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Fluid biomarkers in atypical Parkinsonism: current state and future perspectives

Anastasia Bougea[1] · Carlo Colosimo[2] · Cristian Falup-Pecurariu[3,4] · Giovanni Palermo[4] · Yildiz Degirmenci[5]

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Abstract

Diagnosing Atypical Parkinsonian Syndromes (APS) may be challenging due to overlapping clinical features of Parkinson's disease (PD), and the lack of pathognomonic diagnostic tests. Fluid biomarkers can be useful tools that make it easier to identify and track different APS. Objectives: this narrative review aim to update the current state of fluid biomarker research in APS and their potential implications in clinical practice. A comprehensive literature search was conducted in PubMed and Scopus using the following terms: "Aβ42 amyloid beta with 42 amino acids'', " alpha-synuclein'', "Atypical Parkinsonian Syndromes'', "corticobasaldegeneration'', "C reactive protein'', "cerebrospinal fluid'', "dementia with Lewy bodies'', "multiple system atrophy'', "neurofilament light, oligomericαsyn, phosphorylated α –syn'', "tau phosphorylated at threonine 181'', "progressive supranuclear palsy'', "Seeding Amplification Assay'', "t-tau; total tau". The lack of high-affinity α-syn antibodies and ligands may contribute to α-syn's low efficacy as a diagnostic biomarker of APS. Cerebrospinal fluid (CSF) biomarkers reflecting Alzheimer pathology, axonal damage (neurofilament light chain) add valuable diagnostic and prognostic information in the neurochemical characterization of APS. Inflammatoryand microRNAs markers need to be further validated before their clinical use. Seeding Amplification Assays (SAA), despite their high sensitivity and specificity, are at this point used only as a research tool, and they are not quantitative or reflective of disease severity. Biomarker research for early identification and prognosis of APS patients requires multicenter collaboration, validation, and AI-based diagnostics, despite immature biological classification systems.

Keywords Atypical Parkinsonian Syndromes (APS) · Multiple system atrophy (MSA) · Progressive supranuclear palsy (PSP) · Corticobasal degeneration (CBD) · Dementia with Lewy bodies (DLB) · Biomarkers

✉ Anastasia Bougea
abougea@med.uoa.gr

Carlo Colosimo
c.colosimo@aospterni.it

Cristian Falup-Pecurariu
crisfp100@yahoo.co.uk

Giovanni Palermo
palermo.giovanni85@gmail.com

Yildiz Degirmenci
yildiz.degirmenci@kolanhastanesi.com.t

[1] 1st Department of Neurology, Medical School, Eginition Hospital, National and Kapodistrian University of Athens, 11528 Athens, Greece

[2] Department of Neurology, Santa Maria University Hospital, Terni, Italy

[3] Department of Neurology, County Clinic Hospital, Transilvania University Brasov, Brasov, Romania

[4] Center for Neurodegenerative Diseases, Parkinson's Disease and Movement Disorders Unit of Neurology, Department of Neuroscience, University of Pisa, Santa Chiara Hospital, Pisa, Italy

[5] Head of Neurology Department, ISTUN) ZincirlikuyuMedicana Hospital Neurology ClinicParkinson's Disease and Movement Disorders Unit, Istanbul Health and Technology University, Istanbul, Turkey

Introduction

Atypical Parkinsonian Syndromes (APS) are a group of proteinopathies, characterized by the degeneration of the dopaminergic system and other brain neurotransmitter systems (McFarland 2016). Multiple system atrophy (MSA) is characterized by alpha-synuclein (α-syn) aggregates of glial cytoplasmic inclusions (GCIs) affecting the striatonigral, olivopontocerebellar, and central autonomicsystems (Wenning et al. 2022). Progressive supranuclear palsy (PSP) is associated with a 4R-tau protein deposition, predominantly in the basal ganglia, brainstem, and cortical regions (Höglinger et al. 2017). Corticobasal degeneration (CBD) also involves 4R- tau pathology, predominantly in the cortex and basal ganglia (Armstrong et al. 2013). Dementia with Lewy bodies (DLB) is characterized by α-syn pathology, mainly affecting the limbic areas (Colom-Cadena et al. 2013). Although tau pathology has been observed in DLB, the interplay between tau and α-syn is poorly understood at a molecular level. However, the classification of patients according to phenotype does not always allow a precisealignment with pathological diagnosis (Respondek et al. 2019). Disease-specific diagnostic biomarkers are therefore vital in order to enable the early identification of abnormal protein buildup and disease progression.

The "perfect" biomarker would be affordable, non-invasive, highly correlated with the disease process or pharmacological responses to a therapeutic intervention, sensitive, and repeatable (Biomarkers 2001). Cerebrospinal fluid (CSF) may be an appropriate source of biomarkers for the identification and tracking of the pathophysiological processes of APS, but repeated lumbar puncture makes CSF inappropriate for drug monitoring. Blood samples provide OMICS with less invasive biomarkers, that capture complex biological processes (Pasqualotto et al. 2024). However, the use of OMICS in thesebiofluids is generally problematic because of the generalized influence of comorbidities in the properties of these matrices the fact that these biofluids are isolated from the brain.

Current CSF and blood protein biomarkers like α-syn, neurofilament light chains (NFL), amyloid beta with 42 amino acids (Aβ42), total tau(t-tau) protein, and tau phosphorylated at threonine 181(p-Tau 181), lack sufficientspecificity to diagnose MSA and PSPdefinitively (Schirinzi et al. 2018; Laurens et al. 2015; Angelopoulou et al. 2021). Speculative central nervous system (CNS)-enriched extracellular vesicles (EVs), as biological cargos of several cell types, may offer a unique perspective on biological procedures of the brain because of their capacity to cross the blood–brain barrier and enter the peripheral circulation. This would allow the detection of potential biomarkers, but currently with poor diagnostic accuracy (Taha and Bogoniewski 2024). MicroRNAs are stable, tissue-specific molecules that are easier to test with standard laboratory procedures than protein biomarkers, such asreal-time quaking-induced conversion (RT-qPCR). The newly developed Seed Amplification Assay (SAA) for CSF α-syn may be useful for distinguishing between iPD and PSP, but the ability to distinguish MSA from iPD and PSP is still under discussion (Svenningsson 2019; Goolla et al. 2023).

The use of the BIOMARKAPD/ABSI and AT(N) systems for biomarker profiling in cohorts of patients with typical (amnestic) and atypical (non-amnestic) anti-drug resistant disease, including CBD, is of major importance (Molinuevo et al. 2014; Simonsen et al. 2017). Recently, a proposal of biological definition of neuronal α-syn disease through the Neuronal α-synuclein Integrated Staging System (NSD-ISS) relies on biomarkers of synucleinopathy and dopaminergic dysfunction (Simuni et al. 2024). The debate on biological definition of APS and the biomarkers available has sparked further research, even though the clinical definition of APS remains valid.

This comprehensive review explores the potential of fluid biomarker-based systems for APS, focusing on established AD proteins, α-syn, inflammatory cytokines, NFL and microRNAs. We also discuss challenges, limitations, and future directions in APS biomarker research.

Methods

We systematically reviewed articles published during the 2000–2024 period, focusing on fluid biomarker data in APS patients. The PRISMA guidelines for reporting systemic reviews were not adhered to because this is a narrative review rather than a systematic one. We searched PUBMED, SCOPUS and EMBASE from 2000 to 1/1/2024 using the following terms: "Aβ42 amyloid beta with 42 amino acids'', "alpha-synuclein", "Atypical Parkinsonian Syndromes", "corticobasal degeneration", "C reactive protein", "cerebrospinal fluid", "dementia with Lewy bodies", "glial cytoplasmic inclusions", "glial fibrillary acidic protein", "haemoglobin-binding α-syn", "multiple system atrophy", "neurofilament light, oligomericαsyn, phosphorylated α –syn", "tau phosphorylated at threonine 181", "protein misfolding cyclic amplification", "progressive supranuclear palsy", "Seeding Amplification Assay", "t-tau; total tau". Including criteria were original research papers, reviews, and meta-analyses that have been published in peer-reviewed publications in English language. Abstracts and titles were screened as part of the review process following by a full-text evaluation of pertinent research. Data extraction focused on biological fluids, measurement techniques, relevant

conclusions and proposed mechanisms related to fluid biomarkers and APS.

Results

Established AD CSF biomarker profile for APS

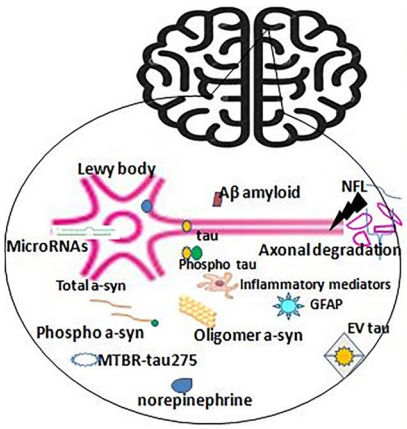
Researchers are developing biomarker classification systems forAlzheimer's disease (AD) to create APS biochemical profiles, including CSF biomarkers ratios, such as t-tau/Aβ42, p-tau/Aβ42 and p-tau/t-tau, as to address the lack of a single specific biomarker (Table 1). Figure 1 shows how these studies can be in distinguishing these syndromes.

Patients with unusual features may be identified by abnormal values in the profile of the AD CSF (e.g. CBS), which is essential for individualized symptom management and accurate stratification of patients in clinical trials (Mitani et al. 1998). However, there are missing data on AT status in several studies(Mitani et al. 1998; Urakami et al. 2001; Süssmuth et al. 2010; Aerts et al. 2011; Nutu et al. 2013; Wagshal et al. 2015; Constantinides et al. 2017; Bougea et al. 2020) (Table 1). Few studies included data on CSF AD biomarker profiling in the PSP. In a large cohort of various neurodegenerative disorders, 10% of patients with PSP had a CSF-AD profile, as measured by an index that included CSF Aβ42 and p-tau values (Schoonenboom et al. 2012). However, the CSF Aβ42 level is not useful to distinguish MSA from other

Table 1 Summary of selected studies of Aβ42, total tau protein and $tau_{p\text{-}181}$ in CSF and plasma of patients with APS providing information about AT(N) status

References	Biological liquid	Sample	Method	CSF or plasma$A\beta_{42}$	CSF or plasma t-tau	CSF or plasma $t\text{-}tau_{p\text{-}181}$
Mitani et al. (1998)	CSF	9 CBD, 12 NC (missing data on AT status)	ELISA	NR	↑ CBD	NR
Urakami et al. (2001)	CSF	10 CBD, 12PSP, 36 C(missing data on AT status)	ELISA	NR	↑ CBD vs PSP	NR
Süssmuth et al. (2010)	CSF	20RS,7PSP-P,25MSA,23PD,20 C(missing data on AT status)	ELISA		↑ MSA vs RS,PD,C	↑ MSA vs RS,PD,C
Aerts et al. (2011)	CSF	21PSP,12 CBS, 28PD(missing data on AT status)	ELISA		↑ CBS vs PSP, C	↑ CBS vs PSP, C
Bech et al. (2012)	CSF	10 MSA, 10 PSP, 11 DLB, 22 PD, 3 PDD,3 CBD(missing data on AT status)	ELISA	↓ in DLB vs all	NS	↔
Hall et al. (2012)	CSF	PD 90, PDD 33, DLB 70, PSP 45,CBD 12, MSA 48, AD48, NC107(missing data on AT status)	Luminex	↔	↑AD vs DLB + PDD	↑AD vs DLB + PDD
Schoonenboom et al. (2012)	CSF	512 AD, 16 CBD, 6 CJD, 52DLB, 20PSP,144 FTLD, 34 VaD, 410 C(missing data on AT status)	ELISA	↓ in DLB vs other groups	↑ DLB	↑ DLB
Nutu et al. (2013)	CSF	90 PD, 32 PDD, 68 DLB, 48 AD, 45 PSP, 46 MSA, 12 CBD(missing data on AT status)	Luminex	↓ in DLB vs other groups	↔	NR
Wagshal et al. (2015)	CSF	37 AD, 24PSP,26 NC(missing data on AT status)	ELISA	NR	↑AD vs PSP, NC	↑ADvs PSP, NC
Constantinides et al. (2017)	CSF	19 PSP, 15 MSA, 17 CBD, 17 PD, 18 C(missing data on AT status)	In house ELISA	↑ CBD vs all	↑ CBD vs all ↑t-tau/$A\beta_{42}$ ratio MSA vs PD	
Schirinzi et al. (2018)	CSF	423PD, 64SWEDD, 196HC(missing data on AT status)		↔	↓PD vs SWEDD,HC	↓ PD vs SWEDD, HC
Bougea et al. (2020)	CSF	30PD,18PDD,29DLB,30HC(missing data on AT status)	In house ELISA	↓ DLB vs PD,PDD,HC	↔	↑ DLB vs PD
Chouliaras et al. (2022)	Plasma	63 AD, 117 PDD/DLB (29 A−, 30 A+, 58 missing data on AT status), 28 FTLD, 19 PSP, 73 C	Simoa digital ELISA	↔ PDD/DLB vs C nor A+ versus A− LBD cases	NR	↔ PDD/DLB vs C nor A+ versus A− LBD cases
Baiardi et al. (2022)	CSF + plasma	59 FTLD, 31PSP, 29 CBS, 49 DLB (31 A−, 18 A+), 97 AD, 67 C	CSF: CLEIA Plasma: Simoa digital ELISA)	NR	NR	CSF: ↑ in DLB and CBS A+ vs A- Plasma: ↑ in A+ versus A− DLB cases

A+ amyloid, *AD* Alzheimer's disease, *CBD* corticobasal degeneration, *CJD* Creutzfeldt–Jakob disease, *CLEIA* chemiluminescent enzyme immunoassays, *CSF* cerebrospinal fluid, *DLB* dementia with Lewy bodies, *FTLD* frontotemporal dementia, *HC* healthy controls, *MSA* multiple system atrophy, *NC* normal control, *NR* Non reported, *PD* Parkinson's disease, *PDD* Parkinson's disease dementia, *PSP* progressive supranuclear palsy, *SWEDD* Scans without evidence of dopaminergic deficit, *VaD* vascular dementia



Fluid biomarkers included in the Present review	PSP	CBS	MSA	DLB
CSF or blood amyloid/tau/phospho-tau MTBR-tau275/t-tau /EV tau)	Unhelpful	Positive if AD pathology underlies the CBS	Unclear value	Positive or negative
CSF or blood a-syn (total/phospho/oligomer/Hb-α-syn	Unclear value	Unclear value	Unclear value	Unclear value
CSF or blood NFL	Unclear value	Unclear value	Predictive value	Unclear value
CSF or blood inflammatory mediators	Unclear value	Unclear value	Unclear value	Unclear value
SAA assays in CSF	Usually negative	Usually negative	Usually positive	Usually positive
Plasma norepinephrine	Unhelpful	Unhelpful	for MSA vs. isolated autonomic failure sensitivity: 82%–100%, specificity: 75%–100%	Unhelpful

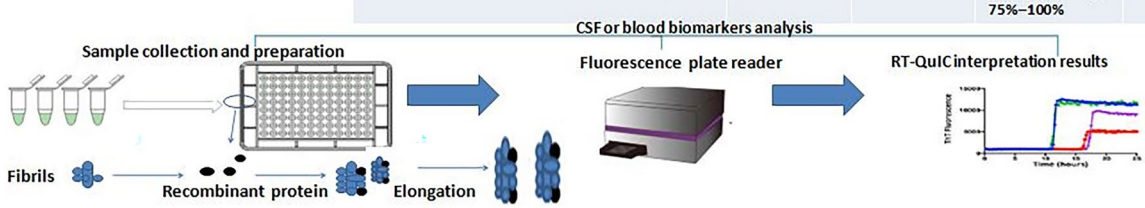


Fig. 1 Synopsis of fluid biomarkers in APSs that can be detected in CSF and blood (plasma/serum/erythrocytes/extracellular vesicles) and which of them has proven potent in distinguishing these syndromes. Experimental design and the multi-analysis workflow of RT-qPCR, including the sample collection and preparation, multiplatform analysis of, and data interpretation. *APS* atypical Parkinsonian syndromes, *EV* extracellular vesicles, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy, *CBD* corticobasal degeneration, *DLB* dementia with Lewy bodies, *RT-qPCR* real-time quaking-induced conversion

parkinsonian disorders or to control. Higher t-tau/Aβ42 ratio may distinguish MSA from PD with high specificity but suboptimal sensitivity (Constantinides et al. 2017). A percentage of 20% of CBS patients harbored a CSF AD profile. One study by Aerts et al. (2012) reported an higher t-tau/Aβ42 ratio in CBS compared to PD patients and controls, and a lower p-tau/t-tau ratio compared to control subjects. In CBS, most research failed to reveal a discernible difference between CBS and MSA patients or controls with regards to CSF p-tau levels (Noguchi et al. 2005; Hall et al. 2012). The third study concluded that a typical CSF-AD profile was observed in approximately 30 percent of CBS patients, with increased t-tau and reduced Aβ42 in the CBS group (Constantinides et al. 2017). When the CBS patients with a CSF profilein AD were excluded, these differences disappeared, suggesting that the admixture of AD patients was responsible for these differences (Paraskevas et al. 2019).

Unlike CBD without these biomarkers, CSF with MTBR-tau275/t-tau or MTBR-tau282/t-tau can identify CBD patients with up to 83 percent accuracy, regardless of clinical syndromes (such as CBS, bvFTD, and PSP-RS) (Horie et al. 2022). Although classified as a 4R tauopathies, CSF MTBR-tau275/t-tau and MTBR-tau282/t-tau were specifically reduced in CBD and FTLD-MAPT but not in PSP. This might be because PSP patients may show a greater variation in the level of pathology burden in the neocortex than CBD patients and most patients with FTLD-MAPT.

AD blood biomarker profile for APS

Importantly, the recent validation of ultrasensitive biomarker quantification techniques (e.g. digital immunoassays) for AD have made it possible to assess AD core biomarkers in the blood, with very encouraging results for possible future blood-based diagnostics (Table 1). Conversely, blood Aβ and tau protein levels showed relatively small or no changes in LBD studies (Chouliaras et al. 2022; Baiardi et al. 2022) (Table 1). In fact, blood Aβ42/40 levels in LBD were found to be unaffected. The lower levels of Aβ42 or Aβ40 in APS compared to PD and HCs may help differentiate APS from PD and HCs, supporting their earlier identification (Chen et al. 2024; Li et al. 2022). The pathophysiology of AD in APS may be associated with a decreased in plasma or serum Aβ42 levels (Robinson et al. 2018). However, a recent meta-analysis suggested that Aβ42 does not distinguish between APS, PD, and healthy controls (Cong et al. 2021). Existence of Aβ-positive controls in a healthy control group, where approximately onethird of the Aβ-positive pathology has been documented in some earlier studies (Huang et al. 2023), may help to explain these results.

In the PSP group, the plasma EV 3R/4R tau ratios were correlated with clinical, neurological and cognitive signs severity; low plasma ratios indicated increased severity of the disease (Chatterjee et al. 2024) and could potentially be used as a marker of progression and as a surrogate for clinical trials. EV 3R/4R tau ratios also can additionally discriminate patients with ALS and PSP from healthy controls and patients with neurodegenerative diseases with high diagnostic accuracy (AUC > 0.91).

Alpha-synuclein as biomarker in APS

Several studies have examined on total CSF α-syn as a potential MSA biomarker. Researchers initially focused on total CSF α-syn as a candidate biomarker for synucleinopathies. However, the focus has shifted over time to the phosphorylated (p) and oligomeric (o) forms of α-syn, as post-translational alterations in α-syn seem to be driving neurodegeneration (Beyer and Ariza 2013). The following section provides an overview of the CSF α-syn studies in APS (Table 2).

Total CSF α-syn in APS

Several studies measured total CSF α-syn in MSA, most of which reported a slight decrease in total α-syn levels compared with control subjects (Mollenhauer et al. 2011). However, there is significant overlap between MSA and healthy subjects in the levels of α-syn, which makes CSF alpha-syn not a clinically useful biomarker for the detection of MSA (Aerts et al. 2012). No significant differences were reported when MSA was compared with other synucleinopathies, CBS and PSP (Shi et al. 2011). A comparative study reported that CSF α-syn showed that high positive predictive value for PD, MSA, and DLB, indicating that clinical studies stratified patients (Mollenhauer et al. 2011). Another approach is measure panels of multiple biomarkers for the identification of composite biomarkers (Magdalinou et al. 2015; Tateno et al. 2012; Spies et al. 2009; Mollenhauer et al. 2008). In these cohorts,the total α-syn was significantly decreased in all synucleinopathies, but no independent distinction between the different synucleinopathies could be made.

Phosphorylated and oligomeric CSF α-syn in APS

Wang et al. (2012) found that the total and phosphorylated levels of CSF α-syn were decreased in MSA, PD, PSP, AD, and control subjects compared to controls. The PD group had increased phosphorylated α-syn levels whereas MSA patients had decreased phosphorylated α-syn levels (Brudek et al. 2017; Li et al. 2020). The phosphorylated/total α-syn ratio was significantly increased in both groups. However, these α-syn forms were not useful in differentiating PD from MSA or MSA and PD from CBD and PSP (Constantinides et al. 2021; Tokuda et al. 2010) (Table 2). Another study found a lower total α-syn and higher phosphorylated to total ratio of α-syn in MSA compared to tauopathy (Yamasaki et al. 2019). Foulds et al. (2012) found that MSA had higher mean values for total, oligomeric and phosphorylated α-syn levels, suggesting that this α-syn form of MSA may be a candidate biomarker.

Plasma/serumα-syn in APS

Studies of plasma t-α-syn in patients with MSA show non-significant increases compared with control groups and significant differences between groups (Lee et al. 2006; Seino et al. 2019). A significant increase was observed only in MSA-P patients (Sun et al. 2014). However, there is considerable variability within the MSA group. Plasma or serum t- α- syn was not useful distinguishing between MSA, DLB, PSP, CBD or both groups of patients in the control group (Seino et al. 2019; Schulz et al. 2021; Wang et al. 2019; Singh et al. 2019), whereas the levels of autoantibodies against t-α–syn should be taken in account for interpretation of these results (Maetzler et al. 2011; Folke et al. 2021). Table 2**.** summarized selected studies of α-syn in serum and plasma in patients with APS and Fig. 1 showed how powerfulthese studies may be in discriminating these syndromes **.**

A-syn in erythrocytes, exosomes in APS

Extracellular vesicles (EVs) with α-synhave been investigated as potential peripheral biomarkers in APS. A meta-analysis suggested that the combined concentration of α-syn in speculative neuronal and oligodendroglial EVs may be higher in patients with PD than healthy controls (Taha and Bogoniewski 2024). Plasma levels of Neuronal derived exosomes (NDE) were higher in PD than in MSA or control.NDE ratio significantly correlated with UPDRS part III scores for MSA-P (Ohmichi et al. 2019).Oligodendrocyte-derived exosomes (ODE) did not correlate with disease duration or severity in MSA-C but did correlate in MSA-P (Ohmichi et al. 2019). However, more evidence is needed to confirm the role of NDEs in APS.

Zhang et al. (2022) measured haemoglobin-binding α-syn (Hb-α-syn) in erythrocytes in a large cohort of MSA patients, demonstrating that Hb-α-syn could be a good surrogate marker of brain α-syn accumulation. Dutta et al. (2021) measured the total amount of α-syn in neuronal and oligodendroglial exosomes showed that patients with MSA had a significantly elevated amount of α-syn, especially in

Table 2 Summary of selected α-syn CSF and plasma/serum studies of patients with atypical parkinsonism

References	Biofluid	Sample	Method	A-Syn type	Main outcomes
Mollenhauer et al. (2008)	CSF	PD8, DLB38, AD13, CJD8,13 C	ELISA	t-α-syn	↓DLB + PD vs AD, CJD,C
Spies et al. (2009)	CSF	40DLB, 131 AD, 28 VaD,39 FTD	ELISA	t-α-syn	↔
Tokuda et al. (2010)	CSF	1o cohort (all analytes): 32PD, 28 C 2o cohort (o-asyn): 25PD, 35 AD, 18PSP, 43 C	ELISA	t-α-syn o-α-syn o-α-syn: t-α-syn ratio	↓t-α-syn: trend PD ↑o-α-syn + ratio in PD
Mollenhauer et al. (2011)	CSF	51PD, 55DLB, 29MSA, 62 AD, 76 NC	ELISA	t-α-syn	↓AD > DLB > MSA > PD vs NC
Shi et al. (2011)	CSF	Discovery cohort: 126PD, 32MSA, 50 AD, 137 C Validation cohort: 83 PD	Luminex	t-α-syn	↓PD, vs AD + C
Hall et al. (2012)	CSF	PD90, PDD33, DLB70, PSP45,CBD12, MSA48, AD48, NC107	Luminex	t-α-syn	↓AD > DLB + PDD > PD + MSA vs C, AD and PSP
Aerts et al. (2012)	CSF	PD58, MSA47, DLB3, VaD22, PSP 10, CBD2	ELISA(Ab 211/ FL-140)	t-α-syn	↔
Foulds et al. (2012)	CSF	38PD, 16DLB, 8MSA, 20HC	ELISA	t-α-syn	↔
Tateno et al. (2012)	CSF	11PD, 6DLB, 11MSA, 9 AD, 11 C	ELISA	t-α-syn	↓PD, DLB, MSA vs AD + C
Wang et al. (2012)	CSF	Discovery cohort: 83PD, 14MSA, 30PSD, 25 AD,51HC Validation cohort: 109PD, 20MSA, 22PSP, 50 AD, 71 HC	Luminex	t-α-syn p-α-syn p-α-syn: t-α-syn ratio	↓t-α-syn σε PD + MSA vs C ↑ α-Syn ratio σε PD vs C, PSP
Wennström et al. (2013)	CSF	38PD, 22PDD, 33DLB, 46 AD, 52HC	ELISA	t-α-syn	↓PDD > PD > DLB vs AD + HC
Magdalinou et al. (2015)	CSF	31PD, 33PSP,14 CBS,31MSA,26 AD,16 FTD, 30HC	ELISA	t-α-syn	MSA < HC
Constantinides et al. (2017)	CSF	19 PSP, 15 MSA, 17 CBD, 17 PD, 18 C	In house ELISA	t-α-syn	
Bougea et al. (2020)	CSF	30 PD, 19 PDD, 29DLB, 30HC	In house ELISA	t-α-syn	DLB > HC > PDD > PD
Constantinides et al. (2021)	CSF	13PD, 9MSA, 13PSP,9 CBD,51 AD, 26 FTD, 14 VD	ELISA	t-α-syn pS129-α-syn pS129-α-syn to t-α-syn ratio o-α-syn	o-α-syn, pS129-α-syn: ↔ pS129-α-syn/α-syn ratio:PD, MSA > other groups
Lee et al. (2006)	Plasma	105PD, 38MSA, 51HC	ELISA	t- α -syn	↑PD, vs MSA, HC
Maetzler et al. (2011)	Serum	14DLB + 31HC		t- α -syn	↑serum autoantibody levels against t- α -syn in DLB

Table 2 (continued)

References	Biofluid	Sample	Method	A-Syn type	Main outcomes
Sun et al. (2014)	Plasma	74MSA, 90HC	ELISA	t- α -syn	↑MSA, vs HC
Wang et al. (2015)	Oligomer	100PD, 22MSA,102 C	ELISA	RBC t- α -syn	↑RBC α-syn oligomer/ total protein MSA vs C
Brudeck et al. (2017)	Plasma	18MSA, 41HC	ELISA + MSD	pS-α-syn	↓ MSA
Folke et al. (2019)	Plasma	34MSA + 59HC	In house ELISA	t- α -syn	↔
Seino et al. (2019)		22PD,15MSA, 8 CBD, 14PSP	ELISA	t- α -syn	↔
Singh et al. (2019)	Serum	34MSA + PSP + 68HC	SPR	t- α -syn	↑MSA, PSP vs HC
Liu et al. (2019)	Oligomeric	77MSA, 133HC	ELISA	t- α -syn	↑MSA, vs HC
Bougea et. (2020)	Serum + plasma	29DLB + 18PDD + 30HC	ELISA	t- α -syn	↑DLB vs HC
Wang et al. (2019)	Serum	20MSA + 19PSP + 60HC	IMR	t- α -syn	↔
Li et al. (2019)	RBC	33PD + 114MSA + 334 C	ELISA	RBC t- α -syn oligomer	↔ MSA vs PD
Li et al. (2020)	RBC	107MSA, 220HC	ELISA	pS- α -syn-RBC	↓ MSA vs C
Folke et al. (2021)	Plasma	28MSA, 43PD, 15 C	ELISA	t- α -syn	↓ MSA vs C
Dutta et al. (2021)	Plasma, serum, oligodendroglial exosomes	51PD, 30MSA, 50 HC	IMR	Exosomal, t- α -syn	↑ α-syn serum/a-syn plasma MSA, neuronal α-syn PD vs MSA, oligodendroglial exosomal α-synMSAvsPD, HC
Schulz et al. (2021)	Serum	151PD + 17 MSA + 38PSP + 16 CBS + 45DLB + 20HC	ELISA	t- α –syn	↔ PSP vs HC
Stuendl et al. (2021)	Plasma	50PSP + 50DLB + 41HC	MSD	t- α –syn, EV α -syn	↔ PSP vs HC
Jiang et al. (2021)	Serum	88 CBD + 116PSP + 191HC	MSD	Exosomal α –syn	↔ PSP, CBD vs HC
Zhang et al. (2022)		149MSA, 149HC	ELISA	Hb-t- α -syn	↑ MSA vs HC (71.8% sensitivity, 80.5% specificity)
Cristiani et al. (2024)	RBC	8PSP + 19PD + 18HC	ELISA	Total, oligomeric, and p129-α-syn	RBC total a-syn ↑ PSP vs PD, HC

AD Alzheimer's disease, *CBD* corticobasal degeneration, *CJD* Creutzfeldt–Jakob disease, *CSF* cerebrospinal fluid, *DLB* dementia with Lewy bodies, *EV* extravesicular, *IMR* ultra-sensitiveimmunoassayutilizingimmunomagneticreduction, *HC* healthy controls, *FTD* frontotemporal dementia, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy, *p-α-Syn* phosphorylated-α-Synuclein, *SNCA t-α-Syn* total -α-Synuclein, *SPR* Real-time label-free surface plasmon resonance VaD, ↔ without statistically significant differences between groups

oligodendroglial exosomes. Liu et al. (2019) quantified total and oligomericα-syn in erythrocyte membranes and cytoplasm, and found that MSA patients had increased total and oligomericα-syn compared to controls, while no differences were observed in other study (Li et al. 2019). Li et al. (2020) focused on erythrocyte phosphorylated-α-syn as a candidate biomarker for MSA, resulting in 70% sensitivity and 90% specificity for diagnosis of MSA. Wang et al. (2015) focused on oligomericα-syn quantification in red blood cells (RBC), but this ratio did not provide sufficient diagnostic precision for distinguishing MSA from PD or control groups. So far, exosomalα- syn cannot distinguish PSP or CBS from controls (Jiang et al. 2020).For the first time, Cristiani et al. (2024) observed increased levels of total α-syn in erythrocytes in patients with PSP patients compared to both patients with PD and HC. This suggests that a significant part of the protein buildup may be the normal form resulting from neuronal transmission.

Seeding assays as promising tool in APS

CSF α-syn SAA was studied as a possible alternative to traditional CSF analysis. The main strengths of this biomarker are: (i) the possibility of distinguishing between different

synucleinopathies, as the assay can distinguish between the neuronal α-synuclein pathology characteristic of Lewy bodies disorders (PD and DLB) and the pathology associated with the predominantly glial inclusions of MSA; (ii) may be able to discriminate between synucleinopathies and tauopathies, although further optimization is warranted; (iii) it may be possible to use the test for quantitative purposespossibly providing prognostic information, taking into account the SAA kinetics.

Shahnawaz et al. (2020) implemented a seeding assay (protein misfolding cyclic amplification—PMCA) in CSF of MSA and PD patients. Using different amyloid-conformity-specific dyes, the detection of α-syn PMCA in CSF samples is easily distinguished from PD and MSA (95% sensitivity), by differences in the conformations of the α-syn strains in these disorders. Similarly, Rossi et al. (2020)applied RT-QuIC in 172 CSF samples of MSA, DLB, PD, iRBD, and PAF. Only two of 31 MSA patients exhibited seeding activity in this assay, supporting the current view that are intrinsic differences between the conformational strains MSA and LBD. SAA had a sensitivity of 95.3% and specificity of 98% for detecting the presence of the α-syn in different LBDs. RT-QuIC assay for MSA was moderate sensitive (75%), with differences in reaction kinetics compared to PD (longer T50 and lower Vmax) (Poggiolini et al. 2022). Reaction kinetics predicted progression of disease only in the MSA group.

Another approach to biomarker identification is to use composite markers including > 1 biomarker. This dual approach of the α-syn PMCA and CSF NFL differentiated MSA from controls (NFL) andPD/DLB (PMCA) (Singer et al. 2020). It is noteworthy that almost all MSA were reactive to the alpha-syn PMCA but with different kinetics of reaction (MSA showed an earlier but significantly lower fluorescence compared to LBD).

The same approach was followed by another study group, combining α-syn RT-QuIC with CSF and plasma NFL (Quadalti et al. 2021). RT-QuIC produced a positive seeding reaction in 3/65 MSA patients. The RT-QuIC kinetic curves in MSA patients differed significantly from the corresponding PD curves (significantly lower relative fluorescent units). The combined use of the α-syn RT-QuIC and NFL further optimized the MSA-PD differentiation.

However, promising results were obtained by combining the seeding activity and immunoprecipitation assays for concentrate α-syn seeds. Okuzumi et al. (2023) combined immunoprecipitation (IP), in an attempt to concentrate α-syn seeds from serum, followed by real-time quaking-induced conversion (RT-QuIC) assay (IP/RT-QuIC), in a cohort of MSA, PSP/CBD, DLB. The serum αS-SAA can accurately distinguish patients with PD and DLB from those without PD or DLB. Interestingly, the assay was less successful in MSA, probably due to the lower concentrations of α-syn seeds in the blood of MSA patients (Fig. 1).

In PSP, Vaughan et al. (2024) confirmed the high frequency of primary 4RT pathology at post-mortem and diagnostic consistency time, as previously shown (Respondek et al. 2017); therefore, a positive SAA of PD type is very unlikely to reflect cases with major PD pathology. A high incidence of Lewy body co-pathology was observed in post-mortem PSP investigations (Jecmenica Lukic et al. 2020). On the other hand, a recent study found that that 4 out of 16 (25%) PSP CSF samples were positive for PD-type SAA comparable to the proportion of Lewy body co-pathology (22%) in a smaller postmortem PSP cohort. Interestingly, older patients with PSP may have a higher prevalence of PD co-pathology, suggesting that age-related proteostatic dysfunction contributes to the accumulation of multiple co-pathologies (Robinson et al. 2018). The rate of Lewy body co-pathology observed in CBD in previous neuropathological studies (10%) was lower than the positive rate in SAA. This suggests that the CBS group may include a mix of patients with primary 4-repeat tau pathology (PSP or CBD) and co-pathology with Lewy body, as well as patients with clinically misdiagnosed primary PD pathology, which may explain the higher rate of positive SAA. On the other hand, it might suggest that the specificity of α-synSAAin CBD patients is insufficient. The positivity of the α-synSAA in PSP and CBS is of relevance because it provides an early indication that co-pathology with PD may worsen the severity and rate of disease progression, which differs from the earlier clinicopathological studies.

The novel Amprion's SAAmplify-αSYN Biomarker Test provides a breakthrough, by consistently and reproducibly distinguishing MSA from other synucleinopathies (Ma et al. 2024). This study classifies synuclein seeds based on fluorescence levels: Type 1 seeds, linked to PD, DLB, and idiopathic REM sleep behavior disorder (iRBD), exhibit high fluorescence, while Type 2 seeds, associated with MSA, display intermediate fluorescence. Conducted across seven medical institutions in four countries, the study achieved 100% agreement with the gold standard of pathology for brain tissue and pathology-confirmed CSF samples, the diagnosis of these participants is probably very accurate, and the novel synSAA reached 95% sensitivity for PD and IRBD, and 95% specificity for healthy controls, confirming the clear detection of the disease-associated biomarker. In line with their anticipated underlying Lewy body pathology, type 1α-syn seeds were found in all samples from synSAA-positive patients with PD and IRBD. Research showed higher specificity for type 2 seeds in people with MSA than in real-life cohorts, most likely because follow-up subjects showed better concordance between clinical diagnosis and neuropathology.These results underscore synSAA's potential for high-accuracy patient stratification, differential diagnosis, and early detection of MSA.

Neurofilament light chain (NFL)

Neurofilament light chain (NFL) is a non-specific marker of neuroaxonal damage, but there are only a few studies in APS. CSF NFL levels were significantly elevated in the MSA and PSP groups compared to PD patients (Bech et al. 2012), with some overlap between PSP/MSA and PD (Holmberg et al. 1998). NFL levels correlated with disease progression in APS. A later study involving a CBS group confirmed these results and further established NFL as a useful marker for distinguishing PD from APS. Moreover, NFL remained unaltered in subsequent analyses, suggesting a stable axonal injury rate in APSs (Constantinescu et al. 2010). These results have been replicated in the follow-up studies comparing MSA with PD (Chelban et al. 2022) and PSP with synucleinopathies (Oliveira Hauer et al. 2023). CSF NFL levels in PSP and MSA patients are significantly higher than in controls, suggesting that this may be a biomarker for monitoring of APS progression, to be used in trials of new disease-modifying therapies (Angelopoulou et al. 2021).

When neurons are damaged or degenerated, NfL are released into the CSF can be detected in the blood, which makes them a potential biomarker for APS. Our recent meta-analysis reported higher CSF and blood NfL levels in APS patients compared to PD patients, with a high diagnostic accuracy in discriminating between the two groups (Angelopoulou et al. 2021). These results suggest that NfL may be a useful biomarker to help distinguish APS from other parkinsonian disorders. The Parchi's group developed assays using plasma NfL with a sensitivity and specificity of nearly 90 percent that can distinguish between individuals with PD and those with MSA, PSP, and APS. These results were similar to those obtained with CSF NfL (Quadalti et al. 2021). The longitudinal study by Donker et al. (2018) found that higher levels of serum NfL were associated with a more rapid decline in gait and postural instability in patients with PSP, suggesting that NfL may be predictive of future mobility disorders in these patients. By stratifying patients based on NfL levels, clinicians could potentially better tailor treatment strategies and provide patients and their families with more accurate prognostic information.

Supine plasma norepinephrine as biomarker in MSA

In addition to increased plasma or CSF NfL, the updated MDS criteria also suggested supine norepinephrine as supportive MSA biomarker but not a requirement for MSA diagnosis (Wenning et al. 2022). To distinguish between MSA and PD, supine plasma norepinephrine levels have been employed. In MSA, supine norepinephrine levels are relatively unaffected, whereas in PD, decreased levels are reported. Notwithstanding this, it is noteworthy that the test has high specificity but low sensitivity. The most sensitive and specific indicator in predicting phenoconversion to MSA in individuals with isolated autonomic failure is supine norepinephrine > 100 pg/mL (Singer et al. 2017). More evidence is needed to demonstrate their utility as biomarkers to formally qualify for the MDS criteria.

General inflammatory markers

Although the time relationship between neuroinflammation and neurodegeneration is complex, it is now clear that neuroinflammation is involved in APS pathogenesis (Balistreri and Monastero 2023). Elevated levels of inflammatory markers were found in MSA patients compared to healthy controls, including tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-1beta (IL-1β) (Brodacki et al. 2008; Kaufman et al. 2013; Starhof et al. 2018; Compta et al. 2019), suggesting a role for neuroinflammation in disease pathogenesis. Kim et al. (2019) reported no difference between MSA and controls in serum levels of IL-1β, IL-2, IL-6, IL-10, TNF-α, or high-sensitivity C reactive protein (CRP). Inflammatory processes contribute to the progression of disease and clinical symptoms in PSP (Starhof et al. 2018). Increased CRP, TNF-alpha, IL-1-beta, IL-4, and IL-6 wereobserved in the comparison of the PSP and PD (Starhof et al. 2018). CSF analysis revealed a significant increase in microglialderived cytokines in PSP (Hall et al. 2018).

Neuroinflammatory protein YKL-40 is increased in neurodegenerative diseases such as AD, and frontotemporal lobar degeneration (Llorens et al. 2017; Wennström et al. 2015). Individuals with PD and MSA had considerably lower CSF YKL-40 levels than those with PSP and CBD (Olsson et al. 2013). In addition, this study did not show any increase in YKL-40 in CSF during the prodromal phase of DLB compared to cognitively normal controls (Morenas-Rodríguez et al. 2019). Despite not recommended as a CSF biomarker for DLB, it may be useful for the evaluation of the concurrent AD pathology in DLB patients. The discovery of generic inflammation markers is sensitive and non-specific, but it is hoped that they can be used in combination to create a model that can be used.

Glial fibrillary acidic protein (GFAP) in APS

Astrocytes, the main cell type in the CNS, contain a medium- sized protein called glial fibrillary acidic protein (GFAP). When astrocytes are damaged, they release the products of the GFAP and GFAP breakdown into the CSF and serum. Its presence highly specific to the source of intracranial insult (Lotankar et al. 2017). Therefore, higher levels in MSA compared to controls and its breakdown products indicate astrocytic damage but are not statistically significant (Brouillette et al. 2015; Santaella et al. 2020).

Although non-significant, the increase in GFAP in CSF in PSP patients indicates abnormal disease progression, astrogliosis is only one of the steps in the pathogenesis of APS (Süssmuth et al. 2010).

MicroRNAsin APS

Non-coding RNAs, such as microRNAs, long non-coding RNAs, and circular RNAs (circRNAs), are gaining emphasis in addition to messenger RNAs (mRNAs), which make up 1–2% of the human transcriptome. This is because these RNAs are stable in biological liquids and play regulatory roles in transcription, splicing, and translation, which makes them potential APS transcription biomarkers (Bougea 2022).

MicroRNAs in MSA

Ubhi et al. (2014) studied the microRNA profiles in transgenic MSA muscle models and MSA patients and showed significant miRNA dysregulation. They found that miR-96 complex has been modified and that increased miR-96 expression was observed. These findings are consistent with a recent study conducted by Vallelunga et al. (2021). The same authors found (Vallelunga et al. 2014) that the target genes for SLC1 A1 and SLC6 A6 mRNA and protein levels were decreased, while the miR-96 expression was increased. Vallelungaet al. (2014) found 12 novel miRNAs in the serum of MSA, PD, and healthy controls, nine of which showedincreased MSArelated expression compared to healthy controls. Functional analysis revealed associations with fatty acid metabolism, prion disease, and NOTCH signaling which are thought to be involved in demyelination of oligodendrocytes.

Uwatoko et al. (2019) reported conflicting findings, with miR-671-5p, miR-19b-3p, and miR-24-3p being DE in MSA and PD, but miR-24-3p was downregulated in MSA. Marques et al. (2017)demonstrated that the cerebellar striatum is a good source of miRNAs in PD, MSA, and healthy controls. An intriguing discovery was the correlation between cerebellar ataxia and miR-24 and miR-148b in MSA patients, indicating a potential role for these miRNAs in the cerebellar degeneration observed in MSA patients. Valera et al. (2017) showed showed a significant increase in let-7b and miR-101, a decrease in miR34c, and a tendency to increase miR-30a, miR-96, and miR-183 in the striatum of an MSA-P patient. In vitro studies have confirmed this theory by showing that α-Syn accumulation and the lack of autophagy were caused by overexpression miR-101 in CG-4 oligodendroglial cells. Conversely, anti-miR-10 reduced the accumulation of α-syn in oligodendroglial cells and increased autophagy in cell and mouse models (Bai et al. 2017). Increased miR-96 levels agree with Ubhi et al. findings and RAB5 A plays a role in the classification of intracellular vesicles in autophagy (Table 3).

MicroRNAs in PSP

Only three studies are available on microRNAs and PSP. Using the TargetScan method, Smith et al. (2011) have shown that miRNAs can control tau protein splicing, affecting the tau 4R:3R ratio. In PSP patients, miR-132, miR-132*, and miR-212 were downregulated, while miR-9, miR-124, miR-137, and miR-132 reduced tau protein levels. In conclusion, alterations in the miR132/PTBP2 pathway might be a factor in the aberrant tau protein exon 10 attachment to these patients'brains. Further analysis of PTBP2 and miR-132 in iPSC neural cells derived from patients with PSP may provide insight into the role of miRNAs in the pathophysiology of PSP (Table 4). Tatura et al. (2016) found that PSP represses target genes for miR-147a and miR-518e. The results of Smith et al., showed that themiR-132 expression was significantly lower in the temporal, parietal, and prefrontal regions of the brains of eight patients with PSP as compared to eight healthy controls; however, due to the smalle sample size, this difference was not statistically significant. These findings imply that miRNAs regulate the overexpression of neurotoxic proteins, which plays a role in the pathogenesis of PSP. Nonaka et al. (2022) assessed CSF miRNA expression levels in 11 PSP patients and eight age-matched healthy controls. The most significantly elevated or downregulated miRNAs in the early-onset of PSP were miR-204-3p, miR-873-3p, and miR-6840-5p. These findings suggest that miRNAs regulate the overexpression of neurotoxic proteins that contribute to the pathogenesis of PSP.

Research suggests miRNA transcriptomics could be a useful biomarker for APS, but lacks standardized detection and multi-center initiative. Future studies may require large-cohort research including CBD patients.

Challenges and limitations

Hypothesis-free proteomic methods, also referred to as "omics," (such as genomics, proteomics, and metabolomics) begin by looking for patterns in typically large-scale data analytics and attempting to link those patterns with biological states in combination with predictive modeling (Krassowski et al. 2020). Attempts to understand the pattern begin when it is, to identify the patterns of up-regulation and down-regulation of genes that arelinked to specific cellular physiological pathways not begin until the pattern has been identified (Tables 4 and 5). This type of methodology has been made feasible by the technical capacity to gather and analyze vast amounts of data, but it has also produced a large

Table 3 Overview of microRNAs in MSA patients

Author	Sample	Biological liquid/tissue	Method	Upregulated miRNAs	Downregulated miRNAs
Vallelunga et al.	25PD, 25MSA,25HC	Serum	TaqMan low density array	miR-24, miR-29c, miR-148b, miR223*, miR-324-3p, miR-483-5p, miR1274 A, miR-1274B andmiR-1291	miR-339-5p, miR-652, and miR-744
Marques et al.	28PD, 17MSA,28HC	CSF	RT-qPCR	miR-19a, miR-19b, miR-24, and miR34c	NS
Ubhi et al.	Patients: 3MSA,3 AD, 3DLB,3 CBD, 3PSP,4HC	Human + mice frontal cortex	RT-qPCR	miR-96, miR-182, and miR-183	
Wakabayashi et al.	13MSA,13HC	Formalinfixed paraffinembedded MSA sample	miRCURY LNA Array	In Pons (miR-1290, miR-21-5p, miR30b-5p, miR-4428, miR-23a-3p). In cerebellum (miR-4428, miR4732-5p, miR-1290, miR-3619-3p, miR4725-3p)	In Pons (miR-128-3p, miR-371b-3p, miR3928-3p, miR-1915-3p, miR-129–2-3p, miR1203, miR-584-5p, miR-1910-5p, miR-675- 5p, miR-149-5p, miR1233-3p, miR-3173-5p, miR-1539, miR-513a5p, miR-3663-5p, miR4723-3p, miR-4739, miR-4440, miR-1909- 5p, miR-129-5p, miR330-5p, miR-572, miR4632-3p, miR-940, miR-1231, miR-124-3p, miR-34a-5p, miR-210-3p, miR-4687-5p, miR127-3p, miR-138-5p, miR-379-5p, and miR219a-5p). In cerebellum (miR-4739, miR-4726-3p, miR1228-3p, miR-346, miR-134-5p, miR-1233- 3p, miR-484, miR-138- 5p, miR-132-3p, miR3663-5p, miR-4440, miR-3184-5p, miR-557, miR-3907, miR-129-5p, miR-219a-2-3p, miR129-1-3p and miR-129-2-3p)
Valera et al.	17MSA,7HC	Striatum	RT-qPCR	miR-183, miR-30a, miR-96, let-7b and miR-101	miR-34c

Table 3 (continued)

Author	Sample	Biological liquid/tissue	Method	Upregulated miRNAs	Downregulated miRNAs
Kume et al.	5MSA-P,5MSA-P,10HC	Serum	Microarray	miR-16, miR451, miR-103a, miR223, miR-486- 5p, miR-107, miR25, miR-3135b, miR15b, miR-185, miR939, miR-92a, miR4298, miR-92b, let-7c, miR-17, miR-4693-3p, miR-130a, let7 d, let-7i, miR484, miR-4791, miR522, miR-26a, let7b, miR-3605-3p, miR-30 d, miR4434, miR-4281, miR106a, miR-3667-3p, miR-99a, miR24, miR-221, miR31, miR-1285, miR218-2, let-7a, miR27a, miR-20a, miR518a-3p, miR19b, miR-10b, miR377, miR-4698, miR186, miR-126, miR1303, miR-500b, miR3622a-5p, mr3139	miR-4325, miR-380, miR3912, miR-4661-3p, miR4795-3p, miR-4458, miR3155, miR-590-3p, miR147b, miR-4439, miR378i, miR-3939, miR4495, miR-526b, miR548z, miR-3183
Lee et al.	4MSA,4HC	Cerebellumpost-mortem	Microarray	miR-202 and miR199a-5p	miR-129-3p, miR-129-5p, miR-337-3p, miR-380, miR-433, miR-132, miR410, miR-206, and miR409-5p
Uwatoko et al.	Study set: 11 MSA, 6 HC Validation set: 31 MSA-C, 30 MSA-P, 28 PD, 28 HC	Plasma	3D-Gene® Human miRNA oligo chip Ver. 17.0 (1720 miRNAs)	Study set: MSA vs. HC: miR-371b-5p, miR-4708-3p, miR-4736, and miR-663a) Validation set: miR-19b-3p στηνPD	Study set MSA vs. HC: 75 miR-NAs Validation set: miRNAs NS MSA vs.HC. MiR-671-5p ⬇ in PD vs. MSA-P; miR-24-3p ⬇ in MSA-C vs. PD
Starhof et al.	Pilot cohort: 10 MSA, 10 PD, 10 HC, 10 PSP Validation cohort: 29 MSA, 37 PD, 32 PSP, 23 HC	CSF, EDTA, plasma	Pilot study: Exiqon miRCURY PCR Panel I version IV (372 miRNAs) Validation study: Fluidigm Biomark RTqPCR system (46 miRNAs)	All patient group CSF: let-7b-5p, miR-106b5p, miR-184, miR-218-5p, miR-331-5p, miR-34c-3p, miR-7-5p, and miR-99a-5p Plasma: miR-218-5p, miR574-3p, miR-191-5p, miR30c-5p, and miR-873-3p	
Vallelunga et al.	51 PD,52 MSA,56HC	Serum	qRT-PCR	MSA vs. HC: miR-96-5p PD vs MSA: miR-339-5p	MSA vs. HC: miR-339-5p

Table 3 (continued)

Author	Sample	Biological liquid/tissue	Method	Upregulated miRNAs	Downregulated miRNAs
Perez-Soriano et al.	Discovery set: 7MSA-C,13MSA-P, 19PD,40HC Validation set: 8MSA-C,12MSA-P, 18PD,40HC	Serum	GeneChip miRNA 4.0 array (2,025 miRNA). FC > 11.51 $p < 0.05$	hsa-mir-16-5p, hsa-mir-191-5p, hsa-mir-24-3p, hsa-mir-7641, hsa-let-7b-5p, hsa-mir-425-5p, hsa-mir-23a-3p, hsa-mir-93-5p, hsa-mir-122-5p, hsa-mir-103a-3p, hsa-mir-4530, hsa-mir-17-5p, hsa-mir-140-3p, hsa-mir-106a-5p, hsa-mir-107, hsa-mir-25-3p, hsa-mir-7704, hsa-mir-181a-5p, hsa-mir-4487	hsa-mir-6797-3p, hsa-mir-940, hsa-mir-6796-3p, hsa-mir-3648, hsa-mir-1225-5p, hsa-mir-3197

CSF cerebrospinal liquid, *EDTA* ethylenediaminetetraacetic acid, *HC* Healthy control, *MSA* Multiple system atrophy, *NS* non significant, *PD* Parkinson's disease, *P-MSA* Parkinsonian variant of Multiple system atrophy, *C-MSA* Cerebellar variant of Multiple system atrophy, *SN* Substantia nigra, *PSP* Progressive supranuclear palsy, *qRT-PCR* Real-Time Quantitative Reverse Transcription

number of false positives; seemingly solid findings with great statistical significance are typically not reproducible. The lack of clinically used "omics" markers might be due to the fact that these technologies are still in their infancy and the lengthy period of time it takes for a biomarker to be validated and clinically established hasn't passed yet (Oldoni et al. 2022). However, it's possible that this study methodology is just ineffective as a firstpass strategy and will need significant additional refinement.

Longitudinal studies on fluid biomarkers, particularly for CSF, are limited, particularly for patient stratification in future APS drug trials (Magdalinou et al. 2015). Conflicting results from different techniques, such as isolating RNA and exosomes, and downstream miRNA detection, quantification, and normalization, make it difficult to accurately distinguish patients with RBD from MSA from healthy controls (Taha and Bogoniewski 2024). Blood contamination during lumbar puncture and hemolysis during sample collection and processing also pose challenges (Simonsen et al. 2017).The α-syn RT-QuIC is a rather robust SAA regarding the effect of preanalytical variables since only blood contamination and adding detergentmay significantly influence the outcome (Mammana et al. 2024). Therefore, blood contamination should be excluded by cytological routine testing and, as previously recommended for biomarker studies, the first 2 mL of CSF collected should not be used where contamination is most likely to occur, as contamination in the blood that impacts the assay kinetics is not always visible by visual inspection. The number of positivereplicates in serially diluted CSF samples improved the discrimination between samples with high and low seedingactivity, and the time to threshold (LAG) was the most reliablekinetic parameter in multiple- test conditions (Mammana et al. 2024).

The lack of antibodies and ligands with high affinity for α-syn contributes to the poor efficacy of the α-syn as a diagnostic marker for APS. Innovative methods such as strain-specific assays (SSAs) have been developed for the detection of strain-specific α-syn in CSF and tissue samples. However, SAAs in MSA lack specificity in detecting α-syn aggregates, and there is a lack of standardization in experimental protocols and techniques (van Rumund et al. 2019). Additionally, the limited availability of post-mortem brain tissue in MSA may further limit research on α-syn aggregates in MSA (Magalhães and Lashuel 2022). In the same line, the connection between CSF and brain MTBR-tau antemortem was hampered by the absence of complementary techniques to detect brain tau pathology in living individuals (such as tau PET imaging with a tracer unique to primary tauopathies).

Future directions

APSs area rare fatal neurodegenerative disorders without cure. The difficulty in effectively managing these diseasesis

Table 4 Overview of microRNAs in PSP patients

Authors	Sample	Biological fluid/tissue	Method	Upregulated miRNAs	Downregulated miRNAs
Smith et al.	8PSP, 8HC	Human temporal, parietal and prefrontal lobes	RT–PCR	ns	miR-132 (and their cluster miR-132, miR132* and miR-212)
Tatura et al.	40PSP, 40HC	Human inferior frontal gyri	qRTPCR	miR-147 (miR-147a) and miR-518e	miR-132
Nonaka et al.	11PSP, 8HC	CSF	3D-Gene 3000 miRNA microarray	hsa-miR-204-3p, hsa-miR-4476, hsa-miR-6132, hsa-miR-4638-5p, hsa-miR-7110-5p, hsa-miR-3679-5p, hsa-miR-1236-5p, hsa-miR-6867-3p, hsa-miR-6761-3p, hsa-miR-423-5p, hsa-miR-7111-3p, hsa-miR-3156-3p, hsa-miR-12114, hsa-miR-6889-5p, hsa-miR-6740-3p, hsa-miR-885-5p, hsa-miR-6894-3p, hsa-miR-487b-5p, hsa-miR-6820-5p, hsa-miR-873-3p, hsa-miR-7109-3p, hsa-miR-5193, hsa-miR 4648, hsa-miR-10398-5p,hsa-miR-1825,hsa-miR-6870-5p,hsa-miR-6825-5p, hsa-miR-4700-3p, hsa-miR-3622a-3p, hsa-miR-5001-5p, hsa-miR-6510-5p, hsa-miR-4505, hsa-miR-4665-5p, hsa-miR-8485, hsa-miR-7110-3p, hsa-miR-6862-3p, hsa-miR-6886-3p, hsa-miR-328-5p	hsa-miR-6840-5p

CSF cerebrospinal liquid, *HC* healthy control, *MSA* multiple system atrophy, *ns* non significant, *PSP* Progressivesupranuclear palsy

not only attributed to the incomplete knowledge of neuropathogenesis, but the lack of diagnostic methods such as specific biomarkers. Recent advances in fluid biomarkers offer promising possibilities for detecting MSA at earlier stages, allowing for timely intervention and treatment. For example, CSF biomarkers such as α-syn and NfL have the potential to distinguish MSA from other neurodegenerative diseases with higher accuracy. Although these biomarkers have great promise to improve diagnosis and treatment, their implementation in clinical practice requires overcoming a number of challenges. First, standardised protocols and guidelines for the collection and analysis of biomarker data should be established to ensure their reliability and consistency across different health care settings.In addition, health professionals will need adequate training and resources to accurately interpret biomarker results and to integrate them effectively into patient care plans. Collaborative efforts between researchers, clinicians and industry partners will also be essential to develop and validate biomarker tests for diagnosis and monitoring of APSs. Despite these challenges, the integration of fluid and imaging biomarkers into clinical practice may ultimately improve the accuracy and effectiveness of MSA diagnosis and treatment, leading to improved outcomes and quality of life for patients.

Promising novel molecules are in mid-stage development. ATH434, an alpha-synuclein inhibitor, is expected to secure approximately 30% of the total MSA market across the 7 major markets (United States, Germany, France, Italy, Spain, the United Kingdom, and Japan), by 2034. Insights from ongoing assessments, like those involving ATH434, underscore the potential of these markers to detect iron accumulation in specific brain regions, advancing both early diagnosis and the development of targeted therapeutic approaches.In an observational research, total free and oligomericα-synucleinwere evaluated to see if MSA patients had higher levels of oligomericα-synuclein than controls (NCT01485549). Furthermore, TRACK-MSA, an observational research, is being conducted in MSA patients to identify alterations in CSF and plasma biomarkers, such as α-synuclein, aggregated α-synuclein, Nfl, Tau/phosphorylated Tau in CSF, and plasma Nfl (NCT04450992). When combined, the aforementioned biomarkers have the potential to be both diagnostic and prognostic, provided that the clinical studies yield some trustworthy profiles. Although significant progress has been made on biomarker discovery for MSA, three recent observational clinical studies are underway to demonstrate the biomarker profiles across the synucleinopathies (NCT05453058, NCT05638815, NCT05699460). These

advancements aim to enhance the precision and efficacy of MSA clinical research and management strategies. Moreover, advancements in omics technologies, such as proteomics and metabolomics, offer the opportunity to identify novel biomarkers and pathways involved in MSA pathogenesis, paving the way for personalized medicine approaches and targeted therapies.

Research on biomarkers for APS has made significant progress, but more needs to be done to ensure consistency and effectiveness. Standardization and validation studies are needed to verify the diagnostic and prognostic effectiveness of biomarkers in various patient populations. Longitudinal studies are required to identify inflammatory biomarkers that reflect specific neuropathological processes in MSA, PSP, CBD, and DLB. Fluid biomarkers could aid in differential diagnosis, predicting disease progression, identifying therapeutic targets, and assessing disease-modifying therapies efficacy. In vivo biomarkers, such as CSF SAAs, can help distinguish atypical parkinsonism and advance our understanding of the disease (Coughlin et al. 2022). By addressing the technical challenges and limitations of SAAs in MSA, researchers can improve the sensitivity and specificity of these assays, enhance the reproducibility of results, and establish a standardized protocol for studying α-syn aggregates in MSA. To evaluate the positive and negative predictive values of both assays, it will be crucial to integrate the testing of α-syn and 4-repeat tau SAAs across the APSs. Assessing fluid biomarker and neuropathological correlates of AD co-pathology, their influence on the course of the illness, and their correlation with common genetic variations of interest, such as MAPT and APOE4 status, will also be crucial.In doing so, SAAs may offer new opportunities for developing targeted therapies and diagnostic tools for this devastating neurodegenerative disorder.

Advanced technologies such as next-generation sequencing (NGS), and liquid biopsies are expected to become commonplace in normal clinical settings as the diagnostics industry shifts toward more integrated and tailored approaches over the course of the next five to ten years. Artificial intelligence (AI) may revolutionizethe conventional statistical analysis of atypical parkinsonism biomarker data, allowing a broader number of variables and outcomes. Deep learning offers benefits like accurate classification, similar analysis to experts, personalized networks, and improved performance (Kanatani et al. 2022). More studies are needed to confirm these results. Regulatory bodies are modifying their criteria to accommodate cutting-edge methods that surpass conventional methods as the need for individualized treatments increases. Traditional diagnostic techniques should pave the avenue for faster more precise, and noninvasive testing alternatives that allow for real-time patient health monitoring.

Conclusion

Redefining APS based on biology is crucial, but current classification criteriaare still based mainly on clinical features. Although they have been confirmed as indicators for AD, emerging diagnostic techniques including CSF tau, total tau (t-tau), and phosphorylated tau (p-tau) are not consistently changed in PSP. Glial fibrillary acid protein (GFAP) and CSF/serum neurofilament light chain (NfL) are arguably the most important biomarkers being researched for distinguishing APS from PD and from one another.Translating biomarker research into clinical practice of APS requires multicentercollaboration, validation, and AI based diagnostics.

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Data availability The data supporting the results of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest relevant to this work.

Ethical approval The authors confirm that neither the approval of an institutional review board nor patient consent was required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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