

Review

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Review

Autoimmune Encephalitis and Paraneoplastic Neurological Syndromes with Progressive Supranuclear Palsy-Like Manifestations

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Abstract: Advances in diagnostic procedures have led to an increasing rate of diagnosis of autoimmune encephalitis or paraneoplastic neurological syndrome (AE/PNS) among patients with progressive supranuclear palsy (PSP)-like manifestations. The antibodies involved in these conditions include anti-IgLON5, -Ma2, and -Ri antibodies, each of which has a characteristic clinical presentation. The steps in the diagnosis of AE/PNS in patients with PSP-like manifestations include (i) suspicion of AE/PNS based on clinical presentations atypical of PSP and (ii) antibody detection measures. Methods used to identify antibodies include a combination of tissue-based assays and confirmatory tests. The primary confirmatory tests include cell-based assays and immunoblotting (line or western blot). Treatments can be divided into immunotherapy and tumor therapies, the former of which includes acute and maintenance therapies comprising corticosteroids, intravenous immunoglobulins, plasmapheresis, rituximab, and cyclophosphamide. One of the major challenges of diagnosis is that existing reports on PSP-like patients with AE/PNS include only case reports, with the majority discussing antibodies other than anti-IgLON5 antibody. As such, more patients need to be evaluated to establish the relationship between antibodies and PSP-like manifestations.

Keywords: progressive supranuclear palsy; autoimmune encephalitis; paraneoplastic neurological syndrome

1. Introduction

Progressive supranuclear palsy (PSP), first described by Steele, Richardson, and Olszewski in 1964, typically presents with vertical supranuclear gaze palsy and repeated falls within 3 years. This disease is characterized by a resistance to levodopa therapy and a more rapid progression than Parkinson's disease [1,2]. Diagnosis is currently made using the Movement Disorder Society clinical diagnostic criteria for PSP (MDS-PSP) [3]. Although the detailed pathophysiology is unclear, the accumulation of abnormal forms of the microtubule-associated protein tau plays an important role [4].

Recently, the importance of autoimmune encephalitis (AE) and paraneoplastic neurological syndrome (PNS) as mimics of Parkinsonian syndromes, including PSP, is being increasingly recognized [5,6]. The pathogenesis of AE/PNS is thought to be divided into two types: humoral and cellular immunity-driven [7]. Pathogenic autoantibodies are present in disorders predominantly caused by humoral immunity. Autoantibodies can also exist in many cellular immunity-mediated cases, although most are considered secondary occurrences without pathological significance. Over the past decade, advances in antibody identification techniques, such as cell-based assays (CBA), immunoprecipitation methods, and protein microarrays, have led to the discovery of many novel autoantibodies that can cause AE/PNS, some of which have been associated with symptoms and signs that imitate PSP.

As AE/PNS can be treated with immunotherapies and tumor therapies, clinicians should differentiate between these conditions. In this review, we discuss the following topics: (i) the

antibodies causing PSP-like manifestations and (ii) the diagnosis and management of diseases associated with these antibodies.

2. Methods

We performed a narrative review of articles searched from the PubMed database (search date: Jun 18, 2024) using the following search string: ((progressive supranuclear palsy[MeSH Terms] OR "progressive supranuclear pals*" [Title/Abstract] OR PSPRS[Title/Abstract] OR "Richardson* syndrome"[Title/Abstract] OR "progressive gait freezing"[Title/Abstract] OR "pure akinesia with gait freezing"[Title/Abstract]) AND (antibod*[Title/Abstract] OR autoantibod*[Title/Abstract] OR immunolog*[Title/Abstract] OR autoimmune*[Title/Abstract] OR immune*[Title/Abstract] OR neoplas*[Title/Abstract] OR paraneoplas*[Title/Abstract])) AND ((english[Language]) OR (japanese[Language])). The inclusion period was unlimited. A total of 334 articles matched the search criteria, from which 37 case reports, case series, clinical studies, reviews, and basic research articles regarding AE/PNS causing PSP-like manifestations were selected. Furthermore, an additional 32 articles were identified by manual searching and referring to bibliographies.

3. Autoantibodies Related to AE/PNS Mimicking PSP

3.1. Overview of Autoantibodies Mimicking PSP

Since the early 2000s, a series of AE/PNS patients with PSP-like phenotypes have been reported (Table 1). The most discussed condition resembling PSP is anti-IgLON5 disease, a disorder associated with the anti-IgLON5 antibody, with ten patients with PSP-like manifestations examined in one case series [8]. The second most notable condition is associated with anti-Ma2 and anti-Ri antibodies. Although actual patients resembling those with PSP have been discussed only in case reports, clinical studies have shown that symptoms and findings can be somewhat similar to those of PSP. In addition to these antibodies, one case report presented a patient mimicking PSP with each of the following antibodies: anti-CV2/collapsin response mediator protein 5 (CV2/CRMP5), anti-dipeptidyl-peptidase-like protein 6 (DPPX), anti-Hu, and anti-leucine-rich glioma-inactivated 1 protein (LGI1). Uncharacterized antibodies and anti-NH2 terminus of alpha-enolase antibodies have also been detected in AE/PNS-mimicking PSP [9–12].

To suspect an association between these antibodies in patients presenting with PSP-like manifestations, it is important to understand the typical symptoms and signs related to the antibodies, as well as their differences from those of PSP, a neurodegenerative disease. The following sections summarize the topics related to each antibody.

Table 1. Summary of previously published cases of PSP-like patients due to AE/PNS.

Author	Year	Related autoantibody	Sample	No. of patients	Age	Sex	Progression pattern	Associated tumor	Atypical features other than the progression pattern	Abnormal CSF findings	Immunotherapies and/or tumor therapies	Outcome
Dash et al.	2016	CV2/CRMP5	Serum, CSF	1	65	M	Subacute	SCLC	Weight loss (10 kg over 6 months) and T2 hyperintensity of the basal ganglia in MRI	Cells	IVIG, and chemotherapy	Effective
Tobin et al.	2014	DPPX	Serum (CSF analysis also performed, but results unavailable)	1	36	F	NA	None	Diarrhea, weight loss (45 kg), dysgeusia, and myoclonus	NA	Corticosteroids	Not effective
Ohyagi et al.	2017	Hu	Serum	1	57	M	Subacute	SCLC	T2 hyperintensity in the extreme capsule on MRI	Proteins	IVIG, chemotherapy, and radiotherapy	Not effective
González-Ávila et al.	2020	IgLON5	CSF	1	66	M	Chronic	None	Facial myokymia and myorhythmia, hypersomnia, sleep-related breathing disorder, and MRI without typical PSP appearance	NA	Not done	NA
Gaig et al.	2021	IgLON5	Serum (CSF analysis also performed, but results unavailable)	10	Median: 62 (44-71)	M=7 F=3	Chronic	NA	Mild downward GP (6), sleep dysfunction (3), limb ataxia (3), OH (1), vocal cord palsy (2), respiratory failure (2), limb stiffness with spasms (1), chorea (1)	NA	NA	NA
Berger-Sieczkowski et al.	2023	IgLON5	CSF	1	67	M	Chronic	None	Prominent bulbar symptoms, severe dysphagia with vocal	Normal	Not done	NA

									cord paresis, and nocturnal stridor with severe hypoxemic episodes			
Vogrig et al.	2021	KLHL11	NA	1	79	M	NA	None	Weight loss (9 kg over 2 months), hypersomnia, and T2 hyperintensity of the mesial temporal region in MRI	Cells, proteins, and OCB	IVIG and corticosteroids	Not effective
Hierro et al.	2020	LGI1	Serum	1	60	M	Subacute	None	Parinaud's syndrome, and MRI without typical PSP appearance	Cells and proteins	IVIG, corticosteroids, and RTX	Effective
Adams et al.	2011	Ma1, Ma2	Serum	1	55	M	Subacute	Tonsillar carcinoma	Narcolepsy with cataplexy, diplopia	Proteins	Corticosteroids, cyclophosphamide	Effective
Sankhla et al.	2024	Ma2	Serum	1	49	F	Subacute	Breast cancer	None	OCB	Corticosteroids, and RTX	Effective
Inoue et al.	2012	NAE	Serum	1	63	F	Subacute	None	No rigidity in the neck, extremity edema, arthralgia, and MRI without typical PSP appearance	Cells and proteins	Corticosteroids	Effective
Takkar et al.	2020	Ri	Serum, CSF	1	45	F	Subacute	Breast cancer	Leg spasticity, and MRI without typical PSP appearance	Normal	IVIG, and chemotherapy	Temporarily effective
Borsche et al.	2019	Sez6l2	Serum	1	55	F	Subacute	None	Prominent cerebellar ataxia and MRI without typical PSP appearance	Normal	IVIG and RTX	Effective
Kannoth et al.	2016	Uncharacterized abs	NA	1	66	M	Subacute	None	MRI without typical PSP appearance	Proteins	Corticosteroids	Effective
Dale et al.	2018	Uncharacterized abs	CSF	1	72	M	Subacute	None	None	Proteins and OCB	IVIG and corticosteroids	Not effective

Abbreviations: antibodies, abs; cerebrospinal fluid, CSF; CV2/collapsin response mediator protein 5, CV2/CRMP5; dipeptidyl-peptidase-like protein-6, DPPX; gaze palsy, GP; intravenous immunoglobulin, IVIG; Kelch-like protein 11, KLHL11; leucine-rich glioma-inactivated 1, LGI1; magnetic resonance imaging, MRI; not applicable, NA; NH2 terminal of alpha-enolase, NAE; oligoclonal band, OCB; progressive supranuclear palsy, PSP; rituximab, RTX; small cell lung cancer, SCLC.

3.2. Anti-IgLON5 Antibody

3.2.1. Summary of Anti-IgLON5 Antibody

IgLON5 is a cell surface antigen primarily expressed in the brain tissue, which is related to the development and formation of neural networks [13]. Anti-IgLON5 disease manifests as low-risk (10-15%) tumor association. Related tumors include breast, thyroid, and kidney cancers [13]. Approximately 75% of the cases have a chronic course, while the remaining 25% have an acute or subacute course. Typical patients have a combination of the following symptoms: (1) bulbar symptoms, (2) sleep disturbances, (3) movement disorders (primarily gait disturbance, generalized chorea, and craniofacial dyskinesias), (4) neuromuscular symptoms (primarily fasciculations, weakness, and stiff-person syndrome), (5) cognitive decline, (6) gaze palsy and blepharoptosis, and (7) autonomic dysfunctions [14]. In suspicious cases, the anti-IgLON5 antibody was measured by CBA. Both serum and cerebrospinal fluid (CSF) analyses are sensitive [15]. Immunotherapies are occasionally successful, with response rates ranging from 10-60% [15–18].

3.2.2. Anti-IgLON5 Antibody Associated with PSP-like Manifestations

Three key points regarding anti-IgLON5 antibodies must be addressed:

First, the associations between PSP-like syndromes and anti-IgLON5 disease have been discussed more frequently than those with other antibodies [8,19]. There is one case series study conducting a case-by-case analysis of patients with PSP-like manifestations only in this disease [8]. In this study, twenty-seven patients with anti-IgLON5 disease had movement disorders as the main symptom. Ten of the 27 patients presented with signs and symptoms of PSP. Nine patients resembled PSP-Richardson syndrome, whereas one resembled PSP-corticobasal syndrome. All patients had a chronic disease course, with a median time to diagnosis of 96 months. Atypical features of PSP included minimal downward gaze palsy and prominent sleep disturbances, including abnormal behavior, limb ataxia, orthostatic hypotension, and stridor due to vocal cord paralysis.

Second, the probability of patients clinically diagnosed with PSP testing positive for anti-IgLON5 antibodies is very low. In one study of 33 patients clinically diagnosed with PSP, Mangesius et al. reported that not a single patient tested positive for anti-IgLON5 antibodies. [20] Sabater et al. showed that only one of 32 patients with PSP tested positive for anti-IgLON5 antibodies [18], suggesting that it is impractical to measure IgLON5 antibodies in all patients clinically diagnosed with PSP.

Third, anti-IgLON5 antibodies may cause tau pathology [21]. Growing evidence had indicated that these antibodies frequently cause 3-repeat and 4-repeat tauopathy in the later stages, which is considered a secondary phenomenon [14]. Moreover, 4-repeat tauopathy was also found to be present alone, in a patient with tufted astrocytes mimicking PSP; however, these features were reported only in a single patient [22]. In this patient, the only finding considered atypical of PSP was the presence of neurofibrillary tangles and neuropil threads in the synaptic glomeruli of the cerebellar cortex.

3.3. Anti-Ma2 Antibodies

3.3.1. Summary of Anti-Ma2 Antibody

Ma2 is an intracellular antigen that is normally expressed in the brain tissue, and there is an important isoform called Ma1. Notably, in most cases where autoantibodies are pathogenic, anti-Ma2 antibodies alone or both anti-Ma2 and -Ma1 antibodies are positive. Anti-Ma1 antibodies are rarely detected alone.

Diseases associated with the anti-Ma2 antibody are at a high risk (>75%) of tumor co-existence, which primarily includes testicular tumors and non-small cell lung cancer (NSCLC) [23]. Typical clinical presentations include subacute limbic encephalitis (e.g., amnesia, seizures, and disturbance of consciousness), brainstem encephalitis (e.g., oculomotor dysfunction, dysarthria, dysphagia, and

Parkinsonism), and narcolepsy [24]. In suspected patients, anti-Ma2 antibodies can be measured by immunoblot [25–27]. The response to immunotherapy and tumor treatment is moderate, and may be superior to that of other diseases associated with antibodies against intracellular antigens. Dalmau et al. showed that 14 of 17 patients treated with tumor treatment (nine of whom were also treated with immunotherapy) improved, while four of 10 patients receiving only immunotherapy responded [24].

3.3.2. Anti-Ma2 Antibody Associated with PSP-like Manifestations

There have been two case reports describing actual PSP-like patients in detail, while one clinical study has shown that at least some of the manifestations caused by anti-Ma2 antibodies can masquerade as PSP. In the two existing case reports, the first patient was a 55-year-old male with no tumors or subacute progressive disease. Unlike PSP, the patient also exhibited elevated protein levels in the CSF and narcolepsy with cataplexy [28]. Sankhla et al. also reported a case of a 49-year-old woman with breast cancer with a subacute course and positive CSF-specific oligoclonal bands, which are atypical features of PSP [29]. Immunotherapy was effective in both of these patients. In another study containing 38 patients with symptoms associated with the anti-Ma2 antibody, 12 had vertical gaze palsy, 12 had excessive daytime sleepiness, five had unsteady gait or mild ataxia, and three had parkinsonism [24].

3.4. *Anti-CV2/CRMP5 Antibody*

3.4.1. Summary of Anti-CV2/CRMP5 Antibody

The anti-CV2/CRMP5 antibody recognizes CRMP5, an intracellular antigen [30] primarily expressed in the brain and spinal cord whose functions include neuronal migration, axonal guidance, and dendritic growth.

Regarding diseases associated with anti-CV2/CRMP5 antibodies, tumors coexist at a high risk (>80%), and frequently include thymoma and SCLC [31]. This condition typically occurs in a subacute fashion, manifesting as encephalomyelitis (a term that should only be used to describe patients presenting with multiple neurological manifestations including limbic encephalitis, brainstem encephalitis, cerebellar degeneration, myelitis, sensory neuronopathy, and chronic gastrointestinal pseudo-obstruction [31,32]), neuropathy (primarily asymmetric polyradiculoneuropathy), chorea, or ocular manifestations (mainly optic neuritis, retinitis, and uveitis) [30,33–35]. When suspected, immunoblotting can be performed for antibody detection. The effects of immunotherapy and tumor treatment are limited [30,35].

3.4.2. Anti-CV2/CRMP5 Antibody Associated with PSP-like Manifestations

Only one case report has yet discussed the relationship between anti-CV2/CRMP5 antibody and PSP [36]. A 65-year-old man with SCLC had subacute onset of the disease, with PSP-like symptoms and signs, including vertical supranuclear gaze palsy, bradykinesia, rigidity, postural instability, and personality change. Symptoms not typically present in PSP include a weight loss of 10 kg over 6 months and T2 hyperintensity in the basal ganglia on magnetic resonance imaging (MRI). Intravenous immunoglobulin (IVIG) and chemotherapy were effective.

3.5. *Anti-Hu Antibody*

3.5.1. Summary of Anti-Hu Antibody

Anti-Hu antibodies act against intracellular antigens belonging to the Hu family, particularly embryonic lethal abnormal vision like 4 (ELAVL4), which is primarily expressed in the brain and plays a role in the binding and stabilization of mRNA. Diseases associated with anti-Hu antibodies are at high risk (85%) of tumor co-existence, most commonly SCLC [31]. The typical clinical presentations include subacute sensory neuropathy, limbic encephalitis, and cerebellar ataxia. Immunotherapy and oncological therapy are only partially effective [37].

3.5.2. Anti-Hu Antibody Associated with PSP-like Manifestations

To date, only one patient with PSP-like symptoms has been reported [38]. This patient was a 57-year-old man with SCLC who had a subacute disease course. His symptoms, also common in PSP, included supranuclear vertical gaze palsy, whereas the symptoms atypical of PSP included T2 hyperintensity in the extreme capsule on MRI and elevated protein and IgG index in the CSF. The patient was treated with IVIG, chemotherapy, and radiotherapy, all of which were ineffective.

3.6. *Anti-Ri (ANNA-2) Antibody*

3.6.1. Summary of Anti-Ri Antibody

The anti-Ri antibody binds to two intracellular antigens, the neuro-oncologic ventral antigens (NOVA) 1 and 2, which are expressed in tissues throughout the body, and are involved in the regulation of the alternative splicing of pre-mRNAs. Diseases related to anti-Ri antibodies are commonly associated with tumors (> 70 %), of which breast cancer is the most frequently observed, followed by lung cancer (including NSCLC and SCLC) [31]. They show a female predominance. Historically, anti-Ri antibody was known as the causative antibody of opsoclonus-myoclonus syndrome (OMS); however, it subsequently became clear that this antibody is associated with a variety of clinical manifestations. The typical presentation is subacute and stepwise or chronic and progressive cerebellar ataxia (which is the most common), oculomotor dysfunction, opsoclonus with/without myoclonus, spasticity, dystonia, and parkinsonism [39]. Immunotherapy and tumor therapy have limited benefit [39,40].

3.6.2. Anti-Ri Antibody Associated with PSP-like Manifestations

Although only one case report described an actual patient with PSP, a larger case series showed that signs and symptoms of the disease associated with anti-Ri antibodies can also occur in PSP, at least in part [39]. In one review of 36 patients, six presented with parkinsonism (bradykinesia and rigidity) and five presented with supranuclear gaze palsy or ophthalmoplegia. Because this disease tends to cause cerebellar ataxia, it is also a differential diagnosis in patients with PSP and cerebellar ataxia (PSP-C).

One exemplar case report presented the case of a 45-year-old woman with breast cancer [41] who presented with subacute progression of PSP-like manifestations, including gait bradykinesia, gait freezing, dysphagia, urinary urgency, complete external ophthalmoplegia (both horizontally and vertically), and axial rigidity. However, symptoms were atypical for PSP as the patient also presented with leg spasticity with no MRI abnormalities characteristic of PSP. The patient was treated with IVIG and chemotherapy; however, the treatment efficacy was only temporary.

3.7. *Anti-Kelch-like Protein 11 (KLHL11) Antibody*

3.7.1. Summary of Anti-KLHL11 Antibody

KLHL11 is an intracellular antigen expressed in tissues throughout the body and is associated with ubiquitination. Diseases associated with the anti-KLHL11 antibody have a high risk (80%) of association with tumors, the most common being germ cell tumors (mainly teratomas and seminomas). Most patients are male, and typical clinical presentations include acute or subacute cerebellar ataxia and brainstem encephalitis [42,43]. Antibodies can be detected using CBA. Immunotherapy and tumor treatments have limited efficacy [43].

3.7.2. Anti-KLHL11 Antibody Associated with PSP-like Manifestations

One case report described a 79-year-old man without tumors [44]. The typical symptoms of PSP include hypersomnia, micrographia, vertical gaze palsy, gait instability, and a tendency to fall backward. Non-PSP-like signs included high signal intensity in the medial temporal region on MRI, and pleocytosis and elevated protein levels in the CSF. Corticosteroids and IVIG are ineffective.

3.8. *Anti-DPPX Antibody*

3.8.1. Summary of Anti-DPPX Antibody

DPPX is a cell surface antigen expressed predominantly in the brain tissue. Its functions include binding to the voltage-gated A-type Kv4.2, which regulates channel gating and participates in somatodendritic signal integration [45,46]. Patients with diseases associated with anti-DPPX antibodies rarely (10%) have tumors [31]. Common symptoms include subacute to chronic weight loss, gastrointestinal dysfunction, cognitive/mental disorders, and CNS hyperexcitability [47]. Immunotherapy is effective to some extent. One case series and literature review showed that 23 of 39 patients treated with immunotherapy showed marked improvement, nine showed incomplete improvement, three showed no change, and four died [48].

3.8.2. Anti-DPPX Antibody Associated with PSP-like Manifestations

One case report showed that a 36-year-old woman with a 5-year disease course initially misdiagnosed with PSP presented with diarrhea, weight loss (-45 kg), dysgeusia, and myoclonus [49]. Corticosteroid therapy was found to be ineffective.

3.9. *Anti-LGI1 Antibody*

3.9.1. Summary of Anti-LGI1 Antibody

LGI1 is a cell surface antigen primarily located in the brain. One of its functions is to bind voltage-gated potassium channels (VGKCs) in the presynaptic membrane to α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) in the postsynaptic membrane via disintegrin and metalloproteinase domain-containing protein 22 (ADAM22), ADAM23, and postsynaptic density 95 (PSD95). When this binding function is impaired, AMPARs are transported extrasynaptically [50].

Diseases associated with anti-LGI antibodies are associated with a low risk (10%) of tumors, while the types of tumors vary [51,52]. The typical clinical presentation is subacute, in which faciobrachial dystonic seizures are followed by limbic encephalitis, cognitive decline, and seizures (mainly focal). These patients commonly develop hyponatremia. Immunotherapy is effective in most cases [50,53].

3.9.2. Anti-LGI1 Antibody Associated with PSP-like Manifestations

PSP-like syndromes have been discussed in only one prior case report [54] of a 60-year-old male with no concomitant tumors who complained of subacute neurological deterioration. Frequent falls, abnormal optokinetic responses with absent vertical saccades, impaired executive function, and rigidity are common in patients with PSP. In contrast, atypical symptoms and signs of PSP include Parinaud syndrome, no radiological changes in PSP, and CSF with pleocytosis and elevated protein levels. Treatment with IVIG, corticosteroids, and rituximab (RTX) were effective.

3.10. *Anti-Sez6l2 Antibody*

3.10.1. Summary of Anti-Sez6l2 Antibody

Sez6l2 functions as a cell surface antigen in the cerebellum, binds to AMPARs on neuronal synaptic membranes, and maintains intracellular signaling [55]. Tumor involvement is not adequately known; however, in one case series of four patients, one had an ovarian tumor [56]. Patients usually have subacute progressive cerebellar ataxia and Parkinsonism. Immunotherapies are ineffective and the efficacy of tumor therapy is unknown.

3.10.2. Anti-Sez6l2 Antibody Associated with PSP-like Manifestations

One patient with PSP-like symptoms, particularly PSP-C, was reported in a case report [57]. This patient was a 55-year-old woman with no tumors who presented with subacute strong postural instability, mildly slurred speech, and ataxia resembling PSP-C. Subacute progression ruled out the presence of PSP-C. IVIG and RTX therapies were unsuccessful.

4. Diagnosis of AE/PNS Mimicking PSP

4.1. Suspecting AE/PNS Mimicking PSP

AE/PNS should be suspected in patients with atypical PSP manifestations (Table 2). The key diagnostic clues are as follows: young age of onset (< 40 years of age), acute or subacute disease course, coexisting neoplasms, CSF abnormalities (elevated protein, pleocytosis, increased IgG index, and positive CSF-specific OCB), and brain MRI with no findings typical of PSP (e.g., atrophy of the midbrain tegmentum or superior cerebellar peduncle). It is also important to note the characteristic findings of each antibody, which include significant sleep disorders, behavioral manifestations, respiratory failure, and orthostatic hypotension in anti-IgLON5 disease; narcolepsy in the presence of anti-Ma2 antibody; and diarrhea and severe weight loss in diseases associated with anti-DPPX antibody [6].

Table 2. Clinical features that suggestive of AE/PNS mimicking PSP.

- | |
|---|
| 1) Younger age of onset (<40 years of age) |
| 2) Acute or subacute progression |
| 3) Concurrent neoplasms |
| 4) Abnormal CSF (i.e. elevated protein, pleocytosis, increased IgG index, and positive CSF-specific OCB) |
| 5) No MRI findings suggestive of PSP |
| 6) Antibody-specific manifestations atypical for PSP (i.e. significant sleep disorder, behavioral alterations, respiratory failure, orthostatic hypotension for anti-IgLON5 antibody; narcolepsy for anti-Ma2 antibody; and diarrhea and severe weight loss for anti-DPPX antibody) |
| 7) Other symptoms and signs much less common in PSP |

Abbreviations: autoimmune encephalitis or paraneoplastic neurological syndromes AE/PNS, cerebrospinal fluid; CSF, dipeptidyl-peptidase-like protein-6; DPPX, magnetic resonance imaging; MRI, oligoclonal band; OCB, progressive supranuclear palsy; PSP, progressive supranuclear palsy.

4.2. Confirmation of Diagnosis

4.2.1. General Considerations

Laboratory assessment is the final step if an AE/PNS mimicking PSP is suspected. This can be achieved in two steps: a tissue-based assay (TBA) and a confirmatory test. One of two different confirmatory tests can be performed, depending on the target antibodies. One is CBA, and the other is immunoblotting. Although the results of a TBA and a confirmatory test should essentially be concordant, if this is not the case, the sensitivity and specificity of each test must be considered [31,58–61].

In addition to laboratory results, it is often necessary to confirm that the clinical course is typical [31,62]. However, the number of reported patients with AE/PNS mimicking PSP is not sufficiently large to establish these PSP-like manifestations as true clinical entities, particularly for antibodies other than anti-IgLON5. Therefore, careful differential diagnosis is important. When the results are uncertain, first-line treatment can be considered for diagnostic purposes. In the following sections, we discuss the details of laboratory tests.

4.2.2. TBA

TBA is generally performed by preparing frozen rat brain sections and treating them with patient serum or CSF containing primary antibodies, followed by incubation with a secondary antibody conjugated with probes. This is typically performed as an in-house test. All nine of the aforementioned antibodies are suitable; however, there are also undetectable antibodies, such as the anti-glycine receptor (GlyR) antibody and the anti-myelin oligodendrocyte glycoprotein (MOG) antibody. Sensitivity is considered high because it has the potential to detect antibodies targeted at every part of the rat brain, and is not limited to well-characterized brain regions, although this factor may depend on the experience at each institution. One drawback of this method is the inability to identify the exact name of the antibody.

4.2.3. CBA

The general principle of CBA is to express an antigen of interest on the surface of a suitable cell, such as human embryonic kidney 293 (HEK293) cells, by transfecting a plasmid encoding its gene. These cells are then subjected to patient serum or CSF, followed by a detection using secondary antibodies. Commercial kits as well as in-house CBA methods are available. Among the nine antibodies described previously, the target antibodies were anti-IgLON5, -DPPX, -LGI1, -Sez6l2, and -KLHL11 antibodies, which attach to cell-surface antigens except for the anti-KLHL11 antibody, which is directed to an intracellular antigen. The sensitivity and specificity of the test are high because of the use of proteins that retain their structures. However, a combination of CBA and TBA is still recommended as the sensitivity and specificity of CBA alone are not yet clear [60]. Both the serum and CSF should ideally be tested because a superiority of serum or CSF has not yet been determined for detecting these antibodies, except for the anti-LGI1 antibody, whose serum is more sensitive than CSF with no sacrifice for specificity [63,64].

4.2.4. Immunoblot

Immunoblotting techniques include both line and western blot analyses. Line blotting is a method in which a purified antigen is directly bound to a membrane for reaction with patient samples and secondary antibodies, while in western blotting, antigens are stuck to a membrane following electrophoresis. Although the former can be performed using a commercial kit, the latter is based on in-house testing. Anti-Ma2, -Hu, -Ri, and -CV2/CRMP5 antibodies of the nine described above, ones targeting intracellular antigens, are suitable for these assays. Because there is no evidence that either serum or CSF is better, both should be tested if possible [60]. The sensitivity of these assays is good, but the specificity was moderate to low, particularly for commercial line blots with low titers. In particular, the false-positive rate is likely to increase in PSP-like patients as this clinical syndrome is not established, and the pre-test probability may be low, leading to recommendations to confirm concordance of the results of TBA and immunoblot [26,62,65].

5. Management of AE/PNS Mimicking PSP

Immunotherapy and the management of neoplasms are the mainstays of treatment. As there is no treatment with a high level of evidence for AE/PNS mimicking PSP, commonly recommended treatments for AE/PNS are typically followed [66–69]. Immunotherapy can be divided into acute and maintenance therapies. The first-line acute therapy is often intravenous methylprednisolone (IVMP), either alone or in combination with IVIG or plasmapheresis. The regimen for a single cycle comprises 1000 mg of intravenous methylprednisolone for three days for IVMP; 2 g/kg divided into five days for IVIG; and five to ten sessions of therapeutic plasma exchange every alternate day for plasmapheresis.

If these treatments are deemed inadequate at follow-up performed two to four weeks following the completion of acute treatment, rituximab (RTX) or cyclophosphamide is considered as a second-line therapy [67]. However, it is crucial to re-evaluate the diagnosis before initiating these therapies, particularly when the first-line therapies are completely ineffective, or laboratory tests are

indeterminate. RTX can be administered at a dose of 375 mg/m² four times weekly, whereas cyclophosphamide can be administered at 600–1000 mg/m² monthly for up to six months.

Maintenance therapy should be considered following the completion of acute therapy. If it is the first attack, oral corticosteroids can be prescribed as a bridging therapy, with tapering over several months; long-term maintenance therapy is not common. In contrast, maintenance therapy is common in patients who test positive for cell-surface antibodies and experience recurrence. The common regimen includes either periodic RTX alone, or azathioprine (AZA) or mycophenolate mofetil (MMF) with oral corticosteroids tapered over three to six months as a bridging therapy. Periodic RTX can also be administered at a dose of 375 mg/m² every four to six months. AZA can be administered initially at a dose of 1.5 mg/kg/day titrated to 2-3 mg/kg/day over one to several months, while MMF is initially dosed at 500 mg twice daily, increasing to 1000 mg twice daily after two weeks. The duration of maintenance treatment can initially be considered as three years [68].

Coexisting neoplasms should be treated simultaneously. If a related tumor is detected, complete resection can be initially considered. If this is not possible, debulking surgery, chemotherapy, or radiotherapy should be considered.

6. Conclusion and Future Directions

With advances in antibody detection technologies, autoimmune parkinsonism has become attractive as a treatable condition. When we encounter a patient with PSP-like syndromes, the possibility of an autoimmune disease should always be considered, rather than simply assuming that the symptoms are caused by PSP as a neurodegenerative disease. However, as yet, the association between AE/PNS and PSP-like manifestations has not been adequately proven. Antibody detection assays unfortunately have a relatively high risk of presenting with false-positive and false-negative results. Moreover, only a single or handful of PSP-like patients have been described in detail for all antibodies, except for the anti-IgLON5 antibody. The accumulation of patients with similar clinical courses is essential to overcome these problems.

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