

Redefinition of Atypical Parkinsonian Syndromes



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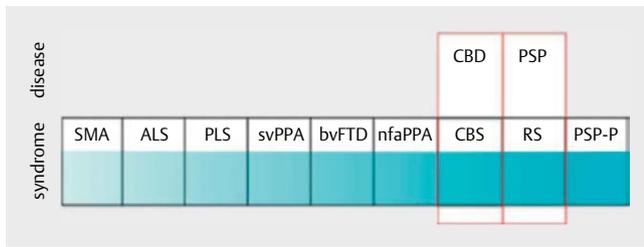
ABSTRACT

The definition of atypical parkinsonian syndromes is undergoing a change. The umbrella concept of atypical parkinsonian syndromes includes diseases with different underlying pathologies. These are, on the one hand, multiple system atrophy (MSA) and dementia with Lewy bodies (DLB), both of which are characterized by intracellular aggregates of the protein alpha-synuclein, and on the other hand, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), which are characterized by aggregates of the protein tau. The current syndrome-based classification of these diseases no longer meets current requirements since 1) numerous clinico-pathological studies have shown that the clinical syndromes do not always coincide with the molecular-pathological diagnosis, 2) a clinical parkinsonian syndrome is sometimes not even present in patients with a pathological diagnosis of an atypical parkinsonian syndrome, and 3) current therapeutic trials that intervene in the molecular disease mechanisms require no symptom-oriented, but a pathogenetically oriented diagnosis. The early and correct prediction of the underlying molecular pathology as a prerequisite for a causative therapy therefore presents a challenge that the old disease concept is no longer capable of meeting.

Traditional Disease Concept

The term “atypical parkinsonian syndrome” is traditionally used for several neurodegenerative diseases, including multiple system atrophy (MSA), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). Their defining commonality consists in their akinetic-rigid extrapyramidal movement disorder. In contrast to idiopathic Parkinson’s disease (PD), the atypical parkinsonian syndromes often have additional clinical characteristics, such as poor response to dopaminergic therapy, more rapid disease progression, and poorer prognosis [1]. MSA, DLB and PSP are still predominantly considered as clinico-pathologically coherent disease entities. However, this concept has already been abandoned in CBD, which is now considered a purely neuropathologically defined disease entity; the clinically defined corticobasal syndrome (CBS) can be traced back only to a relatively small extent (about 25 %) to the neuropathological diagnosis of CBD. To a considerable extent, CBS is also caused by PSP pathology or Alzheimer’s disease (AD) pathology. Conversely, the neuropathological diagnosis of CBD frequently presents with

clinical syndromes other than CBS. In this regard, the classification system of CBS/CBD is already more advanced than that of the other atypical parkinsonian syndromes, since a clear distinction has been made in the nomenclature between clinical syndrome (CBS) and the underlying neuropathology (CBD). For historical reasons, the classification of atypical parkinsonian syndromes has been made in accordance with their clinical appearance (► **Fig. 1**). The use of such a clinically-guided classification system stands to reason, because the constellation of clinical signs and symptoms has always been the physician’s first basis for the generation of a diagnosis. Such a clinical-descriptive categorization allowed initial observations regarding the typical symptoms, demography and epidemiology, as well as the first theories on the cause of the diseases. Precise clinical characterization generally is an essential prerequisite for an etiological and pathogenetic understanding of a disease. The latter should explain the causes and mechanisms of the disease and help derive therapeutic approaches from the pathophysiological processes. According to the traditional disease concept, atypical parkinsonian syndromes defined a disease clinically. The purpose



► **Fig. 1** Traditional disease concept. The clinical syndrome, e.g., corticobasal syndrome (CBS) or Richardson syndrome (RS), defined the disease (corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP)), and helped to differentiate these diseases from other entities, e.g., ALS: amyotrophic lateral sclerosis, bvFTD: behavioral variant of frontotemporal dementia, nfaPPA: non-fluent agrammatic variant of primary progressive aphasia, PLS: primary lateral sclerosis, PSP-P: progressive supranuclear palsy with predominant parkinsonism, SMA: spinal muscular atrophy, svPPA: semantic variant primary progressive aphasia.

of neuropathology was essentially that of comparing the clinical disease entity to the observed pathology and thereby uncovering common disease patterns. PSP, for example, was first described in 1964 by the neurologists John Steele and Cliff Richardson as well as the neuropathologist Jerzy Olszewski as a clinico-pathological entity [2]. The authors reported on 8 patients who had a characteristic neurological symptom constellation with common neuropathological features. They thus characterized a clinical syndrome, which is known today also as Richardson syndrome [3]. The same was true for the CBD, which was first described by Jean J. Rebeiz and colleagues on the basis of the joint clinical and neuropathological findings of 3 patients [4]. Since the clinical symptoms are determined by the anatomical distribution of the neurodegenerative processes, but not by the underlying molecular pathology (proteinopathy), clinical and neuropathological findings were largely coherent in the past. This changed dramatically, however, as molecular biological methods of investigation enabled more accurate insights into the proteinopathies underlying neurodegenerative diseases. In particular, the immunohistochemical characterization of the diverse protein aggregates in atypical parkinsonian syndromes enabled a new way of looking at clinico-pathological correlations.

Changing Disease Concept

Recent discoveries in the field of electron microscopy, immunohistochemistry, biochemistry and genetics have helped to identify typical molecular fingerprints for neurodegenerative diseases, which made it possible to precisely categorize brain tissue from deceased patients on molecular grounds. Thus, in the 1970s, at the ultrastructural level, the intraneurally occurring neurofibrillary tangles (NFTs) in PSP, as described by J. Olszewski [2], were distinguished from those in AD [5]. Subsequently, the microtubule-associated protein tau was identified immunohistochemically as its main component [6]. Using antibody-based methods, the aggregated tau in the brain of PSP patients was shown to consist mainly of isoforms with 4 microtubule-binding repeats (4R-tau). In contrast, a combination of tau with 3 microtubule-binding repeats (3R-tau) and 4R-tau is present in a balanced proportion in AD [7]. In frontotemporal lobar degeneration with tau pathology (FTLD-tau),

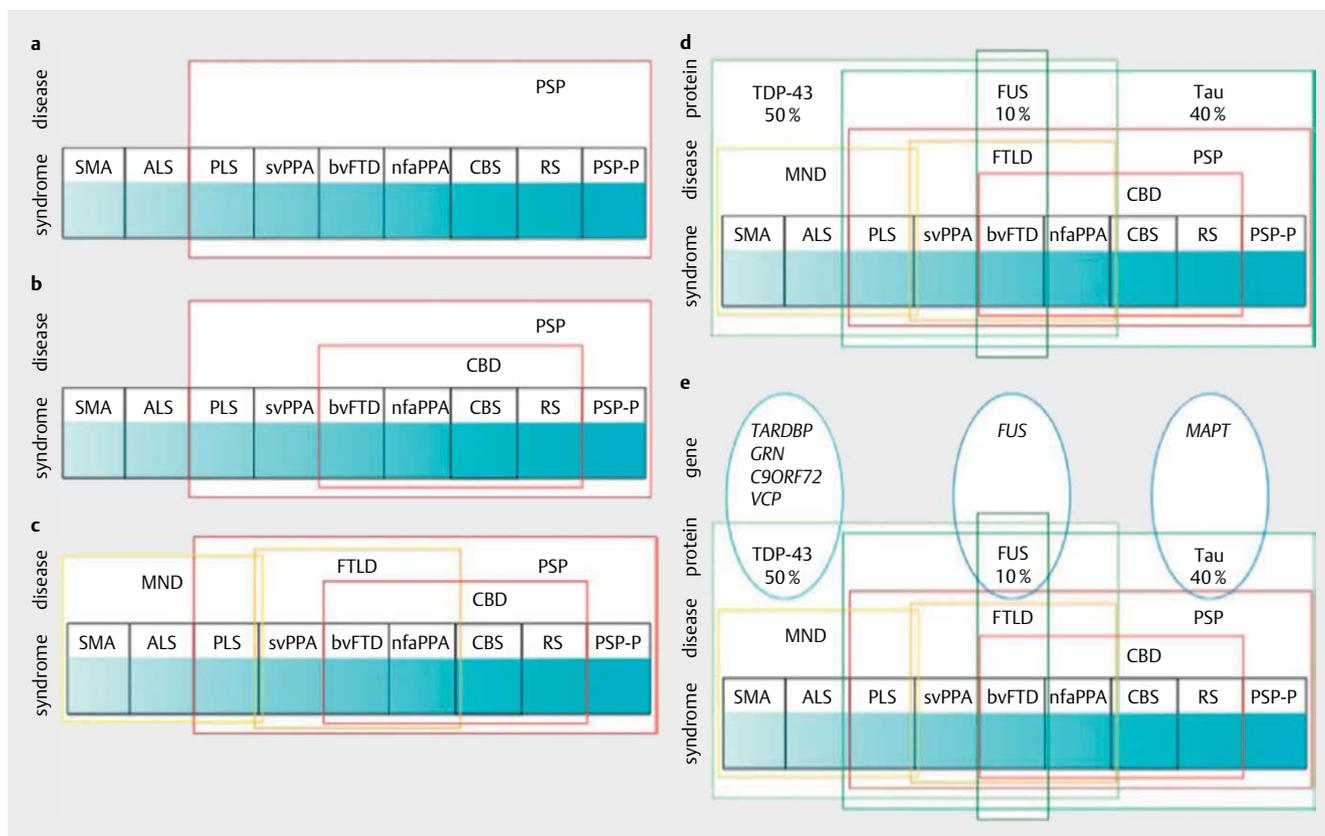
there is predominantly 3R-tau (e.g., in Pick's disease), 4R-tau or a combination of both [8]. Remarkably, intracellular aggregates of 4R-tau are found in CBD as well as in PSP, but they also show morphological differences in astrocytes (PSP: astrocytic tufts, CBD: astrocytic plaques). Intracellular aggregates of the protein alpha-synuclein are characteristic for MSA and DLB (MSA: oligodendroglial cytoplasmic inclusions, DLB: cortical Lewy bodies). This neuropathologically based disease definition proved to be very successful, since e.g., genome-wide association studies on the basis of these neuropathological disease definitions have shown highly characteristic and reproducible profiles [9, 10]. These neuropathological definitions thus seem to delineate etiologically coherent disease entities. The precise molecular-pathological and genetic characterization revealed relevant new findings, which necessitate a redefinition of the atypical parkinsonian syndromes. In ► **Fig. 2a–e**, we would like to delineate the complex clinical and pathological heterogeneity of neurodegenerative diseases using PSP for illustrative purposes. The following are the consequences:

1. Neuropathologically defined diseases show a broader clinical spectrum than assumed in the traditional disease concept

Over the past few years, there has been an increasing number of reports of cases in which the neuropathological diagnosis differed from the initial clinical diagnosis. In the example of PSP, the clinical Richardson syndrome, i.e., supranuclear vertical gaze palsy with early postural instability, specifically predicts the neuropathological diagnosis of PSP [3]. However, this syndrome does not occur in every PSP patient. Supranuclear vertical gaze palsy is missing in a quarter of pathologically diagnosed PSP cases, or develops only late in the course of the disease [11]. Thus, these typical symptoms have a limited sensitivity to detect pathologically defined PSP. On the other hand, patients with a neuropathological diagnosis of PSP can develop symptoms that are similar to those of PD, CBS, primary progressive aphasia (PPA), frontotemporal dementia (FTD), or even primary lateral sclerosis (PLS) (► **Fig. 2a**). However, many of these syndromes are defined as exclusion criteria in current clinical diagnostic criteria [3]. The pathologically defined disease thus crosses the historically determined boundaries of movement disorders (parkinsonian syndrome) into cognitive neurology (dementia). In other words, a traditional atypical parkinsonian syndrome (here: PSP) can paradoxically present clinically as pure dementia without any movement disorder. The clinical spectrum of pathologically defined PSP therefore comprises syndromes which differ significantly from the classical clinical picture [2, 11, 12]. Richardson syndrome probably represents only a minority (about 25%) of all cases with pathologically confirmed PSP [11]. The defining commonality of all these newly described clinical PSP variants are their histopathological and biochemical characteristics, which are also very well related to their typical genetic profile [9].

2. A protein can cause multiple clinical syndromes and neuropathologically defined diseases

In PSP, as well as in CBD, the aggregated tau protein is predominantly found in the 4R form. Structural differences between the tau aggregates of PSP and CBD, however, do exist at cellular level and enable pathological differentiation between them. In PSP, the tau



► **Fig. 2 a–e** Changing disease concept. **a** Neuropathologically defined diseases show a broader clinical spectrum than in the traditional disease concept. The diseases cross historical boundaries between cognitive neurology (dementia) and movement disorders (parkinsonian syndromes). **b** A protein (e. g., tau) can cause multiple clinical syndromes and neuropathologically defined diseases (e. g., CBD and PSP). **c** Clinical syndromes show an overlapping neuropathological spectrum. **d** Clinical syndromes and neuropathological diseases show overlapping proteinopathies *. **e** A proteinopathy can be caused by different genes *. ALS: amyotrophic lateral sclerosis, bvFTD: behavioral variant frontotemporal dementia, CBS: corticobasal syndrome, CBD: corticobasal degeneration, FTLD: frontotemporal lobar degeneration, FUS: fused in sarcoma protein, MND: motor neuron disease, nfaPPA: non-fluent agrammatical variant primary progressive aphasia, PLS: primary lateral sclerosis, PSP: progressive supranuclear palsy, PSP-P: progressive supranuclear palsy with predominant parkinsonism, RS: Richardson syndrome, SMA: spinal muscular atrophy, svPPA: semantic variant primary progressive aphasia, TDP-43: TAR DNA-binding protein-43, VCP: valosin-containing protein. * % values indicate the approximate distribution of proteinopathies in the syndromic spectrum presented.

aggregates in astrocytes are found in the form of tufts, while in CBD they occur in the form of plaques [13]. The clinical spectrum of the two tauopathies PSP and CBD partially overlaps (► **Fig. 2b**). Apart from PSP and CBD, tau is also a major player in a broad spectrum of other neuropathologically defined disease entities.

3. Clinical syndromes show an overlapping neuropathological spectrum

There are numerous clinico-pathological reports according to which syndromes traditionally defined on the basis of clinical symptoms can have different underlying pathological diagnoses (► **Fig. 2c**). For instance, it has become clear that the clinical features of CBD [4], as initially described by Rebeiz, are associated with a variety of other pathologies, e. g., with the neuropathological diagnosis of AD, frontotemporal lobar degeneration (FTLD) or PSP [14]. This led to the definition of the term CBS, which refers solely to the clinical phenotype independent of the neuropathological diagnosis, whereas CBD now describes exclusively the neuropathological diagnosis independent of the clinical picture [15]. On the other hand, neuropsychological syndromes are also caused by different neuropathologically de-

defined diseases: a non-fluent, agrammatic variant (nfaPPA) or a semantic variant (svPPA) of primary progressive aphasia and a behavioral variant of FTD (bvFTD) can neuropathologically present as PSP, CBD or FTLD [16, 17]. Thus, there is an overlap of the clinical spectra of PSP, CBD, FTLD, motor neuron disease (MND) and AD. Hence, the traditional boundaries between movement disorders and dementia therefore do not meet the modern disease concept. Paradoxically, some patients with an atypical parkinsonian syndrome according to neuropathological criteria can even manifest without any movement disorder but purely with cognitive or behavioral deficits. This is due to the fact that type and severity of symptoms are not correlated with the underlying molecular nature of the pathology on which the diagnosis is based, but only with the localization of this pathology. ► **Table 1** gives an overview of the clinical syndromes shown in the figure and the associated pathologies and genes.

4. Clinical syndromes and neuropathological diseases show overlapping proteinopathies

The clinical differentiation of proteinopathies has so far played a minor role in patient care, since the available therapies were pure-

► **Table 1** Pathologically defined diseases and clinically defined syndromes.

| Diseases/Syndromes: Definition |
|--|
| A) Pathologically defined diseases |
| Progressive supranuclear palsy (PSP) |
| Neuropathological disease entity characterized by the intracellular aggregation of the tau protein (i. e., 4-repeat isoforms) in neurons (neurofibrillary tangles), oligodendrocytes (coiled bodies) and astrocytes (tufted astrocytes) [13] |
| Corticobasal degeneration (CBD) |
| Neuropathological disease entity characterized by intracellular aggregation of tau protein (i. e., 4-repeat isoforms) in neurons (neurofibrillary tangles), oligodendrocytes (coiled bodies) and astrocytes (astrocytic plaques) [13] |
| Frontotemporal lobar degeneration (FTLD) |
| Neuropathologically heterogeneous group of diseases with primary frontotemporal degeneration and different histopathological features. In the majority of FTLD cases, pathology with TDP-43-positive inclusion bodies is present. Some of the TDP-43-positive FTLD patients develop amyotrophic lateral sclerosis (ALS). The second most common pathology is caused by the tau protein. The term Pick's disease is reserved for FTLD cases with spherical intraneuronal tau and ubiquitin-positive inclusion bodies with predominantly 3-repeat tau, the so-called pick bodies. More rarely is there a pathology with FUS inclusion bodies. [19] |
| Motor neuron disease (MND) |
| Neuropathologically heterogeneous group of diseases with degeneration of the first, second, or both motor neurons. In the majority of cases, characteristic TDP-43-positive cytoplasmic inclusions are found in the degenerated motor neurons. [32] |
| B) Clinically defined syndromes |
| Richardson syndrome (RS) |
| Core symptoms are progressive postural instability and vertical supranuclear gaze palsy early in the course of the disease. [2, 11–12] |
| Progressive supranuclear palsy with predominant parkinsonism (PSP-P) |
| A characteristic symptom is the predominant parkinsonism (tremor, bradykinesia, rigidity). It is only late in the course of the disease that patients develop clinical features typical seen in Richardson syndrome. [11–12] |
| Corticobasal syndrome (CBS) |
| Syndrome comprising at least one cortical symptom (apraxia, cortical sensory loss, alien limb phenomenon) and at least one extrapyramidal symptom (akinesia, rigidity, dystonia, myoclonus), often with asymmetric presentation. |
| Behavioral variant frontotemporal dementia (bvFTD) |
| Predominant behavioral abnormalities, such as apathy, loss of empathy, disinhibition, increased irritability, and executive dysfunction. [17] |
| Non-fluent variant primary progressive aphasia (nfvPPA) |
| Core symptom is non-fluent speech production with grammatical and phonematic errors as well as disturbances of the syntax without loss of single-word understanding. [17] |
| Semantic variant primary progressive aphasia (svPPA) |
| Core symptom is a naming disorder. Linguistic expression shows a diminished vocabulary while the grammar is not impaired. [17] |
| Amyotrophic lateral sclerosis (ALS) |
| Belongs to the group of motor neuron diseases (MND). Characteristic clinical features of ALS are signs of progressive degeneration of both the upper and the lower motor neurons such as paresis, positive pyramidal signs, muscular atrophy and (pseudo)-bulbar dysarthria and dysphagia. Approximately 20% of ALS patients also develop frontotemporal dementia. [32] |
| Primary lateral sclerosis (PLS) |
| Rare variant of the group of motor neuron diseases (MND) with degeneration of the upper motor neuron. Typical symptoms are increased reflexes, spastic paresis, positive pyramidal signs, and pseudobulbar symptoms such as spastic dysarthria. [32] |
| Spinal muscular atrophy (SMA) |
| Rare variant of the group of motor neuron diseases (MND) with degeneration of the lower motor neuron. This is manifested by progressive peripheral paresis with hypo- or areflexia without spasticity. [32] |

ly symptomatic. In the meantime, however, neuroprotective therapeutic approaches are in preclinical and clinical evaluation. In contrast to a symptom-oriented treatment, neuroprotective treatment does not primarily specific clinical deficits, but specific biochemical features of the disease. All the more important is the realization that there can be different proteinopathies underlying the very same clinical phenotype [18]. In particular, the syndromes of the

FTLD spectrum can be classified into at least three distinct proteinopathies (► **Fig. 2d**): (1) Tau (FTLD-Tau), (2) TAR DNA-binding protein-43 (FTLD-TDP), and (3) fused in sarcoma protein (FTLD-FUS) [17]. Likewise, the syndromes of the parkinsonian spectrum can be classified into at least two proteinopathies: (1) tau (PSP, CBD) and (2) alpha-synuclein (PD, DLB, MSA).

5. A proteinopathy can be triggered by different genes

The majority of the diseases described here occur sporadically. In hereditary variants, a broad spectrum of pathogenic gene variants was identified as possible triggers for specific proteinopathies (► Fig. 2e). Various, mostly autosomal dominantly inherited mutations in the tau gene (MAPT) on chromosome 17 are associated with hereditary forms of FTLD-Tau [19]. Genome-wide association studies also found gene variants in the sporadic tauopathies, among others, the H1 haplotype of the tau gene, which are associated with an increased risk of PSP [9]. Hereditary forms of FTLD and motor neuron disease (MND) with TDP pathology can be caused by mutations in different genes. These include mutations in the TARDBP gene on chromosome 20, the progranulin gene (GRN) on chromosome 17, the VCP gene on chromosome 9, and also hexanucleotide expansions (GGGGCC) in an intron of the C9orf72 gene (C9orf72 = open reading frame 72 on chromosome 9) [17]. In patients with FTLD-FUS and MND with FUS pathology, mutations in the FUS gene were identified [20]. In Central Europe, next to C9orf72 hexanucleotide expansions, a variety of GRN mutations are the second most common cause of the hereditary forms of FTLD [17]. Not much is known about the genetic risk factors in sporadic FTLD. Gene variants of TMEM106B on chromosome 7 might be associated with an increased risk of sporadic FTLD-TDP [21]. The deciphering of genetic associations can contribute significantly to an understanding of the molecular pathogenesis of neurodegenerative diseases. The increasing importance of histopathological, neurobiological and molecular genetic findings for diagnostic and therapeutic procedures ultimately led to a redefinition of parkinsonian syndromes, which are now understood less by their clinical presentation, but rather by their molecular pathogenesis.

Diagnostic Challenges

In view of the emerging therapeutic opportunities, it is all the more important to be able to predict the molecular pathology underlying the neurodegenerative disease at an early stage. The neuropathological disease concept is reflected in the current internationally recognized diagnostic criteria of atypical parkinsonian syndromes, as they define the histopathological examination as diagnostic gold standard (MSA: [22], LBD: [23], PSP: [3]). The latest revisions of the diagnostic criteria for CBD [15] and PSP [24] also take into account the breadth of the clinical phenotypic spectrum and the overlap of the disease entities. However, postmortem neuropathological examination of brain tissue is necessary for a definitive diagnosis. Since suitable methods to detect the pathologically aggregated tau or alpha-synuclein *in vivo* are missing, the syndrome-based antemortem and the pathology-based postmortem diagnosis are, unfortunately, all too often not identical [25, 26]. Currently, the *in vivo* detection of pathological tau and alpha-synuclein aggregates using specific PET tracers is promising, and is under intensive investigation [27]. The detection of pathological aggregates of tau [28], alpha-synuclein [28–30] and TDP-43 [31] in the peripheral tissue has so far been achieved with differing sensitivity and specificity. Their diagnostic value is yet unclear. However, these methods might enable ante mortem diagnosis at the protein level. Both, tau PET and diagnostic biopsies from peripheral tissue would

be very attractive for the pathology-oriented diagnosis, and for monitoring disease progression as well as the efficacy of a protective treatment of neurodegenerative diseases. Multicentric prospective studies for the investigation of early disease-specific symptoms and biomarkers, such as the German ProPSP study (“Prospective observation study for the investigation of demography, clinical course and biomarkers of the progressive progressive supranuclear gaze palsy”) are therefore very important to develop diagnostic modalities for an *ante mortem* detection of the underlying proteinopathy.

Conclusions

Fortunately, rapid progress is being made in the area of atypical parkinsonian syndromes, away from the symptom-based classification approach towards a molecular-pathological classification. This precision medicine is the basis for causative therapies of the future. In summary, the following aspects are the cornerstones of this paradigm shift:

1. Clinical syndromes of neurodegenerative diseases follow the neuroanatomy of the affected brain areas, but not the underlying molecular pathogenesis. As a result, clinical syndromes provide only diagnostic indications but not definite evidence for pathologically defined disease entities.
2. The traditional clinico-anatomical definition of diseases was sufficient for recognizing the affected brain regions and associated neurotransmitter imbalances as a basis for symptomatic therapy (e. g., akinesia and rigidity related to dopamine deficiency).
3. The foreseeable causal therapies (e. g., aggregation-inhibitors/antibodies targeting tau or alpha-synuclein) presuppose, however, an identification of the molecular pathogenesis.
4. Therefore, the traditional clinico-anatomical understanding of the diseases is being increasingly replaced by a molecular-neuropathological definition.

This new complexity requires neurologists, psychiatrists, geneticists and pathologists to overcome traditional conceptual boundaries and to pursue interdisciplinary cooperation.

Conflict of interest

No conflict of interest has been declared by the authors.

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