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Validation of the Movement Disorder Society criteria for the diagnosis of four-repeat tauopathies

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Abstract

Background: The Movement Disorder Society criteria for progressive supranuclear palsy introduced the category “probable 4-repeat (4R)-tauopathy” for joint clinical diagnosis of progressive supranuclear palsy and corticobasal degeneration.

Objectives: To validate the accuracy of these clinical criteria for “probable 4R-tauopathy” to predict underlying 4R-tau pathology.

Methods: Diagnostic accuracy for 4R-tauopathies according to established criteria was estimated retrospectively in autopsy-confirmed patients with progressive supranuclear palsy and corticobasal degeneration (grouped as 4R-tauopathies), and Parkinson’s disease, multiple system atrophy and frontotemporal lobar degeneration (grouped as non-4R-tauopathies).

Results: We identified 250 cases with progressive supranuclear palsy (N=195), corticobasal degeneration (N=55), and with non-4R-tauopathies (N=161). Sensitivity and specificity of “probable 4R-tauopathy” was 10% and 99% in the first year and 59% and 88% at final record.

Conclusions: The new diagnostic category “probable 4R-tauopathy” showed high specificity and may be suitable for recruitment of patients with progressive supranuclear palsy and corticobasal degeneration into therapeutic trials targeting 4R-tau.

Introduction

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are tauopathies with predominant aggregation of 4-repeat (4R) tau isoforms. Their neuropathological distinctions include the morphology of the astrocytic tau deposits and the neuroanatomical distribution of tau-pathology and neurodegeneration.[1] Clinically, they are often difficult to differentiate from one another, because symptoms of PSP and CBD largely overlap.[1] Common clinical presentations of both diseases include Richardsoń s syndrome (RS), corticobasal syndrome (CBS), frontal cognitive/behavioral presentation, and speech/language (SL) dysfunction.[2,3]

PSP and CBD also share many pathological mechanisms and genetic risk factors.[1] Therefore, joint diagnosis of both diseases as 4R-tauopathy may offer unique opportunities for neurobiological investigations and therapeutic interventions. Development of causal, tau-directed therapies for these rapidly progressive diseases is paramount and several compounds are already under clinical evaluation.[4]

With this in mind, the Movement Disorder Society criteria for the clinical diagnosis of PSP (MDS-PSP criteria) introduced the novel diagnostic category "probable 4R-tauopathy" to allow for joint *ante mortem* recognition of patients with PSP and CBD pathology. [2] This new category was introduced for joint recognition of patients with clinical syndromes predicting with high specificity the presence of underlying 4R-tauopathy, i.e. either PSP-or CBD-pathology. This comprises of course all "probable PSP" diagnostic categories being highly specific in predicting PSP pathology. Additionally, also "possible PSP with SL" and "possible PSP with CBS" were included in this concept, since they are considered as being highly specific in predicting either PSP- or CBD pathology ("probable 4R-tauopathy"), albeit being only moderately specific for PSP-pathology ("possible PSP").[2]

While the MDS-PSP criteria have been retrospectively validated in two independent cohorts[5,6], the category of "probable 4R-tauopathy" has not been investigated before.

Here, we retrospectively validate the accuracy of the newly proposed MDS-PSP criteria to predict 4R-tauopathy and compare it against the entire MDS-PSP criteria[2] and the Armstrong criteria for CBD[3], since each might qualify as clinical trial eligibility criteria.

Methods

Patients

This work was approved by the ethics committees of the Technical University of Munich and the participating centers. Cases with detailed clinical information and a pathological diagnosis according to published criteria of patients with PSP[7–9], CBD[8,10], multiple system atrophy (MSA)[11], Lewy body disease with a clinical diagnosis of Parkinsońs disease (PD)[12], and 4R-tau-negative frontotemporal lobar degeneration (FTLD)[13] were identified from collaborating brain banks (Ludwig-Maximilians-University, Munich, Germany; University Hospital, Bordeaux, France; King's College, London, UK; Lund University, Sweden; Erasmus Medical Center, Rotterdam, Netherlands; Hospital Clinic–IDIBAPS, Barcelona, Spain; University of Saskatchewan, Canada; Johns Hopkins University, Baltimore, USA; University of Pennsylvania, Philadelphia, USA). All donors and/or relatives provided written informed consent for the scientific use of their brains and medical records. Part of this cohort has been reported previously.[14,15]

Clinical assessment

Detailed clinical information was obtained for each case by retrospective chart review. Features that were systematically abstracted are shown in Supplementary Table 1. Equivocal findings were not considered as solid findings and thus coded as absent.

Validation of MDS-PSP criteria for 4R-tauopathy

Based on inclusion and exclusion criteria[2], all autopsy cases with pathologically confirmed PSP, CBD, MSA, PD, and 4R-tau-negative FTLD were retrospectively assigned to the clinical diagnoses "probable PSP", "possible PSP-CBS" and "possible PSP-SL" according to the MDS-PSP criteria[2] for the first 3 years of disease and for final ante-mortem record.

Frequency of the diagnosis “probable 4R-tauopathy” was assessed for each group, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for definite PSP and CBD (independent and jointly grouped as 4R-tauopathy) were determined.

In the definition of CBS in the original publication of the MDS-PSP criteria[2], “limb dystonia” was unintentionally omitted, but was considered as the fourth qualifying movement disorder sign for CBS in our analysis, as recommended before.[15]

Validation of MDS-PSP criteria for PSP and Armstrong criteria for CBD

To compare the diagnostic accuracy of the MDS-PSP criteria for “probable 4R-tauopathy” [2] with the standard diagnostic criteria for PSP[2] and CBD[3], we also assessed sensitivity, specificity, PPV, and NPV for the MDS-PSP criteria for PSP[2] and for the clinical diagnostic criteria for likely CBD pathology by Armstrong and colleagues[3] in our cohort as described above.

Results

Characteristics of all cases

We excluded ~400 cases from our analysis due to insufficient clinical information. Sufficient clinical details were available for 250 cases with 4R-tau pathology (N=195 PSP, N=55 CBD), and for 161 cases with non-4R-tau pathology (N=50 MSA, N=51 PD, N=60 4R-tau-negative FTLD). The demographic data of these 411 patients are presented in Table 1. Autopsy cases with 4R-tau-negative FTLD comprised 46 patients with TAR DNA-binding protein 43 (TDP-43) pathology, 10 patients with three-repeat (3R)-tau pathology, and four patients with fused in sarcoma (FUS) protein pathology.

Accuracy of MDS-PSP criteria for “probable 4R-tauopathy”

The frequencies of the diagnosis of “probable 4R-tauopathy” according to the MDS-PSP criteria[2] for each pathological group (within 1, 2, and 3 years of disease onset and at final record) are shown in Supplementary Table 2. From these, the accuracy of the diagnosis of “probable 4R-tauopathy” was calculated (Table 2).

The diagnosis “probable 4R-tauopathy” for 4R-tauopathies (jointly including PSP and CBD) had 23% sensitivity and 98% specificity in the third year after disease onset, and 59% sensitivity and 88% specificity at final record. Sensitivity in the first and second year after disease onset was low (<20%).

According to the MDS-PSP criteria for “probable 4R-tauopathy”, sensitivity for CBD was lower than for PSP, being 16% in the third year and 36% at final record for CBD, and 26% in the third year and 65% at final record for PSP (Table 2).

A diagnosis of “probable 4R-tauopathy” comprised mainly cases diagnosed with “probable PSP”. All but one case that classified as “possible PSP-CBS” or “possible PSP-SL” had frontal behavioral deficits or postural instability at the same time, and thus also qualified for

"probable PSP"[2] (Supplementary Table 3). These cases received a final diagnosis of "probable PSP" according to recently published guidelines.[15]

Accuracy of MDS-PSP criteria for PSP

Frequencies of the clinical diagnosis of PSP according to the MDS-PSP criteria (including all predominance types and all diagnostic certainties)[2] are shown in Supplementary Table 4.

From these, the accuracy of the diagnosis of PSP according to the MDS-PSP criteria was calculated (Table 2).

For 4R-tauopathies, an MDS-PSP diagnosis of PSP had 59% sensitivity and 82% specificity in the third year of disease, and 81% sensitivity and 48% specificity at final record.

Sensitivity for CBD was lower than for PSP, being 42% in the third year and 64% at final record for CBD, and 64% in the third year and 86% at final record for PSP.

Accuracy of Armstrong criteria for CBD

Frequencies of the clinical diagnosis of CBD according to the Armstrong criteria[3] are shown in Supplementary Table 5.

From these, the accuracy of the diagnosis of CBD was calculated (Table 2). For 4R-tauopathies, a diagnosis according to the Armstrong criteria had 3% sensitivity and 100% specificity in the third year of disease, and 17% sensitivity and 99% specificity at final record.

Sensitivity of the Armstrong criteria was similar for CBD and PSP, which was 7% in the third year and 16% at final record for CBD, and 2% in the third year and 17% at final record for PSP.

Discussion

For the first time we assessed the diagnostic accuracy of the MDS-PSP criteria for "probable 4R-tauopathy" in a large, retrospective, autopsy-confirmed cohort and compared their diagnostic value against the overall MDS-PSP criteria and the Armstong criteria for CBD. Our findings suggest that a diagnosis of "probable 4R-tauopathy" may be applied when *specificity* for the underlying pathology is crucial, e.g., in disease-modifying interventional trials and for investigations related to pathogenesis.

Benefits of a joint diagnosis of 4R-tauopathy according to our analysis include a) higher sensitivity for patients with CBD, as compared to the Armstrong criteria and b) higher specificity for patients with PSP and CBD as compared to the overall MDS-PSP criteria for PSP (when applied regardless of predominance type and diagnostic certainty).

Specificity of "probable 4R-tauopathy" decreased towards the final clinical record, which was mainly due to the documentation of vertical supranuclear gaze palsy and postural instability in cases with MSA and Lewy body pathology in later disease stages.

The low sensitivity and high specificity of the Armstrong criteria for CBD in our cohort may be caused by stricter exclusion criteria as compared to the MDS-PSP criteria, including resting tremor, which was present in 20% of PSP and 13% of CBD cases. A previous retrospective study found poor specificity of the Armstrong criteria.[16] However, this group explicitly included clinical CBD mimics in their analysis.[16]

The sensitivity of the MDS-PSP criteria for "probable 4R-tauopathy" for both PSP and CBD was low in our cohort, especially in the first 3 years. This may be partly explained by the lack of supranuclear gaze palsy and slow saccades, of which at least one feature is required for a diagnosis of "probable 4R-tauopathy". Both features were reported as absent in 8% of PSP cases and in 22% of CBD cases and were not reported at all in 10% of PSP, 29% CBD, 24% MSA, 33% PD, and 23% 4R-tau-negative FTLD cases. Exclusion of cases with missing record on oculomotor features did not produce significant changes to our results (not shown). The year of onset for either feature was not reported in 15% of PSP cases and in 4% of CBD cases, which is a limitation of our retrospective chart analysis.

Other limitations of this study are those intrinsic to all retrospective clinico-pathological studies. Medical records had variable quality and lacked standards for examination and documentation of clinical features. Moreover, the specificity of a diagnosis depends on the population and sample size of control cases. The fact that we did not include AD cases may have increased the specificity of the applied criteria in our analysis. From the clinical perspective, CBS has been associated with AD-pathology in as many as 20–30% of cases.[18] However, compared to the typical amnestic syndrome, CBS is a rare AD-phenotype.[19] To reflect a real-world scenario, inclusion of a very high number of AD cases and evaluation of amyloid PET imaging and CSF biomarkers to exclude AD pathology in CBS, as recommended by the MDS-PSP criteria[2] would have been necessary. Unfortunately, this exceeded the scope of the current project. Another bias might have been produced by the fact that the neurologists who reviewed the clinical charts were not blinded to the pathological diagnosis.

Therefore, our results must be interpreted with caution and will need prospective confirmation.

Despite these shortcomings in our methodology, it is likely that clinical features alone will not be able to diagnose 4R-tauopathies early on with good sensitivity. Furthermore, other 4R-tauopathies, such as argyrophilic grain disease and globular glial tauopathy are not represented by the MDS-PSP criteria[2], and their detailed clinical characterization is still pending.[17] These constraints underscore the crucial need for in vivo biomarkers such as biofluid protein levels and tau PET ligands.

In conclusion, the concept of 4R-tauopathies imposes clear advantages for clinical diagnosis and research. In the light of potential tau-specific interventions, early clinical recognition of 4R-tauopathies is crucial and will require more research, especially into 4R-tau specific *in vivo* biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Demographic data

	4RT			Non-4RT			
	Total	***PSP***	***CBD***	***Total***	***MSA***	***PD***	***T-neg. FTLD***
N	250	195	55	161	50	51	60
M:F	132:118	102:93	30:25	82:79	16:34	25:26	41:19
(N, [%])	[53:47]	[52:48]	[55:45]	[51:49]	[32:68]	[49:51]	[68:32]
Age at onset	65.7±0.6	66.3±0.6	63.8±1.2	58.2±0.7	59.7±1.3	58.7±1.5	56.8±1.0
(yrs., mean±S.E.M [range])	[41–91]	[41–91]	[42–81]	[42–80]	[45–80]	[42–76]	[42–74]
Age at death	73.3±0.6	74.1±0.6	70.4±1.2	67.7±0.7	67.1±1.2	73.4±1.2	63.5±1.2
(yrs., mean±S.E.M [range])	[51–94]	[54–94]	[51–85]	[47–92]	[51–90]	[59–92]	[47–84]
Disease duration	7.5±0.3	7.7±0.3	6.7±0.4	9.3±0.5	7.4±0.3	14.7±1.0	6.7±0.6
(yrs., mean±S.E.M [range])	[0–27]	[0–27]	[1–12]	[1–35]	[2–15]	[3–35]	[1–20]

Demographic data of all autopsy-confirmed patients, sub-grouped according to underlying pathology.

Table 2:

Diagnostic values for MDS-PSP criteria for “probable 4R-tauopathy”, MDS PSP criteria for PSP, and Armstrong criteria for CBD

		4RT				PSP				CBD			
		Sens.	***Spec.***	***PPV***	***NPV***	***Sens.***	***Spec.***	***PPV***	***NPV***	***Sens.***	***Spec.***	***PPV***	***NPV***
	MDS PSP criteria for prob. 4RT	9.6	99.4	96.0	41.5	10.8	98.1	84.0	39.2	5.5	93.7	12.0	86.2
1. year	**MDS PSP criteria for PSP**	47.2	88.2	86.1	51.8	52.8	70.7	75.2	47.1	27.3	65.7	11.0	85.4
	Armstrong criteria for CBD	0.8	100	100	39.4	0.5	99.5	50.0	52.6	1.8	99.7	50.0	86.8
	MDS PSP criteria for prob. 4RT	17.2	99.4	97.7	43.6	19.5	97.2	86.4	57.2	9.1	89.0	11.4	86.4
2. year	**MDS PSP criteria for PSP**	45.6	88.2	85.7	51.1	58.5	81.9	74.5	68.6	36.4	62.6	13.1	86.4
	Armstrong criteria for CBD	2.8	100	100	39.9	2.1	98.6	57.1	52.7	5.5	98.9	42.9	87.1
	MDS PSP criteria for prob. 4RT	23.6	98.1	95.2	45.3	25.6	94.4	80.7	58.5	16.4	85.1	14.5	86.8
3. year	**MDS PSP criteria for PSP**	59.2	82.0	83.6	56.4	64.1	75.9	70.6	70.1	41.8	56.7	13.0	86.3
	Armstrong criteria for CBD	3.2	100	100	40.0	2.1	98.2	50.0	52.6	7.3	98.9	50.0	87.3
	MDS PSP criteria for prob. 4RT	58.8	88.2	88.6	58.0	65.1	82.4	76.5	72.8	36.4	58.9	12.1	85.7
Final record	**MDS PSP criteria for PSP**	81.2	51.6	72.2	63.9	86.2	47.7	59.8	79.2	63.6	30.9	12.5	35.3
	Armstrong criteria for CBD	17.2	99.4	97.7	43.6	17.4	95.4	77.3	56.1	16.4	90.2	20.5	87.5

Sensitivity (Sens.), specificity (Spec.), positive predictive value (PPV), negative predictive value (NPV) in % for clinical diagnostic criteria when applied to our autopsy cases with 4R-tauopathy (PSP, N=195; CBD, N=55), and non-4R-tauopathy (MSA, N=50; PD, N=51; 4R-tau negative FTLD, N=60) within 1. - 3. year of disease and at final record.