Classification of atypical parkinsonism per pathology versus phenotype

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Contents

Abstract

The umbrella term "atypical parkinsonism" refers to a clinical presentation with various causes, emphasizing the clinical commonality of diseases in which atypical parkinsonism can present. This term is useful for describing the phenomenology of a movement disorder and to classify patients according to their clinical presentation. In contrast to this classification per phenotype, a classification per pathology is needed when it comes to understanding the pathogenesis and designing and delivering disease-modifying therapeutic interventions. Clinico-pathological correlation studies have revealed enormous clinical heterogeneity and vast clinical overlap in pathologically defined diseases related to atypical parkinsonism. Thus, the classification of patients with atypical parkinsonism per phenotype has limited validity for predicting the underlying pathology. This chapter will contrast the phenotype-driven classification

International Review of Neurobiology, Volume 149
ISSN 0074-7742
https://doi.org/10.1016/bs.irn.2019.10.003

and the pathology-driven classification of neurodegenerative diseases related to atypical parkinsonism and discuss future directions to improve pathology-specific diagnosis.

1. Introduction

"Atypical parkinsonism", in the strict sense, describes a syndrome which comprises of parkinsonian features, such as akinesia, rigidity and tremor, and further clinical signs which are atypical for Parkinson's disease (PD). The latter are also referred to as "red flags" and are outlined in Chapter 1. Diseases that are classically summarized under the term "atypical parkinsonian disorders" are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). However, this concept is not clear-cut, because PSP, CBD, MSA, and LBD are defined by their distinctive pathological characteristics (Dickson, 1999; Dickson et al., 2002; Hauw et al., 1994; McKeith et al., 2017; Trojanowski, Revesz, & Neuropathology Working Group on MSA, 2007), and do not always present with parkinsonism (Armstrong et al., 2013; Gilman et al., 2008; Höglinger et al., 2017; McKeith et al., 2017). Moreover, atypical parkinsonism is not exclusively confined to PSP, CBD, MSA, and DLB. It can also occur in other conditions, including other forms of frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), vascular, drug-induced, autoimmune, infectious, metabolic, toxic, and hereditary diseases (Stamelou, Quinn, & Bhatia, 2013). Thus, the different conceptual interpretations of the term "atypical parkinsonism" need a clearer framework.

PSP, CBD, MSA, and DLB are distinct diseases, but they share some common pathological mechanisms: they all resemble intracellular protein aggregation of either tau or α-synuclein in the brain, which in each case is thought to play the key role in the pathogenesis of these sporadic diseases (Outeiro et al., 2019; Rösler et al., 2019). Variations in genes encoding tau and α-synuclein and in genes related to the degradation of these proteins have been identified as risk factors for PSP, CBD and DLB (Outeiro et al., 2019; Rösler et al., 2019). Prion-like spreading mechanisms of tau and α-synuclein, respectively, are thought to promote disease propagation in PSP, CBD, MSA, and DLB (Kaufmann et al., 2017; Peelaerts, Bousset, Baekelandt, & Melki, 2018). Only clear understanding of their neuropathological hallmarks and distinctions as well as their variable clinical presentations will lead to further discoveries of underlying molecular mechanisms, genetic risk factors, and treatment strategies.

In this chapter, we will introduce the pathological classification, and the clinical classification of PSP, CBD, MSA, and DLB, and put them into a greater context with related neurodegenerative diseases. Finally, we will discuss future directions for the classification of patients with neurodegenerative diseases related to atypical parkinsonism.

2. Classification per pathology

Despite some clinical and pathogenetic commonalities, neurodegenerative diseases related to atypical parkinsonism differ in terms of their neuropathological characteristics on a macroscopic, molecular, and ultrastructural level. On the macroscopic level, they are characterized by distinct anatomical patterns of brain atrophy. On the molecular level, abnormal intracellular protein deposition and aggregation can be found, yet, the protein and the affected cell types differ between each disease. On the ultrastructural level, the protein deposits display disease-specific characteristics. Together, these characteristics form the histopathological hallmarks of these diseases and are used to establish the neuropathological diagnosis *post mortem* (Dickson, 1999; Dickson et al., 2002; Hauw et al., 1994; McKeith et al., 2017; Trojanowski et al., 2007).

On the molecular level, atypical parkinsonian disorders are essentially divided into two groups, depending on the pathological protein aggregates which are found in the brain. These are (1) *tauopathies*, which include PSP and CBD and are characterized by the intracellular aggregation of the microtubule associated protein tau (MAPT), and (2) *α-synucleinopathies*, which include MSA und DLB and are characterized by the intracellular aggregation of the presynaptic protein α-synuclein.

3. Tauopathies

The pathological classification of *PSP* and *CBD* as tauopathies places both diseases into a larger context. On the one hand, tauopathies extent to a much broader spectrum of diseases other than PSP and CBD, which includes Pick's disease (PiD), argyrophilic grain disease (AGD), globular glial tauopathy (GGT), hereditary tauopathies with *MAPT* mutations, and also AD as a secondary tauopathy, to name some examples (Kovacs, 2015; Rösler et al., 2019). Tauopathies are further characterized by the predominant tau isoforms in intracellular aggregates. In PSP and CBD, these aggregates are predominantly formed of tau isoforms with four microtubule-binding repeats (*4R-tau*), while Pick's disease (*PiD*) is characterized by aggregates of

predominantly three microtubule-binding repeats (*3R-tau*), and AD among other tauopathies has an equal ratio of both (*3R/4R-tau*) (Kovacs, 2015).

On the other hand, PSP and CBD belong to the higher-level class of *frontotemporal lobar degeneration* (FTLD) which include not only tau pathology (*FTLD-tau*), but also proteinopathies other than tau, such as FTLD with TAR DNA-binding protein-43 (*FTLD-TDP43*), and FTLD with fused in sarcoma protein (*FTLD-FUS*) (Mackenzie et al., 2010).

In PSP and CBD, 4R-tau aggregates are found within neurons and glial cells (Rösler et al., 2019). Among other histological features that allow the differentiation between both diseases, the tau deposits in astrocytes differ morphologically, and are called astrocytic tufts in PSP and astrocytic plaques in CBD, respectively (Dickson, 1999; Dickson et al., 2002; Hauw et al., 1994). While typical anatomical patterns of tau-associated pathology are described for each, PSP and CBD, the affected brain regions can vary in both diseases (Rösler et al., 2019). This is possibly triggered by distinct tau strains with unique seeding pattern (Rösler et al., 2019). Differential distribution of tau pathology likely produces the heterogeneity of clinical presentations in PSP and CBD (Williams et al., 2005; Yoshida et al. 2017).

The classification of PSP and CBD in the larger context of tauopathies and FTLD is shown in Fig. 1.

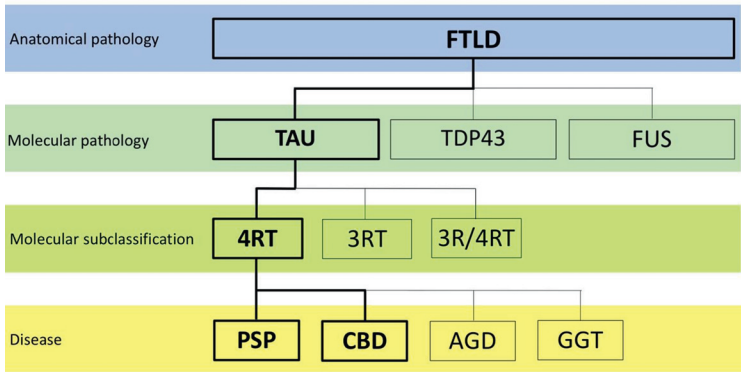

Fig. 1 ***Pathological classification of tauopathies.*** Classification of tauopathies according to their molecular characteristics. Tauopathies are part of the FTLD-spectrum, which include FTLD-tau, FTLD-TDP43, and FTLD-FUS. Tauopathies are further classified into 3RT, 4RT, and 3R/4RT, according to the predominant tau isoform. *AGD*, argyrophilic grain disease; *CBD*, corticobasal degeneration; *GGT*, globular glial tauopathy; *FTLD*, frontotemporal lobar degeneration; *FUS*, fused in sarcoma protein; Pick's disease; *PSP*, progressive supranuclear palsy; *Tau*, tauoathy; TDP43,TAR DNA-binding protein-43; *3RT*, 3-repeat tauopathy; *4RT*, 4-repeat tauopathy; *3R/4RT*, mixed 3-repeat tau/4-repeat tauopathy.

4. α-synucleinopathies

From the pathological perspective, *PD*, *DLB*, and *MSA* are jointly classified as α-synucleinopathies (McCann, Stevens, Cartwright, & Halliday, 2014). They again are subclassified into 1) *Lewy body disease (LBD)*, which comprises PD and DLB, and 2) *MSA* (McCann et al., 2014). LBD is characterized by neuronal inclusions composed of α-synuclein, which are referred to as *Lewy bodies* (Dickson et al., 2009; McKeith et al., 2017). The pathology of PD and DLB does not differ on the molecular nor the ultrastructural level. However, in patients with PD, the pathology is primarily found in the brainstem, while patients with DLB show widespread pathology through almost all brain areas, which also reflects the severe cortical and autonomic clinical features in the latter (Dickson et al., 2009; McKeith et al., 2017). In MSA, α-synuclein aggregates are primarily found in oligodendroglial cells, which are referred to as *glial cytoplasmic inclusions* (GCI) (Ahmed et al., 2012; Trojanowski et al., 2007). The distribution of pathology in MSA correlates with the clinical phenotype. In the parkinsonian subtype (MSA-P), the pathology is pronounced in substantia nigra, pons and striatum, while the cerebellar subtype (MSA-C) displays marked pathology in cerebellum and cerebellar circuits (Ahmed et al., 2012; Trojanowski et al., 2007). The pathological classification of synucleinopathies is shown in Fig. 2.

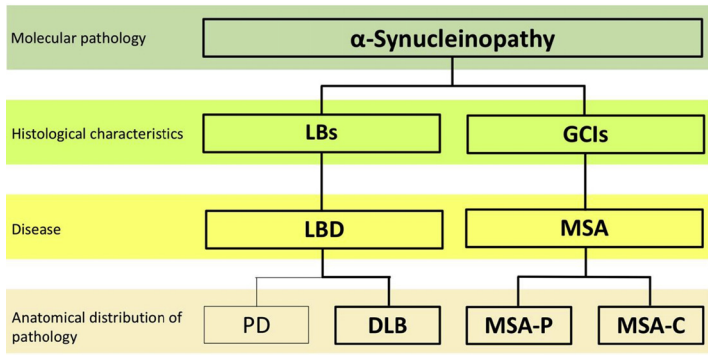

Fig. 2 ***Pathological classification α-synucleinopathies.*** Classification of α-synucleinopathies according to their molecular and histological characteristics. The anatomical distribution of pathology determines the disease subtype (PD, DLB, MSA-P, and MSA-C). *DLB*, dementia with Lewy bodies; *GCI*, glial cytoplasmatic inclusions; *LBs*, Lewy bodies; *LBD*, Lewy body disease; *MSA*, multiple system atrophy; *MSA-C*, multiple system atrophy – cerebellar subtype; *MSA-P*, multiple system atrophy – parkinsonian subtype; *PD*, Parkinson's disease.

5. Classification per phenotype

While the neuropathological examination post mortem represents the diagnostic gold standard of PSP, CBD, DLB, and MSA, the clinician relies on the description and classification of patients according to their phenotype. This is also reflected by the clinical diagnostic criteria of atypical parkinsonian disorders (Armstrong et al., 2013; Gilman et al., 2008; Höglinger et al., 2017; McKeith et al., 2017). Due to phenotypic overlaps among different pathologies, the neuropathological diagnosis cannot be predicted with definite certainty (Armstrong et al., 2013; Gilman et al., 2008; Höglinger et al., 2017; McKeith et al., 2017). However, a classification of patients per phenotype allows an approximation to the pathological diagnosis. Moreover, it is essential for placing appropriate symptomatic therapies and helpful for predicting the later clinical course, because some phenotypes exhibit less rapid disease progression and increased survival times (Petrovic et al. 2012; Respondek & Höglinger, 2016). As mentioned previously, patients with PSP, CBD, MSA, and DLB may present without parkinsonian features (Armstrong et al., 2013; Gilman et al., 2008; Höglinger et al., 2017; McKeith et al., 2017). Importantly, many phenotypes fall into the cognitive spectrum with mnestic, behavioral, and language dysfunction and can resemble AD, frontotemporal dementia (FTD) and other dementias (Armstrong et al., 2013; Höglinger et al., 2017; McKeith et al., 2017).

5.1 Clinical spectrum of the tauopathies PSP and CBD (Table 1)

Especially in PSP and CBD, clinico-pathological studies of the last two decades resulted in an expansion of the clinical spectrum (Armstrong et al., 2013; Höglinger et al., 2017; Respondek et al., 2017). This led to a refinement of the clinical diagnostic criteria for PSP and CBD, which now include a variety of clinical phenotypes in order to increase diagnostic sensitivity (Armstrong et al., 2013; Höglinger et al., 2017). On the other hand, all phenotypes linked to PSP and CBD have been related to other neuropathologies. For example, *corticobasal syndrome (CBS)* was originally only described for CBD, and now is linked to several other neuropathologies, including PSP, AD, PiD and FTLD-TDP (Alexander et al., 2014; Ling et al., 2010). *Richardsoń syndrome (RS)* was long considered the archetypical clinical phenotypes of PSP but was observed in patients with CBD pathology as well (Armstrong et al., 2013; Ling et al., 2010).

Table 1 Classification of PSP and CBD per phenotype, associated pathologies and differential diagnoses.

Phenotype		Pathology	Differential diagnoses
Predominantly cognitive phenotypes			
bvFTD	Behavioral variant of FTD	PSP, CBD	TDP-43 positive FTLD, PiD
nfaPPA	Non-fluent, agrammatic variant of primary progressive aphasia	PSP, CBD	PiD, Tau-negative FTLD, AD
AOS	Apraxia of speech	PSP, CBD	TDP-43 positive FTLD
AS	Amnestic syndrome of the hippocampal type	CBD	AD, GGT, AGD, PART, Tau-negative FTLD
Cognitive and motor overlap phenotypes			
RS	Richardson's syndrome	PSP, CBD	
CBS	Corticobasal syndrome	CBD, PSP	AD, Tau-negative FTLD
Predominantly motor phenotypes			
PSP-P	PSP with parkinsonism	PSP	PD
PGF	Progressive gait freezing	PSP, CBD	LBD, MSA, PNLD
LOCA	Late onset cerebellar ataxia	PSP	MSA, SCA
PLS	Primary lateral sclerosis	PSP	MND, Tau-negative FTLD

AD, Alzheimer's disease; *AGD*, argyrophilic grain disease; *CBD*, corticobasal degeneration; *FTD*, frontotemporal dementia; *FTLD*, frontotemporal lobar degeneration; *GGT*, globular glial tauopathy; *LBD*, Lewy body disease; *MSA*, multiple system atrophy; *PART*, primary age-related tauopathy; *PiD*, Pick's disease; *PNLD*, pallidonigroluysian degeneration; *PSP*, progressive supranuclear palsy; *SCA*, spinocerebellar ataxia.

Beyond RS and CBS, additional phenotypes have been reported in autopsy-confirmed PSP and CBD cases. Some phenotypes present in both, PSP and CBD, including *nonfluent/agrammatic variant of primary progressive aphasia (nfaPPA), apraxia of speech (AOS)*, and *behavioral variant of frontotemporal dementia (bvFTD)* (Armstrong et al., 2013; Respondek et al., 2017; Respondek & Höglinger, 2016). In PSP, *predominant parkinsonism (PSP-P)*, *progressive gait freezing (PGF)*, *primary lateral sclerosis (PLS)*, and *predominant cerebellar presentation (PSP-C)* were also described (Respondek et al., 2017; Respondek & Höglinger, 2016). Due to the vast clinical overlap between PSP and CBD, criteria for the clinical diagnosis of *"probable 4-repeat tauopathy"* have been established (Höglinger et al., 2017).

5.2 Clinical spectrum of α-synucleinopathies (Table 2)

The clinical spectrum of α-synucleinopathies includes *PD* and *PD dementia (PDD)*, as well as diseases which are referred to as "atypical parkinsonian disorders", namely *DLB* and *MSA* (McCann et al., 2014). The essential clinical feature of DLB is early dementia (McKeith et al., 2017). Patients with DLB frequently present with parkinsonism, but it is not crucial for the clinical diagnosis (McKeith et al., 2017). Other frequent clinical characteristics include spontaneous visual hallucinations, fluctuations in cognition, attention and alertness and autonomic dysfunction (McKeith et al., 2017). The onset of dementia versus parkinsonism determines whether a patient is classified as DLB or PDD: a patient with dementia prior or within the first year after onset of parkinsonism is diagnosed with DLB, and vice versa (McCann et al., 2014; McKeith et al., 2017). Thus, AD is an important differential diagnosis of DLB (McKeith et al., 2017). This again demonstrates how the clinical classification of atypical parkinsonian disorders expands into cognitive phenotypes. In MSA, autonomic dysfunction is an early and prominent clinical feature and is required for the clinical diagnosis (Gilman

Table 2 Classification of α-synucleinopathies per phenotype, associated pathologies and differential diagnoses.

Phenotype		Pathology	Differential diagnoses
Cognitive and motor overlap phenotypes			
DLB	Dementia with Lewy bodies	LBD	PD, PDD, AD, Tau-negative FTLD, PiD.
PDD	Parkinson's disease dementia	LBD	PD, DLB, AD, PSP, Tau-negative FTLD, PiD.
Predominantly motor phenotypes			
MSA-P	MSA-parkinsonian type	MSA	PD, PSP
MSA-C	MSA-cerebellar type	MSA	SCA, PSP
Prodromal phenotypes			
RBD	REM-sleep behavior disorder	LBD, MSA	RBD
PAF	Pure autonomic failure	LBD, MSA	PAF

AD, Alzheimer's disease; *FTLD*, frontotemporal lobar degeneration; *LBD*, Lewy body disease; *MSA*, multiple system atrophy; *PD*, Parkinson's disease; *PDD*, Parkinson's disease dementia; *PiD*, Pick's disease; PNLD; *PSP*, progressive supranuclear palsy; *SCA*, spinocerebellar ataxia.

et al., 2008). The phenotypes of MSA are classified according to the predominant motor symptoms. These include *MSA-P* with predominant parkinsonism, and *MSA-C* with predominant cerebellar features (Gilman et al., 2008). Cognitive changes may be observed in MSA (Stankovic et al., 2014), but they are far less pronounced than in DLB. Clinical differential diagnoses for MSA-P include any diseases presenting with parkinsonism, and for MSA-C other late onset cerebellar ataxia (LOCA), such as PSP-C, and spinocerebellar ataxia (SCA) (Gilman et al., 2008; Koga et al., 2016). The phenotypic spectrum of α-synucleinopathies has recently expanded to include pre-motor presentations. These are *REM-sleep behavior disorder (RBD)*, and *pure autonomic failure (PAF)*, which have been associated with highly increased risk for developing PD, DLB or MSA later (Kaufmann et al., 2017; St Louis, Boeve, & Boeve, 2017).

6. Conclusions and outlook

The pathological classification of neurodegenerative diseases related to atypical parkinsonism has a number of advantages. First of all, only the histopathological characteristics allow for a definite diagnosis of these diseases. Moreover, the classification per pathology increases our understanding of disease pathogenesis, because it reveals histological, neurochemical, and molecular changes and facilitates the identification of genetic and environmental risk factors of these diseases. Last but not least, the specific underlying pathology represents the target of disease-modifying investigational drugs (Boxer et al., 2017; Levin et al., 2019), and thus, therapeutic trials require a classification of patients per pathology.

At present however, the clinical diagnosis of sporadic neurodegenerative diseases relies on the exact description of the clinical phenotype, because pathology-specific biomarkers are lacking (Armstrong et al., 2013; Gilman et al., 2008; Höglinger et al., 2017; McKeith et al., 2017).

The umbrella term "atypical parkinsonism" can be misleading. A number of clinical phenotypes related to atypical parkinsonian disorders completely lack features of parkinsonism and extent into the spectrum of cognitive disorders. It is important to have a clear understanding of all phenotypes and related pathologies to overcome the diagnostic obstacles created by the heterogeneity of clinical manifestations and terminology, to define biomarkers for early diagnosis, and to identify disease-modifying therapies. Molecular imaging techniques, such as Tau-PET, are matter of investigation, and hold potential for pathology-specific *in vivo* diagnosis (Niccolini

et al., 2018; Passamonti et al., 2017). Natural history studies on variant clinical phenotypes will lead to a better understanding and description of the phenotypic spectrum of atypical parkinsonian disorders.

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