the splenium and the body of the corpus callosum, the middle cingulate bundle, and the white matter tracts in the superior parietal, premotor, and motor regions [47]. On the other hand, a functional MRI study focuses more on task performance than simple MRI. A sample of CBS patients with limb apraxia showed diminished activity in the premotor cortex alongside heightened activity in the parietal cortex, suggesting a potential compensatory mechanism through neural recruitment [48]. Planning non-functional or structural grasp-to-pass movements for inconveniently oriented tools, regardless of which hand was used, significantly activated the left parietal and prefrontal nodes more than simple, undemanding functional grasps [49]. Therefore, because of the compensation between the premotor and parietal cortices, apraxia is a less expressed symptom. Key MRI findings in MSA include atrophy of the cerebellum and brainstem. The “hot cross bun” (HCB) sign, characterized by cruciform T2 hyperintensity in the pons, is a hallmark of MSA, and it has sometimes been noted in other neurological conditions, such as autopsy-confirmed CBD [50] or autoimmune cerebellar ataxia [51]. These features are usually symmetrical [52]. Coronal fluid-attenuated inversion recovery (FLAIR) images confirmed asymmetric atrophy in the posterior putamen, resulting in the near-total loss of neurons in this structure. This MRI finding is often called the “putamina rim” sign. The putamen and the globus pallidus are parts of the striatum. The striatum plays a crucial role in numerous brain functions, such as motor control and learning, language processing, reward mechanisms, and cognitive functioning [53]. In the neuropsychological context, Broca’s and Wernicke’s areas (located in the frontal and temporal lobes, respectively) are involved in speech functions, but the role of the putamen in language involves a network of coactivations in both the left and right putamina, with the left putamen playing a significant role in additional language functions, including bilingual language processing [54]. Hypointensity in the atrophic putamen on coronal FLAIR images suggested iron deposition linked to neurodegeneration, distinguishing it from age-related changes in the external globus pallidus. The patient’s initial asymmetric parkinsonism aligns with previous reports of asymmetrical parkinsonism in early-stage MSA-P cases [55].

7. Single-Photon Emission Computed Tomography (SPECT)

A DaTscan examination is used for dopamine transporter density imaging with Ioflupane I123, which is a good marker of presynaptic nigrostriatal dysfunction [56]. The use of presynaptic dopaminergic imaging, such as dopamine transporter imaging, is constrained in distinguishing among different parkinsonian syndromes. This limitation results from the fact that the presynaptic dopaminergic system is affected not only in APSs but also in PD [57]. However, there is a more precise and meticulous imaging method based on DaTscan.

Dopamine transporter single-photon emission computed tomography (DaT-SPECT) software facilitates the automated computation of three quantitative indices: the specific binding ratio, putamen-to-caudate ratio, and asymmetry index (AI), which are quantitative parkinsonian type indices calculated from DaT-SPECT. The AI is often used to indicate the asymmetry of reduced striatal 123I-Ioflupane accumulation on DaT-SPECT. AI values on DaT-SPECT measured in the PD group (n = 311), PSP group (n = 33), and MSA-P group (n = 20) were significantly greater than those observed in the control group (n = 137) [58]. The asymmetry of striatal 123I-Ioflupane binding appears to be less prominent in MSA and PSP (n = 24 cumulatively) compared to PD (n = 48), although no statistical difference was observed. Greater binding symmetry was detected in MSA-P compared to PD, and this was also observed in another study. It remains unclear how the asymmetry of motor symptoms at various stages of PD correlates with DaT-SPECT imaging and whether the asymmetric reduction in striatal 123I-Ioflupane accumulation on DaT-SPECT will prove valuable in distinguishing PD from PSP and MSA-P [59,60]. In patients with MSA, a decrease in perfusion was observed bilaterally in the cerebellar cortex and vermis, along with reduced perfusion in the left and right posterior putamina. The inverse contrast indicated higher relative perfusion in the occipital and right primary motor cortices compared to IPD [35]. In another study, 16 CBS cases were examined. All of these patients had cerebral atrophy, which was symmetric in 81%. Cerebral peduncle atrophy stood out as the most prominent imaging feature of CBS. Atrophy in the midbrain tegmentum was observed in eight patients, with three of them presenting vertical gaze palsy. Additionally, atrophy in the corpus callosum was observed in 15 patients (94%), which can seemingly be the first sign of developing atrophy in the future. In the SPECT examination, all of the individuals exhibited asymmetric hypoperfusion in the frontoparietal lobes. The left frontal area was linked to reduced planning time without affecting strategy implementation. The right frontal lobe was engaged in making adjustments to the previously established plan. Therefore, it has an influence on visuospatial working memory, which is necessary during execution, except in the initial planning phase [61]. Cerebellar hemisphere hypoperfusion was identified in 10 patients (63%), occurring on the side contralateral to the affected cerebral cortex [62]. Cerebral blood flow asymmetry in this group of subjects was also confirmed, with greater involvement of the frontoparietal cortex and subcortical structures [63]. Additionally, hypoperfusion in the basal ganglia, particularly the putamina, was observed in 11 patients (69%), and hypoperfusion in the thalamus was noted in 14 patients (88%). CBS patients exhibited the greatest absolute differences in SPECT perfusion between the right and left sides. PSP-P patients presented the greatest variation in perfusion values between brain regions: they were highest in the insular lobe and lowest in the temporal lobe. The basal ganglia in the right brain hemisphere are more involved in the retrieval of lexical items, and they act to suppress right frontal activity to keep it from interfering with word generation processes in the left hemisphere [64]. Individuals with PSP-RS and CBS who had insular and temporal lobe involvement showed a tendency to possess nearly identical absolute SPECT perfusion differences between the left and right sides [39]. In a meta-analysis of functional MRI studies on empathy conducted by Fan and colleagues, it was discovered that the right anterior insula is linked to the affective-perceptual type of empathy. In contrast, the left insula is involved in both the affective-perceptual and cognitive-evaluative types of empathy [65]. SUVRs (standardized uptake value ratios) were determined for the striatum and the caudate and putamen separately and compared among the study

groups. In addition, hemispherical and caudate-putamen differences were evaluated in atypical parkinsonism cases. After consolidating various forms of atypical parkinsonism into a unified group, the study delved into individual assessments of striatal metabolism among these distinct types. Across all types, the highest SUVRs were observed in patients with MSA (striatal SUVR: 1.50 ± 0.02). In the caudate, lower SUVRs in the left hemisphere were evident for all atypical parkinsonism types, with statistical significance observed in CBD and MSA. In contrast, the putamen displayed higher SUVRs in the left hemisphere compared to the right, with statistically significant differences across all parkinsonism types. Following a similar caudate pattern, in the striatum, the SUVRs were once again lower in the left hemisphere than the right, and statistically significant differences were observed in the MSA and CBD groups. Relying exclusively on SUVRs from the caudate and putamen and aiming to predict the specific type of atypical parkinsonism, the model demonstrated statistical significance and an overall accuracy of 55.2%. It successfully predicted PSP with 80.0% accuracy, CBD with 33.3% accuracy, and MSA with 100.0% accuracy [66].

8. PET

The most reliable distinction in metabolic activity between APSs and PD lies in the reduced striatal glucose metabolism observed in patients with atypical parkinsonism [57]. Through the assessment of these metabolic patterns, FDG PET imaging has secured a significant position as a supportive feature in distinguishing between different subtypes of APSs [67]. To perform PET, two groups of specific tracers are in use. The first generation includes 18F-THK5317, 18F-AV-1451 (18F-flortaucipir or [18F]FDG PET), and 11C-PBB3 [13]. The second-generation PET tracers, such as PI2620 and PMPBB3 (also known as APN1607), not only bind strongly to Alzheimer's disease brain tissue but also significantly bind to the brain tissues of those with PSP/CBD [68]. There is increased 18F-flortaucipir retention among PSP patients in the thalamus, midbrain, caudate nucleus, putamen, and globus pallidus, even when adjusting for age, with the largest effect sizes in the last structure [39]. Predominantly in the prefrontal cortices, the anterior cingulate gyrus, and the midbrain, asymmetrical or bilateral hypometabolism was observed, depending on the type of PSP [69]. Additionally, a localized region of reduced metabolic activity in the midbrain was observed in some patients with PSP using [18F]FDG PET scans [70]. In both symmetrical and asymmetrical PSP types, notable bilateral mesiofrontal hypometabolism and, to a lesser extent, dorsolateral frontal hypometabolism are observed. In contrast, hemi-PSP patients display more asymmetric thalamic and sensorimotor cortex metabolism, and the middle cingulate cortex appears more hypometabolic compared to that in symPSP patients [26]. [18F]FDG PET (F-18-AV1451 tracer) imaging in CBS reveals asymmetric reduced glucose metabolism in several areas, including the parietal lobes extending into the posterior frontal lobes, paracentral lobule, sensorimotor cortex, thalamus, basal ganglia, middle cingulate, parietal lobe, substantia nigra [30,40], and putamen [30]. The above-mentioned structures are contralateral to the clinically more affected body side. [28]. CBD subjects are characterized by asymmetrical decreases, which are more pronounced in the hemisphere opposite to the body side that is more severely affected in the cerebrum, lateral parietal and frontal regions, and thalamus, accompanied by relative bilateral enhancements in occipital regions [65]. In cases of low-level or high-variability 18F-fluorodeoxyglucose uptake for assessing metabolic activation, it is necessary to use alternative radiopharmaceuticals. 18F-dihydroxyphenylalanine (18F-DOPA) has been introduced as a marker of dopamine uptake for imaging metabolism in the brain's basal ganglia [71]. Striatal dopaminergic deficiency is connected with APSs [72], and because of this, 18F-DOPA has found application in APS recognition. In three patients diagnosed with clinical PSP, there was a noticeable decrease in 18F-dopa in the bilateral dorsal striatum, ventral striatum, and orbitofrontal cortex, as well as in the right amygdala, when compared to normal controls. Additionally, there were no areas where 18F-DOPA was found to be increased [73]. In six individuals with CBS, distinct abnormalities with significant asymmetry were identified in the parietal cortex, the thalamus, the caudate nucleus, and the putamen of the hemisphere predominantly

affected by clinical symptoms. Additionally, reduced 18F-DOPA uptake was observed to have an asymmetric pattern in both the caudate nucleus and the putamen in four CBS patients [74]. In research in which 27 individuals were examined via PET, 9 of them (33.5%) suffering from CBS exhibited abnormalities in 18F-DOPA PET, whereas semi-quantitative analysis showed putaminal asymmetry in 17 CBS patients (63%). Uniformly diminished striatal uptake was observed in both the putamen and caudate nucleus. This contrasts with the pattern seen in PSP and PD, where the reduction in striatal uptake tends to be heterogeneous. Importantly, there were no identified correlations between 18F-DOPA PET and the clinical features of the patients [75]. Amyloid PET scans do not show positive results for CBD. However, recent studies using tau PET imaging in CBD have identified tau protein accumulation in several regions, such as the supplementary motor area, midbrain, subthalamus, perirolandic area, basal ganglia, and both cerebral and cerebellar white matter. Notably, this tau accumulation is more pronounced in areas opposite to the side more severely affected by the disease [46]. Twenty-eight patients (disease duration of 5 years or less) with MSA-P exhibited a marked decrease in 18F-DOPA uptake in the bilateral striatum. Subsequent [18F]FDG PET scans revealed a notable reduction in the bilateral putamen in patients diagnosed with MSA-P [76]. In another study, MSA-P subjects showed asymmetric diffuse hypometabolism in the putamen-pallidum, with the relative sparing of the caudate nuclei, while in MSA-C patients, hypometabolism was seen in the cerebellum and brainstem. In mixed subtypes, variable hypometabolism in the basal ganglia, cerebellum, and brainstem was associated with that in frontoparietal regions [77]. The pattern associated with CBS effectively differentiates CBS from MSA but not from PSP due to the 24% overlap in spatial metabolic patterns between CBS and PSP. By assessing the extent of hemispheric asymmetry at the network level and comparing it to the PSP-related pattern, the authors succeeded in distinguishing between CBS and PSP with a specificity of 92–94% [57].

9. Transcranial Sonography

Transcranial sonography (TCS) is a non-invasive diagnostic method using diverse brain structures' echogenicity to identify a range of neurodegenerative conditions, such as APSs [78]. Elevated substantia nigra (SN) echogenicity is characteristic of PD (70–90%), frequently observed in CBD (>80%), and uncommon in MSA-P (ranging from 10% to 25%), whereas lenticular nucleus (LN) hyperechogenicity is more common in the last two diseases [79]. Similar results were obtained in another study [80]. In a study including 366 individuals suffering from various PSP types, marked enlargement of the third ventricle (≥1 cm) was noticed in 71%, whereas for LN hyperechogenicity, it was 70%. SN hyperechogenicity is seen in 22% of cases [74]. Research differentiating between PSP-RS and PSP-P showed that in the first PSP type, there is almost no SN hyperechogenicity (only 1 to 26 cases), but 86% of PSP-P patients demonstrate this symptom [81]. Notably, SN hyperechogenicity is more pronounced in PD, whereas a hyperechogenic LN, as well as an enlarged third ventricle, is more common in individuals with APSs [80]. For CBD, bilateral symmetric hyperechogenic SN areas or bilateral or unilateral hyperechogenic LN regions are quite common. The SN is often enlarged (>0.25 cm^3 vs. <0.20 cm^3). In PSP and MSA, there is no asymmetry in the SN range, but there may be asymmetry in the LN [82]. It is worth noting that TCS is only used as an additional examination to either diagnose an APS or determine symmetry in these disorders. Furthermore, it was found that PD individuals with levodopa-induced dyskinesia (LID) had significantly higher SN echogenicity compared to those without LID, which can explain the poor levodopa responses in PSP and MSA [83]. Additionally, a recent study confirms that TCS might be a good diagnostic tool, combined with clinical and demographic characteristics, for predicting cognitive impairments in PD. Thus, TCS appears to be a promising approach to gaining a better understanding of the mechanisms and natural disease course of atypical parkinsonian syndromes. The findings are summarized in the Table 1.

Table 1. Imaging findings in APS in the context of symmetry.

Imaging	Often Occuring Disease	Finding	Morphology	Symmetry	Specificity	Sensivity
MRI	PSP-RS	Hummingbird sign/penguin sign	A midbrain tegmental atrophy without pontine atrophy	Unpaired structure	99.5%	57%
	PSP-RS	Morning glory sign	An increased lateral concavity of the midbrain tegmentum	Unpaired structure	97%	37%
	PSP	Basal ganglia, brain stem and frontal cortex atrophy		Symmetric		
	MSA	Hot cross bun sign	A linear T2-hyperintensity extending across the rostral pons	Symmetric	98.5%	50%
	MSA	Putamina rim sign	A near-total loss of neurons in the putamen	Asymmetric	90%	72%
	CBS	Basal ganglia, brain stem and frontal cortex atrophy		Asymmetric		
SPECT	PSP, MSA-P, CBS	Basal ganglia, brain stem and frontal cortex	Hypoperfusion	Asymmetric (less than in PD)		
PET	PSP	Pimple sign	A reduced metabolism in the midbrain	Unpaired structure		
	PSP	Frontal cortices, the anterior cingulate gyrus, and the midbrain	A reduced glucose metabolism	Symmetric or asymmetric		
	CBS	Disseminated: Parieto-frontal thalamus, basal ganglia, middle cingulate, parietal lobe	A reduced glucose metabolism	Asymmetric		
	MSA-P	Striatum	A reduced glucose metabolism	Symmetric or asymmetric	95%	
	MSA-C	Cerebellum and brainstem	A reduced glucose metabolism	Asymmetric	95%	
	Undifferentiated (mixed) MSA	Cerebellum, brainstem, stratium, fronto-parietal regions	A reduced glucose metabolism	Asymmetric	95%	
TCS	PSP and MSA	SN	Hyperechogenicity	Symmetric	PSP (86%) PSP-RS (3.8%)	
	PSP and MSA	LN	Hyperechogenicity	Asymmetric	PSP—70%	
	CBD	SN	Hyperechogenicity	Symmetric		
	CBD	LN	Hyperechogenicity	Symmetric or asymmetric		

10. Discussion

There are many hypotheses attempting to explain the cause of neurodegeneration. They include the interplay between environmental toxins and tau or α-synuclein, inflammatory factors such as oxidative stress or microglial activation [84], and vascular components,

including vascular malformations or ischemic events [85]. While there is much literature on atypical parkinsonism, little is known about the symmetry in these diseases, especially when it comes to MSA's potential symmetry. Neuroimaging studies have demonstrated a range of metabolic, structural, and functional abnormalities, leading to a better understanding of the pathophysiological mechanisms contributing to asymmetry in APSs. On the basis of MRI, a PSP degeneration mechanism was proposed based on the correlation between clinical dysfunction and white matter tract degeneration in the superior cerebellar peduncles, body of the corpus callosum, and association fibers [86]. Aside from assessing symmetry, evaluating the unpaired structures of the brain in imaging studies also seems important. The hummingbird and morning glory signs have high specificity (99.5% and 97%, respectively), but their sensitivity is relatively low (57% and 37%, respectively) [4,37–39]. Monitoring the progression of midbrain atrophy and the pontine-to-midbrain ratio showed high sensitivity and specificity in differentiating PSP from PD [41]. Nevertheless, there is justification for expanding the diagnostics to PSP when at least one of these signs occurs, regardless of clinical symmetry expression. Both of these signs are good indicators for distinguishing between PSP and CBS as well [87]. The asymmetry in CBS is possibly caused by a variable asymmetric reduction in striatal D2 receptor binding, which was demonstrated through SPECT examination. This finding might explain why CBS has an asymmetric disease manifestation and why this asymmetry is the most prominent among the APSs, as well as the lack of response to dopaminergic therapy, especially for motor symptoms [63]. The atrophy in MSA most often involves the pons, putamen, and cerebellum [88]. The diagnostic specificity of the HCBs and the hyperintensity of the middle cerebellar peduncle on MRI for MSA reaches 98.5%, but it can be found in other disturbances [51], so the sensitivity of this sign is relatively low (around 50%). Higher sensitivity was obtained with the "putamina rim" sign. Its sensitivity is 72%, and its specificity is around 90%. Notably, the "putamina rim" is more often asymmetrical than the HCBs [89]. It is worth noting that even in the most sensitive imaging studies performed by experienced radiologists, small changes, such as those disrupting symmetry, can remain undetected. Therefore, the risk of false results is relatively high. Presumably, the clinical symmetry in PSP and MSA, to a great extent, depends on the atrophy symmetry. The asymmetry of atrophy or hypoperfusion in specific brain structures affects different psychosocial behaviors in patients because these structures play different roles in determining behaviors such as empathy, word generation, movement planning, and others, depending on whether they are located on the left or right side.

Data can contain errors caused by incorrect diagnosis—the incorrect classification of the patient for a given disease, as is common in the case of APSs. The degree of symmetry changes over the course of PD. According to the Hoehn and Yahr scale, which illustrates the natural, typical progression of PD, the initially asymmetric manifestation of symptoms evolves into a bilateral form, which can be mistakenly interpreted as an APS [90]. Additionally, there are no specific data regarding APS symmetry evolution. Therefore, it seems that symmetry assessment is most useful at the early stage of illness. Notably, it is observed that the symmetry of abnormalities in imaging studies does not always correlate with the symmetry of symptoms in clinical examinations, which may be attributed to two factors. First, the clinical assessment of symmetry is highly subjective and based on varying criteria, leading to the potential misclassification of the disease's level of symmetry. Second, it is possible that the clinical abnormalities might not occur simultaneously with the imaging abnormalities. Clinically, CBS is regarded (according to the latest criteria and current publications) as a highly asymmetrical disease, whereas atrophic changes on MRI are seen to become more symmetrical as the disease progresses. It is suggested that atrophy may precede clinical abnormalities, as individuals in very advanced stages of APSs are less frequently examined by experienced clinicians due to severe symptoms and severely limited mobility. It should be noted that the study groups are relatively small, which is probably due to the fact that APSs are rare in the population, and it is difficult to find a sufficiently large group of patients. Naturally, given the very limited size of the studied

cohorts, drawing definitive statistical conclusions is impossible. However, summarizing the collected data from these studies reveals a clear trend in the rates of symmetry across the various types of APSs. Additionally, in some studies, APS evaluation was not based on the newest criteria dedicated to the particular entity. The symmetry evaluation is highly subjective; therefore, the results obtained may vary between different studies, especially when they are based on different diagnostic criteria. In the authors' opinion, the cited studies do not provide sufficient information on whether the patients were receiving pharmacotherapy during their symptoms' severity assessment and, if so, what they were taking. Many drugs may intensify parkinsonism (i.e., neuroleptics or metoclopramide), which can also potentially affect the symptoms' symmetry. In most of the cited studies, a neuropathological evaluation had not been performed; therefore, establishing a particular diagnosis and exact statistical proportions in the context of symmetry could be flawed. However, the data indicate that there are clear differences between particular APSs in terms of the symmetry of clinical symptoms and the signs present in imaging tests.

Although, in some cases, particular disease types were not differentiated, PSP-RS appears to be the most symmetrical PSP subtype [16], and MSA typically manifests with relatively symmetrical symptoms, whereas MSA-P might express marked asymmetry, with asymmetric dystonia of the limbs and asymmetric myoclonic jerks, leading to the wrong CBS diagnosis [27]. CBS is the most asymmetrical form of APS, and the lack of symmetry is included in its diagnostic criteria. However, CBS is not always asymmetric like the criteria describe. CBS is conventionally viewed as a sporadic disorder, implying a potential genetic predisposition to the development of symmetric degeneration [26]. Because of all of the above-mentioned factors, establishing the exact and proper diagnosis distinguishing a particular APS type or IPD is not straightforward. A misdiagnosis can lead to the initiation of inappropriate drug therapy and significant health deterioration.

11. Conclusions

Asymmetry may initially seem like an unhelpful diagnostic tool; however, determining which side has undergone degeneration can be taken into consideration as an additional diagnostic criterion to help minimize the risk of misdiagnosis, especially in the case of an ambiguous clinical presentation in a suspected APS. It is important to assess the clinical condition after a meticulous analysis of patient symptoms, imaging tests, and current pharmacotherapy. Additionally, determining neurodegeneration symmetry may be highly significant in identifying potential functional deficits in both the motor and neuropsychological contexts. Patients with significant asymmetry in neurodegeneration, expressed through asymmetry in motor symptoms, may exhibit different neuropsychological symptoms depending on their individual brain lateralization, especially due to frequent frontal or parietal lobe atrophy in this kind of neurodegeneration. This significantly affects already-impaired cognitive functioning; additionally, it can be exacerbated throughout the progression of the disease, because it might have a critical impact on the remaining life of the individual affected by the APS. It is also worth emphasizing that there is a great need to determine whether and how the symmetry of APS symptoms changes over the course of the disease. Furthermore, due to the connection between brain lateralization and handedness, hand dominance should be routinely examined to assess potential neuropsychological damage.

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Abbreviations

APSs	atypical parkinsonian syndromes
IPD	idiopathic Parkinson's disease
MSA	multiple system atrophy
PSP	progressive supranuclear palsy
CBS	corticobasal syndrome
DLB	dementia with Lewy bodies
SPECT	single-photon emission computed tomography
PD	Parkinson's disease
PSP-RS	progressive supranuclear palsy-Richardson syndrome
NNIPPS	Neuroprotection and natural history in Parkinson plus syndromes
PSP-P	progressive supranuclear palsy-parkinsonism
PSP-CBS	progressive supranuclear palsy-corticobasal syndrome
MDS	Movement Disorder Society
PSP-PAGF	progressive supranuclear palsy-pure akinesia with gait freezing
PSP-FTD	progressive supranuclear palsy-frontotemporal dementia
PSP-AOS	progressive supranuclear palsy-apraxia of speech syndrome
PSP-PNFA	progressive supranuclear palsy-progressive non-fluent aphasia
Hemi-PSP	progressive supranuclear palsy with a lateralized disease manifestation
SymPSP	progressive supranuclear palsy with symmetric clinical presentation, a symmetric disease manifestation
CBD	corticobasal degeneration
S-CBD	symmetric corticobasal degeneration
CBD-CBS	corticobasal degeneration-corticobasal syndrome
CBD-RS	corticobasal degeneration-Richardson syndrome
MSA-P	multiple system atrophy-parkinsonism
MSA-C	multiple system atrophy-cerebellum
MRI	magnetic resonance imaging
PET	positron emission tomography
DTI	diffusion tensor imaging
MD	mean diffusivity
FA	fractional anisotropy
FLAIR	fluid-attenuated inversion recovery
HCB	"hot cross bun" sign
DaTscan	dopamine transporter scan
DaT-SPECT	dopamine transporter single-photon emission computed tomography
AI	asymmetry index
SUVRs	standardized uptake value ratios
FDG PET	fludeoxyglucose-18 positron emission tomography
18F-DOPA	18F-dihydroxyphenylalanine
TCS	transcranial sonography
SN	substantia nigra
LN	lenticular nucleus
LID	levodopa-induced dyskinesia

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The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study

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Introduction: Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are tauopathic atypical parkinsonisms. Given their overlap in terms of clinical manifestation, there is growing interest in the mechanisms leading to these entities.

Materials and methods: In total, 71 patients were included in the study, 19 of whom were clinically diagnosed with CBS, 37 with PSP, and 15 with Parkinson's disease (PD). The mean ages of the participants were 72.8, 72.9, and 64.0 years, respectively, and the disease duration varied from 3 to 6 years. Each individual underwent blood collection. Morphological and biochemical evaluation of blood samples was performed to analyze the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-high-density lipoprotein ratio (NHR). A single-photon emission computed tomography (SPECT) with technetium-99m hexamethylpropyleneamine oxime (^{99}Tc-HMPAO) tracer was used to assess perfusion in two regions of interest (ROI): the thalamus and insula. Using Pearson correlation to assess the linear relationship between NHR and perfusion in the insula and thalamus for CBS, PSP, and PD patients, the authors intended to verify possible correlations between NLR, PLR, and NHR and perfusion in the indicated ROIs.

Results: The study revealed a negative linear correlation between NHR and perfusion of both the left (Insula L; $R = -0.59$) and right (Insula R; $R = -0.58$) insula regions. Similar to the insula, a linear correlation between NHR and activity in both the left (Thalamus L) and right (Thalamus R) thalamus regions in CBS subjects with a relatively stronger correlation in the right thalamus ($R = -0.64$ vs. $R = -0.58$) was found. These observations were not confirmed in PSP and PD patients.

Conclusion: Simultaneously using non-specific parameters for peripheral inflammation (NLR, PLR, and NHR) and perfusion, SPECT may be an interesting beginning point for further analysis of inflammatory disease mechanisms. To the

best of our knowledge, this is the first study to address the potential correlation between the peripheral neuroinflammatory markers NLR, PLR, and NHR and perfusion disturbances in particular ROIs.

KEYWORDS

NLR, PLR, NHR, atypical parkinsonism, SPECT, neuroinflammation

Introduction

Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are complex, clinically diverse conditions that are often referred to as "atypical Parkinsonian" disorders (1). PSP and CBS are very rare conditions; the prevalence of PSP is ~3–7 per 100,000, and the CBS prevalence ranges from 5 to 7 per 100,000 (2). The neuropathological identification of PSP relies on detecting neurofibrillary tangles and threads in the subcortical nuclei, along with the presence of tufted astrocytes. In addition, observations may include the presence of coiled oligodendroglia and diffuse cytoplasmic immunoreactivity in neuronal tissue (3). PSP manifests through substantial postural instability, recurrent falls, axial rigidity, cognitive dysfunction, and vertical supranuclear gaze palsy (4, 5). Clinically, CBS is characterized by asymmetric parkinsonism, limb apraxia, and cortical sensory deficits, accompanied by progressive dystonia, myoclonus, and alien limb phenomenon (6–8). CBS is associated with morphologically asymmetric cortical atrophy, variable basal ganglia, and nigral degeneration (9). CBS can be a manifestation of various pathologies, including corticobasal degeneration (CBD), PSP, frontotemporal dementia (FTD) (10), posterior cortical atrophy (11), and Alzheimer's disease (AD) (12–14). CBD is a neurodegenerative disorder in which a neuropathological evaluation can find abnormal neurons and glial cells (notably astrocytic plaques), tau protein accumulations in both the gray and white matter of the neocortex and striatum, along with swollen neurons, and localized loss of neurons in the neocortex and substantia nigra (6). CBD can clinically manifest through various syndromes, among which can include, apart from CBS, the non-fluent/agrammatic variant of primary progressive aphasia or frontal behavioral-spatial syndrome (11). They often manifest in individuals in their 60s or older, with some cases presenting in individuals in their 50s or even younger. Both diseases are classified as four-repeat tauopathies. Tau is encoded by the microtubule-associated protein tau (MAPT) gene, producing six protein isoforms that are tightly regulated. The inclusion or exclusion of exon 10 results in the formation of 4-repeat (4R) tau and 3-repeat (3R) tau, respectively (15). Various tauopathies' pathogenesis results from disruption of the 3R:4R tau ratio (16). It is implicated in several 4R diseases (other than PSP and CBD), such as FTLD-MAPT, argyrophilic grain disease (AGD), and globular glial tauopathy (GGT). AGD is most often found among patients over 80 years old as a single neurodegenerative condition or as a manifestation of AD or PSP (17). Another 4R tauopathy is a GGT that is divided into three types. The first type is indicative of a sporadic multiple system tauopathy associated with presenile dementia. The second type is distinguished by being more indicative of motor neuron disease, and the third type is a peculiar mix of two previous entities (18). There are many hypotheses attempting to explain the exact pathomechanism of the disease. Among the hypotheses concerning pathogenesis, inflammatory (19–21), vascular (19, 22, 23), and environmental (19, 22) theories were considered. The vascular hypothesis is based on brain hypoperfusion, which leads to neurodegeneration (19). The inflammatory hypothesis is linked with microglial activation. Microglial cells are part of the innate immune system and serve as the primary macrophages within the central nervous system (CNS). Astrocytes are the most prevalent cell type and can be found throughout all areas of the CNS. Physiologically, microglial cells provide physical and metabolic support to neurons, assist in detoxification, guide cell migration, and facilitate the regulation of metabolic energy. In response to a disease or injury, astrocytes experience a persistent activation known as astrogliosis. Similar to microglia, reactive astrocytes can develop a pro-inflammatory phenotype (24).

The inflammation is characterized by the activation of microglia and subsequent astrocyte response, accompanied by heightened cytokine expression and immune system mediators in both the cerebrospinal fluid (CSF) and the brain (25). The inflammatory hypothesis is linked to reactive astrocytes and microglia accumulation around amyloid deposits (4). The infiltration of peripheral immune cells influences microglia to adapt to a pro-inflammatory state, thereby accelerating disease progression. Microglia have the capacity to curb the spread of tau through phagocytosis. It can also intensify neurodegeneration by facilitating the distribution of these proteins (26). It is uncertain whether tau is the cause or the effect of the neuroinflammatory response (27). There is an increasing interest in peripheral inflammatory markers in the context of neurodegeneration. This research aimed to evaluate the possible correlation between peripheral inflammation and atrophic changes in certain regions of interest (ROIs) in PSP, CBS, and PD.

Methods and data collection

Study group

The analyzed group involved 71 patients: 19 with CBS, 37 with PSP, and 15 with Parkinson's disease (PD). Eligible patients diagnosed with CBS were identified and confirmed according to

Armstrong's criteria (8). PSP individuals fulfilled the MDS criteria for PSP (5), and a PD diagnosis was established based on Postuma's clinical criteria. (28). The mean age of the groups was 72.8, 72.9, and 64.0 years, respectively. In the first group, there were eighteen women and one man; in the second group, there were eighteen women and nineteen men; while the last cohort was represented by seven women and eight men aged-matched in relation to the research group.

Data collection

Neutrophil counts serve as parameters of inflammation (29, 30), and high-density lipoprotein cholesterol (HDL-C) is a component of atherosclerosis (29, 31). The neutrophil-to-lymphocyte ratio (NLR) can be used to assess the background of inflammatory illness (32, 33). The measure is derived by dividing the neutrophil count by the lymphocyte count in peripheral blood. NLR reflects the balance between acute and chronic inflammation, as shown by neutrophils, and adaptive immunity, as represented by lymphocytes (34).

Similarly, the platelet-to-lymphocyte ratio (PLR), determined by the ratio of platelet-to-lymphocyte counts in the blood, serves as an indicator of changes in the balance between the platelet count, which is linked to acute inflammatory responses and clot formation tendencies, and the lymphocyte count, reflecting the state of adaptive immunity (35). The neutrophil-to-high-density lipoprotein-C ratio (NHR) is a combined indicator of both inflammation and lipid metabolism (36). All patients underwent a comprehensive blood analysis at the Mazovian Brodno Hospital Laboratory Diagnostics Department. This analysis provided morphological and biochemical evaluations, including absolute neutrophil and lymphocyte counts, platelet counts, and lipid profiles. All three parameters (NLR, PLR, and NHR) were calculated according to the aforementioned patterns based on the blood sample obtained from a single sample.

Cerebral blood flow was examined after administering 740 MBq technetium-99m hexamethylpropyleneamine oxime ([99mTc]Tc-HMPAO) in a quiet room. The data were acquired with a single-photon emission computed tomography/computed tomography (SPECT/CT) scan (Symbia T6, Siemens) on a dual-head gamma camera with a low-energy, high-resolution parallel-hole collimator. The step-and-shoot acquisition mode was used. Sequences of 128 frames on a 128 $\times$ 128 matrix were used (64 projections per head, 30 s per projection). The photopeak was set at 140 keV with a 10% window on each side. Repetitive reconstruction (eight iterations, eight subsets, 7 mm Gauss filter), scatter correction, and computed tomography (CT) attenuation correction were performed. The post-processing was examined using Scenium software (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). The SPECT ROIs were pre-planned using Scenium software (an integral part of the Siemens workstation) based on the T1-weighted MRI images of a standard brain dataset. The analysis and definition of subregions were based on a program offered by Siemens Healthineers (SCENIUM, Syngovia).

Software aided in assessing the human brain scans, enabling automated analysis by quantifying mean pixel values within the standard ROI. This also allowed for comparison with existing databases using the healthy control group and the reference parameters derived from these databases, which were derived from SPECT studies, e.g., the calculation of uptake ratios between ROIs and subtraction between two functional scans. The database contained the defined regions and subregions of the brain and the related radiopharmaceutical accumulation values. The data bank was created from images for which reconstructions of Flash3D and CT-based attenuation revision were executed, and intensity normalization was based on the brainstem and the whole brain, respectively. All databases comprised 20 HMPAO-SPECT scans of asymptomatic control individuals aged 64–86 years from a mixed population of men and women. The ROIs used in the Database Comparison (37) were defined on a high-resolution T1 MRI volume scan. In the Database Comparison edition, the statistics are displayed and computed on voxel-by-voxel grounds.

The Database Comparison computed the standard number deviations from each voxel mean value, where the standard deviation and mean values were obtained from the corresponding voxel in the control group brain scans. According to this model, these statistics follow a T-distribution.

The differences in radiopharmaceutical accumulation in the selected ROIs were compared to the database, and these values were reflected in SD. Statistically significant differences in the radiopharmaceutical distribution in the selected ROI are considered if the accumulation exceeded 2 SD values. This method was used in the SCENIUM program (Siemens). The analysis was based on the SD value assessment. The total minimum and maximum counts were automatically measured in each ROI of the investigated brain SPECT examination and were compared using Scenium with measurements from the standard brain SPECT datasets. All comparisons were automatically presented as SDs. This parameter, taken from the ROIs, was evaluated statistically in multiple brain locations. The sizes and shapes of the SPECT-examined brain scans were calibrated per the same parameters as the standard brain scan received from the dataset. The pre-planned ROIs were extrapolated to the SPECT images of the assessed brains.

Finally, the total minimum and maximum counts were automatically assessed in each ROI of the investigated brain during the SPECT examination. Subsequently, they were differentiated with Scenium using measurements from standard brain SPECT datasets. All data were evaluated by an experienced nuclear medicine specialist.

This study assessed many ROIs; however, reduced activity emerged in the thalamus and insula. It has been proposed that decreasing thalamic activation through ascending projections from the brainstem may lead to postural instability in PSP (38). Patients who showed negative results on the [11C]Pittsburgh Compound-B (PIB)-PET (PIB-PET) scans exhibited two primary groups of decreased thalamus metabolism, extending toward the mesencephalon and diencephalon (39). In the insula, imaging

TABLE 1 Descriptive statistics and subgroup comparison.

Parameters	CBS (N = 19)		PSP (N = 37)		PD (N = 15)		p
	Mean	SD	Mean	SD	Mean	SD	
Age	72.8	7.2	72.9	6.3	64.0	10.8	0.0575
Biochemical parameters							
NLR	2.5	1.6	2.3	0.8	2.4	0.9	0.8635
PLR	164.5	77.9	145.4	54.9	124.9	49.1	0.2584
NHR	0.08	0.05	0.08	0.04	0.09	0.04	0.7335
SPECT							
Thalamus R	−4.4	2.4	−4.4	2.2	−1.7	1.7	0.0003
Thalamus L	−4.2	1.8	−4.1	1.9	−1.9	1.5	0.0008
Insula R	−1.9	1.8	−1.5	2.0	0.2	1.8	0.0049
Insula L	−3.2	2.6	−3.1	3.2	−0.7	1.9	0.0167

SD, standard deviation; p, p-value for Kruskal–Wallis test.

revealed gray matter loss in the premotor cortices, supplementary motor area, and insula in the CBS pathologic groups (40). Decreased [11C]UCB-J binding has been observed in the insula, among other areas, in both PSP and CBD patients (41).

Statistical analysis

The collected data were analyzed using Statistica software (version 13.1, Dell Inc., Statsoft). Data distribution was assessed using the Shapiro-Wilk test. Due to normal distribution, all parameters are expressed as means with standard deviations (SD) and 95% confidence intervals (95% CI). For group comparisons, we used the Student's t-test. Further analysis of the possible correlations in each group of patients between biochemical parameters (NLR, PLR, and NHR) and perfusion in the thalamus and insula was performed using Pearson's correlation coefficient. In the final determination of statistical significance, a p-value of 0.05 was used.

Results

Biochemical parameters

The mean age of CBS and PSP patients was similar (72.8 vs. 72.9 years), but the mean age of patients with PD was younger (64.0 years), with a p-value of 0.0575.

The NLR, as a marker of systemic inflammation, also showed similar mean values across all groups: CBS (2.5), PSP (2.3), and PD patients (2.4). Group comparison implies that, based on NLR alone, there was no strong evidence to suggest a difference in systemic inflammation between the groups ($p = 0.8635$).

The second marker of inflammation, PLR, also exhibited mean values within a comparable range (CBS: 164.5 vs. PSP: 145.4 vs. PD: 124.9; $p = 0.2584$) in analyzed groups of patients.

TABLE 2 PD patients in relation to CBS and PSP patients.

	CBS vs. PD	PSP vs. PD
Thalamus R	0.0024	0.003
Thalamus L	0.0036	0.0012
Insula R	0.0064	0.0160
Insula L	0.0253	0.0349

The third inflammation marker, NHR, which can also potentially relate to oxygenation status, showed a non-significant p-value (0.7335) compared to its values for CBS, PSP, and PD patients (Table 1).

SPECT

There were statistically significant differences between the tauopathic atypical parkinsonisms and PD; simultaneously, crucial differences between PSP and CBS were not found in terms of SPECT values in the compared regions (right thalamus $p = 0.003$, left thalamus $p = 0.008$, right insula $p = 0.0049$, left insula $p = 0.0167$) as shown in Table 1. After post-hoc analysis, we observed no statistically significant differences between CBS and PSP patients in terms of SPECT measurements for any of these regions. However, these values differed significantly for PD patients relative to CBS and PSP patients (Table 2).

NHR and the insula

We observed a negative linear correlation between NHR and activity of both the left (Insula L; $R = -0.59$, Figure 1) and right (Insula R; $R = -0.58$, Figure 2) insula regions, suggesting that higher values were associated with lower activity levels in these areas. For both PSP patients and PD patients, correlations were insignificant ($p > 0.05$).

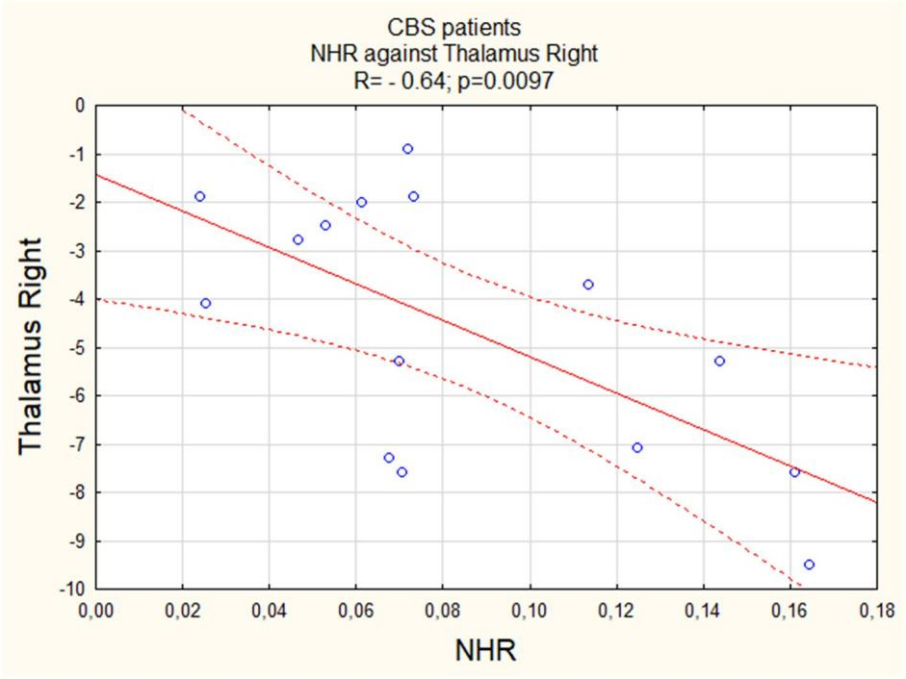

FIGURE 1
The correlation between perfusion of the left insula and NHR in CBS.

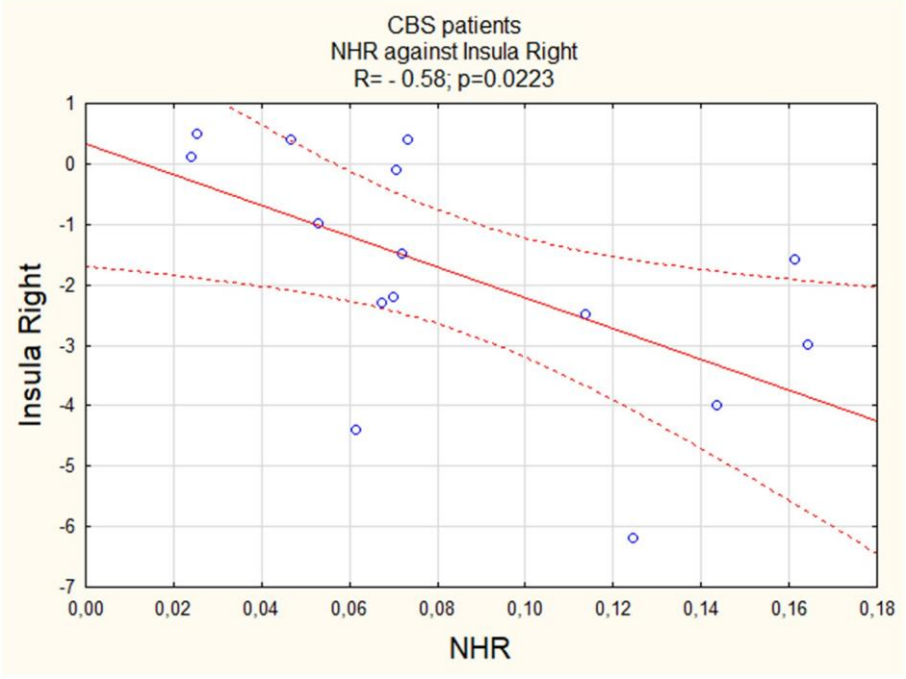

FIGURE 2
The correlation between perfusion of the right insula and NHR in CBS.

NHR and the thalamus

Similar to the insula, we observed a negative linear correlation between NHR and activity in both the left (Thalamus L) and right (Thalamus R) thalamus regions, with a relatively stronger correlation in the right thalamus ($R = -0.64$, Figure 3 vs. $R = -0.58$, Figure 4). For both PSP patients and PD patients, correlations were insignificant ($p > 0.05$).

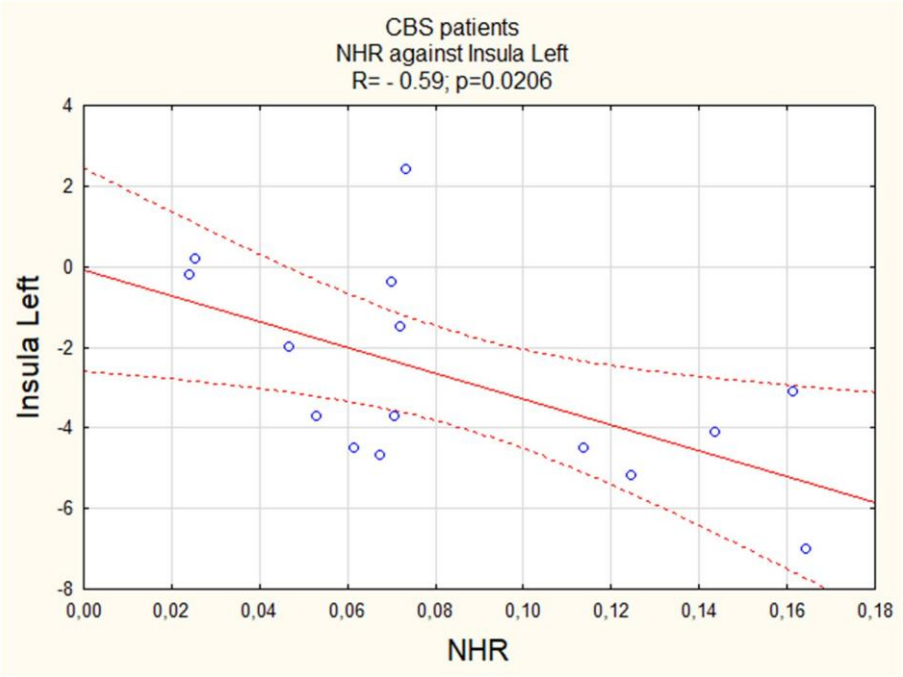

FIGURE 3
The correlation between perfusion of the right thalamus and NHR in CBS.

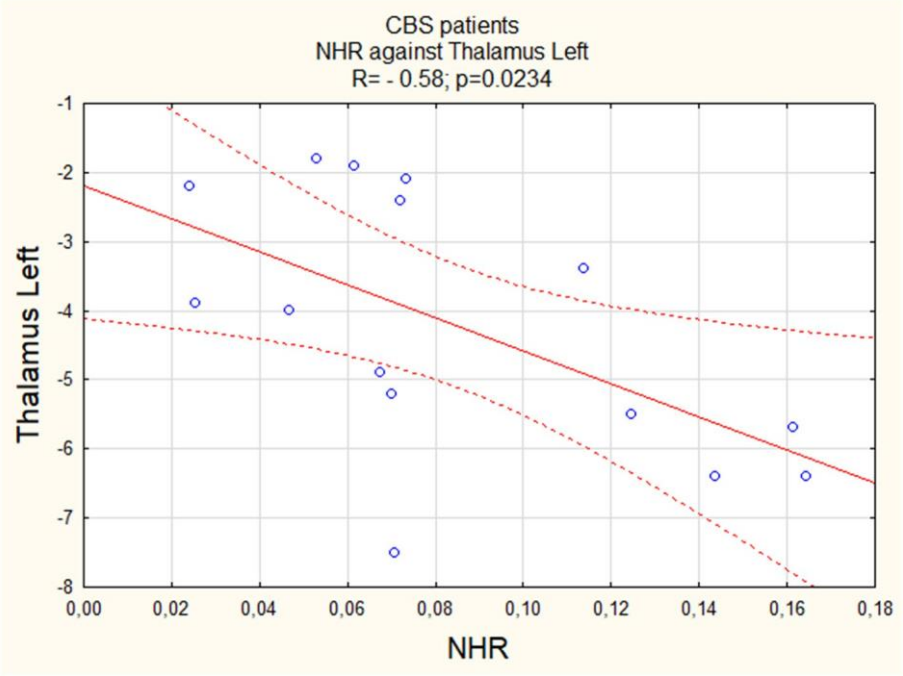

FIGURE 4
The correlation between perfusion of the left thalamus and NHR in CBS.

Discussion

A statistically significant negative correlation was observed between NHR and perfusion in the insula and thalamus in patients with CBS (Table 3). The correlation was not detected among patients with PSP and PD. The group of individuals suffering from PD was, on average, ~9 years younger than the other two groups. This was due to the fact that as Parkinson's disease progresses, the

TABLE 3 Correlation between NHR and insula and thalamus perfusion for CBS, PSP, and PD patients.

	CBS		PSP		PD	
	Rp	p	Rp	p	Rs	p
NHR and insula L	−0.59	0.0206	0.14	>0.05	0.13	>0.05
NHR and insula R	−0.58	0.0223	0.15	>0.05	−0.39	>0.05
NHR and thalamus L	−0.58	0.0234	0.14	>0.05	−0.49	>0.05
NHR and thalamus R	−0.64	0.009	0.11	>0.05	−0.31	>0.05

Rp, Pearson coefficient; Rs, Spearman coefficient; p, p-value for Pearson or Spearman coefficient correlation.

average lipid levels decrease, which could potentially disrupt the comparison of NHR values between the groups. (42) NHR is a peripheral inflammatory factor likely associated with inflammation caused by extensive microglial activation, which is linked to this phenomenon. The inflammation and microglial activation appear to be key factors in neurodegeneration in atypical parkinsonism and other neurodegenerative diseases. The presence of a highly oxidizing, pro-inflammatory environment combined with a high concentration of microglia makes dopaminergic neurons in the substantia nigra especially susceptible to neuroinflammation (43). Glial cells are crucial for cholesterol synthesis and metabolic balance in the brain, where a particle resembling HDL containing apolipoprotein E (ApoE) facilitates cholesterol transport. Astrocytes and microglia are responsible for the secretion of ApoEs found in these HDL-like particles (44). There is a strong possibility that dyslipidemia is causally related to impaired blood–brain barrier (BBB) function (45). Higher HDL-C levels are linked to reduced BBB permeability (44). Breakdowns in both the structure and performance of the BBB occur naturally with aging. However, this deterioration is significantly amplified in numerous neurodegenerative conditions and serves as a prominent sign of cognitive impairment or even dementia (46).

HDL facilitates reverse cholesterol transport (RCT), a mechanism that extracts excess cholesterol from peripheral tissues and delivers it to liver cells. Therefore, cholesterol is metabolized and eliminated (47). Additional beneficial roles of HDL include anti-inflammatory, antioxidant, and vasodilatory activities. HDL also plays a role in regulating insulin secretion and insulin sensitivity. HDL functions relate to the structure and composition of its particles, which is evident in the varying biological activities of its two primary subclasses, HDL2 and HDL3. Smaller and denser HDL3 particles play a more significant role in cholesterol effiux, whereas larger HDL2 particles are more actively involved in antithrombotic activities (48). The described HDL properties negatively correlate with the proposed mechanisms leading to diseases such as PSP or CBS. Considering the functions of the HDL subclasses, HDL2 appears to be a greater protective factor than HDL3. This only confirms the importance of further research on the relationship between HDL and these tauopathies.

As it turns out, HDL influences the risk of diseases such as AD or FTD, which may clinically manifest. Research has indicated a relationship between higher plasma levels of HDL-C and ApoE levels and a lower risk of dementia (49). Similar to ApoE, Apolipoprotein J (ApoJ) attaches to HDL and HDL-like particles and plays a vital role in cholesterol metabolism in the brain. ApoJ prevents the aggregation of both amorphous and amyloidogenic proteins triggered by stress in various ways. It binds to the hydrophobic sections of aggregated or misfolded proteins, either breaking them down or reducing their toxicity. Additionally, under normal physiological conditions, ApoJ plays a neuroprotective role by blocking the aggregation of Aβ. (50). ApoJ was found to be increased in AD patients (51). HDL defends against cognitive deterioration in AD (52). The behavioral variant FTD (bvFTD) cohort (N = 31) showed reduced levels of HDL compared with the control group (53). The difference in the correlation between CBS and PSP may be attributed to the fact that CBS can be a symptom of many diseases, such as AD or FTD, whereas PSP is a more suggestive clinical diagnosis than CBS (54). There is a significant overlap between the diagnosis of CBS and PSP (55). In FTD, cognitive phenotypes frequently overlap with motor phenotypes, including motor neuron diseases, parkinsonian symptoms, and syndromes such as CBS or PSP (56). Extrapyramidal symptoms combined with apraxia suggest the presence of CBS, which is predominantly associated with Tau disease. In contrast, dementia in the context of FTD with motor neuron disease (FTD-MND) syndrome is mainly linked to TDP-43 pathology (57). AD also might resemble CBS and PSP, but AD is more connected with the Tau protein phosphorylated at threonine 181 (p-tau181) (58). Both markers are potentially present in the CSF.

SPECT examination is widely used in the differential diagnosis of 4R tauopathies (4RT). Research employing the same radiotracer identified perfusion abnormalities in the prefrontal cortex in PSP, but in CBS, the irregularities occurred in the inferior prefrontal, sensorimotor, and posterior parietal cortices. Furthermore, another study demonstrated a more pronounced asymmetry in blood flow in CBS (59). SPECT allows for the distinguishing of CBS patients from PD patients. CBS patients exhibited reduced perfusion in the temporoinsular area, insula, or thalamus (60). The anterior insula's increased functionality was correlated with Interleukin-6 elevation in the serum of the CBS patients (61). The correlation between NHR and perfusion of the insula suggests a potential relationship between systemic inflammation (as reflected by NHR) and reduced activity in the insula, which could contribute to the symptomatology observed in CBS patients, such as motor dysfunction and cognitive impairment. Reduced activity in this region can affect, among other functions, sensory perception, motor control, and regulation of consciousness. It is worth adding that impaired judgment, lack of empathy, and impulsivity/disinhibition are clinical characteristics of the behavioral variant of bvFTD. These deficits are consistent with the roles of the anterior insula region (62). Patients with AD express atrophy of the insular cortex, which may reflect typical symptoms such as progressive memory loss, diminished activities of daily life, language impairment, motor skill disorders, and loss of perception (63, 64). Additionally, the thalamus, among other structures, is likely responsible for sleep disturbances observed in individuals with AD (65). Individuals with bvFTD and AD exhibit marked bilateral volume losses in the thalamus (66, 67). Differential thalamic involvement, identified through diffusion measurements, may be useful in distinguishing PSP from CBD. In PSP, the

anterior and medial thalamic nuclei were found to be more affected, whereas, in CBD, the motor thalamus region was predominantly affected (60). To the best of our knowledge, the correlation between the perfusion of these mentioned ROI and NHR levels has not been explored previously.

It should be noted that NLR and NHR are widely used as peripheral inflammatory indicators in other diseases than 4RT. The average NLR value in the PSP group was notably higher than that in both the PD group and healthy control subjects (68). As a reference point for the study group, we adopted laboratory norms for neutrophils, blood platelets, and HDL. Moreover, the NLR can predict mortality in the general population and is significantly associated with higher overall mortality rates (69). Studies have claimed that inflammation plays a pivotal role in PD pathogenesis, assessing, among other things, NLR and NHR contributions. In the PD group, there was a significant increase in neutrophil count, NHR, and NLR. In contrast, hypertension, body mass index, and lymphocyte count, as well as total cholesterol levels, triglycerides, LDL cholesterol, and uric acid were substantially reduced compared to the control group. Meanwhile, correlation analysis revealed that the NHR was significantly negatively associated with disease duration. The NHR has significant predictive power for PD and is intricately linked to the disease's duration. These findings suggest that the NHR could be a superior indicator of long-term clinical outcomes in PD patients compared with the NLR (70, 71). There are many reports about neutrophils and HDL having a significant association with cardiovascular diseases (72, 73).

Additionally, during acute cardiovascular events, abundant neutrophil aggregates lead to increased expression of local inflammatory mediators, which heightens inflammation and exacerbates the condition. HDL-C supports endothelial function and blood viscosity and possesses anti-atherosclerotic properties (72). The NHR can be used, for example, to evaluate survival prognosis in ischemic strokes. The NHR is assumed to facilitate the identification of suitable symptomatic therapies for patients (73).

However, there are no data on the influence of the NHR on the development of symptoms, selection of more appropriate therapy, and, consequently, survival rate in the context of 4RT tauopathies. PSP and CBS contributed to the elevation of the NLR. A significant difference in the NLR increase was observed exclusively in PSP, whereas the rise in NLR within CBS cases was less marked and lacked significant differences (27). It seems that, as seen in the case of PD and vascular diseases, a proper understanding of the precise mechanism of action of peripheral inflammatory markers such as NLR, PLR, and NHR will not only allow better prediction of survival duration but also enable the selection of the appropriate therapies. Consequently, this approach could extend the survival time of patients suffering from 4RT.

Neuroinflammatory PSP pathogenesis was also associated with a significant increase in pro-inflammatory and microglia-related cytokines (IL-1β, IL-6, and TNF-α) and IL-4 (74, 75). Additionally, PSP individuals expressed elevated IL-2 levels associated with malfunctioning peripheral inflammation (74). One study postulated that patients with PSP express higher levels of TGFβ in cortical areas, as well as IL-1β, which is more concentrated in the substantia nigra (76). There was a correlation found between IL-6 serum levels and PSP severity (77). Data related to the CBS interleukin profile were not found. However, CBS can be a symptom of FTD. In individuals with autosomal dominant FTD, elevated IL-6 levels were linked to a more rapid functional decline, while TNFα was associated with both this deterioration and temporal lobe atrophy (78).

This study primarily evaluated the utility of assessing peripheral inflammation in the context of diagnosing CBS or PSP. It is especially crucial because these diseases exhibit considerable phenotypic overlap; therefore, an additional diagnostic tool will be extremely important for establishing an accurate diagnosis (55). Identifying a specific target within the pathomechanism of CBS may provide the opportunity to find effective targeted future therapies for patients suffering from the syndrome. Both inflammation and brain hypoperfusion caused by modifiable factors, e.g., atherosclerosis, narrowing of the blood vessels, chronic infections, and many environmental factors, can be mitigated through appropriately chosen pharmacotherapy, which can impact the quality of life of these subjects in the future.

Limitations

The research was constrained by several limitations. The study lacked neuropathological evaluation because all patients are currently alive. Additionally, the cohort is relatively small, comprising 71 subjects, of whom 19 were diagnosed with CBS, 37 with PSP, and 15 with PD. The relatively small proportion of patients and the CBS cohort was insufficiently balanced in terms of gender. These two aspects were associated with the fact that both CBS and PSP are rare diseases; moreover, patients affected by the clinical entities suffer due to limited mobility. Additionally, PD patients' average age was lower than in the case of the other study groups. In this study, particular CBS and PSP and specific subclasses of HDL were not acknowledged. Assessments were based on a singular examination. Due to the rapid clinical deterioration, conducting a reliable subsequent evaluation of these diseases was not possible. The study is based on non-specific, easily accessible diagnostic tools.

Conclusion

This study showed a negative correlation between the NHR increase and perfusion concerning the thalamus and insula via SPECT examination in the context of CBS. The NHR is a non-specific indicator of peripheral inflammation. The NHR index may be a good indicator of hypoperfusion due to the negative correlation of HDL with atherosclerotic plaques and neutrophils, which significantly increases the risk of blood vessel stenosis and, consequently, hypoperfusion. It appears that a high level of HDL (which is negatively correlated with the NHR) has a protective effect on the BBB and, consequently, on the degeneration process. Decreased perfusion may suggest the evolution of neurodegenerative changes. The same correlation was not observed in the case of the PSP and PD. This finding may arise from the fact that CBS can occur in a more heterogeneous group

of pathologies when compared to PSP or PD. Additionally, this may suggest possible differences in the pathomechanism of these two diseases. There is currently a lack of efficient treatment options, and an analysis of the course of inflammation may enable further studies into possible effective treatments. Additional studies involving larger groups of patients with neuropathological verification are necessary.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by BioEthical Committee of the Medical University of Warsaw. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. BM: Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. NM-A: Formal analysis, Investigation, Project administration, Validation, Writing – original draft, Writing – review & editing. AM: Investigation, Writing – original draft, Writing – review & editing. MK: Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. LK: Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. PA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Article

Possible Impact of Peripheral Inflammatory Factors and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy–Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy–Predominant Parkinsonism (PSP-P)

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Abstract: Progressive supranuclear palsy (PSP) is a tauopathic atypical parkinsonian syndrome. Recent studies suggest that inflammation may play a role in PSP pathogenesis, highlighting markers like the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and cytokines such as IL-1β and IL-6. This study aimed to assess the relationship between peripheral inflammatory markers and psychological abnormalities in PSP-RS and PSP-P patients. The study included 24 participants: 12 with PSP-RS, 12 with PSP-P, and 12 controls. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA); however, the executive functions were evaluated using the Frontal Assessment Battery (FAB), while inflammatory markers such as IL-1β, IL6, NLR, and PLR were measured. The parameter correlation was executed using Spearman's correlation (rs). The analysis revealed significant negative correlations between NLR and MoCA (rs = −0.48), as well as between PLR and MoCA (rs = −0.60). The negative correlation between IL-1β and MoCA was statistically significant but relatively weak. This study highlights the relevance of inflammatory markers such as NLR and PLR in reflecting cognitive decline in PSP patients, with IL-1β potentially playing a protective role in cognitive function.

Keywords: interleukin-1β (IL-1β); interleukin-6 (IL-6); peripheral inflammatory markers; Montreal Cognitive Assessment (MoCA); Frontal Assessment Battery (FAB); progressive supranuclear palsy (PSP)

1. Introduction

Progressive supranuclear palsy (PSP) belongs to atypical parkinsonisms; generally, it is characterized by bradykinesia, impaired postural reflexes, eye movement disturbances, and language or cognitive difficulties [1,2]. Among the hypotheses attempting to explain the pathophysiological mechanism of PSP are the vascular, environmental [3–5], genetic [6], and increasingly popular inflammatory mechanisms. PSP is a four-repeat (4R) tauopathy. Neuropathologically, the diagnosis of PSP relies on identifying neurofibrillary tangles and threads within subcortical nuclei, along with the presence of tufted astrocytes [7]. The definitive diagnosis of PSP can be established based on neuropathological examination. Without the possibility of neuropathological confirmation, a diagnosis of probable PSP can be made based on the gradual progression of symptoms, sporadic occurrence, and

an onset after the age of 40 [2], but the last two criteria are questioned, especially in relation to the genetic form of PSP [6]. This tau pathology leads to the development of several clinical phenotypes, with the two most common being PSP–Richardson's syndrome (PSP-RS) and PSP with predominant parkinsonism (PSP-P). Together, these two subtypes account for 80–90% of all PSP cases [8]. According to the most contemporary diagnostic criteria, both PSP types are diagnosed based on an onset of symptoms at age 40 or older, gradual progression of symptoms, and sporadic occurrence [2]. The diagnosis of PSP-RS is established on the basis of vertical eye movement and the tendency to fall within 3 years. In PSP-P, the criteria indicate a marked severity of symptoms commonly linked to parkinsonism, such as freezing and rigidity, which could be accompanied by resistance to levodopa treatment. The diagnostic criteria for PSP include the assessment of cognitive dysfunction [2]. There are various manifestations of cognitive deterioration in PSP, among which mild deficits ranging to pronounced dementia could be mentioned [9]. It comprises a broad range of cognitive abnormalities, including impairments in attention, executive functioning, learning, and memory [10]. In the early stages of the disease, mild cognitive impairment (MCI) is the most prevalent type of cognitive dysfunction, affecting 43% of patients, followed by dementia in 41%, and normal cognition in 16% of subjects is observed. Over time, most PSP patients advance to dementia with an incidence rate of 241 per 1000 patients per year [9]. However, PSP-RS also affects the executive functions, which are related to but not synonymous with frontal lobe function. Research has shown deficits in short-term memory and spatial working memory, along with poor memory strategies [11]. The research indicates that cognitive decline among PSP patients is linked to microscopic indicators of the disease, such as the accumulation of tau [12]. PSP individuals present brain atrophy, which is more pronounced in the frontal lobe [13], hippocampus [14], insula [15], or thalamus [16]. SPECT examination also showed a reduced perfusion among the patients with elevated HbA1C levels in these regions [17]. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil high-density lipoprotein ratio (NHR) [18] as well as cytokines released by activated microglia, including TNF-α, IL-1β, and IL-6, are linked to neurodegeneration including atypical parkinsonism disorders like PSP [19]. However, the mechanisms underlying the development of PSP are still not fully recognized [20]. Microglia might be activated by environmental toxins, cytokines, neuronal damage [21], and β-amyloid or tau [22]. The objective of the study was to investigate the association between readily accessible peripheral inflammatory markers, including NLR, PLR, IL-1, and IL-6, and cognitive decline as measured by the widely available MoCA screening tool. Furthermore, the relationship between these inflammatory markers and executive function impairments was examined using the FAB, another standardized screening measure. The study was conducted on cohorts with PSP-RS and PSP-P, with comparisons drawn against a healthy control group.

2. Results

Correlation analysis:

A statistically significant negative correlation was found between NLR and MoCA (rs = −0.48, p value < 0.009), PLR and MoCA (rs = −0.60, p value < 0.001), and NLR and FAB (rs = −0.38, p value < 0.03). We also found a positive correlation between IL-1β and MoCA (rs = 0.38, p value < 0.03). These results are presented in Figures 1–4. The correlations between IL-6 along with other measured parameters and either MoCA or FAB revealed insignificant findings.

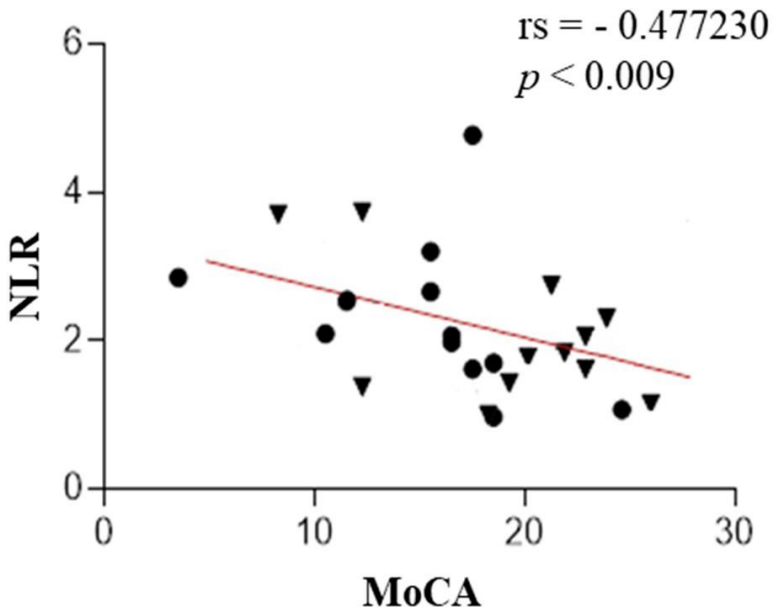

Figure 1. The correlation analysis between the neutrophil-to-lymphocyte ratio (NLR) and test MoCA in patients with PSP (the PSP-RS and PSP-P groups are combined). CirclPSP-RS. Triangle—PSP-P.

Scatter plots show that the NLR was negatively correlated with test MoCA.

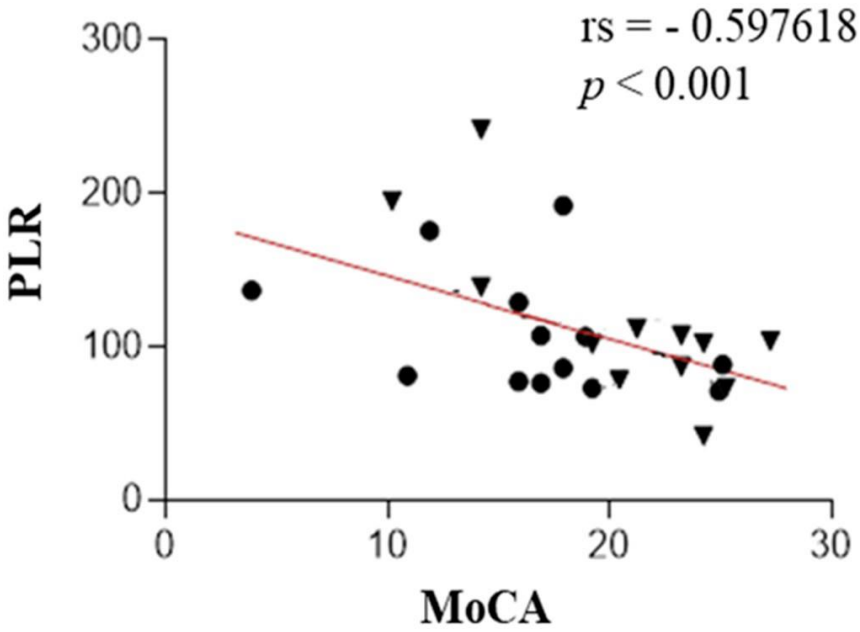

Figure 2. The correlation analysis between the platelet–lymphocyte ratio (PLR) and test MoCA in patients with PSP (the PSP-RS and PSP-P groups are combined). Circle—PSP-RS. Triangle—PSP-P.

Scatter plots show that the PLR was negatively correlated with test MoCA.

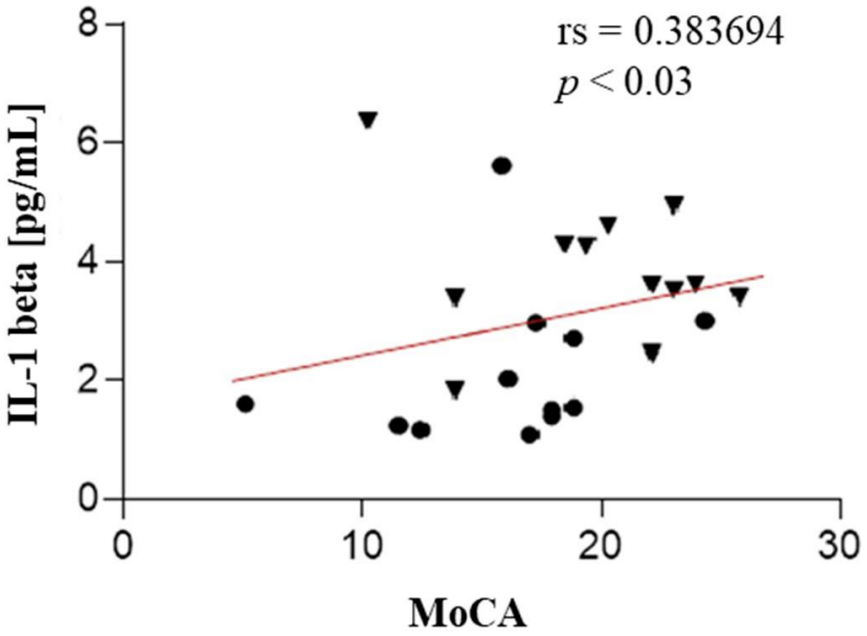

Figure 3. The correlation analysis between the serum IL-1 beta and test MoCA in patients with PSP (the PSP-RS and PSP-P groups are combined). Circle—PSP-RS. Triangle—PSP-P.

Scatter plots show that the serum IL-1 beta was positively correlated with test MoCA.

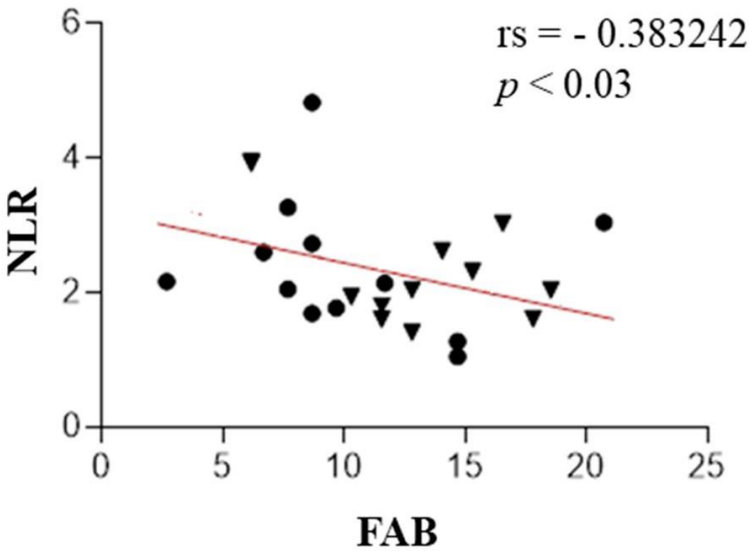

Figure 4. The correlation analysis between the neutrophil-to-lymphocyte ratio (NLR) and test FAB in patients with PSP (the PSP-RS and PSP-P groups are combined). Circle—PSP-RS. Triangle—PSP-P.

Scatter plots show that the NLR was negatively correlated with test FAB.

3. Discussion

In this research, the authors evaluated the correlation of IL-1-beta concentration, IL-6, NLR, and PLR with cognitive function assessed in screening, easily accessible tests—MoCA and FAB. IL-1 and IL-6, which are microglial-derived, share common functions in the body's inflammatory response. IL-1 acts as a leukocytic pyrogen, a mediator of fever, an endogenous leukocytic mediator, and an inducer of components in the acute-phase response. Similarly, IL-6 is produced at the onset of inflammation, traveling through the bloodstream to the liver, where it rapidly stimulates the production of numerous acute-phase proteins. Together, both cytokines play crucial roles in initiating and regulating the

acute-phase response during inflammation [23,24]. The role of the mentioned interleukins in the neurodegeneration development is unambiguous. Both IL-1β and IL-6 play crucial roles in driving neuroinflammatory processes, serving as possible mediators in the progression of neurodegeneration [25–27]. However, their roles differ in certain aspects. IL-1β primarily acts as a potent pro-inflammatory cytokine, intensifying neural damage [27], whereas IL-6 exhibits a dual function, participating not only in inflammation but also in neuronal and cerebrovascular repair mechanisms [25]. Elevated levels of IL-6 have been linked to the early onset of PD [25,26], suggesting its potential as a biomarker and therapeutic target [25]. Hepcidin, which regulates iron metabolism, is also a component of the nonspecific immune system involved in pathogen response, connecting it to the issue of neuroinflammation in the development of neurodegenerative diseases. Hepcidin suggests a potential acceleration of neurodegeneration as a result of disrupted metal homeostasis [28]. Munoz-Delgado et al. conducted a meta-analysis of 121 individuals, concluding that patients with PSP had a higher PLR [29] and NLR in peripheral blood compared to HCs [29,30]. Our study also shows that, widely described in the literature, elevated NLR and PLR parameters in PSP are associated with lower scores on the MoCA test. This research also shows that the elevated NLR parameter in this disease is associated with lower MoCA test scores. Consequently, increased peripheral inflammatory parameters correlate with poorer performance in executive functions (verbal fluency, cognitive flexibility) and memory (short-term verbal memory, retrieval). Additionally, NLR is negatively correlated with the FAB test to a similar degree; interestingly, no such relationship was observed for PLR.

These findings are consistent with the literature, where patients with PSP are reported to have lower scores on MoCA and FAB tests compared to the control group. It is hypothesized that this may be linked, among other factors, to hypometabolism [31] or cortical atrophy [32,33]. It should be noted that both the MoCA and FAB test are the screening tools for assessing executive functions and memory. However, further research should employ more advanced neuropsychological batteries to analyze which areas of executive functions, language functions, and/or memory are impaired due to elevated levels of peripheral inflammatory factors, and IL-1β. Most studies have indicated a general link between microglial activation, IL-1β, IL-6 secretion, and tau pathology [19]. Regarding Alzheimer's disease (AD), it is postulated that increased levels of activated microglia are linked to reduced rates of amyloid accumulation as well as slower tau deposition, resulting in cognitive decline. Similarly, stimulated microglial macrophages predicted slower tau accumulation with mitigated cognitive decline as a consequence [22]. Thus, it seems that a similar mechanism may occur in the case of PSP, which aligns with the obtained results, showing a positive correlation between IL-1β, which is microglia-derived, and better cognitive or executive functions among PSP patients. However, the exact mechanism behind this correlation remains unclear. A statistical analysis showed that the mean IL-1β concentration in CSF was significantly higher in patients with PSP-P compared to those with PSP-RS, and in the control group compared to the PSP-RS group [34]. In our study, there is a positive correlation between the IL-1β level and MoCA score; moreover, in the control group, IL-1β concentration is the highest, which may suggest a protective function of interleukins against the development of inflammation. Considering that IL-1β levels are statistically higher in PSP-P than in PSP-RS, and the cognitive function deterioration is more pronounced in PSP-RS, it therefore supports the hypothesis of the protective effect of IL-1β. This may result from the fact that IL-1β, released during the initiation of inflammation, has a self-limiting effect on the microglial cells that secrete interleukins and it secondarily limits inflammation and reduces the decline in cognitive function. Probably due to the correlations obtained are relatively low; nonetheless, a clear negative trend exists between peripheral inflammatory factors and the results of screening psychological tests, along with a positive trend between IL-1β concentration and MoCA scores. No significant correlation was observed between IL-1β concentration and FAB, which may be related to the protective role of interleukins in memory and language functions, without a significant effect on executive functions mainly depending on the frontal lobe. The relationship between IL-6 and the MoCA and FAB

tests was also examined in this publication; however, no statistically significant correlation was found between these parameters. Screening tests assessing cognitive functions were used due to their wide availability and ease of use; moreover, the MoCA and the FAB were used due to their broad range of cognitive domains assessed by the tests. As a pilot study, we aimed to use a screening diagnostic tool that evaluates multiple domains to determine whether there is any correlation between cognitive functioning and peripheral inflammatory factors in the most common PSP subtypes.

To our knowledge, no prior studies have examined the relationship between this parameter and peripheral inflammatory factors. However, in the future, more advanced neuropsychological batteries should be employed to identify the specific domains of neuropsychological functioning affected by inflammation. Moreover, both apathy and depression negatively impact on overall cognitive performance [35]. It is estimated that more than half of individuals with PSP exhibit features of depression and/or apathy, although these symptoms are relatively mild in intensity. Major Depressive Disorders are relatively rare. However, there are no adequate tools for making a definitive diagnosis, and much of the data on affective disorders in PSP rely on subjective responses from participants. Nevertheless, even mild affective disturbances can slightly affect the results of tests assessing cognitive functions [35,36]. This implies the need to study these factors using appropriately dedicated tests in future research.

Both PSP groups exhibited decreased thickness and volume in the frontal lobe regions; however, PSP-P showed more extensive cortical thinning, also affecting the temporal and parietal lobes in comparison to PSP-RS [37]. Greater cortical atrophy (especially in the frontal cortex) among PSP-P patients, along with less pronounced cognitive deterioration compared to PSP-RS, strongly supports an inflammatory etiology for the reduction in the cognitive reserve in PSP. However, the studies are not congruent in this field. Another study claims that there is a greater volume loss in the frontal lobe in PSP-RS compared to PSP-P [38]. In other imaging examinations such as SPECT and FDG PET, frontal lobe hypoperfusion and frontal lobe hypometabolism might be observed, respectively, regarding PSP [39,40]. In SPECT, the D2 receptor radiotracer proved to be useful for distinguishing PSP-RS from PSP-P, as striatal uptake was decreased in PSP-RS and slightly elevated in PSP-P. However, there is insufficient data to definitively differentiate PSP-RS from PSP-P based on frontal lobe hypoperfusion [25] or frontal lobe hypometabolism [40]. According to Black and colleagues, frontal hypometabolism is not useful for distinguishing between PSP-RS and PSP-P [31]. The correlation of the obtained results with imaging examination would allow for an assessment of the extent to which cognitive impairments in PSP are caused by general brain atrophy, particularly in the frontal lobe region, versus the contribution of inflammation, most likely triggered by excessive microglial activation in response to the presence of the neurodegenerative tau. Another important marker of PSP is tau quantitative assessment, reflecting the neurodegenerative nature of the disease. The average regional tau severity was higher in PSP-RS than in PSP-P across all brain regions, with a significant difference observed in every region. The PSP-RS group showed a significantly higher total tau concentration compared to the PSP-P group [41]. A higher concentration of tau is most likely directly proportional to the degree of CNS degeneration; therefore, it seems reasonable to conclude that the level of neurodegeneration is positively correlated with cognitive impairment. While PET has a limited functionality in differentiating PSP-RS and PSP-P based on frontal lobe hypometabolism, PET radiotracers bind tau effectively. The inclusion of tau PET significantly increased confidence in determining the underlying etiology. The largest effect sizes for the certainty of etiology and diagnosis were observed in the Aβ-positive group [42]. The 11C-PK11195 radiotracer (TSPO) receptor is rapidly identified as over-expressed in brain lesions and is considered a useful marker for neurodegeneration [43] such as cognitive impairments. The combined use of C-labeled Pittsburgh Compound B ([11C]PiB) and 18F-labeled AV-1451 enables researchers to assess β-amyloid and tau accumulation [44]. In PSP, increased binding has been observed in the basal ganglia, midbrain, frontal lobe, and cerebellum and in the putamen, thalamus, and pallidum.

The radiotracer binding in the pallidum, midbrain, and pons has been associated with disease severity [45]. Furthermore, both mentioned radiotracers are linked to microglial activation [44]. PET molecular imaging of microglial activation and tau pathology can potentially forecast clinical progression in PSP, but the exact mechanism of this connection remains unclear.

This study has several limitations. Neuropathological evaluation was not conducted in the study as all patients remain alive. The study is based on possible and probable diagnoses of PSP. Due to the pilot character of the study, no neuroimaging was conducted; however, the authors plan to extend the evaluation in future works. The results of both the MoCA and FAB tests are influenced not only by inflammatory factors but also by years of education, intelligence, affect presented during the examination, and the presence of other conditions. A methodological limitation in this study is that both tests were conducted only once, so the patient's well-being on the day of testing may have also affected the results. Additionally, the study group was relatively small (24 subjects and 12 subjects in the healthy control group). Study participants were not divided into PSP-RS and PSP-P subgroups, which might slightly alter final results.

4. Materials and Methods

4.1. Study Group

The research group consisted of 36 individuals: 12 with PSP-RS, 12 with PSP-P, and 12 healthy individuals as the HC. Patients enrolled in the study had to meet the following criteria: provide written informed consent to participate in the clinical trial, be over 55 years of age, show no clinical signs of infection during the internal medicine examination, and have no prior diagnosis of any psychiatric disorder before the PSP diagnosis. Eligible patients diagnosed with either PSP-RS or PSP-P fulfilled the MDS criteria for PSP [2]. The disease duration ranged from 3 to 6 years. In the first group, there were 5 females and 7 males, and in the second group, there were 4 females and 8 males. The mean age of PSP-RS and PSP-P patients was similar (70.3 vs. 68.8); HC was age- and sex-matched. HC had to meet the same criteria as the study group, except for the diagnosis of PSP. Both research groups were separately compared to the control group. Data concerning the individuals participating in the study are summarized in Table 1.

Table 1. Clinical and biochemical data of the study group.

	PSP-RS Patients (n = 12)	PSP-P Patients (n = 12)	Healthy Control (n = 12)
Age [years]—Mean ± SD	70.3 ± 3.6	68.8 ± 6.7	50 ± 8.8
Sex distribution [female/male]	5/7	4/8	7/5
Average disease duration [years]	3.5	4.5	-
CRP [mg/L]	<5	<5	<5
Average NLR—Mean ± SD	2.4 ± 1.0	2.3 ± 0.8	3.03 ± 1.8
Average PLR—Mean ± SD	112.3 ± 28.1	113.2 ± 45.6	97.6 ± 60.2
Average IL-1β [pg/mL] in serum—Mean ± SD	2.2 ± 0.6	3.9 ± 1.1	1.5 ± 0.9
Average IL-6 [pg/mL] in serum—Mean ± SD	4.4 ± 1.5	7.2 ± 2.6	3.9 ± 1.2

PSP-RS, Progressive Supranuclear Palsy–Richardson Syndrome; PSP-P, Progressive Supranuclear Palsy–Predominant Parkinsonism; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet–Lymphocyte Ratio; SD, Standard Deviation.

4.2. Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) provides an overall score along with six index scores for specific cognitive domains, which include language, attention, orientation, memory, executive functioning, and visuospatial ones [46]. The MoCA is a screening

10 min paper-and-pencil test with a maximum score of 30 points, where a score below 26 indicates cognitive deficits [47]. MoCA was used.

4.3. Frontal Assessment Battery (FAB)

The Frontal Assessment Battery (FAB) test effectively detects frontal lobe dysfunction in PSP [31]. It provides an overall score along with six index scores for specific cognitive domains, which include mental flexibility, conceptualization, environmental autonomy, inhibitory control, programming, and sensitivity to interference [48]. A limitation of this scale is its incomplete assessment of cognitive functioning [49].

4.4. Patient Materials

Blood and cerebrospinal fluid (CSF) samples were collected from 24 patients with progressive supranuclear palsy (PSP) hospitalized in the Department of Neurology at the Medical University of Warsaw. The control group comprised 12 healthy individuals who were admitted to the Department of Infectious Diseases, Tropical Diseases, and Hepatology at the same university. These individuals did not have any comorbidities likely impacting the level of inflammatory factors. Blood samples (5 mL) were collected in tubes without anticoagulants, centrifuged, and stored at −80 °C. Similarly, CSF (10 mL) was obtained through a lumbar puncture, frozen, and kept at −80 °C until the analysis.

4.5. Biochemical Analysis

Commercial enzyme-linked immunosorbent assays (ELISAs) were employed to measure the levels of IL-6 and IL-1β. Human IL-6 HS and IL-1β ELISA kits (Diaclone SAS, Besancon, France) were used for this purpose. The absorbance was recorded at 450 nm with a plate reader, and concentrations of the markers were determined based on standard curves.

All patients underwent laboratory testing, which involved a full blood count, an evaluation of C-reactive protein (CRP) levels, and biochemical tests, including lipid profiling and ferritin measurement. None of the patients had elevated inflammatory markers such as CRP or leukocytosis. The ratios including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-HDL-C ratio (NHR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-monocyte ratio (NMR) were calculated by dividing the number of neutrophils by lymphocytes, lymphocytes by monocytes, neutrophils by HDL-C, platelets by lymphocytes, and neutrophils by monocytes, respectively. The Sysmex XT 4000i automatic hematology analyzer, located at the Laboratory Diagnostics Department of the Mazovian Hospital in Brodno, was used for the counts.

4.6. Statistical Analysis

A data analysis was performed using GraphPad Prism 8 software (GraphPad Software, San Diego, CA, USA). Arithmetic means (X) and standard deviations (SDs) were computed. Statistical significance was established at $p < 0.05$. The normality of the data was evaluated using the Shapiro–Wilk test. Group comparisons were made using the Mann–Whitney U test, and Spearman's Rank-Order Correlation was applied to assess the relationships between clinical markers and FAB, as well as MoCA test scores.

5. Conclusions

In this research, the authors evaluated the association of IL-1-beta concentration, IL-6, NLR, and PLR with cognitive function assessed in screening, easily accessible tests—MoCA and FAB. Nonspecific inflammatory parameters suggest that this process may play a role in cognitive and executive functioning impairments observed in PSP; however, a further detailed analysis is required to elucidate its significance. Although there is increasing interest in studying neuroinflammation and its connection to immune status in various neurodegenerative disorders, limited information is available on PSP. Gaining a deeper understanding of the factors accelerating PSP progression including cognitive deterioration could ultimately lead to the development of new therapeutic strategies.

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Errata

Strona nr **52**

Jest „The negative correlation between IL-1β and MoCA was statistically significant but relatively weak.”
Powinno być „The positive correlation between IL-1β and MoCA was statistically significant but relatively weak.”

Warszawa, 21.12.2024
(miejscowość, data)

Natalia Madetko-Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Asymmetry in Atypical Parkinsonian Syndromes-A Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbieranie danych, pisanie artykułu.
Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

dr hab. n. med.
Natalia Madetko-Alster
specjalista neurolog
PWZ 3376620

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Piotr Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Asymmetry in Atypical Parkinsonian Syndromes-A Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Przegląd koncepcji i projektu, analiza danych i interpretacja danych, zbieranie danych, metodologia, pisanie artykułu oraz superwizja
Mój udział procentowy w przygotowaniu publikacji określam jako 30 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

dr hab. n. med. Piotr Alster
specjalista neurolog

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Bartosz Migda
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study” oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Analiza statystyczna, pisanie manuskryptu.
Mój udział procentowy w przygotowaniu publikacji określam jako 9 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on koncepcję i aranżację badań, zbiór danych, analizę statystyczną i interpretację danych, metodologię, pisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Natalia Madetko-Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Zbiór danych, pisanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,

(imię i nazwisko kandydata do stopnia)

obejmował on koncepcję i aranżację badań, zbiór danych, analizę statystyczną i interpretację danych, metodologię, pisanie manuskryptu

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego

(imię i nazwisko kandydata do stopnia)

dr hab. n. med.
Natalia Madetko-Alster
specjalista neurolog
PWZ 3375629

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Anna Migda
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbiór danych, pisanie manuskryptu.
Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on koncepcję i aranżację badań, zbiór danych, analizę statystyczną i interpretację danych, metodologię, pisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Michał Kutyłowski
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbiór danych, pisanie manuskryptu.
Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on koncepcję i aranżację badań, zbiór danych, analizę statystyczną i interpretację danych, metodologię, pisanie manuskryptu.
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Leszek Królicki
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study” oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Metodologia, pisanie manuskryptu.
Mój udział procentowy w przygotowaniu publikacji określam jako 8 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on koncepcję i aranżację badań, zbiór danych, analizę statystyczną i interpretację danych, metodologię, pisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

Leszek Królicki
Elektronicznie podpisany przez Leszek Królicki
Data: 2024.12.22 18:23:47 +01'00'

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Piotr Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „The possible connection between neutrophil-to-high-density lipoprotein ratio and cerebral perfusion in clinically established corticobasal syndrome: a pilot study" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Koncepcja i aranżacja badań, analiza statystyczna i interpretacja danych, metodologia, pisanie manuskryptu, superwizja.
Mój udział procentowy w przygotowaniu publikacji określam jako 20 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on koncepcję i aranżację badań, zbiór danych, analizę statystyczną i interpretację danych, metodologię, pisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

dr hab. n. med. Piotr Alster
specjalista neurolog
6168373

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Dagmara Otto-Ślusarczyk
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factots and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Metodologia, zbieranie danych, analiza danych, pisanie artykułu.
Mój udział procentowy w przygotowaniu publikacji określam jako 16 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,
(imię i nazwisko kandydata do stopnia)
obejmował on Przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 20.12.2024
(miejscowość, data)

Karolina Duszyńska-Wąs
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factors and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P), oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Zbieranie danych, analiza danych, pisanie artykułu

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: Przegląd koncepcji i projektu, analiza danych i interpretacja danych, zbieranie danych, metodologia oraz pisanie artykułu

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego

(imię i nazwisko kandydata do stopnia)

Karolina Duszyńska-Wąs
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 20.12.2024
(miejscowość, data)

Agnieszka Drzewińska
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factors and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P), oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

Zbieranie danych, analiza danych, pisanie artykułu

Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.

Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: Przegląd koncepcji i projektu, analiza danych i interpretacja danych, zbieranie danych, metodologia oraz pisanie artykułu

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Andrzej Załęski
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factots and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbieranie danych, analiza danych, pisanie artykułu.
Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,
(imię i nazwisko kandydata do stopnia)
obejmował on Przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

dr n.med. Andrzej Załęski
Specjalista pediatrii
Specjalista chorób zakaźnych

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Natalia Madetko-Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factots and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbieranie danych, analiza danych, pisanie artykułu.
Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,
(imię i nazwisko kandydata do stopnia)
obejmował on Przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu.
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

dr hab. n. med.
Natalia Madetko-Alster
specjalista neurolog
PWZ 3/1/6620
.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Alicja Wiercińska-Drapało
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factots and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbieranie danych, analiza danych, pisanie artykułu.
Mój udział procentowy w przygotowaniu publikacji określam jako 1 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,
(imię i nazwisko kandydata do stopnia)
obejmował on Przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

Alicja Wiercińska-Drapało
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Marta Struga
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factots and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Zbieranie danych, analiza danych, pisanie artykułu.
Mój udział procentowy w przygotowaniu publikacji określam jako 2 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,
(imię i nazwisko kandydata do stopnia)
obejmował on Przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Katedry i Zakładu Biochemii
prof. dr. hab. n. med. Marta Struga
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 21.12.2024
(miejscowość, data)

Piotr Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Impact of Peripheral Inflammatory Factots and Interleukin-1β (IL-1β) on Cognitive Functioning in Progressive Supranuclear Palsy-Richardson Syndrome (PSP-RS) and Progressive Supranuclear Palsy-Predominant Parkinsonism (PSP-P) oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
Przegląd koncepcji i projektu, analiza danych i interpretacja danych, zbieranie danych, metodologia, pisanie artykułu oraz superwizja
Mój udział procentowy w przygotowaniu publikacji określam jako 16 %.
Wkład Patryka Chunowskiego w powstawanie publikacji określam jako 61 %,
(imię i nazwisko kandydata do stopnia)
obejmował on Przegląd koncepcji i projektu, analizę danych i interpretację danych, zbieranie danych, metodologię oraz pisanie artykułu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek/mgr Patryka Chunowskiego
(imię i nazwisko kandydata do stopnia)

dr hab. n. med. Piotr Alster
specjalista neurolog
31[illegible]

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników