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Zaburzenia depresyjne i jakości życia w postępującym porażeniu nadjądrowym

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

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Atypowy parkinsonizm, depresja, jakość życia, postępujące porażenie nadjądrowe, PSP, zapalenie, neurozapalenie, neurodegeneracja, N/HGBR, NLR, PLR, NHR

Key words

Atypical parkinsonism, depression, quality of life, progressive supranuclear palsy, PSP, inflammation, neuroinflammation, neurodegeneration, N/HGBR, NLR, PLR, NHR

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Spis treści

Wykaz używanych skrótów

- AD- choroba Alzheimera
- APS- atypowy parkinsonizm
- BDI- skala depresji Becka
- CBD- zwyrodnienie korowo-podstawne
- CBS- zespół korowo-podstawny
- 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
- IL-10- interleukina 10
- LDL- lipoproteina o niskiej gęstości
- MSA- zanik wieloukładowy
- NHR- stosunek neutrofili do lipoproteiny o wysokiej gęstości
- NLR- stosunek neutrofili do limfocytów
- OUN- ośrodkowy układ nerwowy
- PD- choroba Parkinsona
- PLR- stosunek płytek krwi do limfocytów
- PMR- płyn mózgowo-rdzeniowy
- PPS- zespół(y) Parkinsonizm-Plus
- PSP- postępujące porażenie nadjądrowe
- PSP-P- postępujące porażenie nadjądrowe typu parkinsonowskiego
- PSP-RS- postępujące porażenie nadjądrowe–zespół Richardsona
- TNFβ- czynnik martwicy nowotworu β
- QoL jakość życia

Zaburzenia depresyjne i jakości życia w postępującym porażeniu nadjądrowym

Streszczenie w języku polskim

Wstęp:

Postępujące porażenie nadjądrowe (PSP) stanowi obok zespołu korowo-podstawnego (CBS) i zaniku wieloukładowego (MSA) heterogenną grupę jednostek chorobowych określanych wspólną nazwą atypowych parkinsonizmów (APS) lub zespołami Parkinsonizm-Plus (PPS). Fenotypy tych zaburzeń nakładają się na siebie, co nastręcza trudności diagnostycznych. Pewna diagnoza stawiana jest jednak tylko na podstawie badania neuropatologicznego wykonywanego post mortem. Przyżyciowo, stawiane jest tylko prawdopodobne rozpoznanie APS, co prowadzić może do stosunkowo wysokiego ryzyka popełnienia błędu. Celem niniejszego cyklu publikacji jest przedstawienie znaczenia stanu zapalnego jak również jego powiązań z zaburzeniami depresyjnymi w patofizjologii PSP.

Metodologia:

Przy tworzeniu pracy przeglądowej przeprowadzono szczegółowy przegląd aktualnej literatury, korzystając ze źródeł dostępnych w bazie PubMed. Wyselekcjonowane pod względem wartości naukowej badania poddano ocenie i analizie pod kątem możliwej przydatności w ocenie jakości życia (QoL) pacjentów z rozpoznaniem PSP. W pierwszej pracy badawczej zbadano pacjentów z PSP (u części z nich dodatkowo współwystępowała depresja, co oceniano m. in. przy użyciu Skali Depresji Becka, BDI); wykorzystano podstawowe badania biochemiczne krwi obwodowej. Badania pozwoliły na ocenę powiązań wykładników stanu zapalnego z zaburzeniami depresyjnymi w PSP. Trzecia praca umożliwiła ocenę profilu niektórych parametrów stanu zapalnego u osób z postępującym porażeniu nadjądrowym w porównaniu do prawidłowo dobranej pod względem metodologicznym grupy kontrolnej. Badania pozwoliły na uzyskanie podstawowych celów pod postacią wstępnej weryfikacji znaczenia stanu zapalnego w kontekście zaburzeń depresyjnych i jakości życia w PSP.

Wyniki:

W pierwszej pracy poglądowej podkreślono znaczenie precyzyjnej oceny jakości życia w PSP i przedstawiono narzędzia umożliwiające taką ewaluację. Praca badawcza dotycząca oceny laboratoryjnych markerów zapalenia w PSP i depresji pozwoliła na identyfikację parametru korelującego z obecnością i nasileniem depresji. Ponadto stwierdzono korelację pomiędzy wspomnianym wskaźnikiem a innymi parametrami morfologii. Badania te są spójne z dotychczasowymi doniesieniami o profilu zapalnym w podobnych jednostkach chorobowych. Praca badawcza porównująca profil niektórych markerów stanu zapalnego i neurotroficznych u pacjentów z PSP oraz grupy kontrolnej uwidacznia niektóre podobieństwa i różnice między nimi.

Podsumowanie:

Przedstawione publikacje sugerują potencją użyteczność badań markerów stanu zapalnego i ich znaczenia w patofizjologii PSP. W ramach omawianego cyklu wskazano na zasadność dalszych badań na większych grupach pacjentów, przy użyciu bardziej szczegółowych paneli parametrów stanu zapalnego, co może przyczynić się do lepszego zrozumienia mechanizmów choroby i identyfikacji potencjalnych celów terapeutycznych w tych zaburzeniach w przyszłości.

Depressive disorders and Quality of Life disorders in Progressive Supranuclear Palsy

Streszczenie w języku angielskim

Introduction:

Progressive supranuclear palsy (PSP), along with corticobasal syndrome (CBS) and multiple system atrophy (MSA), constitutes a heterogeneous group of disorders collectively known as atypical parkinsonisms (APS) or Parkinsonism-Plus syndromes (PPS). The phenotypes of these disorders overlap, which poses diagnostic challenges. However, a definitive diagnosis is made only based on post-mortem neuropathological examination. Ante-mortem, only a probable diagnosis of APS is made, which can lead to a relatively high risk of error. The aim of this series of publications is to present the importance of inflammation and its association with depressive disorders in the pathophysiology of PSP.

Methodology:

In preparing this review, a detailed search of the current literature was conducted, using sources available in the PubMed database. Studies selected for their scientific merit were evaluated and analyzed for their potential usefulness in assessing the quality of life (QoL) of patients diagnosed with PSP. The first study examined patients with PSP (some of whom also had comorbid depression, as assessed, among other tools, using the Beck Depression Inventory (BDI); basic biochemical tests of peripheral blood were used. The study allowed for the assessment of the association between inflammatory markers and major depressive disorder in PSP. The third study assessed the profile of certain inflammatory parameters in individuals with progressive supranuclear palsy compared to a methodologically appropriately matched control group. The study achieved its primary objectives of providing preliminary verification of the significance of inflammation in the context of depressive disorders and quality of life in PSP.

Results:

The first review paper emphasized the importance of precise assessment of quality of life in PSP and presented tools enabling such evaluation. Research evaluating laboratory markers of inflammation in PSP and depression identified a parameter that correlates with the presence and severity of depression. Furthermore, a correlation was found between this marker and other morphological parameters. These studies are consistent with previous reports on the inflammatory profile in similar conditions. Research comparing the profiles of certain inflammatory and neurotrophic markers in patients with PSP and a control group highlights some similarities and differences between them.

Summary:

The presented publications suggest the potential usefulness of inflammatory marker studies and their importance in the pathophysiology of PSP. This series highlights the merits of further studies in larger patient groups, using more detailed panels of inflammatory parameters, which may contribute to a better understanding of the disease mechanisms and the identification of potential therapeutic targets for these disorders in the future.

Hipoteza badawcza

Potencjalne powiązanie zaburzeń jakości życia i depresyjnych z wybranymi czynnikami patofizjologicznymi w postępującym porażeniu nadjądrowym.

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Sumaryczna punktacja IF: 10,7
Sumaryczna punktacja MNiSW: 260

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Wprowadzenie

W niniejszym cyklu prac analizowane są wybrane aspekty symptomatologii w postępującym porażeniu nadjądrowym (PSP).

PSP stanowi obok zespołu korowo-podstawnego (CBS) i zaniku wieloukładowego (MSA) heterogenną pod względem neuropatologicznym grupę jednostek chorobowych określanych wspólną nazwą atypowych parkinsonizmów (APS) lub zespołami Parkinsonizm-Plus (PPS). Postuluje się preferowanie tego ostatniego terminu celem uniknięcia stygmatyzacji chorych (terminy: „typowy" – „atypowy" sugerują odstępstwo od „normy") [1]. Patofizjologia choroby obejmuje m. in. zaburzenia przemian białka tau (taopatia). Jak wskazuje nazewnictwo, oprócz objawów pozapiramidowych jak w chorobie Parkinsona (PD), we wszystkich z wymienionych jednostek występują dodatkowe w stosunku do PD objawy, które w PSP obejmują m.in.: zaburzenia poznawcze na wczesnym etapie choroby (w przeciwieństwie do PD), zaburzenia opuszkowe (dysfagia, dysfonia i dyzartria), wczesne i częste upadki. Podejmowane próby leczenia objawowego zgodnie z zasadami terapii zespołów parkinsonowskich skutkują w PSP jedynie słabą i nietrwałą odpowiedzią na leczenie lewodopę. W przebiegu APS stwierdzana jest szybsza progresja w połączeniu z niewielką skutecznością leczenia objawowego wiąże się z niepomyślnym rokowaniem. W obrazie klinicznym występują także objawy pozaruchowe, do których należą m. in. zaburzenia nastroju (głównie depresyjne o różnym stopniu nasilenia) oraz zachowania. Zaburzenia sfery psychicznej wydają się grupą objawów najsłabiej poznaną w przypadku PSP, co częściowo wynika z rzadkiego występowania APS, koncentracji neurologów na objawach dostępnych badaniu neurologicznemu, a także subiektywną perspektywą pacjentów i ich opiekunów. Wobec bardzo ograniczonych możliwości terapeutycznych w zakresie objawów motorycznych, co prowadzi do dynamicznie narastającej niesprawności pacjentów – istotne wydaje się ocena i monitorowanie zaburzeń nastroju, które w dużej mierze decydują o jakości życia (QoL) chorych i ich opiekunów.

W literaturze obserwuje się rosnące zainteresowanie perspektywą pacjenta w odniesieniu do choroby, a także podkreśla się potrzebę wczesnego wykrywania i oddziaływania także na zaburzenia nastroju, jako szczególnie istotne dla chorych z uwagi na niebagatelny wpływ na QoL i perspektywy terapii. Pogłębienie znajomości tych aspektów choroby było przesłanką do powstania tego cyklu.

Rozpoznanie APS stanowi na wczesnym etapie choroby duże wyzwanie diagnostyczne, także w kontekście rzadkiej zachorowalności, daleko mniejszej niż w PD. Aktualnie obowiązujące kryteria rozpoznania PSP [2], a także CBD i MSA umożliwiają postawienie pewnego rozpoznania wyłącznie na podstawie badania neuropatologicznego. Na obecnym etapie wiedzy przyżyciowo możliwe jest postawienie jedynie możliwej lub prawdopodobnej diagnozy każdej z tych jednostek chorobowych. W obrębie PSP wyróżnia się liczne podtypy choroby, niektóre bardzo słabo poznane, z istotnie odmiennym przebiegiem klinicznym i wynikającym z tego zróżnicowanym rokowaniem [3]. Z uwagi na wyjątkowo ograniczone dane na temat niektórych z nich, dla wielu nie zostały dotychczas sprecyzowane kryteria diagnostyczne. Najczęściej występujący i historycznie opisany jako pierwszy, typ Richardsona (PSP-RS) charakteryzuje się wcześnie występującymi zaburzeniami mięśni osiowych (co implikuje zaburzenia równowagi i upadki), zaburzeniami gałkoruchowymi i poznawczymi; przebieg choroby jest w tym przypadku bardziej agresywny. PSP-RS stanowi w kohortach potwierdzonych badaniem pośmiertnym ok. 76% wszystkich przypadków PSP [4]. Postać typu parkinsonowskiego (PSP-P) z bardziej zaznaczonym asymetrycznym drżeniem, wcześnie ujawniającą się bradykinezją i cechami dystonii cechuje się względnie dobrą odpowiedzią na leczenie lewodopą; stanowi większe wyzwanie do odróżnienia od PD.

W obu przytoczonych fenotypach PSP, za najbardziej uciążliwe z objawów pozaruchowych uznane zostały tak przez pacjentów, jak ich opiekunów zaburzenia snu, tym niemniej jako istotnie zaburzające QoL wskazano zaburzenia poznawcze i afektywne (wiodące w PSP-RS) oraz ze strony przewodu pokarmowego (bardziej zaznaczone w PSP-P)[5]. Wszystkie z wyżej wymienionych objawów istotnie obniżały QoL, będącą wskaźnikiem mierzącym satysfakcję z życia i zdolność do realizacji oczekiwań, pozwalającym na ocenę wpływu chorób i ewentualnych ich terapii na dobrostan jednostki [6]. Precyzyjna i powtarzalna ocena QoL, przeprowadzana ze pomocą kwestionariuszy klinicznych ewaluowanych na potrzeby poszczególnych zaburzeń, umożliwia ilościową ocenę subiektywnego dobrostanu pacjentów lub/i ich opiekunów. W odniesieniu do PSP, dostępne są kwestionariusze zaprojektowane dla tej jednostki chorobowej lub adaptowane z doświadczeń pacjentów z PD; niektóre z nich scharakteryzowano w przeglądzie [7], otwierającym cykl publikacji doktoranta. Poza ich charakterystyką zaznaczono ograniczenia w zastosowaniu, podobieństwa i różnice, a także praktyczne aspekty zastosowania w codziennej praktyce klinicznej.

Cykl składa się 3 powiązanych tematycznie ze sobą publikacji, wśród których znajduje się jedna praca poglądowa i dwie prace oryginalne o łącznej punktacji Impact Factor wynoszącej 10,7 oraz łącznej punktacji Ministerstwa Nauki i Szkolnictwa Wyższego wynoszącej 260 punktów. Omawiane zagadnienia dotyczą zaburzeń depresyjnych w PSP, o nasileniu odzwierciedlanym w ocenie QoL. Celem niniejszego cyklu artykułów, stanowiącego podstawę przewodu doktorskiego, jest przedstawienie powiązań zaburzeń depresyjnych w PSP z ekspresją niektórych parametrów stanu zapalnego o potencjalnym udziale w patomechanizmie tej choroby.

Omówienie cyklu

Celem pierwszej pracy cyklu o charakterze poglądowym [8] było omówienie dostępnych narzędzi do precyzyjnej ilościowej oceny QoL pacjentów z rozpoznaniem PSP.

Jak już wspomniano wyżej, choroba ta cechuje się heterogennością tak na poziomie patomechanizmu, jak i objawów klinicznych, co doprowadziło do scharakteryzowania kilku jej fenotypów, przy czym niektóre z nich są dotychczas wyjątkowo słabo poznane. Wynika to najprawdopodobniej z rzadkiego ich występowania, znacznego zaawansowania choroby w momencie diagnozy (kiedy to niemożliwe jest już zidentyfikowanie wczesnych objawów różnicujących poszczególne podtypy), a także nakładania się objawów między fenotypami. W kontekście badań nad QoL jest to szczególnie istotne z uwagi na zauważalne różnice w zakresie dynamiki przebiegu choroby pomiędzy jej typami, przekładające się na zróżnicowany komfort codziennego funkcjonowania chorych. Szczegółowo omówiono te różnice dla dwóch najczęściej występujących (i najlepiej poznanych) fenotypów: Richardsona i typu parkinsonowskiego, z uwzględnieniem odmienności klinicznych, reakcji na próby terapii lewodopą i średni czas przeżycia chorych na podstawie danych z największych kohort [9]. Wobec wspomnianych trudności diagnostycznych, podkreślono przewagę aktualnie obowiązujących kryteriów rozpoznania [10] nad stosowanymi wcześniej [11], szczególnie w zakresie wyższej czułości diagnostycznej nowego narzędzia. Znaczenie badań nad QoL w nieuleczalnych chorobach układu nerwowego o postępującym przebiegu omówiono na przykładzie choroby Alzheimera (AD) oraz bardziej zbliżonej do PSP w kontekście klinicznym – chorobie Parkinsona (PD); w zakresie podobieństwa nawiązano do wspólnych dla obu tych jednostek objawów pozaruchowych i ich wpływie na funkcjonowanie pacjentów. Z racji na fakt, że część narzędzi do oceny QoL w PSP zaprojektowano pierwotnie na potrzeby PD, zaś inne zostały stworzone do użycia wyłącznie w PSP, przegląd tych kwestionariuszy przeprowadzono właśnie według takiego podziału; zaznaczono ich cechy

charakterystyczne, ewentualną przewagę czy równocenność w oparciu o badania z użyciem tych narzędzi. W przeglądzie umieszczono także wzmianki o niektórych uniwersalnych narzędziach do oceny QoL, które stosowane mogą być także w PSP, choć zaprojektowane były do szerokiego użycia w psychologii i medycynie, niekoniecznie do oceny pacjentów neurologicznych. W publikacji zwrócono także uwagę na ograniczenia metodologiczne, które wpływać mogą na wnioski wysuwane przez badaczy weryfikujących przydatność omawianych narzędzi. Kluczową kwestią jest powszechny w pracach nad PSP brak weryfikacji pośmiertnej rozpoznania. Ponadto, szybka deterioracja stanu somatycznego i poznawczego pacjentów, typowa dla PSP, utrudnia wielokrotną ocenę QoL u tych samych pacjentów, co ogranicza wnioski z przydatności narzędzi. Nie bez znaczenia jest także fakt rekrutacji osób z rozpoznaniem postawionym na podstawie obecnie obowiązujących oraz zdezaktualizowanych kryteriów diagnostycznych (we wcześniejszych z przytaczanych badań), co prowadzi do uzyskiwania niejednorodnych pod względem rozpoznania grup badawczych. Z wyjątkiem ostatniej, uwagi te odnoszą się także do omawianych poniżej dwóch badań oryginalnych.

Eksplorując zagadnienie wpływu niektórych zaburzeń pozaruchowych w PSP (ściśle – zaburzeń depresyjnych) na QoL, badano związek tych zaburzeń z wykładnikami stanu zapalnego, w nawiązaniu do zapalnej teorii obu tych chorób (tj. PSP i depresji).

W pracy oryginalnej [12], będącej na moment publikacji pierwszą analizą markerów obwodowych stanu zapalnego u pacjentów z depresją współistniejącą z PSP, omówiono związek niespecyficznego markeru zapalenia, jakim jest współczynnik neutrofili do hemoglobiny (N/HGBR) z nasileniem zaburzeń depresyjnych, w powiązaniu z parametrem ilościowym, jakim jest wynik w Skali Depresji Becka (BDI). Zwraca się uwagę, że depresja jest istotnie częstsza w populacji pacjentów z rozpoznaniem niektórych chorób neurodegeneracyjnych, w tym AD i PD [13], co koresponduje z podobnymi wnioskami w zakresie zaburzeń QoL w tych jednostkach chorobowych, omawianymi powyżej. Jakkolwiek patomechanizm wszystkich z wymienionych chorób nie został dotychczas precyzyjnie ustalony, to wspólne wydają się być zaburzenia w układzie cytokin pro- i przeciwzapalnych, w szczególności w grupie chorób pozapiramidowych: interleukin 1 beta (IL-1β), 2 (IL-2), 6 (IL-6), 10 (IL-10), czynnika martwicy nowotworów alfa (TNF-α), a nawet rutynowo badanego w praktyce klinicznej białka C-reaktywnego (CRP) [14]. Autorzy pracy będącej

częścią niniejszego cyklu wychodzą naprzeciw rosnącemu zainteresowaniu znaczeniem znanych od dawna niespecyficznych markerów stanu zapalnego, do których należą stężenia niektórych frakcji leukocytów i lipoprotein we krwi obwodowej, a ściśle – ich wzajemne stosunki. Najlepiej poznane w zakresie użyteczności klinicznej są stosunek neutrofili do lipoproteiny o wysokiej gęstości (NHR), stosunek neutrofili do limfocytów (NLR) oraz stosunek płytek krwi do limfocytów (PLR), w tym w przypadku chorób neurologicznych, m. in. PD oraz APS [15]. Powiązania procesu zapalenia w obrębie ośrodkowego układu nerwowego z nasileniem tego zjawiska w obszarze krwi obwodowej (skąd pobierany jest rutynowo materiał do badań diagnostycznych) są obecnie przedmiotem rosnącego zainteresowania nie tylko w zakresie chorób neurozwyrodnieniowych, ale także afektywnych.

W badaniu oceniano różnice w zakresie wspomnianych wskaźników (oraz wskaźnika neutrofilów do hemoglobiny, NHGB-R), oznaczonych z jednorazowego pobrania krwi od 10 pacjentów z PSP ze współwystępowaniem dużego epizodu depresyjnego w porównaniu do 11 pacjentów z PSP, bez rozpoznania depresji. W diagnostyce zespołu depresyjnego u chorych stosowano m. in. badanie przy użyciu BDI, jako narzędzie o użyteczności diagnostycznej zweryfikowanej dla PSP [16]. W zakresie pozostałych obciążeń i leczenia nie obserwowano istotnych różnic między badanymi grupami.

W przypadkach PSP, gdzie rozpoznawano także depresję wskaźnik NHGB-R był istotnie wyższy w stosunku do odpowiednio dobranej grupy chorych z PSP, w której nie występowała depresja. Różnice między analizowanymi grupami pacjentów PSP z depresją oraz bez takiego rozpoznania nie były istotne statystyczne dla pozostałych wskaźników stanu zapalnego analizowanych w tej pracy: NLR, NMR.

Wobec wstępnego zidentyfikowania wskaźnika NHGB-R jako przydatnego diagnostycznie, przeprowadzono analizy potencjalnej korelacji tego wskaźnika z innymi zebranymi danymi (frakcje leukocytów, wymienione wcześniej niespecyficzne wskaźniki stanu zapalnego, BDI). Stwierdzona została silna, istotna statystycznie ($r = 0.95, p < 0.0001$) dodatnia korelacja z całkowitą liczbą neutrofili, a także umiarkowana pozytywna korelacja ze wskaźnikiem neutrofilów do leukocytów (NLR) ($r = 0.67, p = 0.0247$), której istotności statystycznej nie potwierdziły dalsze analizy matematyczne (skorygowany $p = 0.1729$). Analogiczne, tzn. bez znamienności statystycznej po zastosowaniu poprawki Bonferroniego były obliczenia dla stężenia hemoglobiny, limfocytów czy monocytów.

Badanie to ilustruje związek między obecnością objawów zespołu depresyjnego a nasileniem stanu zapalnego w PSP, odzwierciedlonym przez niespecyficzne, szeroko dostępne

diagnostycznie markery w krwi obwodowej. Jednakże, z uwagi na fakt, że na liczbę neutrofilów może wpływać wiele różnych czynników, a zatem jej zmiany są wysoce niespecyficzne – potwierdzenie hipotezy z tego badania należy potwierdzić wnioskami z kolejnych grup chorych. Badania in vitro w taopatiach (w tym w PSP) wykazywały nierównowagę między stężeniami cytokin prozapalnych (IL-1, IL-6) względem cząsteczek o aktywności przeciwzapalnej (IL-4, IL-10, IL-13, TGF-β), z tego powodu koncepcja ośrodkowego zapalenia jako przyczyny chorób neurodegeneracyjnych wydaje się być uproszczona [17]. Podobnie, niejasne jest podłoże molekularne leżące u podłoża zaburzeń depresyjnych [18]. Trudności w zakresie takich badań powoduje wspomniana już wrażliwość ilości leukocytów i ich frakcji w krwi obwodowej na wiele czynników, w tym stres i stymulację adrenergiczną, wpisaną w patomechanizm depresji. Z zależności z omawianymi niespecyficznymi markerami stanu zapalnego, w sposób powtarzalny wielu autorów obserwuje podwyższenie wartości NLR i korelację z nasileniem depresji [19 20]. Tym niemniej inni akcentują dużą zmienność omawianych parametrów w różnych publikacjach, co znajduje odzwierciedlenie w badaniach o najwyższym stopniu wiarygodności [21]. W badaniu będącym składową omawianego cyklu, zwraca się uwagę na ograniczenia jak dyskutowane powyżej.

Dyskutowane powyżej niejasności w zakresie odzwierciedlenia ośrodkowo występującego w PSP stanu zapalnego na niespecyficzne, obwodowe parametry zapalne stanowiły przesłankę do powstania trzeciej pracy niniejszego cyklu [22].

Praca przedstawia nasilenie stanu zapalnego, odzwierciedlonego stężeniem niektórych specyficznych markerów, badanych w surowicy krwi obwodowej (czynnik neurotroficzny pochodzący z linii komórek glejowych [GDNF], hepcydyna, IL-1β, IL-6) oraz płynie mózgowo-rdzeniowym (PMR) (GDNF, IL-1β, IL-6) pacjentów z PSP, w odniesieniu do zdrowych ochotników, w powiązaniu z czynnikami oceny jakości życia.

Analizie poddano 11 osób z rozpoznaniem PSP postawionym na podstawie aktualnie obowiązujących, przytaczanych już powyżej kryteriów oraz 10 osób z grupy kontrolnej, dobranych odpowiednio pod względem wiekowym. W obu grupach nie było istotnej współchorobowości ani innych czynników (np. farmakoterapii) mogącej potencjalnie wpływać na nasilenie ogólnoustrojowego stanu zapalnego. Grupę kontrolną stanowiły osoby, które poddawane były inwazyjnej diagnostyce (m. in. punkcja lędźwiowa i badania pmr, badania krwi) z uwagi na wysuwane początkowo podejrzenie innej niż neurodegeneracyjna jednostki chorobowej (np. neuroinfekcja), lecz w toku diagnostycznym takie podejrzenia

ostatecznie wykluczono. Stan kliniczny oraz QoL badanych osób obiektywizowano przy użyciu kwestionariuszy, odpowiednio: mPSPRS oraz PSP-QoL, przy czym badania te prowadzono min. 1 tydzień od momentu przeprowadzenia omówionej wcześniej inwazyjnej diagnostyki. Istotne statystycznie między grupami były stwierdzone dla stężenia w surowicy: GDNF, hepcycyny, IL-1β i IL-6, a także dla GDNF i IL-6 w PMR. Ustalono, że wystąpiła istotna statystycznie ujemna korelacja między stężeniem GDNF w surowicy oraz wynikami w obu skalach: mPSPRS ($\rho = -0.77,\ p = 0.003$) i PSP-QoL ($\rho = -0.68,\ p = 0.011$). Ponadto, w grupie kontrolnej zaobserwowano ujemną korelację między stężeniem IL-6 w PMR i wynikiem w skali mPSPRS ($\rho = -0.60,\ p = 0.036$). Nie stwierdzono istotnej korelacji dla innych z badanych zmiennych.

Zidentyfikowano istotną statystycznie korelację między wartościami uzyskanymi przy użyciu obu tych kwestionariuszy a stężeniem GDNF, co sugeruje wpływ tej neurotrofiny na przeżycie komórek nerwowych, zaburzonym w sytuacji ośrodkowego zapalenia występującego w przebiegu PSP. W badaniach na niewielkich grupach chorych z PSP, sugeruje się że uwalnianie tego czynnika jest reakcją obronną przed dalszą progresją uszkodzenia neuronów dopaminergicznych [23 24]. Ochronny wpływ tej substancji wykazano w badaniach klinicznych nad zaburzeniami funkcji poznawczych i snu na podłożu różnych chorób oun, w tym o podłożu taopatii [25 26]. Dostępne są również doniesienia o funkcji protekcyjnej w przypadku PSP, szczególnie agresywniej przebiegającej postaci Richardsona [27]. Także dla tej postaci choroby (PSP-RS) stwierdzono podwyższone stężenia hepcydyny. Badania nad innymi z omawianych cząsteczek-mediatorów stanu zapalnego w omawianych chorobach neurozwyrodnieniowych dotychczas nie przyniosły rozstrzygnięcia w oparciu o dane kliniczne.

Mimo ograniczeń metodologicznych (mała liczebność grupy – wiązana z niewielką zachorowalnością, nierozróżnienie na podtypy choroby, niemożność całkowitego wykluczenia wpływu chorób współwystępujących, czy brak analizy wieloczynnikowej), badanie stanowi kolejny argument za tezą o wpływie stanu zapalnego na proces neurozwyrodnieniowy, jaki obserwuje się in vivo w PSP.

Podsumowanie

Brak jest obecnie dedykowanych dla PSP narzędzi umożliwiających kompleksową ocenę jakości życia i współwystępowania zaburzeń depresyjnych; ich stworzenie (a nie adaptacja

skal będących już w użyciu w innych jednostkach chorobowych) mógłby pozwolić na precyzyjniejsze monitorowanie stanu klinicznego chorych, a dalsze wykorzystanie mogło by obejmować ocenę skuteczności potencjalnych terapii. W miarę postępu badań, coraz wyraźniej widoczny jest związek między stanem zapalnym a depresją, także w omawianych tu chorobach neurozwyrodnieniowych (potencjalnie uniwersalny mechanizm depresji), oraz jej wpływ neurotrofin na jakość życia tej grupy chorych.

Uzasadnione jest prowadzenie dalszych badań oceniających korelację obwodowych czynników zapalnych z szeroko rozumianymi aspektami funkcjonowania poznawczo-emocjonalnego chorych z PSP, w kontekście monitorowania jakości ich życia i oddziaływania na nią.

Pogłębienie wiedzy na temat roli konkretnych mediatorów zapalnych może w przyszłości doprowadzić do zidentyfikowania potencjalnych punktów uchwytu terapii umożliwiających modyfikację przebiegu chorób, aktualnie pozostających bez skutecznych metod leczenia.

Wnioski

Wiodące wnioski z poszczególnych składowych cyklu zebrano w Tabeli 1:

Quality of life in patients with progressive supranuclear palsy: a review of literature and implications for practice
Wobec braku leczenia przyczynowego – kluczowa jest identyfikacja aspektów choroby podatnych na interwencję, przez systematyczną, zobiektywizowaną ocenę QoL
Possible Significance of Neutrophil–Hemoglobin Ratio in Differentiating Progressive Supranuclear Palsy from Depression: A Pilot Study
Prawdopodobne jest istnienie wspólnych szlaków w patomechanizmie PSP oraz depresji, w oparciu o mechanizm zapalny
Inflammatory and Neurotrophic Factors and Their Connection to Quality of Life in Progressive Supranuclear Palsy—Single-Center Study
W procesie rozwoju PSP mają miejsce mechanizmy neuroprotekcyjne o działaniu przeciwzapalnym

Uwagi

W pracy cyklu doktorskiego zatytułowanej: „Inflammatory and Neurotrophic Factors and Their Connection to Quality of Life in Progressive Supranuclear Palsy—Single-Center Study" 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.

Niektóre z badań oparte były na odpowiednich zgodach Komisji Bioetycznej udzielonych dla wcześniejszych projektów, w których uzyskiwano dane będące podstawą do prac z niniejszego cyklu. Numery tych zgód znajdują się w publikacjach cyklu. Załączone oświadczenie Komisji (AKBE 140/2024) wystawione zostało na nazwisko Promotora niniejszej pracy doktorskiej, nadzorującego badanie.

Errata

W sekcji Abstractu pracy zatytułowanej: " Quality of life in patients with progressive supranuclear palsy: a review of literature and implications for practice" doszło na etapie redakcyjnym do przypadkowego zbublowania części tekstu.

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Quality of life in patients with progressive supranuclear palsy: a review of literature and implications for practice

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Progressive supranuclear palsy (PSP) is an atypical form of parkinsonism characterized by tauopathy, manifesting as oculomotor dysfunction, postural instability, akinesia, and cognitive/language impairments. The diagnosis and examination of PSP can be challenging, primarily due to the unclear and underexplored pathomechanisms involved, alongside absence of effective treatments. Clinical variants of PSP is the second most common form of neurodegenerative parkinsonism after Parkinson's disease (PD). It is defined by a symmetrical akinetic-rigid syndrome (atypical parkinsonism) and vertical supranuclear gaze palsy. In contrast to PD, PSP often presents with gait instability, backward falls, and cognitive and behavioral changes at early disease stages. The classification of PSP has evolved since Richardson, Steele, and Olszewski's initial reporting of the condition in 1963, which included a cohort of nine patients. Over the years, the definition of this disorder has evolved to encapsulate a group of patients with distinct clinical variants, notably the classical Richardson syndrome (RS) and several atypical phenotypes, each with significant implications for disease progression and quality of life (QoL). The 2017 Movement Disorder Society Diagnostic Criteria by Hoglinger et al., improved the sensitivity for detecting early and variant PSP presentations and provided more specific differential diagnoses for conditions such as PD and other forms of atypical parkinsonian syndromes. Owing to the growing interest in the disease's progression, evaluating the QoL for patients with PSP has become crucial. This review emphasizes the significance of QoL evaluation and its feasibility for practical implications, serving as an initial foundation for future research focused on the well-being of individuals affected by PSP. Progressive supranuclear palsy (PSP) is an atypical form of parkinsonism characterized by tauopathy, manifesting as oculomotor dysfunction, postural instability, akinesia, and cognitive/language impairments. Diagnosing PSP is challenging owing to the lack of tools for differential examination. Additionally, the pathomechanism of this disease is not sufficiently understood, and no treatment is currently available. Owing to the growing interest in the disease's progression, evaluating the quality of life (QoL) for patients with PSP has become crucial. This review emphasizes the significance of QoL evaluation and its feasibility for practical implications, serving as an initial foundation for future research focused on the well-being of individuals affected by PSP.

KEYWORDS

atypical parkinsonism, quality of life, progressive supranuclear palsy, neurodegenerative diseases, tauopathy, patient-reported outcomes

1 Introduction: clinical variants of PSP

Progressive supranuclear palsy (PSP) is a rare neurodegenerative parkinsonism with a prevalence of 1–18 per 100,000 compared to 1–2 per 1,000 in Parkinson's disease (PD). It is characterized by symmetrical akinetic-rigid syndrome (atypical parkinsonism) and vertical supranuclear gaze palsy. In contrast to PD, PSP presents early with gait instability, backward falls, and cognitive and behavioral changes. Since 1963, when Richardson, Steele, and Olszewski (1) reported a series of nine patients, the definition of PSP has evolved to encompass a group of patients with distinct clinical variants. After the description of classical Richardson syndrome (RS), other specific atypical phenotypes of PSP have been discovered over the years (2). The recognition of different variants of PSP has expanded the concept into a group of several "subtypes," with varied progression. These differences in the dynamics of patient deterioration significantly impact their quality of life (QoL).

The Movement Disorder Society Diagnostic Criteria, revised by Hoglinger et al. (4), has enhanced the sensitivity for detecting early and variant presentations of PSP, offering more precise differential diagnoses than the previous guidelines from the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) (3). These guidelines emphasize four core functional domains: postural instability [P], oculomotor dysfunction [O], akinesia [A], and cognitive dysfunction [C]. By utilizing combinations of these domains, healthcare professionals can establish a diagnostic spectrum, classifying patients into three categories: probable PSP, possible PSP, and suggestive of PSP. Additional clinical indicators, such as levodopa resistance, dysphagia, spastic dysarthria, and photophobia, as well as specific radiological findings—such as predominant midbrain atrophy or hypometabolism and postsynaptic striatal dopaminergic degeneration—support the diagnostic process also play supportive roles in diagnosis. Among other symptoms, cognitive and behavioral abnormalities, including dysexecutive syndrome, bradyphrenia, impulsivity, disinhibition, perseveration, and reduced phonemic verbal fluency, can also complicate the assessment process. Currently, a neuropathological examination remains the only definitive diagnostic method for PSP (4).

Differentiating various PSP phenotypes is essential given the prognostic differences and implications for future drug trials. PSP–Richardson syndrome (PSP-RS) encompasses the characteristics originally described by Steele et al., where patients typically present with relatively early falls, cognitive dysfunction, gaze abnormalities, and postural instability (lurching and falls backwards) in the initial stages of the disease (5). PSP-RS is the most common variant, accounting for 76% of autopsy-confirmed cases in a recent series (6), and is associated with a poorer prognosis compared to the PSP-parkinsonism (PSP-P) phenotype, featuring an average disease duration of 5.9 years (ranging from 5 to 8 years) and an average age of death at 72.1 years (7). Conversely, PSP-P is characterized by primary asymmetrical tremor, non-axial dystonia, and early bradykinesia, with a notable response to levodopa therapy. These features resemble those of idiopathic PD. Patients with PSP-P tend to have a longer survival rate (9.1 years) compared to those with PSP-RS. However, the overlap in clinical characteristics between these two variants presents a significant diagnostic challenge. Neuropsychological assessments, such as those utilizing the Frontal Assessment Battery (FAB), can aid in identifying the two most common PSP variants (8). Moreover, due to insufficient data on clinical and pathological patterns, less common variants of PSP have not yet been formally detailed in the MDSPSP criteria (9); consequently, their low incidence means these variants are described only briefly in contemporary literature, typically in case reports or small case series. The most common variants of the disease are outlined in Table 1.

Despite significant progress in understanding PSP, achieving a definitive diagnosis still hinges on neuropathological examination. Achieving early and reliable diagnosis still remains a significant clinical challenge driven by both patient demands for ante-mortem confirmation and clinicians' needs for effective therapeutic trials allocation. As a result, there is an urgent need for improved diagnostic tools. At present, no disease-modifying therapies are available for PSP, and only a limited number of treatments have proven effective. Levodopa can provide symptomatic relief, but its efficacy is typically limited and short-lived in PSP-P patients, with rare benefits seen in those with PSP-RS (10); the impact of this treatment on overall disease duration remains unclear. Physical therapy may yield measurable improvements on clinical rating scales (5). While apraxia of eyelid opening may be improved by pretarsal Botulinum toxin injections, these interventions do not address the major clinical symptoms that ultimately lead to fatality in all PSP cases.

PSP faces significant challenges in clinical examination due to the low specificity of *in vivo* diagnostic tools and the lack of evidence-based methods. There is growing interest in exploring other aspects of the disease, such as the quality of life, which is particularly relevant given the pronounced deterioration and incurable nature of PSP. This review aims to synthesize current knowledge regarding the methods of evaluation of QoL in PSP, using scales specifically dedicated for this clinical entity, as well as those generally applicable to parkinsonisms. Additionally, the significance of QoL assessment was examined in the context of its limitations and future perspectives to enhance understanding and intervention strategies.

2 Methods

We performed a search of the PubMed database for studies published from the date of inception of the database up to August 2024, searching for the following key words: "Progressive Supranuclear Palsy," "Quality of Life," and their abbreviations; and "movement disorders."

3 Importance of QoL studies

Combining preclinical and clinical findings with QoL analysis enhances our understanding of the disease's natural progression and a more precise identification of progression factors. Considered a vital adjunct to clinical data (11), QoL studies provide insights into neurodegenerative diseases beyond PD, which have been insufficiently documented largely due to the low prevalence of parkinsonian syndromes other than PD, and thus the unavailability of large cohorts (12). Gathering subjective data about patients' well-being and other facets of their lives enables healthcare providers to deliver more effective and personalized clinical care. This approach has garnered endorsements from the Food and Drug Administration (FDA) and the World Health Organization (WHO) as vital for ongoing care

TABLE 1 Main symptoms found in the different PSP variants (1).

Richardson's syndrome	PSP-parkinsonism (PSP-P)	PSP-corticobasal syndrome	PSP with predominant cerebellar ataxia (PSP-C)
Unsteady gait, falls, bradykinesia, impaired ocular movement (apraxia of eyelid opening, slowing of vertical saccades, vertical supranuclear gaze palsy) personality changes (apathy, disinhibition), cognitive slowing (bradyphenia), executive dysfunction (difficulty planning, multitasking), speech abnormalities (ataxic slow, spastic and hypophonic), dysphagia	Bradykinesia, tremor (asymmetric onset), rigidity, moderate initial response to levodopa treatment.	Asymmetric limb rigidity, alien limb, cortical sensory loss, dystonia, bradykinesia (unresponsive to levodopa), apraxia	Similar to MSA-C, but less pronounced autonomic dysfunction

PSP, progressive supranuclear palsy; MSA-C, multiple system atrophy-cerebellar type.

improvement and future drug development (13). By prioritizing the patient's perspective on disease progression, we can enhance management strategies. Given that many patients exhibit a lack of insight into their functional deficits (anosognosia)—a phenomenon well studied in extrapyramidal disorders, including PSP and Alzheimer's disease (14)—numerical scales for assessing progression could prove valuable for accurately evaluating patient needs.

QoL is a broad, multidimensional concept that reflects patients' subjective perceptions regarding how their disease affects their overall well-being. It encompasses physical, mental, emotional, and social dimensions. Self-reported tools for QoL assessment, which can be generic (applicable for numerous diseases, i.e., universal) or disease-specific (ie. disease oriented), are continually being developed for clinical studies and practice to quantify disease impact on patients' everyday lives, treatment efficacy, and health policy management (15, 16). Some QoL aspects, such as symptom perception, self-image, and life satisfaction—including social and economic factors—are inherently subjective; however, others can be objectively measured, including clinical manifestations of the disease and patients' financial and social situations. The instruments presented below include both subjective and objective indicators. While data on QoL in PSP is less comprehensive compared to sporadic PD (17), recent years have seen an uptick in interest surrounding QoL in Parkinsonism, and some tools for capturing QoL have been developed, mostly based on quantitative scales (18).

In addition to predominant motor symptoms, non-motor symptoms (NMSs) significantly increase morbidity and disability in PD and other parkinsonian disorders, considerably affecting the QoL for patients and their caregivers (19, 20). Researchers have observed variable patterns in the prevalence of specific NMS that differentially impact individuals' lives. A study involving 50 patients with PSP compared to 100 patients with PD identified insomnia, fatigue, and urinary dysfunction as the most common NMSs in PSP (21). Other studies have also highlighted gastrointestinal problems and fatigue as prevalent issues (22). The authors of the largest PSP cohort study (23) found that the most prevalent domains in both the PSP-RS and PSP-P subgroups were sleep/fatigue and sexual function; however, mood/cognition was severely impaired in RS, while gastrointestinal issues were more pronounced in PSP-P subtype. Despite some methodological limitations—such as the absence of case–control design and lack of comparisons to other parkinsonian disorders or healthy controls—these findings indicated issues that substantially contributed to a decrease in QoL and could be amenable to symptomatic treatment if recognized early in the disease trajectory.

3.1 Scales in parkinsonism (including PSP) for QoL evaluation

Widely used tools for QoL assessment in patients with PSP include the Parkinson's Disease Questionnaire-39 (PDQ-39) (24), the Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL) (25), and the EuroQol instrument (EQ-5D) (26, 27). Although the PDQ-39 was primarily designed for PD, it can also be utilized for evaluating atypical parkinsonism conditions, including PSP. However, since it was not tailored for PSP, it fails to address certain prevalent symptoms of the disorder, such as muddled thinking, ocular motor dysfunction, confusion, and apathy (28).

The validation of these instruments for patients with PSP appears to be limited, as they do not encompass the unique aspects of the disease (including several aforementioned symptoms), which may lead to an underestimation of associated health problems (24).

3.2 Scales dedicated to PSP for QoL evaluation

The PSP-QoL scale was specifically developed to assess the distinct physical and mental domains experienced by patients with PSP. This scale comprises 45 patient-rated items that evaluate difficulties related to mental and physical tasks within the preceding month. It remains the only tool sufficiently validated for QoL assessment in this disease population (25). Its primary disadvantage is the time-consuming nature of its completion, which restricts its applicability in clinical settings; hence, a more streamlined QoL tool is required. Notably, this scale was developed using a large cohort of patients with PSP, focusing on crucial clinical features and including items with good discriminative power for different disease stages, indicating that the tool has good construct validity and high reliability. As such, it is recommended for use as a patient-reported outcome measure in clinical trials (25). However, the study associated with this tool underrepresented late-stage patients (as they were unable to complete the survey), raising questions about the tool's applicability to those in advanced stages of the disease. Researchers did not differentiate between probable and possible PSP, as participants were diagnosed outside the study's centers. Further validation is encouraged in diverse populations. In a study by Patnelyat et al. (29, 30) patients with PSP were evaluated to establish correlations between the PSP Rating Scale and the PSP-QoL. While the study indicated the PSP-QoL as a feasible method of self-assessment and revealed significant associations with the PSP Rating Scale, the authors cautioned that these correlations

might differ between patients with Richardson syndrome and those with non-Richardson syndrome. Somewhat addressing the limitations of the PSP-QoL, the PDQ-8—a condensed version of eight representative questions from the PDQ-39 (31)—has gained traction in PD management, including clinical trials (32). However, its effectiveness specifically within the PSP population requires further investigation. In a larger cohort study ($n = 132$), Xin-Yi et al. (33) found that the PDQ-8 correlated well with the PSP-QoL in assessing QoL, indicating strong relevance of the PDQ-8 with each item of PSP-QoL. The authors highlighted that among the short scales used for QoL assessment in patients with parkinsonian disorders, the PDQ-8 was the most comparable to the PSP-QoL. The most significantly affected domains identified were mobility, activities of daily life, cognition, and communication—elements critical not only for the patients themselves but also for their caregivers in terms of recognizing levels of independence.

Further analysis of the impact of several variables (e.g., disease duration, sex, NMSS, ESS, GDS, and MMSE) on the PSP-QoL total score showed that longer disease duration, depression (assessed using the Geriatric Depression Scale [GDS]), and daytime sleepiness (assessed by the ESS) were the most important determinants of QoL. To determine QoL, the established connections between GDS scores, NMSS, PSP Rating Scale (PSPrs), and ESS scores were all confirmed to be crucial for QoL assessment. Similar findings were noted in earlier studies of multiple system atrophy (MSA-P) and PSP (34). The simplicity of the PDQ-8 contributes to a high completion rate, with favorable feedback from patients. Furthermore, detailed comparisons between the two patient groups (PSP-RS vs. PSP non-RS) indicate a worse clinical course of the disease in patients with RS variant, particularly evident in both motor and non-motor symptoms (including deterioration in mood and cognitive function). A strong correlation between the PDQ-39 and PSP-QoL subscales (physical and mental) was also confirmed by Schrag et al. (25), highlighting the relationship between PSPrs and PSP-QoL along with the relevance of non-motor symptoms in patients' QoL (29). Based on these findings, utilizing both assessment instruments is recommended.

Wiblin et al. emphasized the significance of particular aspects of social life—such as social network strength, family support, and personal disease insight—for the QoL of patients with PSP (17). Among the 19 patient-caregiver pairs studied, reduced QoL was found to be associated with speech difficulties, social life restrictions, and disease stigma. Although their results are based on semistructured interviews rather than formal QoL assessment tools discussed above, they pointed out that further evaluations using standardized scales would allow objective comparisons of patients' well-being.

The Modified Progressive Supranuclear Palsy Rating Scale (PSPRS) has been devised to quantify and track the severity of major symptoms associated with PSP. In this questionnaire, a physician assesses each of the 28 items categorized into six domains: daily activities (based on patient history), mentation, bulbar symptoms, oculomotor function, limb motor skills, and disturbances in gait/midline (based on examination) (35).

Further evaluations of the tool indicate areas for refinement; for example, some items in the questionnaire reflect critical disease aspects, yet calculating maximum scores for these items does not effectively capture variances in clinical severity. In addition, some of the analyzed items were found to be interrelated or overlapping, indicating they may not need to be evaluated separately. Some items and their scores were also classified as minimally changeable over the course of disease progression, failing to accurately represent changes in a patient's status (36). For these reasons, the removal of items such as tremors, limb dystonia, and dysphagia has been proposed to improve the consistency of the scale.

A modified version of the PSPRS, referred to as the mPSPRS, was also designed by Grotch et al. (37) by eliminating the following 14 items from the PSPRS that were identified as insensitive or overlapping: Irritability; sleep difficulty, grasping/imitative/utilizing behavior, voluntary left and right saccades, finger tapping, toe tapping, postural kinetics, or rest tremor. This simplification makes patient evaluation less time-consuming while yielding outcomes comparable in metric power to that of the original PSPRS. This modified version was evaluated by experts from the European section of the International Parkinson and Movement Disorder Society. A comparison between the PSPRS and mPSPRS was performed based on data from 86 participants in the TAUROS trial, which examined both baseline and 52-week follow-up data. They reported a strong positive correlation between the mPSPRS and PSPRS total scores. Some differences were observed between patients with RS and non-RS; however, the implications of these differences remain unclear. Given the equivalence, the authors recommend the mPSPRS for disease monitoring due to its demonstrated sensitivity to change and practicality in clinical practice (29).

Researchers highlight the high dropout rate among study participants, attributed to the rapid progression of the disease, which may influence their results. Nevertheless, they assumed that the mPSPRS could effectively depict changes within intervals as short as 52 or even 26 weeks. They also emphasized that the scale does not account for factors beyond emotional incontinence, despite evidence that problems such as bradyphrenia, disorientation, and behavioral changes play a key role in the mental sphere of the disease. Additionally, the study faced challenges in distinguishing between Richardson's and non-RS forms of PSP, as some recruited patients were diagnosed according to the NINDS-SPSP diagnostic criteria; therefore, the sensitivity to changes in the mPSPRS may vary across these two subpopulations. In rarer forms of PSP phenotypes, a larger sample size would be necessary to detect any changes in mPSPRS scores, and further prospective studies are recommended to confirm the effectiveness of the tool. However, due to its ease of implementation and demonstrated sensitivity to change over time, the authors advocate for the mPSPRS as a valuable resource for routine clinical practice, particularly for assessing treatment effects in forthcoming disease-modifying trials.

The Progressive Supranuclear Palsy Clinical Deficits Scale (PSP-CDS) (38) comprises seven clinical domains: Akinesia-rigidity, Bradyphrenia, Communication, Dysphagia, Eye movements, Finger dexterity, and Gait & balance. Each domain is scored from 0 to 3, indicating no, mild, moderate, or severe deficits. Piot et al. found a good-to-excellent correlation between the total scores from the PSP-CDS and the clinical scales previously discussed for both PSP-RS and variant PSP (vPSP) phenotypes. To date, the PSP-CDS has been evaluated as sensitive, reliable, and easily applicable in both research and clinical contexts.

3.3 Other generic scales

In addition to the previously described tools, various generic questionnaires designed for patients PD are also applicable to other

conditions. These include the Sickness Impact Profile (SIP), the Medical Outcome Study 36-Item Short Form Health Survey (SF-36), the Life Satisfaction Questionnaire (LSQ), the EuroQol EQ-5D, the WHOQOL-BREF, and the Quality of Well-Being Scale (QWBS) (39–43). All of these tools have been proven to be valid and reliable in assessing PD (41).

The Sickness Impact Profile (SIP) questionnaire was developed to assess 12 areas of functioning at the time of study that are sensitive to disease progression and may not be accurately reflected in other scales (e.g., SF-36, EQ-5D). However, the SIP's extensive length (comprising 136 items) leads to a completion time of approximately 30 min. The SIP has also shown associations with key constructs relevant to PD, such as the Hoehn and Yahr scale, the Unified Parkinson's Disease Rating Scale (UPDRS), and the SF-36 (44).

In contrast, the SF-36 is a shorter tool that requires approximately 9 min to complete and evaluates eight aspects of QoL over the 4 weeks preceding the survey. It is particularly effective in predicting disease progression but does possess certain upper and lower thresholds (45). The SF-36 demonstrates good reliability and discriminative validity (41, 46–49) and has been shown to respond partially to changes over time (50) and following intervention (30). One study indicated that it was more responsive than both the PDQ-39 and PDQUALIF (51).

The Life Satisfaction Questionnaire (LSQ) assesses general satisfaction and satisfaction with eight specific life domains, with responses rated on a six-point scale. The EQ-5D scale, with three levels of evaluation, is primarily designed to inform healthcare decision making and detects QoL changes across five health areas, including self-esteem during the study period. While the EQ-5D has a brief completion time of approximately 3 min, it has faced criticism for lacking sensitivity to QoL changes compared to other instruments (43). Nevertheless, some studies have established its correlation with UPDRS and SF-36 scores (52) and its capacity to discriminate between different stages of PD stages (53), as well as to respond to therapeutic interventions (54–56).

The Nottingham Health Profile (NHP) comprises 38 items requiring yes/no responses, covering eight domains. This tool has undergone validation in various populations (57, 58) and has been tested specifically in patients with PD, yielding acceptable validity in this cohort, supported by good internal consistency and a unidimensional factor structure (59). However, the stability of the NHP, as assessed through test–retest procedures, has not yet been evaluated in patients with PD. Unfortunately, floor effects were noticeable in the PDQ-39 results (60). Nevertheless, the NHP is responsive to interventions such as deep brain stimulation (61, 62) and demonstrates changes over time (63, 64).

The QWB system evaluates physical activity, mobility, social activity, and 27 symptoms, categorizing patients into one of 43 functional levels. The assessment is advised to be conducted with the assistance of trained professionals, taking approximately 10–15 min to complete. A specialized version tailored for patients undergoing deep brain stimulation treatment, known as the Questions on Life Satisfaction–Deep Brain Stimulation (QLS-DBS) module, has also been developed. Reports indicate moderate to high convergent validity of the QLS-MD module with the SF-36 and EQ-5D, while moderate convergent validity has been established for the QLSDBS (65).

The Quality-of-Life Questionnaire 15D (15D) comprises 15 questions, each representing 15 distinct dimensions, with five scoring options per question. Although several non-PD populations have indicated good psychometric properties, in the context of PD, the 15D has only undergone partial validation, with one study reporting correlations with the PDQ-39 and UPDRS scores for sections II and III (66).

Among the questionnaires developed exclusively for patients with PD, in addition to the PDQ-39 and PDQL, the PDQUALIF PIMS is a lesser-used questionnaire. This tool contains 32 domain-specific items along with one global item and features seven subscales. It includes many non-motor items, such as autonomic dysfunction, fatigue, sleep disturbances, and sexual function, and has demonstrated sensitivity to changes in clinical trials (67). It is believed that the QoL scales provide greater utility in evaluating the effectiveness of rehabilitation, pharmacological treatments, or neurosurgical interventions in patients compared to other assessment instruments (16).

Table 2 summarizes some strengths and limitations associated with these various assessment tools.

4 Limitations

The evaluation of the QoL of patients with PSP is affected by various limitations. Firstly, many of the aforementioned studies were primarily based on clinical examinations, which enabled only probable or possible diagnoses. Neuropathological verification, which provides the possibility of obtaining a definite diagnosis, is rarely performed following the death of patients who have undergone QoL assessments. The relatively rapid progression of PSP and the short life expectancy following diagnosis complicate the characterization of the disease, which is complicated by difficulties in examination of patients with early stage PSP and the limited access to patients with advanced-stage PSP owing to significant cognitive and motor disability. Additionally, owing to the boundaries in the clinical evaluation of patients with advanced-stage PSP, much of the available information stems predominantly from caregivers' perspectives. Additionally, some studies reviewed herein were conducted prior to the release of the most recent diagnostic criteria established by Hoglinger et al. (4), which may not be as effective in diagnosing patients exhibiting non-Richardson syndrome. PSP being a rare disease makes the interpretation of the statistical outcomes of studies, especially the single-center studies, questionable in the context of the generalization of the results. Despite the notable differences in the disease progression of the two major subtypes—PSP-RS and PSP-P—some studies treat the PSP cohort as a homogeneous group, which may undermine the outcomes of these studies. The COVID-19 pandemic has imposed additional limitations on the examination of patients with significant motor disabilities, such as those seen in PSP. Among other limitations, owing due to limited cooperation with patients with PSP, the assessment of QoL may rely on isolated evaluations and do not allow for trend analyses.

5 Summary and perspectives

Based on data from the Adelphi PSP Disease Specific Programme™, a cross-sectional study including 242 patients, their families, and neurologists, Pillas et al. (68), highlighted the substantial burden of disease experienced by patients with PSP, their caregivers, and healthcare systems across all disease phenotypes. In this study, 67–100% of patients across various phenotypes exhibited moderate-to-severe disease severity at the time of enrollment, necessitating care from multiple healthcare professionals and constant care from a minimum of one caregiver. Despite minor statistical limitations—particularly concerning the

TABLE 2 A simplified overview of scales for QoL assessment.

Scale	Strengths	Limitations
Parkinson's Disease Questionnaire-39 (PDQ-39) (24, 31)	Assesses difficulties across 8 dimensions of daily living. Telephone interview versions available for remote assessments Good internal consistency	Does not provide a comprehensive overview of certain clinical features of PSP.
Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL) (25)	Assess items of high clinical significance and importance from the patient's point of view (19) Highly reliable with good face and construct validity	Responsiveness of the PSP-QoL not tested.
EuroQol instrument (EQ-5D) (26, 27)	Improved sensitivity and reduced ceiling effects. Available in numerous languages and in various modes of administration.	Insensitive to some specific PSP features (19)
Parkinson's Disease Questionnaire (PDQ-8) (31)	Short-form version, derived from PDQ-39	Non-motor impairment (oculomotor, mental) less evaluated (36)
Modified Progressive Supranuclear Palsy Rating Scale (mPSPRS) (37)	Reflects a wide range of functional disabilities in PSP patients. Good sensitivity to change.	Preferred in clinical trials
Progressive Supranuclear Palsy Clinical Deficits Scale (PSP-CDS) (38)	Uncomplicated formula feasible in clinical practice	-
Sickness Impact Profile (SIP) (44)	Widely covers different functional areas.	Formula requiring longer evaluation time, which may affect its use in clinical settings, particularly among patients with advanced deterioration.
Medical Outcome Study 36-Item Short Form Health Survey (SF-36) (45)	Widely used, well-researched – comparable results from different diseases studied	Largely limited by floor and ceiling effects.
Life Satisfaction Questionnaire (LSQ) (43)	Requires a short completion time in clinical settings.	Not designed for motor disorders Very general findings
Nottingham Health Profile (NHP) (57–59)	Requires a short completion time in clinical settings.	Not designed for motor disorders Very general findings
Quality of Well-Being Scale (QWBS) (65)	Assesses last 3 days of QoL experience.	Not designed for motor disorders Very general findings
Quality-of-Life Questionnaire 15D (15D) (66)	Requires a short completion time in clinical settings.	Not designed for motor disorders Very general findings

PSP, progressive supranuclear palsy; QoL quality of life.

representation of diverse patient populations and geographical variations—the authors underline the growing involvement of family and healthcare workers in managing disease progression. They also emphasize the pressing need for comprehensive patient management strategies applicable to all phenotypic manifestations of the disease. Adopting an inter-professional approach, healthcare professionals with family support may influence the QoL of patients with PSP (82).

In conclusion, PSP is regarded as an under-recognized and under-researched disease; thus, patients' multifaceted needs often go unmet. It is recommended that a direct diagnostic journey and systematic follow-up be implemented at specialized movement disorder centers, where individualized education for patients and their caregivers can be provided, which may be potentially affect their QoL. Given the minimal response to symptomatic treatments, rapid disease progression, and short life expectancy, QoL should remain a focal point of attention. As the pathological mechanisms underlying atypical parkinsonism remain unknown, there is a pressing need for further research in this area to explore potential therapeutic interventions and address current patient care requirements. Additionally, more research is warranted regarding QoL, especially within the context of treatments evaluated in clinical trials.

Author contributions

MM: Conceptualization, Formal analysis, Investigation, Project administration, Validation, Writing – original draft, Writing – review & editing. NM-A: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. PA: Formal analysis, Supervision, Validation, 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.

Publisher's note

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diseases

MDPI

Brief Report

Possible Significance of Neutrophil–Hemoglobin Ratio in Differentiating Progressive Supranuclear Palsy from Depression: A Pilot Study

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Abstract: Background: Research has associated chronic inflammation with the evolution of neurological and psychiatric disorders. Neurodegenerative diseases, including Parkinson's Disease (PD), Alzheimer's Disease (AD), and less common ones such as Progressive Supranuclear Palsy (PSP), are commonly linked to depression. However, the pathomechanisms and the role of neuroinflammation in these disorders remain unclear; therefore, interest is increasing in easily accessible inflammatory morphological assessments of blood samples, such as the neutrophil-to-lymphocyte ratio (NLR), the neutrophil-to-monocyte ratio (NMR), and the neutrophil-to-hemoglobin ratio (N/HGBR). Methods: The authors analyzed 15 age-matched controls and 21 patients with PSP; the PSP group was additionally divided into 11 patients without depression (PSP) and 10 with depression (Beck Depression Inventory [BDI] $\geq$ 14) (PSP-D). Results: In the PSP-D group, the level of N/HGBR was significantly lower than in the controls ($p = 0.01$), but there were no significant differences in any other neutrophil-derived parameters or comparisons of morphological blood assessment. Patients with PSP-D exhibited a marginally significant decrease in neutrophil levels compared to the controls. Conclusions: This is the first study highlighting the possible significance of peripheral inflammatory factors in patients with PSP affected by depression. It highlights possible tendencies in the area of non-specific inflammatory markers and suggests their relation to affective disorders in PSP.

Keywords: depression; inflammation; N/HGBR; NLR; PLR; NHR; atypical Parkinsonism

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1. Introduction

The pathophysiology of Parkinsonian syndromes remains not fully recognized; the clinical picture can exhibit motor and non-motor symptoms (NMSs) [1]. NMSs lead to decreased quality of daily life and disability (disproportionately to motor dysfunction). In patients with Parkinson's Disease (PD), depression (as the main NMS) is diagnosed in 30–40%, whereas patients with Progressive Supranuclear Palsy (PSP) present a higher frequency of depressive disorders [2,3].

Factors associated with the pathogenesis of these diseases include neuroinflammation, oxidative stress, and mitophagy disruption. In the context of neuroinflammation, the

specific impact on the course of Parkinsonism has not been uncovered. Moreover, whether neuroinflammation is a cause or consequence is debated. A meta-analysis of peripheral inflammatory markers revealed elevated interleukin 1 beta (IL-1β), interleukin 2 (IL-2), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), interleukin-10 (IL-10), and C-reactive protein (CRP) levels in patients with PD and atypical Parkinsonisms [4]. Recently, there has been growing interest in unspecific ratios of selected blood cells and high-density lipoprotein, in the context of the peripheral pathological inflammatory response. Markers for chronic subclinical inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the monocyte-to-lymphocyte ratio (MLR), and the neutrophil-to-high-density lipoprotein ratio (NHR), have been evaluated in various neurodegenerative disorders. In addition to these approaches, many studies on major depressive disorder (MDD) are now focusing on the role of central and peripheral inflammation as diagnostic and prognostic factors.

Major depressive disorders are among the common mood conditions with the highest prevalence in PSP. Specified diagnostic criteria, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM V) by the American Psychiatric Association (2013), are implemented for precise diagnosis, which are also necessary for treatment evaluation [5]. For the assessment of depression among patients with Parkinsonian syndromes, the Beck Depression Inventory II (BDI-II) is a tool of great reliability for correlating higher BDI-II scores with lower quality of life (QoL), irrespective of motor and cognitive symptoms [6].

2. Materials and Methods

2.1. Group Description

This study analyzed the differences in biochemical parameters between patients with PSP without a diagnosis of MDD (n = 11) and those with MDD comorbidity (PSP-D, n = 10), and compared them to healthy controls (n = 15), who were similar in age and other demographic parameters. Regarding the presence of depression, two subgroups of patients with PSP were categorized based on BDI scores: a PSP (BDI < 14) group and a PSP-D (BDI $\geq$ 14) group [6,7]. All patients were examined by a neurologist and a neuropsychologist experienced in the assessment of movement disorders at the Department of Neurology, Medical University of Warsaw, between 2020 and 2023. The diagnosis of PSP was based on recent criteria [8]. The patients included in the PSP-D group received a BDI score equal to or higher than 14 points. BDI is a standard method of assessment, enabling the evaluation of the core clinical characteristics of depression, which encompass its negative symptoms; this 21-item self-assessment instrument is one of the most popular measures worldwide [9]. All patients underwent a comprehensive blood analysis at the Laboratory Diagnostics Department of Mazovian Brodno Hospital (Sysmex xs-1000i Hematology Analyzer, by Sysmex Corporation, Kobe, Japan), providing morphological and biochemical evaluations (e.g., neutrophil and lymphocyte count, platelet count); all ratios were calculated using aforementioned patterns based on the blood testing obtained from a single sample.

Patients diagnosed with PSP (without comorbidity of MDD) had a mean age of 68.4 years (SD = 6.3), with ages ranging from 59 to 77 years. Patients in the PSP-D group had a mean age of 72.3 years (SD = 6.2), which was very similar to that of the control group, whose mean age was 71.3 years (SD = 5.6). Both PSP subgroups exhibited male predominance, whereas the control group exhibited a distribution with female predominance, consisting of 10 females and 5 males (Table 1).

Table 1. Descriptive statistics of analyzed parameters.

Variables	Control (n = 15)	PSP (n = 11)	PSP-D (n = 10)	p-Value
	Mean ± SD	Mean ± SD	Mean ± SD	
Sex (female/male)	10/5	2/9	4/6	-
Age	71.3 ± 5.6	68.4 ± 6.3	72.3 ± 6.2	-
NEU [$\times 10^9$/L]	6.0 ± 1.9	5.6 ± 1.9	4.4 ± 1.1	0.04 [a]
HGB	13.4 ± 1.2	14.2 ± 1.5	13.8 ± 1.0	-
LYM [$\times 10^9$/L]	2.0 ± 0.9	2.1 ± 0.7	1.7 ± 0.5	-
MONO [$\times 10^9$/L]	0.6 ± 0.2	0.6 ± 0.4	0.6 ± 0.1	-
N/HGBR	0.44 ± 0.1	0.4 ± 0.2	0.3 ± 0.1	0.01 [a]
NLR	4.4 ± 4.1	2.6 ± 1.0	2.7 ± 1.0	-
NMR	12.8 ± 9.4	8.6 ± 2.7	7.9 ± 2.3	-
BDI	5.3 ± 2.4	9.4 ± 2.9	20.7 ± 5.1	-

Statistical significance was calculated using the Mann–Whitney U-test. Significant p-value (α = 0.05). [a], significant for PSP × control; Legend: p—p-values for Student's t test; BDI—Beck Depression Inventory (PSP group—BDI scores below 20; PSP-D group—BDI scores of 20 and above); N/HGBR—neutrophil-to-hemoglobin ratio; NLR—neutrophil-to-lymphocyte ratio; NMR—neutrophil-to-monocytes ratio; NEU—neutrophil; HGB—hemoglobin; LYM—lymphocytes; MONO—monocytes.

Among the exclusion criteria used in this study were neoplasms, chronic inflammatory diseases, autoimmune diseases, infectious diseases, vascular abnormalities, and psychiatric disorders other than depression. The treatment of all patients was analyzed for possible influence on mood disorders, and individuals impacted by drug treatments were excluded. Most of the patients with PSP were not receiving any dopaminergic agents at the time of the study, as these drugs were withdrawn due to their primary or secondary inefficiency. Only treatment for irrelevant comorbidities was deemed eligible for all patients with PSP and healthy controls.

2.2. Statistical Analysis

Statistical analyses were conducted using GraphPad software, ver. 9.3 (GraphPad Software, Boston, MA, USA). Variables following a normal distribution were expressed as mean and standard deviation (SD). Comparisons between two groups were performed using the Mann–Whitney U test, while the Kruskal–Wallis test was utilized for comparisons involving three or more groups. If the Kruskal–Wallis test indicated statistical significance, Dunn's post hoc test was conducted. A two-tailed p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Neutrophil-to-Hemoglobin Ratio (N/HGBR)

The mean N/HGBR for the PSP cohort was 0.4 (SD = 0.2; range: 0.2–0.6) and was significantly higher than for the PSP-D group (mean score: 0.3; SD = 0.1; range: 0.2–0.4; p = 0.01) (Table 1). For parameters with group-to-group differences showing statistical significance, the neutrophil count was also determined (p = 0.04) (Table 1).

3.2. Neutrophil–Lymphocyte Ratio (NLR)

The mean NLR for the PSP cohort was 2.6 (SD = 1.0; range: 1.6–3.6); compared to the PSP-D group (2.7 ± 1.0), the difference was not statistically significant (Table 1).

3.3. Neutrophil-to-Monocyte Ratio (NMR)

The mean NMR for the PSP cohort was 8.6 (SD = 2.7); compared to the PSP-D group (7.9 ± 2.3), the difference was not statistically significant (Table 1, Figure 1).

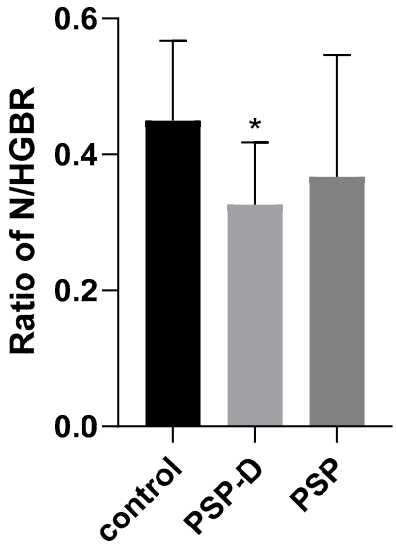

Figure 1. Level of N/HGBR in serum. Comparisons were carried out between the Progressive Supranuclear Palsy (PSP) and PSP with depression (PSP-D) groups and controls. Statistical significance was calculated using analysis of variance followed by Dunne's post hoc test, * $p < 0.01$. Legend: N/HGBR—neutrophil-to-hemoglobin ratio; PSP—Progressive Supranuclear Palsy; PSP-D—PSP with depression.

3.4. Correlations Between N/HGBR and Other Inflammatory Markers and Clinical Measures

Pearson's correlation analyses were performed to explore the relationships between the N/HGBR and various clinical and inflammatory variables, including HGB, LYM, MONO, NEU, NLR, NMR, and BDI. The results of these analyses are summarized in a correlation matrix, with further details presented in a heatmap visualization (Figure 2).

A strong positive correlation was found between the N/HGBR and neutrophil count (NEU) (r = 0.95, $p < 0.0001$), which remained statistically significant after Bonferroni correction (adjusted $p = 0.0007$). This indicates that higher N/HGBR values are strongly associated with elevated neutrophil levels.

A moderate positive correlation was observed between the N/HGBR and the neutrophil-to-lymphocyte ratio (NLR) (r = 0.67, $p = 0.0247$), although this correlation lost statistical significance after Bonferroni correction (adjusted $p = 0.1729$). Similarly, a negative correlation was found between the N/HGBR and hemoglobin levels (HGB) (r = −0.44, $p = 0.1173$), which was also non-significant after correction (adjusted $p = 0.8211$).

The correlation between the N/HGBR and lymphocyte count (LYM) was minimal (r = −0.01, $p = 0.4897$), and this result remained non-significant after correction. A moderate positive correlation between the N/HGBR and monocyte count (MONO) (r = 0.55, $p = 0.0609$) was also observed, but it became non-significant after correction (adjusted $p = 0.4263$). Likewise, the N/HGBR showed a weak positive correlation with NMR (r = 0.45, $p = 0.1141$), which was not statistically significant after the correction (adjusted $p = 0.7987$).

Finally, no significant correlation was found between the N/HGBR and BDI (r = −0.10, $p = 0.3954$), and this result remained non-significant even after correction (adjusted $p = 2.7678$).

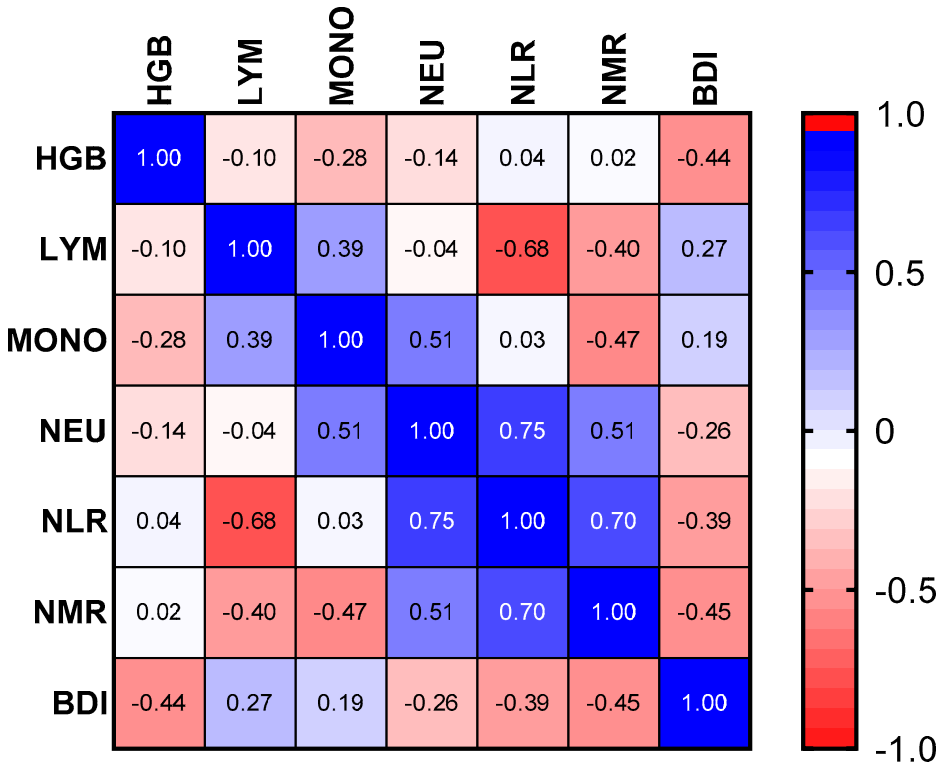

Figure 2. Heatmap showing Pearson's correlation coefficients between the N/HGBR and various clinical and inflammatory markers. The color intensity represents the strength of the correlation, with blue indicating negative correlations, red indicating positive correlations, and white indicating no correlation.

4. Discussion

The outcomes of this study stress the possible significance of peripheral inflammation in the context of clinical severity. This study reveals that the level of neutrophils in patients affected by PSP with depression is lower than in patients with PSP without depression and in healthy controls. This shows that the combined effect of PSP and depression may be affected by an additional factor inhibiting the stimulation of neutrophils; however, the description of this process is not specified.

Depression is associated with increased levels of neutrophils, as stressed in multiple studies regarding non-specific inflammatory factors such as the neutrophil-to-lymphocyte ratio. The increased levels of this parameter were found to be correlated with the severity of depression and cardiovascular risk factors [10]. In this context, an intuitive outcome of this study suggests that the neutrophils and derived factors, like the neutrophil-to-hemoglobin ratio in the group of PSP with depression, should be increased, which is contrary to the actual outcomes. The results of this study may be partly explained by the impact of two clinical aspects: PSP as the primary disease and depression as the co-existing factor. The pathophysiology of PSP is linked to neuroinflammation; however, a more thorough analysis of the recently discovered mechanisms underlying this disease indicates the possible significance of certain cytokines regarded as anti-inflammatory factors. Evaluations of the M2 phenotype of microglia have indicated its possible relevance in tauopathies at their early stages. M2 is related to the production of IL-4, IL-10, IL-13, and TGF-β, which are classified as anti-inflammatory cytokines [11]. In this context, the PSP pathomechanism tends to be a complex process affected by proinflammatory factors, such as IL-1 and IL-6, and the abovementioned anti-inflammatory cytokines [12].

Previous assessments of inflammation in PSP showed a positive correlation between PLR and IL-6 in serum [12]. This may suggest that the microglial activation impacting the levels of IL-6 may play a role in the evolution of certain groups of symptoms in atypical Parkinsonism. Peripheral inflammatory parameters have yet to be used to examine this group. Initially, studies concerning this assessment were based on the analysis of NLR [13]. They indicated the possibly elevated levels of NLR among patients with PSP in comparison with patients with Parkinson's Disease. The examination of PSP and CBS did not show any significant differences in NLR. Patients with PSP-RS had higher levels of NLR than the control group [14]. A meta-analysis on the significance of NLR showed higher levels of neutrophils among patients with PSP and not significantly deviated lymphocytes compared to controls [15]. The activated leukocyte metabolism in PSP and NRF2/HO-1 pathway activation were linked with accumulation in peripheral blood mononuclear cells [16]. The features were found to be negatively correlated with the PSP-rating scale. Examinations concerning the association between peripheral inflammatory parameters and neuroimaging revealed a negative correlation between NHR and perfusion in the insula and thalamus only among patients with CBS [17], which has not been confirmed in PSP. The results obtained from these studies suggest that the inflammatory impact may differ depending on the region of interest in neuroimaging.

Despite multi-dimensional studies, the exact causes of depressive disorders are still unknown, and it is believed that the co-occurrence of various endogenic (genetic predisposition, physical brain structure changes, psychological factors, comorbidity, gender) and environmental factors contributes to MDD [18–20]. Those may be additionally influenced by lifestyle factors (like a highly processed diet leading to gut dysbiosis, poor physical activity, or psychoactive substances use) [21,22]. The progression of the mentioned neurodegenerative disorders worsens with MDD and other mood changes, significantly affecting patients' QoL.

Currently, although not fully discovered, the multi-systemic and entangled pathophysiology pathway of affective disorders includes neurotransmission alterations in monoamines and glutaminate, neurotrophin imbalance, or hypothalamic–pituitary–adrenal axis dysregulation, followed by immune system dysfunctions and local inflammation [23]. Neuroinflammation in mood disorders is currently being intensively explored to uncover promising discoveries that can improve their treatment [24]. Interestingly, a bidirectional relationship has been reported: depression increases inflammatory responses, which in turn increase depression [25]. For neuroinflammation evaluation, numerous peripheral and central biomarkers have been assessed for their feasibility, e.g., C-reactive protein (CRP), several interleukins, cortisol, and tumor necrosis factor-alpha (TNF-α), among others. A complex pathway of inflammatory responses is initiated with neutrophil stimulation, impacting the production of numerous non-specific mediators, leading to phagocytic and apoptotic effects. Moreover, lymphocytes are responsible for immune system regulation and suppression. Thus, neutrophil numbers refer to an unspecific inflammatory process, whereas lymphocyte counts are caused by physiological stress [26]. These ratios are highly accessible due to availability from routine complete blood count, at low costs. Also, for mood disorders and other psychiatric comorbidities, their use is well established [27]. Most studies, including meta-analyses, have indicated that NLR levels are associated with the severity of depression [28,29]. However, in some studies, no significant difference in NLR between patients with depression and controls was found, but the researchers assumed that this was due to the relatively small group samples [30]. In another study, the correlation with MDD severity was not significant in a female subgroup, which was explained by changes in estrogen levels. However, other scientists doubt this explanation, stressing the need for further studies in this field [31,32]. Data from a meta-analysis on inflammation

and depression reveal a noticeable heterogeneity across studies [33]. Despite suggestions for future evaluation, NLR is recognized as suitable for neuroinflammation assessment, but as an unspecified marker, it is also useful as a diagnostic biomarker and predictor of several mood disorders presence, including MDD and psychotic depression [34,35].

Although antidepressants influence neuroinflammation, some data suggest that they do not affect NLR [36,37]. Because it is recognized to be less affected by confounding conditions, NLR may be more informative, compared to other leukocyte parameters or non-leukocyte-based markers. Other markers have not been as well explored as NLR yet. In some studies, NLR and PLR were found to be correlated with depression severity, but other researchers did not find such a correlation, although some suggested a possible link between the clinical profile of MDD with PLR, but not with NLR [31,38]. All individuals diagnosed with MDD showed significantly increased PLR in comparison with healthy controls [39]. A meta-analysis of different studies revealed a significant association between PLR, NLR, and MLR values [31]. The importance of immune dysregulation in mood disorders (including MDD) and its possible treatment target was revealed in randomized controlled studies. The addition of anti-inflammatory drugs (i.e., statins, celecoxib, and omega-3 fatty acids) to a selective serotonin reuptake inhibitor (SSRI) resulted in greater efficiency in MDD treatment, compared with SSRI monotherapy [40,41].

This study has several limitations. As all patients included in the study were alive, no neuropathological examination was performed, and a definitive diagnosis was not accessible. The diagnosis of PSP was based on probable and possible diagnoses according to the most contemporary criteria [8]. The examination was based on non-specific assessment methods of peripheral inflammation; however, the authors intended to evaluate factors with high accessibility, low cost, and minimal invasiveness that were feasible to assess in clinical practice. This study was based on a single examination of patients, which excluded the analysis of time-related tendencies.

The outcomes of this research suggest that depression may be a factor additionally enhancing one of the contrary mechanisms. This study's methodological limitations and characteristics as a pilot study limit the interpretation and applicability of the results. Understanding the co-existing factors impacting the pathophysiology of PSP seems crucial in achieving future optimal therapeutic strategies; in this context, pilot studies highlighting such tendencies are valuable.

5. Conclusions

To the best of our knowledge, this is the first study indicating the possible significance of the inflammatory process in the pathogenesis of both PSP and depression. The pathomechanism of this Parkinsonian syndrome remains unexplained; thus, further research is recommended, preferably including larger groups of participants. As neuroinflammation seems to be one of the common underlying causes for both mood disorders and some neurodegenerative syndromes, there is a need for further exploration. Advances in preclinical studies may lead to the identification of binding points for new drugs with potentially disease-modifying effects.

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Brief Report

Inflammatory and Neurotrophic Factors and Their Connection to Quality of Life in Progressive Supranuclear Palsy—Single-Center Study

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Abstract

Progressive supranuclear palsy (PSP) is a condition classified as atypical parkinsonism. Pathologically, it is a four-repeat tauopathy; clinically, it is a disease comprising oculomotor dysfunction, postural instability, akinesia, and cognitive/language disorders. Its pathogenesis is not fully recognized; however, neuroinflammation is considered to likely be a significant aspect, though it is not known whether inflammation is a cause or consequence of neurodegeneration. In this study, the authors analyzed the association between inflammatory/neurotrophic factors and parameters linked to quality of life, based on examinations of 10 controls and 11 patients with PSP. They found a negative correlation between mPSPRS (Modified Progressive Supranuclear Palsy Rating Scale) and the glial cell-line-derived neurotrophic factor levels (GDNF) ($r = -0.772727$, $p = 0.003$) in the serum, a less pronounced negative correlation between progressive supranuclear palsy–quality of life parameter (PSP-QoL) and GDNF ($r = -0.68390$, $p = 0.011$) in the serum, and no correlations were observed in the analyses of inflammatory factors. The obtained results show the association between lower levels of GDNF and more pronounced clinical deterioration. Further analysis in the field based on larger groups of patients is required.

Keywords: neurodegeneration; neuroinflammation; progressive supranuclear palsy (PSP); quality of life; QoL

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1. Introduction

Progressive supranuclear palsy (PSP), the most common among the atypical parkinsonian disorders (Parkinson-plus syndromes), is a neurodegenerative disease with a largely unknown pathophysiological background [1]. Its clinical manifestation is associated with oculomotor dysfunction and speech/cognitive deterioration, differing from typical parkinsonian syndrome (tremor, akinesia, rigidity, and postural instability) [1]. Although the diagnostic criteria include multiple subtypes of PSP, the vast majority (up to 90% of all cases) are linked with two subtypes: PSP-Richardson's syndrome (PSP-RS) and PSP-parkinsonism

predominant (PSP-P), which have different clinical presentations and prognoses. The leading neuropathological process is the aggregation of microtubule-associated protein tau (MAPT) into neurofibrillary tangles, and it is present in both neurons and glia cells in several cortical and subcortical regions of the brain [2], with continuous accumulation resulting in microgliosis, astrogliosis, and neuronal damage [3]. Factors describing the pathogenesis of PSP include mitophagy disruption, oxidative stress, and neuroinflammation, among others [4]. Apart from the concepts of genetic and epigenetic background, and, recently, proteome-wide expression discoveries, there are convincing data for neuroinflammation's involvement in PSP pathogenesis [5–7].

In several studies, including those conducted posthumously, increased microglia numbers and activation were identified in PSP brains, especially in the subthalamic nucleus, substantia nigra, extrapyramidal motor system, and its cerebellar output [8]. There was a positive correlation between microglial activation and tau concentration [9]. In PET imaging studies, microglial activation was identified in the midbrain, basal ganglia, and other areas crucial for PSP symptomatology [10]. Interestingly, tau accumulation and microglial activation were proven to be positively correlated with clinical course severity and were predictive factors for disease progression [11,12]. These results strongly support the hypothesis of microglial activation being a major pathway of PSP pathology. The results from transgenic animal studies on tau-overexpressed rats suggest that the primary cause of microglial activation is tau deposits, as inflammation starts in tangle areas; in vitro cultures are found to secrete pro-inflammatory cytokines in the presence of full-length tau structures [13]. Pro-inflammatory factor release and neuroinflammation induction further accelerate the hyperphosphorylated tau accumulation process, leading to a high concentration of pro-inflammatory factors such as IL-1β being identified in PSP pathology-related structures [8,14]. It is not clear whether neuroinflammation leads to neurodegeneration or whether it is rather a consequence of the degenerative process [15]. The other mechanism that is common for many neurodegenerative diseases is glial cell senescence, which directly contributes to neuronal tau pathology, resulting in cognitive impairment, although its significance in PSP pathology is unknown and there is currently limited evidence in this field [16]. Also, limited data are available regarding T cell involvement: studies on genetically modified rodents resulting in T cell infiltration suppression suggest its protective role in PSP pathophysiology; therefore, further research is needed [17]. Hepcidin is a peptide of liver origin, primarily identified as an iron homeostasis regulator, and its tissue distribution (including CNS) plays a role in neuroinflammation and the pathogenesis of neurodegenerative diseases; therefore, more data are available for Alzheimer's disease and Parkinson's disease, and its significance in atypical parkinsonism has been described less [18].

Recently, there has been growing interest in neurotrophin dysregulation and tauopathy development. Among others, brain-derived neurotrophic factor (BDNF) is identified as a major agent involved in such processes [19]. Its mRNA and protein concentrations are decreased in post mortem brain studies, followed by clinical decline [20,21]. Neurotrophin dysregulation by tau-mediated pathways seems to be commonly identified in various neurodegenerative disorders; nevertheless, in some studies, the nerve growth factor (NGF) binding site density was noticeably lower in PSP, but not in other parkinsonian syndromes [22]. To the best of our knowledge, the only study to extensively explore the significance of neurotrophins in PSP was performed by Alster et al. [23]; the results indicated potentially striking aspects regarding the pathophysiology of the disease. In clinical practice, measuring non-specific inflammatory factors' concentrations from samples obtained invasively is impractical; therefore, the analysis of easily accessible factors seems feasible. Also, the link between laboratory features and clinical insight is crucial for current assessment and follow-up. Future diagnostic management will possibly include

multimodal diagnostic algorithms integrating structured clinical phenotyping, quantitative imaging, molecular diagnostics, and, optimally, autopsy-linked validation [24]. Evaluating factors important for a patient's everyday life functioning supports the patient-orientated perspective, so we performed our analysis based on quality of life (QoL) parameters.

2. Results

A total of 11 patients with PSP and 10 healthy controls were included in the study. Clinical severity in the PSP group was assessed using the mPSPRS and PSP-QoL scales, with mean values of 6.36 ± 4.23 and 106.73 ± 57.98, respectively.

2.1. Biomarker Concentrations in Serum and CSF

We first compared biomarker concentrations between PSP patients and healthy controls.

Significant group differences were observed for serum GDNF, hepcidin, IL-1β, and IL-6, as well as for CSF GDNF and IL-6 (Table 1). The distribution of serum biomarkers is shown in Figure 1 and CSF biomarkers in Figure 2.

Table 1. Comparison of biomarker concentrations in serum and CSF between PSP patients and healthy controls using the Mann–Whitney U test.

Biomarker	Control (Means ± SD)	PSP (Mean ± SD)	*p*-Value
Serum			
GDNF pg/mL	1.60 ± 0.6	2.23 ± 1.2	**** $p = 0.0001$
Hepcidin ng/mL	0.85 ± 0.1	1.88 ± 1.3	**** $p = 0.0001$
IL-1 beta pg/mL	1.62 ± 0.8	3.06 ± 1.5	* $p = 0.01$
IL-6 pg/mL	3.72 ± 2.2	4.81 ± 2.1	* $p = 0.04$
CSF			
GDNF pg/mL	1.02 ± 0.2	1.28 ± 0.3	* $p = 0.01$
IL-1 beta pg/mL	7.14 ± 1.6	6.19 ± 1.5	$p = 0.07$
IL-6 pg/mL	4.21 ± 0.9	6.92 ± 2.9	* $p = 0.01$

* $p < 0.05$, **** $p < 0.0001$ (Mann–Whitney U test).

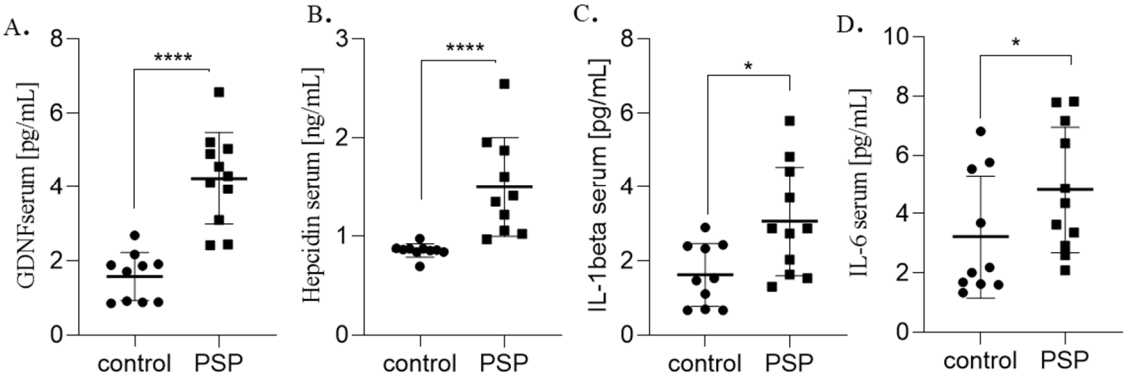

Figure 1. Serum biomarkers levels in PSP patients and healthy controls. Box-and-dot plot showing individual values, mean ± SD for serum (**A**) GDNF, (**B**) hepcidin, (**C**) IL-1 beta, (**D**) IL-6 concentrations in patients with PSP and healthy controls. A higher GDNF and IL-6 level was observed in the PSP group compared to controls (**** $p = 0.0001$, * $p = 0.01$, respectively, Mann–Whitney U test).

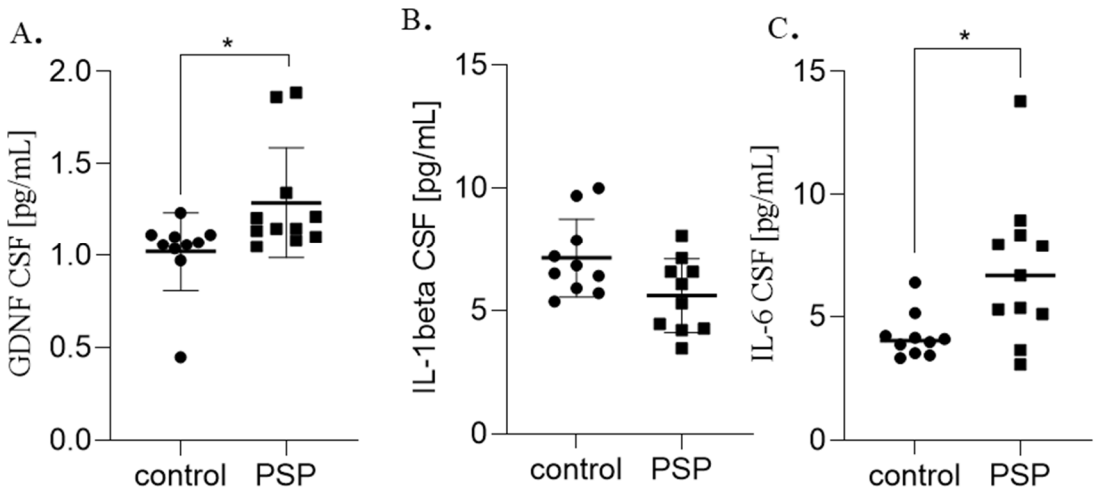

Figure 2. CSF biomarkers levels in PSP patients and healthy controls. Box-and-dot plot showing individual values, mean ± SD for serum (**A**) GDNF, (**B**) IL-1 beta, (**C**) IL-6 concentrations in patients with PSP and healthy controls. A significantly lower all biomarkers level was observed in the PSP group compared to controls (* $p = 0.01$, respectively, Mann–Whitney U test).

2.2. Correlations Between Biomarkers and Clinical Scales

We next investigated associations between biomarker levels and clinical severity within the PSP group.

Significant negative correlations were observed between serum GDNF and both clinical scales: mPSPRS ($\rho = -0.77$, $p = 0.003$) and PSP-QoL ($\rho = -0.68$, $p = 0.011$). These relationships are illustrated in Figure 3 and summarized in Table 2.

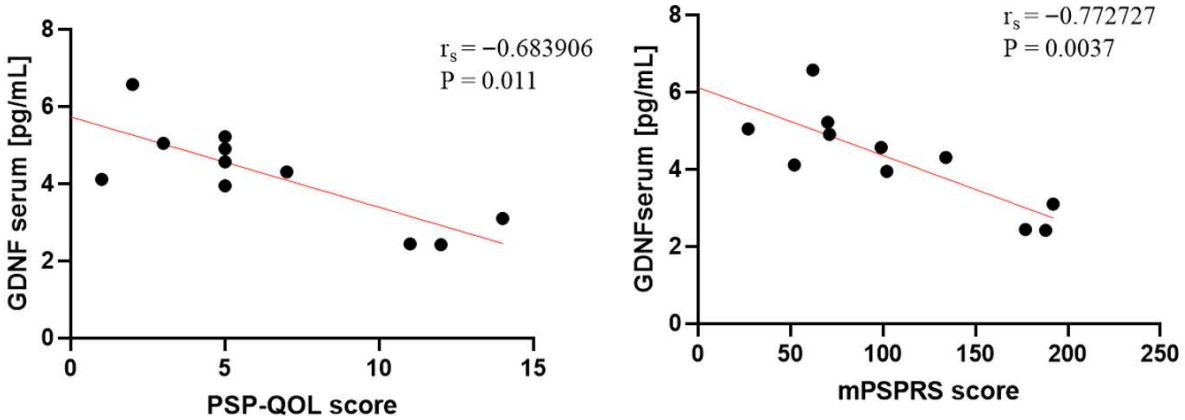

Figure 3. Correlation between clinical scales and biomarkers in PSP patients and healthy controls. Significant negative correlations were observed in the PSP group for mPSPRS ($\rho = -0.77$, $p = 0.003$), and PSP-QoL ($\rho = -0.68$, $p = 0.01$). Each panel shows individual data points (n = 11) with a regression line in red. PSP = progressive supranuclear palsy; GDNF = glial cell line-derived neurotrophic factor.

Table 2. Spearman's correlations between clinical scale scores and serum biomarker concentrations in PSP patients.

Group	Clinical Scale	Biomarker	Specimen	Spearman's r	*p*-Value
PSP	mPSPRS	GDNF	Serum	**−0.772727**	** **p = 0.003**
PSP	PSP-QoL	GDNF	Serum	**−0.683906**	* **p = 0.01**

* $p < 0.05$, ** $p < 0.01$. Spearman's rank correlation was used. Trends toward significance are noted where $p < 0.1$.

No significant correlations were identified for IL-1β, IL-6, or hepcidin in either serum or CSF.

In healthy controls, a negative correlation between CSF IL-6 and mPSPRS was observed ($\rho = -0.60$, $p = 0.036$).

No other significant correlations were observed across the remaining markers and scales in either group.

3. Discussion

Although the etiology of PSP is not specified, in terms of its pathogenesis, inflammation and oxidative damage are thought to greatly contribute to disease development. In this study, we evaluate the neuroinflammation (expressed as the concentration of specific markers) and neurotrophic factors in connection with the functional status of PSP patients.

In patients with PSP, there was a significant correlation between serum GDNF and clinical-scale results: mPSPRS and PSP-QoL ($p = 0.003$, $p = 0.01$, respectively). This suggests that this molecule possibly plays a protective role in neuron survival. GDNF is significant as it is considered a crucial agent for dopaminergic cells preservation, although its role in neurodegenerative diseases is not fully recognized—in Parkinson's disease, it favors dopaminergic neuron survival, and, additionally, the results of certain studies based on a limited cohort of PSP patients suggest that GDNF release may be a mechanism contrary to the neurodegeneration process in PSP-RS [23,25].

From a clinical perspective, the connection between GDNF changes and sleep disturbances [26], some executive functions (especially working memory, inhibitory control and cognitive flexibility) [23], and cognitive status [27] was proven in several works; in each, the protective role of this neurotrophin was highlighted. None of these papers evaluated the overall QoL, different tools to analyze functional decline were chosen, and some of them were based on examining conditions other than PSP, e.g., Parkinson's disease; therefore, a general conclusion cannot be made.

Alster et al. [25] highlighted that this factor had a possibly protective role, especially in more deteriorating forms of PSP, and GDNF release was considered to potentially be a mechanism contrary to rapid neurodegeneration in PSP-RS. In this ante mortem study, it was found that more increased serum GDNF levels were observed in PSP-P, though this observation was not confirmed in PSP-RS, which suggests that serum GDNF levels may primarily increase as a protective mechanism; this hypothesis aligns with the results of GDNF studies in Parkinson's disease, where the factor had an inhibitory influence on the deterioration of certain clinical features (discussed above). As more pronounced atrophy is generally observed in PSP-RS than PSP-P, this suggests that the rise in GDNF may be seen earlier in the disease course of the former than in the latter [28].

On the other hand, if GDNF release is a protective reaction to degeneration, its level may increase proportionally to the atrophy severity regardless of PSP clinical phenotype; due to the undefined and possibly multifactorial pathomechanism of this disease, presumptions such as this are limited. Further studies on PSP patients with a well-established disease subtype diagnosis, ideally with subsequent serial sampling of serum at different disease stages, would verify this prediction. In such a situation, GDNF evaluation could be used as a marker of future neuroprotective therapies' effectiveness in various neurodegenerative diseases, yet further studies are needed to confirm its usefulness in such a role. The results of our research team demonstrate the connection between biochemical and clinical aspects of PSP, resembling similar neurodegenerative diseases like PD. In light of these similarities, the authors intend to enroll patients diagnosed with other atypical parkinsonian syndromes to explore the laboratory and clinical features of the disorders.

Significant differences in some interleukins' (e.g., IL-1 and IL-6) concentrations with respect to different PSP subtypes were identified in a recent study [29]. The authors of that study differentiated between PSP-P and PSP-RS patients and explained several interleukin patterns in specific microglial activity leading to various types of IL release; they also assumed the potential impact of these immune profiles on the natural course of the disease. As in our study, there was only a trend toward significance in terms of IL-1β concentration, so we assume that enrolling a larger cohort (or multi-center data) would make the sample strong enough to achieve statistical significance in studies of that strongly pro-inflammatory cytokine. This is because other animal studies have revealed its role in various degenerative processes in the central nervous system, where the neuroprotective effect of microglia activation via IL-1β pathways was identified [30]. In a study on the mechanisms of microglia activation via the IL-6 pathway in traumatic brain injury, the authors achieved similar results; therefore, cases of severe CNS injury should be included [31].

Preclinical studies on inflammasome activation reveal that in the production of pro-inflammatory cytokines IL-1β and IL-18, tau hyperphosphorylation and accumulation are increased [32]. We assume that further clinical studies on IL-18 in PSP would provide coherent results. The preclinical findings highlight that the inflammasome may be a therapeutic target in PSP and other tauopathies [33].

Apart from more specific cytokines, non-specific peripheral inflammatory parameters were also investigated in PSP and other parkinsonian-plus syndromes. As the inflammatory process in neurodegenerative diseases is generalized, it can be reflected by non-specific parameters. Studies on the serum lymphocyte-to-monocyte ratio (LMR), neutrophil-to-high-density-lipoprotein ratio (NHR), and neutrophil-to-lymphocyte ratio (NLR) revealed elevated NLR and NHR parameters with lower LMR in patients with PD, corresponding with the disease severity; the platelet-to-lymphocyte ratio (PLR) was significantly lower in PD, but not in other parkinsonian syndromes (as MSA and PSP patients were analyzed) [34]. The explanation for these observations remains unclear; therefore, it is suggested that different pathomechanisms are involved in these disorders. As discussed, the parameters are highly unspecific, and the impacts of general patient status and numerous other parameters need to be ruled out.

On the other hand, studies have revealed substantially increased GDNF levels in PSP-P patients and less increased levels in PSP-RS patients; the authors suggest that in PSP, the GDNF levels in the serum initially rise as a protective mechanism [29]. Such a mechanism is considered for dopaminergic neurons protection in PD, a disorder where more data is available, compared to Parkinson-plus syndromes [23]. In PD animal models, a positive effect on various glial cells was observed; this could be a novel therapeutic strategy for such neurodegenerative disease, with potential for similar disorders [23]. Preclinical findings on GDNF's role include promoting the survival of remaining neurons and axons regeneration as well as the promotion of the functional activity of viable neurons [35].

Also, higher hepcidin levels were identified in the serum in PSP-RS [18]. Furthermore, the inclusion of other rare PSP subtypes could be beneficial for exploring this hypothesis, but obtaining results of statistical significance might be challenging due to cohorts probably being small. In further studies, the analysis of comorbidities and their influence on neurotrophic agent concentrations could also bring innovative conclusions.

In studies of small patient cohorts, strong microglial activation and its correlation with tau accumulation were found in both –PSP and corticobasal degeneration (CBD) on brain sections, although there were no clinical (or QoL) analyses of those few cases (for PSP, n = 10) [9]. Also, in larger groups with 95 PSP and 30 CBD cases, it was confirmed at autopsy that they had identified microscopic findings, but without any connection to clinical symptoms and without an impact on QoL [36]. Inconclusive results for the wider

immune profile in PSP (for interleukin 4, tumor necrosis factor α [TNF-α], and transforming growth factor β1 [TGF-β1] analysis) suggest that only a few molecules could be specific markers for neuroinflammation [37]. Promising results (cytokine concentration in PSP in comparison to PD) come from studies on interleukin 10, interleukin 18, interleukin 1β, and interferon γ [38]. A meta-analysis of 29 studies on a total of 1679 patients revealed poor correlation of central with peripheral inflammatory markers [39,40]. The imbalance of pro- and anti-inflammatory homeostasis leads to clinical symptoms that influence patient well-being and disease burden on everyday life, decreasing QoL. As PSP seems to be heterogeneous, further studies on the disease pathophysiology and clinical presentation should be performed with an acknowledgement of its major subtypes. For future studies, in addition to developing our pilot study outcomes, an attempt at a clinical distinction of PSP-P and PSP-RS based on QoL evaluation results should be made.

It is noteworthy that the intervention based on modifying the disease course only via central inflammation suppression is unlikely to stop the pathological process and could therefore delay the clinical deterioration of some patients. The GDNF and its pathway seem to be a promising aim, as they were identified as influencing numerous clinical symptoms of PSP; nevertheless, more real-life data (including QoL studies) are needed.

As in PSP-RS, with clinically relatively rapid deterioration, the most intense inflammatory process is present at the beginning of the disease; the studies revealed higher inflammatory marker concentrations at the beginning of the course. In PSP-P, inflammatory activity seems to be less intense and stable; therefore, the concentrations of pro-inflammatory cytokines are predicted to be lower than in RS cases and stable in subsequent samples. This hypothesis based on clinical observations of the natural PSP course requires further studies focused on changes in interleukin concentrations during the following disease stages.

Limitations

This study has several limitations. Firstly, the number of examined patients and proportionally healthy controls was limited (reflecting a low morbidity and relatively short disease duration), as the research was planned as a pilot single-center study. Given the pilot nature and small sample size, the findings should be considered preliminary.

Limited group size has an influence on limitations in statistical methodology of the study. No formal multiple-comparison adjustments were applied and the results should be interpreted as preliminary. Future studies with larger sample sizes will incorporate appropriate statistical procedures, including false discovery rate (FDR) correction, among others.

Importantly, in the analysis there was no distinction between PSP-RS and PSP-P subtypes. Similar to work by Alster et al. [18], the results are presumably the outcome of an even smaller group of patients that are potentially more heterogeneous (including various disease phenotypes). In that study, serum GDNF levels increased in both PSP subgroups when compared to the controls, which supports the hypothesis that in all cases of PSP, the serum levels are higher than in HCs. In PSP-RS, the concentration in the CSF was significantly increased compared to PSP-P or HCs (and for both of those cohorts, the concentration was comparable). To the best of our knowledge, there are no studies on GDNF concentration in PSP variants other than –RS or –P.

The clinical deterioration observed in PSP limits the possibility of extended follow-up evaluation, and also leads to bounded cooperation of patients in research projects of observational protocol only. As a result of this fact, longitudinal data (including subsequent sampling of the material obtained in an invasive way) was not available. Studies based as a development of this work would contribute novel data, including the dynamic changes in indicators in the disease progression timeline.

Although the authors intended to enroll healthy volunteers of similar age to the patients, some of them were also diagnosed with chronic disorders (e.g., cardiovascular diseases or joint degeneration) that can influence QoL outcomes. However, the detailed analysis of available medical history of all participants of the study did not reveal facts substantially affecting their status.

The patients' clinical diagnoses were not verified neuropathologically; therefore, obtaining a definite diagnosis was not accessible. The study is based on probable/possible diagnosis of PSP. All of the patients were examined by neurologists who are experienced in movement disorders.

As each of the participants was evaluated once, it was not possible to identify any changes in studied values over time, though non-specific peripheral inflammation parameters are known to be variable. Serum and CSF samples were taken before the QoL interview, and the interval was not standardized; the authors plan to analyze the influence of this delay on results in further studies. This makes it difficult to clarify the correlation between the trends in factors such as GDNF and the disease course. Several improvements are considered for future study: longitudinal follow-up, with multi-time biomarker testing and clinical assessments, is planned, which could possibly allow for dynamic changes in indicators to be tracked as the disease progresses.

4. Materials and Methods

4.1. Group Description and Examination Methods

In this study, we analyzed biochemical parameters in the serum and cerebrospinal fluid (CSF) of patients diagnosed with PSP in comparison to healthy controls (HCs) of a similar age. The mean age in the PSP group was 70.5 years (SD = 5.35), ranging from 60 to 81; in the HC group, it was 66.3 years (SD = 5.73), ranging from 59 to 78. Gender distribution showed a noticeable male predominance in the PSP group alone: 63.6% male in the PSP group (4 females, 7 males) and 70.0% female (7 females, 3 males) in the HC group. The disease duration ranged between 3 and 6 years.

All patients in the study were diagnosed in the Department of Neurology of the Medical University of Warsaw based on the current diagnostic criteria by neurologists highly experienced in movement disorders [1], with written consent provided by all participants. Exclusion criteria were the diagnosis of neoplasmatic diseases, autoimmune diseases, infectious diseases, hematologic diseases, diabetes or metabolic syndrome, and using drugs with a possible impact on the analyzed factors; none of the patients used medication that significantly impacted the inflammatory parameters. All participants underwent morphological examination and lumbar puncture in the Department of Neurology of the Medical University of Warsaw, and serum and CSF biochemical examinations were conducted in the Department of Biochemistry. From each patient, 10 mL of CSF and 10 mL of serum were taken for analysis, frozen at -80 °C soon after the collection procedure, and stored in such conditions until evaluation. Each sample was analyzed regarding the four parameters—interleukin 1 β (IL-1β), interleukin 6 (IL-6), hepcidin, and glial cell line neurotrophic factor (GDNF). Commercial ELISA kits from Diaclon SAS (Besançon, France) were used for GDNF concentration assessment (absorbance determination at 450 nm with a plate reader) and calculation was conducted based on standard curves. For each parameter, doubled analysis was performed. The modified PSP Rating Scale (mPSPRS) and PSP-QoL were completed at least 1 week after discharge from the hospital, with caregiver support if necessary.

4.2. Statistical Analysis

All statistical analyses were performed using GraphPad Prism (version 8, GraphPad Software, San Diego, CA, USA) and variables were assessed for normality using the Shapiro-Wilk test. Given the small sample size and non-normal data distribution, non-parametric tests were applied throughout the analysis.

For group comparisons between PSP patients (n = 11) and healthy controls (n = 10), the Mann–Whitney U test was used to evaluate differences in serum and CSF biomarker levels, including GDNF, hepcidin, IL-1β, and IL-6.

To investigate the relationship between clinical scale scores and biomarker concentrations within the PSP group, Spearman's rank correlation coefficients (ρ) were calculated. Clinical scales included the modified PSP Rating Scale (mPSPRS) and PSP-QoL, with statistical significance defined as $p < 0.05$. Spearman's rank correlation was used to explore associations between biomarker concentrations in serum and cerebrospinal fluid (CSF) and clinical scale scores (mPSPRS and PSP-QoL) in both PSP patients and HCs.

5. Conclusions

Further research in neurodegenerative diseases needs to be focused on understanding the role of inflammation as a possibly significant pathogenic factor [33]. So far, none of therapeutic interventions evaluated in PSP have been proven to have sufficient effectiveness, despite over 30 drugs having been tested; the molecules' targets were designed based on discussions of pathophysiology (mostly tau aggregation and accumulation slow-down or microglia activation inhibition) [41]. For innovative therapies, achieving both laboratory and clinical end-points is necessary. Using QoL to indirectly assess clinical outcomes seems to be promising. Future therapies based on neurotrophic agent interference are possibly promising in the context of current therapeutic nihilism regarding atypical parkinsonian syndromes [42].

Inflammation and deviations in neurotrophic parameters play a role in PSP pathophysiology and similar degenerative diseases. In our study, where neuroinflammation corresponds with symptoms and patient functional status, we underline the importance of preclinical and clinical features, encouraging future multi-center and multi-perspective research regarding PSP and related disorders to be conducted.

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Informed Consent Statement: Written informed consent was obtained from the patients to publish this paper.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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

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Warszawa, 9.01.2026r.
(miejscowość i data)

Piotr Alster
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Inflammatory and Neurotrophic Factors and Their Connection to Quality of Life in Progressive Supranuclear Palsy—Single-Center Study

oświadczam, że mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
koncepcja pracy, metodologia, zbieranie danych, analiza danych, pisanie artykułu, superwizja
Mój udział procentowy w przygotowaniu publikacji określam jako 20%
Wkład Michała Markiewicza 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. Michała Markiewicza.
(imię i nazwisko kandydata do stopnia)

dr hab. n. med. Piotr Alster
specjalista neurolog
3168373

.....
Podpis oświadczającego

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

Warszawa, 9.01.2026r.
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analiza danych, superwizja
Mój udział procentowy w przygotowaniu publikacji określam jako 30%
Wkład Michała Markiewicza w powstawanie publikacji określam jako 60%
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OŚWIADCZENIE

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Warszawa, 9.01.2026r.
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Bartosz Migda
(imię i nazwisko)

OŚWIADCZENIE

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Mój udział procentowy w przygotowaniu publikacji określam jako 4%
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Warszawa, 9.01.2026r.
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Natalia Madetko-Alster
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przegląd literatury, analiza danych.
Mój udział procentowy w przygotowaniu publikacji określam jako 10%
Wkład Michała Markiewicza w powstawanie publikacji określam jako 60%
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NWZ 3[illegible]

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Alicja Wiercińska-Drapało
(imię i nazwisko)

OŚWIADCZENIE

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Dagmara Otto-Ślusarczyk
(imię i nazwisko)

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Marta Struga
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KIEROWNIK
Katedry i Zakładu Biochemii
prof. dr. hab. n. med. Marta Struga
Podpis oświadczającego

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Karolina Duszyńska-Wąs
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*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników.

Warszawa, 9.01.2026r.
(miejscowość i data)

Maciej Darewicz
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Inflammatory and Neurotrophic Factors and Their Connection to Quality of Life in Progressive Supranuclear Palsy—Single-Center Study

oświadczam, że mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
analiza danych, analiza statystyczna
Mój udział procentowy w przygotowaniu publikacji określam jako 2%
Wkład Michała Markiewicza 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. Michała Markiewicza.
(imię i nazwisko kandydata do stopnia)

Maciej Darewicz
.....
Podpis oświadczającego

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

Warszawa, 9.01.2026r.
(miejscowość i data)

Patryk Chunowski
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Possible Significance of Neutrophil-Hemoglobin Ratio in Differentiating Progressive Supranuclear Palsy from Depression: A Pilot Study

oświadczam, że mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
zbieranie danych, analiza danych i ich interpretacja, metodologia, pisanie artykułu,
Mój udział procentowy w przygotowaniu publikacji określam jako 2%
Wkład Michała Markiewicza 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. Michała Markiewicza.
(imię i nazwisko kandydata do stopnia)

Dr n. med. Patryk Chunowski
Lekarz
3965044

.....
Podpis oświadczającego

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

Komisja Bioetyczna
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AKBE/ 140 / 2024

Warszawa, dnia 13.05.2024

Dr hab. n. med. Piotr Alster
Klinika Neurologii WNoZ
ul. Kondratowicza 8,
02-091 Warszawa

OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 13 maja 2024 r. przyjęła do wiadomości informację na temat badania pt . "Ocena jakości życia w przebiegu atypowych zespołów parkinsonowskich" Wyżej wymienione badanie jest zgodne z zasadami etyki badań naukowych.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz