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Quantifying apraxia and ophthalmokinetic abnormalities in patients with atypical Parkinsonism: A new way to differential diagnosis?

Vasilios C. Constantinides*, George P. Paraskevas, Constantinos Potagas, Leonidas Stefanis, Elisabeth Kapaki

1st Department of Neurology, National and Kapodistrian University of Athens, School of Medicine, Eginition Hospital, 72-74 Vas. Sophias Ave, 11528, Athens, Greece

1. Introduction

Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are 4-repeat (4R) tauopathies, with distinct pathologic lesions. Multiple system atrophy (MSA) on the other hand is a synucleinopathy. The most common clinical presentation of CBD is the corticobasal syndrome (CBS), which combines cortical and basal ganglionic symptoms and signs [1]. Apraxia is considered the clinical hallmark of CBS [2]. PSP, on the other hand, usually presents with prominent saccade slowing and decrease in vertical gaze amplitude (hypometria) as well as early postural instability. This phenotype is called the "Richardson syndrome" (RS), but a number of other PSP variants have been described more recently [3]. Finally, MSA presents with a combination of dysautonomia, cerebellar, parkinsonian and pyramidal signs. MSA patients do not present with apraxia or saccade slowing/visual hypometria.

Clinical-pathological studies have established that there is significant clinical overlap between CBS and PSP and pathological overlap between CBD and PSP [4–9]. CBD patients can rarely present with a RS-like phenotype (~6%), as indicated by an overall overview of pathologically confirmed cases [1], although some have argued that this frequency can reach 40% [4]. Likewise, PSP can rarely (about 4%) present with a CBS-like phenotype [10]. Importantly, some patients present with mixed symptoms, and are labeled "hybrids" [11].

The major drawback of these studies is their retrospective design [4–9]. Data collection are based on review of patients' charts. Thus, apraxia and ophthalmokinetic abnormalities are usually described as present or absent, without providing information on the severity of these signs. It is not uncommon for these signs not to be examined, leading to missing information. Furthermore, the lack of a standardized method of examining apraxia, can lead to different interpretations on the presence or absence of apraxia.

Many studies have looked into imaging or CSF biomarkers, in order to achieve a more robust *ante mortem* clinical diagnosis in patients with atypical Parkinsonism. This is of particular importance, due to the emergence of protein-targeted, disease-modifying treatments.

The purpose of this study was to prospectively examine a well-characterized cohort of patients with atypical Parkinsonism and assess the quantitative characteristics of apraxia and ophthalmokinetic abnormalities. We aimed at defining a set of clinical indices, based on the severity of apraxia and ophthalmokinetic abnormalities, which would assist in the differential diagnosis of PSP, CBS and MSA.

2. Methods

2.1. Patients

Patients were prospectively recruited from 2011 to 2014 as part of the atypical Parkinsonism Registry of our Department. All patients underwent a thorough evaluation including medical history, physical and neurological examination. Standard laboratory tests were performed to exclude secondary causes of Parkinsonism, such as vascular Parkinsonism, normal pressure hydrocephalus, drug-induced Parkinsonism, etc.

Two cohorts were used for the purposes of this study. The first cohort (*"probable atypical Parkinsonism cohort"*) comprised 35 patients with a diagnosis of "probable" atypical Parkinsonism syndrome, according to latest established diagnostic criteria at the time of the study [1,12,13] (CBS, n = 10; MSA, n = 11; PSP, n = 14).

According to latest established criteria, all patients who fulfill criteria for probable CBS, are also considered probable CBD patients. However, in the absence of pathological confirmation, the pathology underlying CBS cannot be safely established *ante mortem*. For this reason, the term CBS was used, referring to the clinical phenotype of corticobasal syndrome.

By definition, all patients who were assigned as probable PSP patients based on the Litvan criteria [12], are also considered probable PSP-Richardson syndrome patients according to the newest established PSP criteria [3]. All CBS symptoms and signs were prospectively examined and recorded since the initiation of the study. The Armstrong criteria [1] were retrospectively applied to CBS patients included in this study prior to 2013.

* Corresponding author.
E-mail addresses: vassilis.kon@hotmail.com, vconstan@med.uoa.gr (V.C. Constantinides), geoprskvs44@gmail.com (G.P. Paraskevas), cpotagas@otenet.gr (C. Potagas), lstef@med.uoa.gr (L. Stefanis), ekapaki@med.uoa.gr (E. Kapaki).

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All patients were examined independently by three neurologists with experience in movement disorders (EK, GP and VC), and were given a clinical diagnosis of PSP, CBS, MSA, hybrid or other diagnosis. In cases of disagreement, the patients were re-examined and a consensus was reached.

The second cohort ("*possible atypical Parkinsonism cohort*") consisted of 17 patients with a diagnosis of "possible" atypical Parkinsonism syndrome, according to the same criteria [1,12,13] (CBS, n = 4; MSA, n = 4; PSP, n = 5) or "*hybrids*" (patients with mixed PSP and CBS clinical features, n = 4). Patients included in this study were diagnosed as probable or possible atypical Parkinsonism syndrome without using the oculomotor portion of the PSP Rating Scale or Goldenberg apraxia test.

2.2. Opthalmokinetic examination

To examine for saccade speed, a semi-quantitative analysis was performed for each patient. According to this, saccade speed was graded on a 0 to 4 scale (0: normal saccade velocity; 1: mild saccade slowing; 2: moderate saccade slowing; 3: severe saccade slowing; 4: no saccade) in the four primary gaze directions (upwards, downwards, left and right). The sum of these sub-scores produced a composite *saccade speed score*, from 0 to 16.

Likewise, a *hypometria score* (0–16) was introduced, by grading visual hypometria in the four primary visual directions (0: no hypometria; 1: mild hypometria; 2: moderate hypometria; 3: severe hypometria; 4: fixed gaze). This scale was performed independently by two neurologists (GP and VC), with a high agreement ratio (92%).

Furthermore, the voluntary upward, downward and lateral saccade scores of the supranuclear ocular motor examination (score 0–4 for each element), as defined in the progressive supranuclear palsy rating scale (PSP-Rating Scale) were included [14]. In short, this scale incorporates saccade speed as well as gaze amplitude for each primary gaze direction. A total score (upward + downward + lateral saccades; *score 0–12*) was calculated.

All patients were examined independently by two neurologists with experience in movement disorders (GP and VC). In cases of disagreement between examiners, the patient was re-examined by both examiners and a score was agreed upon.

2.3. Neuropsychological and apraxia tests

All patients underwent an extensive neuropsychological evaluation. Tests included the Mini Mental State Examination (MMSE), The Frontal Assessment Battery (FAB), the 15-point clock drawing test (Clox1 & Clox2), the 5-word immediate and delayed recall test.

To test for apraxia, the *Goldenberg apraxia test* (GAT) was implemented [15,16]. In short, the GAT consists of an imitation subscale and a pantomime subscale.

The imitation subscale comprises 10 meaningless hand positions and 10 finger configurations. These gestures are exhibited to the patient by the examiner. The patient is then instructed to imitate them exactly. Each gesture is performed separately with each hand. Two points are awarded if the imitation is correct on the first effort, one point is awarded if it is accomplished on the second try, and no points are awarded if the patient fails to imitate the gesture. Thus the maximum score for the imitation subscale is 80 (40 for each hand; 20 for hand imitation and 20 for finger imitation).

The pantomime subscale comprises 20 learned, everyday gestures which the patient is instructed to perform after verbal command (e.g. show me how you brush your teeth). Each gesture is awarded two to four points, depending on the complexity of the movement, for a total score of 55. The total Goldenberg Apraxia Test score can thus range from 0 to 135.

All patients were videotaped for the purposes of the Goldenberg apraxia test. Each gesture was independently scored by two neurologists (CP and VC). In cases of disagreement, a final score was awarded after re-evaluation by both examiners.

2.4. CSF biochemical analysis

CSF biochemical analysis, with measurement of amyloid beta ($A\beta_{42}$), total tau protein (τ_T), and phosphorylated tau protein ($\tau_{P\text{-}181}$) was performed in all patients of the probable atypical Parkinsonism cohort, as described in detail elsewhere [17]. All patients with abnormal values in all three CSF biomarkers according to cut-off values of our laboratory ($\tau_T > 376$ pg/ml; $\tau_{P\text{-}181} > 56.76$ pg/ml; $A\beta_{42} < 682$ pg/ml), were considered to have a CSF AD profile [18]. All other patients were designated as non-AD patients. All patients, irrespective of their CSF biochemical profile were included in the initial analysis. None of the MSA or PSP patients had an AD CSF profile.

2.5. Ethical considerations

This study was performed according to the ethical guidelines of the declaration of Helsinki, after approval of the Ethical and Scientific Committee of Eginition Hospital. All patients (or the next of kin carer, in cases of compromised mental capacity) gave written informed consent prior to study participation.

2.6. Statistical analysis

Shapiro Wilk and Levene's tests were applied to test for normality of distribution and homogeneity of variances. Two-way analysis of covariance (ANCOVA), with diagnosis and gender as co-factors and age and disease duration as covariates was used to test for differences in opthalmokinetic measurements or neuropsychological/apraxia tests scores. For between-group differences, post-hoc analysis with Bonferroni correction for multiple comparisons was applied. In cases of non-normality, the non-parametric Kruskal-Wallis test (followed by Dunn's post hoc test) was implemented.

The diagnostic value of each marker was analyzed by Receiver Operating Characteristic (ROC) curve analysis. All analyses were performed by IBM SPSS Statistics® version 22.0.0.0 (SPSS Inc., Chicago, IL, 2013). All graphs were designed using GraphPad Prism®, version 5.03 (GraphPad Software Inc., La Jolla, CA, 2009).

Three sets of analyses were performed.

The initial analysis aimed at determining the optimal combination of clinical markers to differentiate among the three atypical Parkinsonism groups. To this end, the most potent opthalmokinetic measurement and the most potent apraxia measurement were selected by use of ROC curve analysis. These two markers were then combined to define clinical fields which would differentiate among probable PSP, CBS and MSA patients. These were designated "CBS field", "MSA field" and "PSP field" (see results).

The second analysis aimed at examining whether the clinical fields, as determined in the first analysis, could differentiate between CBS-AD and CBS-nonAD patients, as defined by CSF biochemical profile.

The third analysis, aimed to determine the predictive value of the three clinical fields ("CBS field", "MSA field" and "PSP field"), as determined in the first analysis, in the "possible atypical Parkinsonism cohort".

3. Results

3.1. Demographic, ophthalmokinetic and neuropsychological characteristics in the "probable atypical Parkinsonism" cohort

CBS patients were significantly older compared to PSP and MSA ($p = 0.041$). PSP patients had significantly worse saccade speed and hypometria scores ($p < 0.001$), as well as worse PSP-Rating Scale ocular motor exam scores ($p < 0.001$ for all elements, with the

Table 1
Demographic, clinical and neuropsychological characteristics of patients. All data are presented as mean (SD). *PSP-RS*: PSP Rating Scale; *UPDRS*: Unified Parkinson's disease Rating Scale; *MMSE*: Mini Mental State Examination; *FAB*: Frontal Assessment Battery; Clox 2: 15-point Clock Drawing Test.

	CBS	MSA	PSP	p value
Demographic – clinical data				
Gender *(m/f)*	6/4	8/3	7/7	0.515
Age *(y)*	69.1 (7.4)	62.8 (8.1)	60.9 (7.3)	0.041
Disease_duration *(m)*	3.2 (1.5)	2.6 (1.3)	3.1 (1.7)	0.677
Opthalmokinetic examination				
Saccade speed score *(max:16)*	3.7 (5.1)	0.1 (0.3)	11.0 (3.5)	< 0.001
Vertical subscore *(max: 8)*	2.3 (2.8)	0.0 (0.0)	6.5 (1.2)	< 0.001
Horizontal subscore *(max: 8)*	1.4 (2.5)	0.1 (0.3)	4.5 (2.7)	0.01
Hypometria score *(max:16)*	0.9 (2.9)	0.0 (0.0)	5.8 (3.8)	< 0.001
Vertical subscore *(max: 8)*	0.5 (1.6)	0.0 (0.0)	4.0 (2.0)	< 0.001
Horizontal subscore *(max:8)*	0.4 (1.3)	0.0 (0.0)	1.8 (2.0)	< 0.001
PSP-RS upward saccades *(max:4)*	0.7 (1.0)	0.0 (0.0)	2.0 (1.1)	< 0.001
PSP-RS downward saccades *(max:4)*	0.6 (0.7)	0.0 (0.0)	2.2 (1.1)	< 0.001
PSP-RS lateral saccades *(max:4)*	0.4 (0.7)	0.0 (0.0)	1.1 (1.0)	0.030
PSP-RS total score *(max:12)*	1.7 (2.3)	0.0 (0.0)	5.2 (2.7)	< 0.001
Neuropsychological tests				
UPDRS III	30.1 (13.1)	17.3 (19.9)	21.8 (10.8)	0.343
MMSE *(max:30)*	21.3 (5.9)	28.4 (2.4)	25.7 (3.3)	0.003
FAB *(max:18)*	8.8 (4.8)	13.9 (2.6)	11.6 (4.5)	0.064
Clox 2 *(max:15)*	7.0 (4.1)	12.6 (1.9)	8.8 (3.3)	0.004
5-word delayed recall	3.9 (1.3)	4.9 (0.3)	4.6 (0.8)	0.149
Goldenberg Apraxia Test				
Total Score *(max:135)*	74.5 (17.3)	131.1 (3.7)	126.0 (9.6)	< 0.001
Imitation *(max:80)*	37.2 (16.1)	78.8 (1.5)	77.1 (5.8)	< 0.001
Pantomime *(max:55)*	37.3 (7.3)	52.3 (2.6)	48.7 (5.5)	0.001

exception of lateral saccades, $p = 0.030$). Separate analysis of horizontal and vertical movements also differed significantly among groups. CBS patients performed worse in the MMSE and Clox2 tests ($p = 0.003$ and $p = 0.004$ respectively). The total GAT score ($p < 0.001$), as well as the imitation ($p < 0.001$) and pantomime subscores ($p = 0.001$) were significantly lower in the CBS group (Table 1).

3.2. ROC curve analysis of the diagnostic accuracy of opthalmokinetic and apraxia measurements

The GAT total score as well as the GAT imitation sub-score provided 100% sensitivity and specificity for a CBS diagnosis in the probable atypical Parkinsonism cohort (cut off ≤ 106 and ≤ 64 respectively (Table 2, Sup. Fig. 1). Regarding opthalmokinetic measurements, hypometria scores were most potent in discriminating PSP from the other two groups, with a cut-off point of ≥ 1 providing 100% sensitivity and 95% specificity. The PSP Rating Scale ocular motor exam score provided similar results (cut-off ≥ 3, sensitivity 100%, specificity 86%) (Table 2, Sup. Fig. 2).

3.3. Construction of "clinical fields"

For the construction of a composite clinical index, the optimal apraxia and the optimal opthalmokinetic indices were selected. To this end, the *total GAT score* was selected, as the optimal apraxia index (Sup. Fig. 3). This was due to its greater range of values (0–135), compared to the *GAT imitation sub-score* (0-80).

Of the opthalmokinetic indices, the *PSP-Rating Scale ocular motor exam score* (≥ 3) was selected (Sup. Fig. 4). The *hypometria score* provided numerically greater specificity. However, the low cut-off point (≥ 1) rendered it susceptible to clinical misclassification of patients.

Based on these two indices (total GAT score, cut-off ≤ 106; saccade speed score, cut off ≥ 3), three clinical fields were constructed: The "*MSA field*" comprised patients with no apraxia (GAT > 106) or saccade slowing (saccade speed score < 5); the "*PSP field*", with saccade slowing (saccade speed score ≥ 3) but no apraxia (GAT > 106); the "*CBS field*", with apraxia (GAT ≤ 106), irrespective of the presence or absence of saccade slowing. When applied on the "*probable* atypical Parkinsonism" cohort, these three fields provided 100% sensitivity and 100% specificity for the respective diagnosis.

3.4. CBS underlying pathology

CSF biochemical analysis revealed that five (50%) of the patients fulfilling criteria for probable CBS, had in fact a CSF AD biochemical profile. All of the CBS-AD and CBS-nonAD patients were allocated in the "CBS field". None of the demographic, ophthalmokinetic, neuropsychological or apraxia measurements were useful in discriminating the two groups (Sup. Table 1).

3.5. Implementation of clinical fields in the "possible atypical Parkinsonism" cohort

The "*MSA field*" had a 100% sensitivity, 77% specificity for an MSA diagnosis in the "possible atypical Parkinsonism" cohort. The "*PSP field*" provided an 80% sensitivity and 100% specificity for a PSP diagnosis. The "*CBS field*" was diagnostic of either CBS or hybrids with a 75% sensitivity and 100% specificity. CBS patients could not be differentiated from hybrids based on their apraxia or ophthalmokinetic profiles (Table 3, Fig. 1).

4. Discussion

In an era of protein-targeted, disease-modifying treatment studies, development of robust biomarkers is pivotal for an accurate diagnosis of patients with atypical Parkinsonism. To this end, many studies have focused on either CSF biochemical markers or MRI markers of various modalities (linear measurements, planimetry, volumetry, diffusion parameters etc.). These studies have produced mixed results, with a degree of overlap among patients [4–9].

The present study aimed at utilizing quantitative ocular motor and apraxia measurements in order to differentiate among patients with atypical Parkinsonism. Based on these measurements, clinical fields were constructed. Interestingly, these fields differentiated "probable" PSP, MSA and CBS patients with 100% sensitivity and specificity in our cohort. Furthermore, when applied to a "possible" atypical Parkinsonism cohort, these fields were highly specific (> 80%) for all diagnoses, with moderate sensitivity for MSA and CBS. These fields could not however differentiate CBS from hybrids, nor could they discriminate CBS patients with AD or non-AD underlying pathology.

Opthalmokinetic abnormalities have been examined previously in patients with Parkinsonism. Electro-oculographic studies support that PSP is characterized by decreased saccade speed and gain early in the disease course [19–22]. These abnormalities seem to be present early, even in atypical cases (i.e. PSP-P) [23]. CBS patients on the other hand mainly present with prolonged saccade latencies [19–22]. Square-wave jerks, gaze-evoked nystagmus, saccadic hypometria and impaired smooth pursuit are encountered in MSA [24]. Although visual hypometria has been described in MSA, it is only mild and usually affects upward gaze. In agreement with these oculographic studies, opthalmokinetic abnormalities, as measured clinically at the bedside by the PSP-Rating Scale ocular motor examination score, were potent discriminators of PSP from other atypical Parkinsonian syndromes in our cohort.

Table 2
Comparison of the discriminative power of various indices in CBS and PSP. *MMSE*: Mini Mental State Examination, *Clox 2*: 15-point Clock Drawing Test; *GB*: Goldenberg Apraxia Test; *Sens*: sensitivity; *Spec*: specificity; *PPV*: positive predictive value; *NPV*: negative predictive value.

	AUC (SD)	p-value	Cut-off	Sens	Spec	PPV	NPV
CBS							
MMSE	0.81 (0.08)	0.030	≤21	50%	95%	83%	81%
Clox2	0.76 (0.09)	0.022	≤11	100%	45%	45%	100%
GB total	1.00 (< 0.01)	< 0.001	≤106	100%	100%	100%	100%
GB pantomime	0.94 (0.04)	< 0.001	≤48	100%	76%	63%	100%
GB imitation	1.00 (< 0.01)	< 0.001	≤64	100%	100%	100%	100%
PSP							
Hypometria score	0.96 (0.04)	< 0.001	≥1	100%	95%	93%	100%
Vertical subscore	0.97 (0.33)	< 0.001	≥3	72%	95%	91%	83%
Horizontal subscore	0.76 (0.91)	0.011	≥2	50%	95%	88%	74%
Saccade speed score	0.93 (0.05)	< 0.001	≥5	100%	86%	83%	100%
Vertical subscore	0.94 (0.04)	< 0.001	≥5	100%	85%	82%	100%
Horizontal subscore	0.86 (0.07)	< 0.001	≥2	86%	85%	80%	90%
PSPRS upward saccades	0.92 (0.05)	< 0.001	≥1	100%	76%	72%	100%
PSPRS downward saccades	0.94 (0.04)	< 0.001	≥1	100%	76%	72%	100%
PSPRS lateral saccades	0.78 (0.09)	0.006	≥1	69%	86%	75%	82%
PSPRS ocular motor examination score	0.95 (0.04)	< 0.001	≥3	100%	86%	82%	100%

Table 3
Diagnostic accuracy of the three clinical fields in the "possible" P-plus cohort. *Sens:* sensitivity; *Spec*: specificity; *PPV*: positive predictive value; *NPV*: negative predictive value.

	Diagnosis	Sens	Spec	PPV	NPV
"MSA field"	MSA vs. other groups	75%	85%	60%	92%
"PSP field"	PSP vs. other groups	100%	92%	83%	100%
"CBS field"	CBD/hybrid vs. other groups	75%	100%	100%	82%

Apraxia is the clinical hallmark of CBS. Some apraxia studies in Parkinsonian syndromes have reported frequencies as high as 75% in PSP [25,26] and 30% in PD patients [27]. In contrast, apraxia is not characteristic of MSA [27]. These studies imply that the presence or absence of apraxia alone cannot discriminate between PSP and CBS.

However, quantitative analyses have demonstrated that there are differences in the severity of apraxia (i.e. more severe in CBS compared to PSP), particularly in intransitive movements [25]. Qualitative analyses, such as error-type profiling, could also differentiate between the two disorders. Thus, it has been supported that CBS is characterized by errors of awkwardness, whereas PSP by sequence errors [26]. This could translate in a limb-kinetic apraxia in CBS, and an ideomotor apraxia in PSP. CBS patients have more severe distal than proximal apraxia, which also supports the notion of limb-kinetic apraxia [28].

Overall, studies on apraxia in patients with Parkinsonism exhibit important discrepancies. These could be attributed to: a) differences in the definition of apraxia types (ideational vs. ideomotor vs. limb-kinetic); b) diverse modalities used to test for apraxia (transitive vs. intransitive, distal vs. proximal, representational vs. non-representational, to verbal or visual command etc.); c) methodological differences (i.e. the apraxia scale used); d) differences in the threshold of "abnormality" used. All these factors have served to increase the uncertainty on the subject. For this reason, we opted to implement a simple apraxia test, which includes finger and hand imitation, as well as pantomime, to ascertain apraxia severity. The Goldenberg apraxia test discriminated CBS from other atypical Parkinsonism patients, and is in our view a clinically useful means to measure apraxia severity.

Our study points to the importance of systematic, quantitative analysis of apraxia and opthalmokinetic abnormalities when examining a patient with Parkinsonism. We support that this approach can assist in the differential diagnosis of atypical Parkinsonism patients. Furthermore, this is feasible at bedside, without the need of elaborate methods (i.e. video-oculography).

Interestingly, implementation of the clinical fields had high specificity even in the cases of "possible" MSA and PSP. This implies that these clinical fields are useful on a clinical level, even in cases that do not exhibit the complete phenotype of MSA and PSP.

These fields however were not useful in patients with "possible" CBS. Only two of the four "possible" CBS patients had apraxia. Moreover, hybrids had apraxia but mixed opthalmokinetic abnormalities (one with normal ocular motility vs. three with hypometria). This could be explained in two ways: Firstly, the CBS phenotype comprises of six cardinal features (myoclonus, alien hand phenomena, cortical sensory deficits, parkinsonism, dystonia, apraxia) [1]. It is conceivable that a patient with CBS presents with symptoms other than apraxia initially, and develops apraxia later in the disease course. This is in contrast with PSP and MSA, where opthalmokinetic abnormalities and dysautonomia respectively are evident early in the disease course. An alternative explanation could be the diverse underlying or mixed pathologies in CBS patients (TDP-43, FTD-tau, PSP, CBD, AD etc.) [29]. Only well characterized clinical cohorts with pathologic confirmation could confidently answer this question.

Importantly, CBS patients could not be differentiated based on their apraxia and opthalmokinetic abnormalities in AD and non-AD patients. This emphasizes the importance of CSF biomarker analysis in CBS patients, as a first step in the determination of underlying pathology. CSF analysis is pivotal in the *ante mortem* recognition of underlying AD pathology. However, CSF analysis cannot assist in cases of mixed pathologies in a single patient (for example concomitant AD and CBD pathology). This is particularly important in elderly patients [29]. More biomarkers are needed to determine *ante mortem* the underlying pathology in patients with Parkinsonism. Until this is accomplished, a systematized analysis of clinical features remains pivotal.

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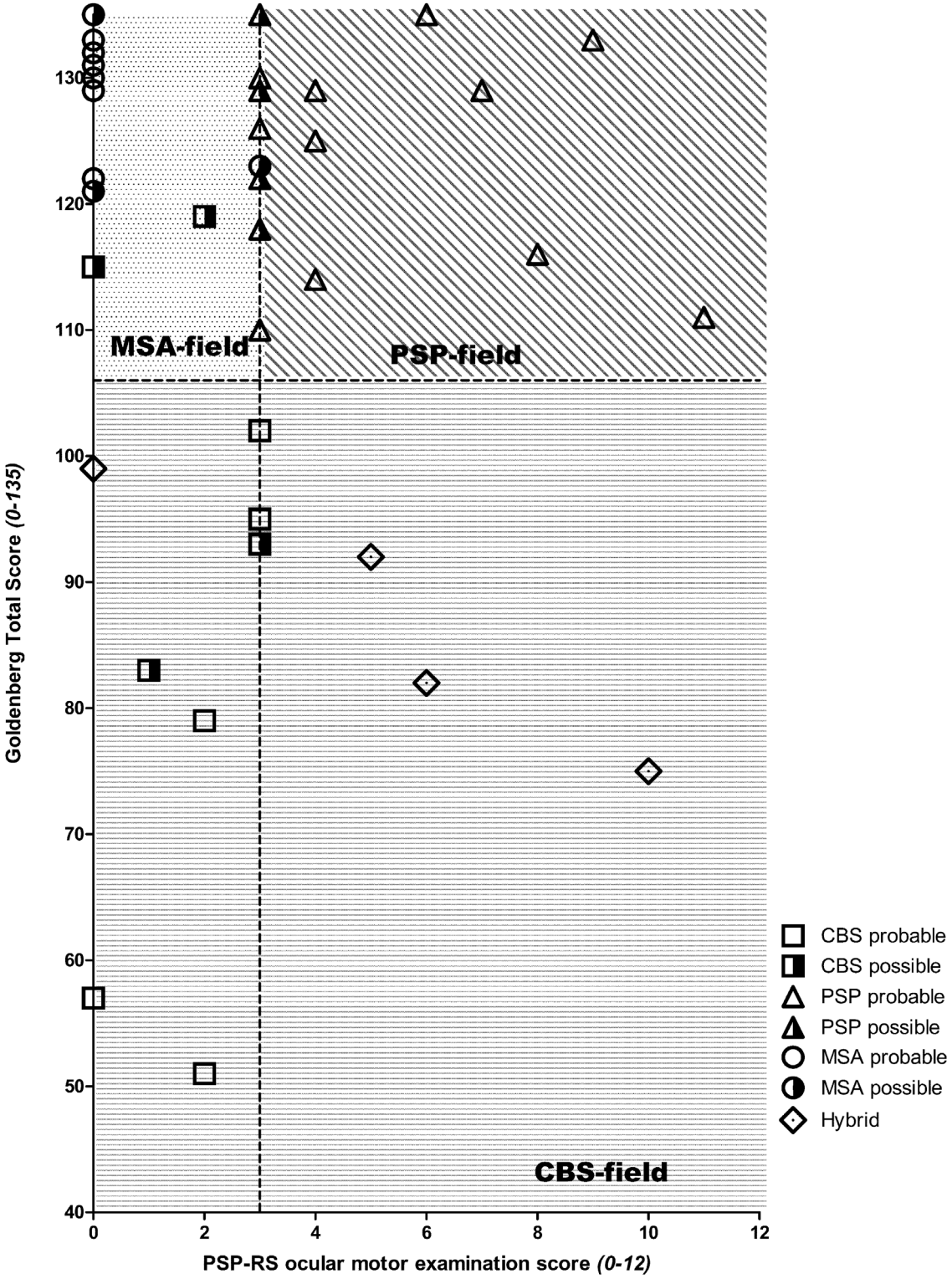

Fig. 1. Scatterplot of combined PSP-Rating Scale and Goldenberg apraxia total scores by diagnostic group.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.12.006.

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