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SHORT COMMENTARY

Asymmetry index of Blink Reflex Recovery Cycle differentiates Parkinson's disease from atypical Parkinsonian syndromes

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Abstract

Background Differential diagnosis between Parkinson's disease (PD) and atypical Parkinsonian syndromes (APS), such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), is often difficult because of overlap of common clinical features. We evaluated R2 Blink Reflex Recovery Cycle (R2BRRC) in drug-naive PD patients and in MSA and PSP patients to differentiate early PD from APS.

Methods We investigated 43 patients: 15 drug-naive PD patients, 16 MSA patients, and 12 PSP patients. R2BRRC was evaluated bilaterally at interstimulus intervals (ISIs) of 100, 150, 200, 300, 400, 500, and 750 ms. An asymmetry index (AI) of R2BRRC for each ISI was computed.

Results R2BRRC of PD patients showed an increased brainstem excitability for less affected side (LAS) stimulation at ISIs of 100, 150, 200 ($p < 0.001$), and 300 ms ($p = 0.03$) compared to more affected side (MAS) stimulation, whereas no differences between LAS and MAS stimulation were found in APS. AI of 0.87 at ISI of 100 ms differentiated PD from MSA with a sensitivity of 86.7% and a specificity of 100%, whereas AI of 0.78 at ISI of 100 ms permitted to discriminate PD from PSP with a sensitivity of 86.7% and a specificity of 91.7%.

Conclusion AI of R2BRRC may represent a reliable tool in differentiating PD from APS, especially at the early stage of the disease.

Keywords Blink Reflex Recovery Cycle · Parkinson's disease · Atypical parkinsonism · Progressive supranuclear palsy · Multiple system atrophy

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, clinically featured by tremor, rigidity, and bradykinesia. Atypical Parkinsonian Syndromes (APS) are rapidly progressive neurodegenerative disorders, characterized by parkinsonism and additional debilitating symptoms. APS differ from PD by a more rapid progression and disabling functional prognosis. However, the differential diagnosis between PD and APS, such as multiple system atrophy (MSA) and the clinical variant of progressive supranuclear palsy (PSP) with predominant parkinsonism, is often difficult because of overlap of common clinical features, which makes APS indistinguishable from PD.

R2 Blink Reflex Recovery Cycle (R2BRRC) is a neurophysiological tool, used to measure brainstem excitability. PD is typically characterized by an enhanced R2BRRC [1]. Only few studies have examined the alterations of excitability in APS, and R2BRRC has been reported to be abnormally enhanced in MSA and PSP, such as in PD [2, 3]. Despite these data, to our knowledge, there are no studies which have focused on possible asymmetric brainstem excitability in untreated PD patients.

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The aim of this study was to evaluate differences of brainstem excitability in drug-naive PD, MSA, and PSP patients through a side-to-side comparison. We computed an asymmetry index (AI) of R2BRRC which may help in differentiating PD from APS, especially at the early stage of the disease.

Methods

Patients affected by untreated PD, PSP, and MSA were enrolled for 24 months, according to the Movement Disorder Society criteria [4, 5] and Gilman's diagnostic criteria [6]. Clinical diagnosis of APS was confirmed by subsequent follow-up visits. The study was approved by the Local Ethics Committee and patients were enrolled after signing the written informed consent.

Clinical evaluation was performed through Unified Parkinson's Disease Rating Scale—Motor Examination section (UPDRS-ME) [7] and Hoehn and Yahr (H&Y) stage [8].

Blink reflex (BR) and R2BRRC [1] were recorded in all patients by a neurophysiologist unaware of clinical data. Bipolar electrical stimulation was applied to supraorbital nerve (intensity: 15–25 mA; duration: 0.2 ms). Electromyographic responses were recorded in orbicularis oculi muscles with surface silver–silver chloride electrodes (filters: 20 Hz–10 kHz) [1].

R2BRRC was performed with the technique of paired stimulation at interstimulus intervals (ISIs) of 100, 150, 200, 300, 400, 500, and 750 ms. For each ISI the R2 amplitude ratio (expressed as percentage ratio between R2 peak-to-peak amplitudes of conditioned and unconditioned responses) was calculated [1]. R2BRRC was evaluated by plotting the R2 amplitude ratio for all the tested ISIs and for both sides.

The absolute value of R2BRRC AI was estimated using the following formula: [(Side1 - Side2)/(Side1 + Side2)], where the two sides are the percentage values of R2BRRC for each ISI, calculated by stimulating both more clinical affected side (MAS) and less affected side (LAS) of each patient. MAS was defined as more clinical impaired side at the time of enrollment, comparing the presence of tremor, rigidity, and bradykinesia through UPDRS-ME scale between the two sides of the body. The subscores of UPDRS-ME scale have been calculated from the item 20–26 to objectively differentiate MAS from LAS for each group of patients.

Treated APS patients were evaluated at least after 12 h of withdrawal of anti-Parkinsonian medication.

Statistical analysis

Shapiro–Wilk test was used to analyze the normality of the data. Differences of means and proportions between two selected groups were evaluated by *t* test and chi-square test, respectively. Differences among the three groups were assessed by analysis of variance (ANOVA), using Tukey post-hoc test for further comparisons. Sensitivity and specificity of AI in differentiating PD from MSA and PSP patients together with 95% confidence intervals (95% CI) were calculated using the optimal cut-off values determined by ROC (receiver operating characteristic) curve analysis.

Results

Forty-three subjects were enrolled: 12 patients with PSP, 16 patients with MSA, and 15 patients with an untreated PD. A diagnosis of probable PSP—Richardson Syndrome was made for 11 out of 12 patients affected by PSP, whilst only one patient presented with a probable PSP-P. Thirteen patients out of sixteen were diagnosed as probable MSA-P, whereas three patients showed a diagnosis of probable MSA-C. Demographics and clinical characteristics are summarized in Table 1.

PSP and MSA patients presented with significantly longer disease duration and higher UPDRS-ME and H&Y scores as compared to PD patients. APS showed almost symmetrical clinical features. However, some differences between MAS and LAS were evident, even if they were more prominent in PD patients than in APS (PSP: UPDRS-ME MAS subscore: 12.9 ± 4.7, LAS subscore: 9.3 ± 4.8; $p < 0.001$; MSA: UPDRS-ME MAS subscore: 15.5 ± 3.9, LAS subscore: 10.6 ± 4.8; $p < 0.001$; PD: UPDRS-ME MAS subscore: 11.5 ± 4.3, LAS subscore: 5.3 ± 4.3; $p < 0.001$).

BR responses to single stimulation were present at a normal latency, similarly in all participants. R2BRRC curves of the three groups are shown in Fig. 1. All PSP and MSA patients showed an early R2 recovery starting at ISI of 100 ms on both sides of stimulation, thus no statistically significant differences were found in a side-to-side

Table 1 Demographic and clinical characteristics of participants

	PSP ($n = 12$)	MSA ($n = 16$)	PD ($n = 15$)
Age (years)[a]	70.3 ± 6.8	68.0 ± 9.1	64.6 ± 7.3
Men (%)	7 (58%)	9 (56%)	10 (67%)
Disease duration (years)[a,*]	3.6 ± 2.6	4.6 ± 2.1	1.7 ± 1.3
UPDRS-ME (score)[a,°]	35.7 ± 15.0	43.2 ± 12.5	25.2 ± 11.7
H&Y (score)[a,*]	3.0 ± 0.6	2.7 ± 0.6	1.9 ± 0.3

PSP progressive supranuclear palsy, *MSA* multiple system atrophy, *PD* Parkinson's disease, *UPDRS-ME* unified Parkinson's disease rating scale-motor examination, *H&Y* Hoehn and Yahr stage

ANOVA test: *$p < 0.001$; °$p = 0.002$

[a]Data are shown as mean ± standard deviation (SD)

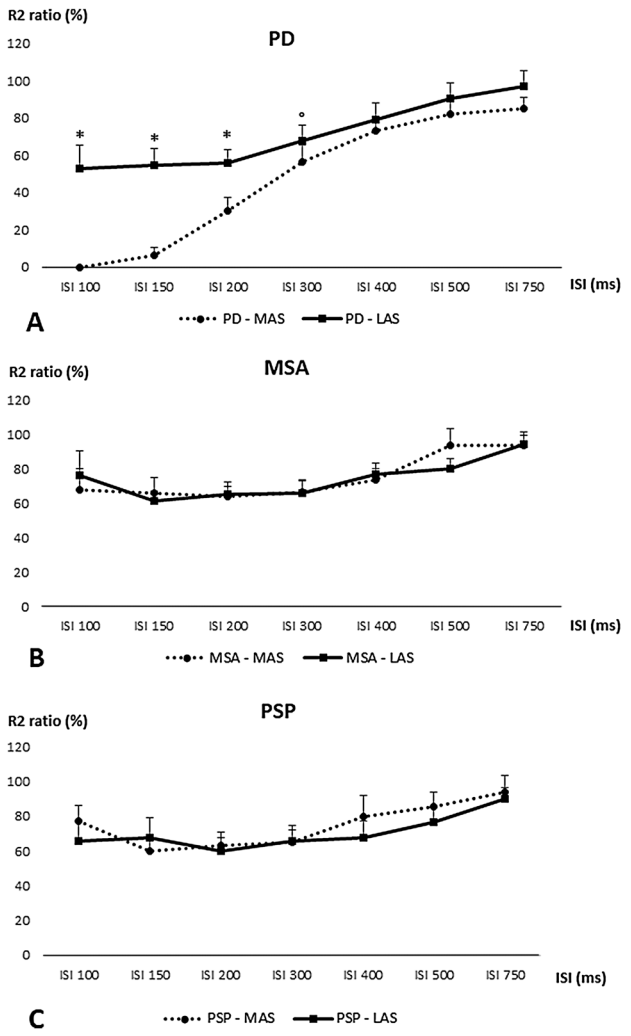

Fig. 1 R2 blink reflex recovery cycle graph-curve for PD, MSA and PSP patients. Ratios of the conditioned R2 component (amplitude) to the unconditioned response are shown as mean + standard error (S.E.). X-axis: interstimulus intervals (ISIs) in milliseconds (ms). Y-axis: ratio of the conditioned to the unconditioned R2 response in percentage (%). **a** R2 blink reflex recovery cycle graph-curve of PD patients; paired *t* test: $*p < 0.001$, $°p = 0.03$ when comparing more affected side (MAS) stimulation vs. less affected side (LAS) stimulation. **b** R2 blink reflex recovery cycle graph-curve of MSA patients; no statistically significant differences were found when comparing MAS stimulation vs. LAS stimulation. **c** R2 blink reflex recovery cycle graph-curve of PSP patients; no statistically significant differences were found when comparing MAS stimulation vs. LAS stimulation. *R2BRRC* R2 blink reflex recovery cycle, *PD* Parkinson's disease, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy, *MAS* more affected side stimulation, *LAS* less affected side stimulation

comparison. R2BRRC of PD patients was increased from ISI of 100 ms stimulating LAS, but it was normal stimulating MAS, revealing a significantly different amplitude of response at ISIs of 100, 150, 200, and 300 ms between LAS and MAS stimulation.

R2BRRC showed a significantly different amplitude of response at ISIs of 100, 150, and 200 ms for MAS stimulation between patients with PD and MSA and also between patients with PD and PSP ($p < 0.01$), whereas no significant differences were found between patients with MSA and PSP. There were no statistically significant differences in R2 amplitude among the three groups for LAS stimulation.

AI of R2BRRC was computed for each ISI. The absolute value of AI ranged between 0 and 1, where 0 represented the absence of asymmetry and 1 represented the maximum asymmetry between the two sides. AI at ISI of 100 ms showed the greatest significant difference among groups (Fig. 2), being higher in PD compared, respectively to PSP and MSA. A cut-off of AI greater than 0.78, estimated using the ROC curve analysis method (accuracy of AI: area under the ROC curve (AUC) = 0.83; $p < 0.001$), differentiated PD from PSP patients with a sensitivity of 86.7% (95% CI 59.5–98.3) and a specificity of 91.7% (95% CI 61.5–99.8). A cut-off of AI greater than 0.87 (accuracy: AUC = 0.87; $p < 0.001$) differentiated PD from MSA patients with a sensitivity of 86.7% (95% CI 59.5–98.3) and a maximum specificity of 100% (95% CI 79.4–100).

To exclude effects related to disease duration or treatment in APS, we conducted further analysis only on drug-naive patients. Thirteen patients affected by APS had never been treated: eight patients with PSP (four men; age 69.1 ± 5.9 years) and five patients with MSA (four men; age 68.2 ± 10.6 years). There were no statistically significant differences in disease duration (PSP: 2 ± 0.8 years; MSA: 2.4 ± 1.1 years) and UPDRS-ME score (PSP: 31.2 ± 16.2; MSA: 35.2 ± 10.9) between drug-naive APS and PD patients. AI at ISI of 100 ms showed the greatest significant difference between drug-naive groups also (supplementary Fig. 1), being higher in PD compared to APS. AI cut-off greater than 0.78 (accuracy: AUC = 0.83; $p < 0.001$), differentiated PD from drug-naive APS patients with a sensitivity of 86.7% (95% CI 59.5–98.3) and a specificity of 92.3% (95% CI 64.0–99.8).

Discussion

Early PD patients exhibited an enhanced brainstem excitability which was found to be contralateral to clinically affected side by R2BRRC. On the other hand, APS did not show any asymmetric pattern of brainstem excitability compared to PD patients. Though APS could be clinically symmetric, it is possible to find an asymmetric presentation, which makes APS indistinguishable from PD as in our sample [5, 6]. The AI, a marker of asymmetric brainstem activity, discriminated PD from PSP and MSA with a good accuracy using a 100 ms ISI stimulation of R2BRRC.

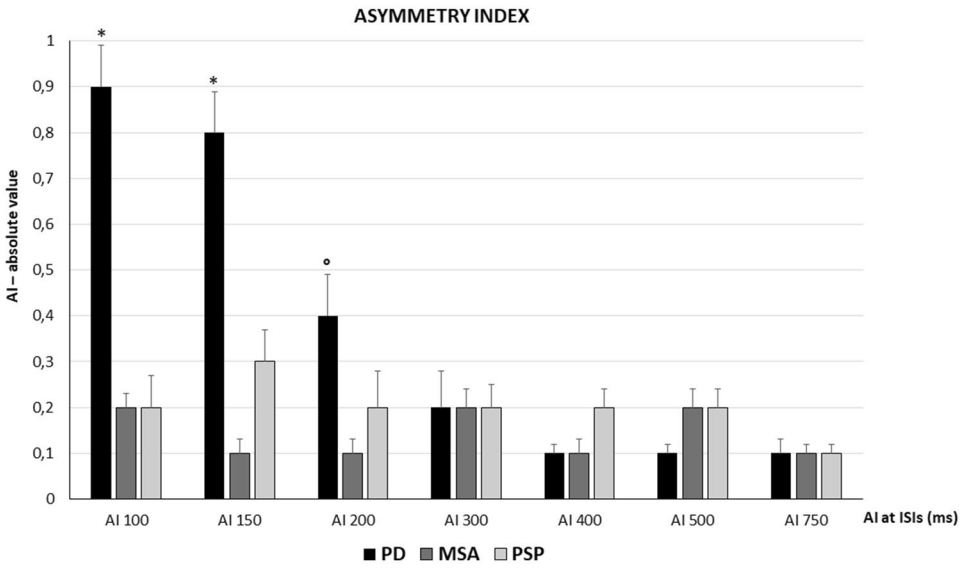

Fig. 2 Asymmetry indexes for PD, MSA, and PSP patients. Asymmetry indexes are shown as mean + standard error (S.E.). X-axis: asymmetry indexes at interstimulus intervals (ISIs) of 100, 150, 200, 300, 400, 500, 750 ms (ms). Y-axis: absolute value of asymmetry index; ANOVA test: $*p < 0.001$ and $°p < 0.02$ when comparing PD, MSA and PSP; Tukey post-hoc test: $p < 0.001$, when comparing PD vs. MSA and PD vs. PSP at AI of 100 and 150 ms; $p = 0.02$ when comparing PD vs. MSA at AI of 200 ms. *AI* asymmetry index, *PD* Parkinson's disease, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy

Previous studies explored R2BRRC in PD and APS [1–3]. The presence of an increased R2BRRC in patients affected of PD was first observed by Kimura and colleagues [1]. Among the few studies that have examined the brainstem excitability in APS, the study conducted by Valls-Solè and colleagues showed that R2BRRC was increased in PSP and MSA as in PD patients [2]. R2BRRC is also discriminant in tauopathies, as it could differentiate PSP from CorticoBasal syndrome with a sensitivity of 91.7% and a specificity of 87.5% [3].

To our knowledge, only two studies were conducted on asymmetric BR responses in PD [9, 10]. Dengler and colleagues evaluated BR in treated PD patients with hemiparkinsonism, observing a decreased EMG activity of the BR components on the clinical affected side (corresponding to MAS) and consequently increased the responses on LAS [9]. Though they did not evaluate recovery cycle, this observation could be considered in agreement with our results on increased R2BRRC for LAS stimulation in PD [9]. Sugiyama and colleagues assessed R2BRRC in treated PD patients with lateral trunk flexion and with normal posture [10]. An asymmetric disinhibition of R2BRRC was found to be associated with the abnormal posture [10]. Nevertheless, the study did not detect correlations between the side of R2BRRC disinhibition and the side of trunk convexity [10].

AI of R2BRRC seems to be a promising neurophysiological tool which permits to distinguish early PD from APS. Moreover, AI differentiates drug-naive PD from untreated PSP and MSA patients with similar disease duration, representing a good marker in early stages also.

We hypothesized that an increased neuronal excitability, probably due to a predominant contralateral dysfunction of basal ganglia structures for loss of cortical inhibitory functions, could explain the asymmetric brainstem disinhibition observed in PD. Therefore, early detection of asymmetric brainstem alterations through the use of AI of R2BRRC could help clinicians in differential diagnosis between PD and APS, especially at the early onset of the disease.

The main limit of our study is the small sample size, given the low frequency of APS in the general population and the difficulty of finding drug-naive patients. Nevertheless, the clinical utility of AI of R2BRRC as aid in differentiating PD from APS should be considered.

Author contributions GS: Research project: conception, organization, execution; Statistical analysis: execution; Manuscript: writing of the first draft, review, and critique. GM: Research project: conception; Statistical analysis: design, review, and critique; Manuscript: review and critique. ID: Research project: execution. GD: Research project: Execution. RM: Research project: execution. GP: Research project: execution. CR: Research project: execution. SS: Statistical analysis: review and critique, Manuscript: Review and critique. FD: Statistical analysis: review and critique, Manuscript: review and critique. AN: Statistical analysis: review and critique, Manuscript: review and critique. MZ: Research project: conception, organization; Statistical analysis: design, execution, review, and critique; Manuscript: review and critique.

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Availability of data and material Data and material of the study are available to be examined.

Compliance with ethical standards

Conflicts of interest The authors declare no financial disclosure or other conflicts of interest.

Ethics approval and consent to participate The study was approved by the Local Ethics Committee and patients were enrolled after signing the written informed consent.

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