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Ocular Motor and Vestibular Video-Oculographic Analysis in Parkinsonian Syndromes

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ABSTRACT

Parkinsonian Syndromes (PS) are neurodegenerative disorders that reflect abnormal function of basal ganglia–cortical circuits. Distinctive CNS impairment leads to specific ocular features in each syndrome, making eye movement analysis crucial for their diagnosis. However, vestibular eye movements have been less studied in PS and multivariate regression methods to find independent ocular motor predictors of clinical disability across groups are lacking.

In this work, we retrospectively review ocular motor and vestibular data from PS patients (Parkinson's disease [PD], Progressive Supranuclear Palsy [PSP], Multiple System Atrophy [MSA], and Cortico-Basal Syndrome [CBS]) who underwent detailed video-oculographic analysis and compared it between groups, correlated it with clinical data at baseline and 1-year after, and applied multivariate regression methods to ascertain their value as an independent predictor of clinical progression.

We found significant ocular fixation instability, slow and hypometric saccades, and lower prevalence of positional nystagmus in PSP, and low gain pursuit and prolonged saccadic latency in CBS. Downward pursuit gain was an independent predictor of motor disability 1 year after ocular assessment across groups, and vertical saccade gain together with horizontal and vertical saccade latency constituted a significant predictor of dopaminergic agonists dosage at baseline and after 1 year.

Ocular motor and vestibular analysis allowed us to clearly distinguish between PD, PSP, MSA and CBS groups. Additionally, vertical pursuit seems to be a helpful predictor of PS disability. Potential correlations between dopaminergic agonists and eye movement data should be cautiously interpreted since these might simply reflect overall clinician's therapeutic strategy in avoiding the use of dopaminergic agonists in atypical parkinsonism. Detailed ocular motor assessment including ocular motor and vestibular data constitutes a powerful diagnostic tool and marker of clinical progression in PS.

KEYWORDS: Parkinson's Disease; Progressive Supranuclear Palsy; Multiple System Atrophy; Cortico-Basal Syndrome; Eye movements

RESUMO

As Síndromes Parkinsonianas (PS) são doenças neurodegenerativas que refletem a função anormal da via cortico-basal. O comprometimento de diferentes partes do SNC leva a diferentes achados oculares em cada síndrome, tornando a análise dos movimentos oculares fulcral para o diagnóstico. No entanto, os movimentos oculares vestibulares nas PS têm sido menos estudados e há falta de análises de regressão multivariável para identificar alterações dos movimentos oculares preditoras da clínica entre os grupos.

Neste trabalho, foi feita uma revisão retrospetiva dos movimentos oculares e dados vestibulares de doentes com PS (Doença de Parkinson [PD], Paralisia Supranuclear Progressiva [PSP], Atrofia de Sistemas Múltiplos [MSA] e Síndrome Cortico-basal [CBS]) que realizaram análise video-oculográfica detalhada e foi comparada entre grupos, correlacionando-a com os dados clínicos iniciais e um ano depois, e foram aplicadas análises de regressão multivariável para determinar o seu valor como preditor independente da progressão clínica.

Encontrámos instabilidade da fixação do olhar significativa, sacadas lentas e hipométricas, e uma menor prevalência do nistagmo posicional na PSP, e diminuição do ganho na perseguição e sacadas com latência prolongada na CBS. O ganho na perseguição descendente foi um preditor independente da disfunção motora 1 ano depois da avaliação ocular entre grupos, e o ganho das sacadas verticais juntamente com a latência das sacadas horizontais e verticais constituíram um preditor significativo da dose de agonistas dopaminérgicos, tanto da dose inicial como da dose após um ano.

A análise vestibular e dos movimentos oculares permitiu-nos distinguir os grupos PD, PSP, MSA e CBS. Adicionalmente, a perseguição vertical parece ser um preditor útil da progressão clínica das PS. A correlação potencial entre os agonistas dopaminérgicos e os movimentos oculares deve ser interpretada com cautela visto que podem simplesmente refletir a estratégia terapêutica de evitar o uso dos agonistas dopaminérgicos no parkinsonismo atípico. A avaliação detalhada dos movimentos oculares e vestibulares constitui uma ferramenta diagnóstica útil e um marcador da progressão clínica nas PS.

PALAVRAS-CHAVE: Doença de Parkinson; Atrofia de Sistemas Múltiplos; Paralisia Supranuclear Progressiva; Síndrome Corticobasal; Movimentos oculares

INTRODUCTION

Parkinsonian Syndromes (PS) include, among other, idiopathic Parkinson's disease (PD), Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), and Cortico-Basal Syndrome (CBS), the former three considered atypical parkinsonisms [1]. They all reflect an abnormal function of the basal ganglia–cortical neuronal circuits, which results in the essential clinical sign for their diagnosis, ie, bradykinesia [2]. Their differential diagnosis is mostly based on clinical aspects, including asymmetric vs. symmetric involvement, early falls, cognitive status, etc, which have allowed for the creation of specific diagnostic criteria for each PS [1,3–6].

Eye movements (ocular fixation, eccentric gaze, smooth pursuit [SP], saccades, and vestibulo-ocular reflex [VOR]) reflect the function of complex brain networks widely spread through the cortex, basal ganglia, cerebellum and brainstem [7]. Therefore, ocular motor analysis able us to assess the functional integrity of these complex networks in PS [2]. Notably, PS have specific ocular features which make eye movement assessment crucial in their differential diagnosis [8]. Importantly, vestibular eye movements however, including the occurrence of positional nystagmus has been only scarcely investigated in PS [9–13]. Additionally, it has been shown, mostly in PD patients, that eye movement performance (e.g., ocular fixation, pursuit gain, saccade latency) correlates with clinical severity and cognitive function [14–16]. Evidence for such correlation is less robust in other PS. Treatment of PS remains purely symptomatic [17]. The basis of symptom management is dopaminergic therapy, either with the dopamine precursor levodopa and/or dopaminergic agonists [1]. PD patients typically respond well to dopaminergic therapies, in contrast with the other PS which respond poorly [18]. Moreover, dopamine agonists, due to their side effects and in addition to their lack of efficacy, tend to be avoided in PS other than PD [19]. Dopaminergic medication effect on eye movements is still controverse. While some studies have shown that dopaminergic therapy may improve saccade latency, gain or amplitude or smooth pursuit gain, others have found no effect [20–24]. Again, this evidence comes mostly from PD patients.

In this work, we retrospectively review ocular motor and vestibular data from PS patients (PD, PSP, MSA, CBS) who underwent detailed video-oculographic analysis in our lab, and further compared it between groups and correlated it with disease severity markers and levodopa equivalent dosage at baseline and after 1 year.

METHODS

Study design and subjects

We performed a retrospective study in which we include patients > 18 years old diagnosed with PS, followed in the Department of Neurology from Coimbra University Hospital Centre, Coimbra, Portugal, who had been referred for detailed ocular motor and vestibular evaluation in our lab, from 2015 to 2019. PS diagnosis had been made at the time of the referral and further confirmed 1 year after eye movement analysis, by experienced neurologists in movement disorders, following the established diagnostic criteria of the Movement Disorder of Society (2015) for PD patients [3]; International Parkinson and Movement Disorder Society (2017) for PSP [6]; Gilman *et al*. consensus statement (2003) for MSA patients [5]; and Armstrong *et al*. (2013) [4] for CBS patients. Patients without assessable clinical records, frank dementia or significant visual impairment were excluded.

Clinical data

Available clinical data from eligible patients was retrieved from their records into anonymised databases, including: gender; age; sex; mean disease duration (i.e., from initial symptom onset to date of eye movement assessment); most affected side (i.e., as defined by the evaluating neurologist as the side with worse bradykinesia when clearly asymmetric); motor disability scores using Unified Parkinson's Disease Rating Scale (UPDRS) motor (part 3) scale (0-72) and modified Hohen & Yahr (HY) scale (0-5) [25,26]; presence of motor fluctuations (i.e., as defined by the evaluating neurologist as more than 10% of "on" time with dyskinesias or more than 20% of "off" time during the day, despite optimized medications); presence of falls (i.e., as defined by the evaluating neurologist as non-provoked falls attributed to parkinsonism); cognitive scores using Mini Mental State Examination (MMSE) score (0-30) and Montreal Cognitive Assessment (MoCA) score (0-30) [27,28]; levodopa dosage (LD) and levodopa equivalent dosage (LED) of dopaminergic agonists [29]. UPDRS, HY, LD and LED were collected at the time of eye movement assessment and 1 year later.

Ocular motor and vestibular data

Eye movements were evaluated using binocular video-oculography (VOG) (Interacoustics VO425, Assen, Denmark; 105 Hz). Presence of spontaneous nystagmus in dark was assessed for 30 seconds. Ocular fixation was assessed while fixating a 1.5-meter distance centred target, for 30 seconds. Gaze evoked nystagmus was assessed while fixating an identical target, located ± 30º horizontally and ±20º vertically. A target was moved sinusoidally 60º horizontally and 40º vertically with a starting velocity of 10º/s for smooth pursuit evaluation. Saccades' paradigm, was based on an randomly appearing target

between 5º and 30º horizontally and vertically, for 60 seconds in each plane. Presence of post-head shaking nystagmus was assessed by observing the eyes for 60 seconds without visual fixation, after manually shaking of patient's head horizontally 30º flexed at a rate of about 3 Hz with an amplitude of about 15º for 15 seconds. Vibration nystagmus was induced by placing a handheld Brookstone Mini Muscle Massager (100 Hz) against the right and left mastoid prominence for 30 seconds on each side. Positional nystagmus was assessed without eye fixation for 60 seconds in the following positions: immediately after lying down from sitting with the head straight and 30º flexed; after a 90º rotation to each side (i.e., Pagnini-McClure maneuver); after head-hanging from sitting, with the head straight and 30º extended (i.e., head-hanging maneuver), followed by a similar maneuver with the head rotated 45º laterally (i.e., Dix-Hallpike maneuver). In all this positions, patients were asked to keep their eyes in the straight-ahead position to avoid contamination from gaze-evoked nystagmus.

Nystagmus mean slow phase velocity (SPV), smooth pursuit mean gain and saccade latency, velocity and precision were analysed using built-in software. SWJ frequency was calculated manually by visually inspecting all ocular fixation tracing recordings. Horizontal asymmetry (right vs. left) ratio of pursuit gain, and saccades latency, gain and velocity was calculated by using the formula: (mean of ocular variable to the right – mean of ocular variable to the left) / (mean of ocular variable to the right + mean of ocular variable to the left). Positional nystagmus was then categorized into paroxysmal (i.e., transient decaying vertical or horizontal nystagmus induced by positional changes which was not resolved with repeated canalith repositioning maneuvers designed for BPPV), persistent (i.e., vertical or horizontal nystagmus induced by positional changes, persisting more than 30 seconds) or mixed (i.e., when the two previously described components [paroxysmal and persistent] where present). Positional nystagmus was further classified as direction-fixed (i.e., beating toward the same direction in both sides), direction-changing apogeotropic (i.e., beating toward the ceiling in both sides), direction-changing geotropic (i.e., beating toward the ground in both sides), downbeat (i.e., beating downward), and upbeat nystagmus (i.e., beating upward). All tracing recordings were visually inspected off-line to ensure correct eye position and nystagmus stability.

Vestibulo-ocular reflex (VOR) during high acceleration head rotations, was quantitively analysed using monocular video-oculography (Video-head impulse test, VHIT) (EyeSeeCam, Munich, Germany; 250 Hz). Patients' head was briskly moved in the maximally excitatory direction for each horizontal semicircular canal plane by the examiner while fixating a 1.5-meter distance target. Twenty valid trials were performed for each side. VOR gain (eye velocity divided by head velocity at 60 milliseconds) was calculated with built-in software.

Ethics

Study protocol was submitted and approved by our Local Ethics Hospital Committee, in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using SPSS 21 (IBM Corp., Armonk, NY). Data normality was determined using the Shapiro–Wilk test. Non-parametric tests were chosen for more rigorous results. Kruskal-Wallis test was used to compare continuous variables, while Pearson chi-square test or Fisher's exact test was used for comparison of discrete variables between PS subgroups. Correlation analysis between oculomotor parameters and clinical data was performed using Spearman univariate regression analysis. Linear regression analysis was performed to find independent ocular motor predictors previously detected in correlation analysis. Benjamini-Hochberg correction for multiple comparisons, using a false discovery rate (FDR) of 10% was applied for between-group, correlation and regression analysis and the corrected level of significance was set at <0.041, <0.005 and <0.047, respectively.

RESULTS

Clinical data

There were 50 patients (PD, n=14; PSP, n=18; MSA, n=8; CBS, n=10), with a mean age of 67.7+/-10.2 years (range 36-85), and 31 were males (62%), Groups were age- and gender-matched. PD patients tended to show greater disease duration than the other groups. PD group demonstrated a significantly lower HY (but not UPDRS) score than all groups at the time of VOG and such difference was still present 1 year later in comparison with PSP and CBS groups. Motor fluctuations were more common in PD group than in PSP and CBS groups. The opposite occurred with falls. Cognitive performance using MoCA (but not with MMSE) was significantly better in PD than CBS patients. LED (but not LD) was significantly higher in PD than in the other groups at the time of VOG and such difference was still present 1 year later in comparison with PSP and CBS groups (see Table 1 for details).

Ocular motor and vestibular data

There were several significant differences between groups in ocular motor data. Square wave jerks were significantly more frequent in PSP than PD patients. Upward pursuit gain was lower in CBS than PD patients. Saccade velocity in all directions and downward

saccades gain were significantly lower in PSP group than in one or more of the other groups. Rightward saccades latency was higher in CBS than PSP group and upward saccades latency was higher in CBS than PD group. The other ocular motor variables did not reach statistical significance between groups. Positional nystagmus in dark was less frequent in PSP group (see Table 2 for details). In 28 (75.6%) patients it was persistent, in 8 (21.6%) was mixed, and in 1 (2.7%) was paroxysmal. PN intensity was mild (horizontal SPV, 2.9+/-1.1º/s; vertical SPV, 41+/-1.5º/s; only one patient, with MSA diagnosis, showed a mean SPV>6º/s) and did not significantly differ between groups (horizontal SPV, p<0.276; vertical SPV, p=0.265) (see Table 3 for details).

Correlation analysis between ocular motor (ie, pursuit and saccades parameters) and clinical data (ie, disease duration, UPDRS and HY score at and 1 year after VOG assessment, and LD and LED at and 1 year after VOG assessment) showed the following significant correlations: (1) downward pursuit gain and HY score at (-0.469, p=0.001) and 1 year after VOG assessment (-0-552, p<0.001); (2) upward pursuit gain and HY score at (-0.409, p=0.005) and 1 year after VOG assessment (-0.502, p=0.001); upward saccade latency and LED at (-0.413, p=0.005) and 1 year after VOG assessment (-0.473, p=0.001); leftward saccade latency and LED 1 year after VOG assessment (-0.416, p=0.005); upward saccade gain and LED 1 year after VOG assessment (0.468, p=0.002); downward saccade gain and LED 1 year after VOG assessment (0.413, p=0.005) (see Figure 1 for details).

To further investigate the influence of the factor “diagnosis” on the results of correlations analysis, a linear regression analysis was performed. Here, downward pursuit gain, saccade latency up and to the left, and downward saccade gain remained as an independent factor of HY score 1 year after VOG assessment, and LED at and 1 year after VOG assessment, respectively (see Table 4 for details). The addition of the UPDRS score in the regression models did not change the results (data not shown).

Finally, horizontal asymmetry ratio of pursuit gain, saccades latency, gain and velocity, and VHIT gain did not correlate with body side asymmetry (data not shown).

Table 1. Demographic and Clinical data.

	PD n=14	PSP n=18	MSA n=8	CBS n=10	p value
Mean age, years +/- SD	63.5+/-12.4	69.7+/-5.3	67.0+/-16.1	70.5+/-6.5	0.335
Gender, males, number of patients (%)	9 (64.3)	12 (66.7)	5 (62.5)	5 (50)	0.847
Mean disease duration, years +/- SD	7.6 (5.6) n=13	3.6 (2.3) n=15	3.5 (2.2) n=8	3.2 (2.3) n=10	0.051
Mean UPDRS score +/- SD	33.1+/-12.3 n=12	37.3+/-9.2 n=9	37.1+/-22.5 n=7	46.0+/-11.7 n=8	0.271
Mean HY score +/- SD	2.1+/-0.6 n=13	2.5+/-0.5 n=14	3.3+/-1.0 n=7	3.3+/-1.2 n=10	**0.010**[a]
Mean UPDRS score 1 year later +/- SD	32.5+/-13.3 n=7	40.4+/-12.5 n=9	35.4+/-18 n=5	52.5+/-9.5 n=4	0.114
Mean HY score 1 year later +/- SD	2.5+/-0.8 n=11	2.9+/-0.5 n=14	3.6+/-1.3 n=5	3.7+/-1.0 n=9	**0.025**[b]
Motor fluctuations, number of patients (%)	7 (53.8) n=13	2 (13.3) n=15	1 (14.3) n=8	0 (0) n=10	**0.010**[c]
Falls, number of patients (%)	7 (53) n=13	14 (93.3) n=15	7 (87.5) n=8	10 (100) n=10	**0.012**[d]
Most affected side, right/left/symmetric, number of patients	3/9/0 n=13	5/2/8 n=15	3/2/3 n=8	5/3/2 n=10	-
Mean MoCA score +/- SD	19.4+/-5.2 n=9	18.2+/-5.1 n=4	- n=0	11.0+/-3.8 n=4	**0.042**[e]
Mean MMSE score +/- SD	25.6+/-3.5 n=3	27.0+/-1.4 n=2	- n=0	23.6+/-2.6 n=5	0.260
Mean LD +/- SD	585.3+/-514.4 n=13	487.5+/-288.3 n=14	518.7+/-349.4 n=8	622.5+/-382.6 n=10	0.870
Mean LED +/- SD	149.2+/-166.4 n=13	28.5+/-65.4 n=14	0.0+/-0.0 n=8	6.0+/-18.9 n=10	**0.003**[f]
Mean LD 1 year later +/- SD	504.3+/-281.9 n=11	596.4+/-306.8 n=15	575.0+/-349.4 n=8	661.1+/-285.8 n=9	0.742
Mean LED 1 year later +/- SD	125.4+/-139.4 n=11	17.3+/-47.1 n=15	34.0+/-63.5 n=8	6.67+/-20.0 n=9	**0.032**[g]

PD, Parkinson's Disease; PSP, Progressive Supranuclear Palsy; MSA, Multiple System Atrophy; CBS, Corticobasal Syndrome; UPDRS III, Unified Parkinson's Disease Rating Scale Part 3; HY, Hohen and Yahr; MoCA, Montreal Cognitive Assessment; MMSE, Minimental State Examination; LD, Levodopa dosage; LED, Levodopa equivalent dosage

[a]PD vs. PSP, p=0.047; PD vs. MSA, p=0.009; PD vs. CBS, p=0.011

[b]PD vs. PSP, p=0.049; PD vs. CBS, p=0.010
[c]PD vs. PSP, p=0.042; PD vs. CBS, p=0.007
[d]PD vs. PSP, p=0.029; PD vs. CBS, p=0.019
[e]PD vs. CBS, p=0.013
[f]PD vs. PSP, p=0.019; PD vs. MSA, p=0.008; PD vs. CBS, p=0.011
[g]PD vs. PSP, p=0.016; PD vs. CBS, p=0.029
Kruskal Wallis, Pearson chi square, and Fisher's exact test were used in between-groups analysis; a $p<0.05$ was considered significant

Table 2. Ocular motor data.

	PD n=14	PSP n=18	MSA n=8	CBS n=10	p value
Mean SWJ number per second +/- SD	0.5+/-0.2	0.8+/-0.2	0.5+/-0.2	0.5+/-0.3	**0.014**[a]
Mean pursuit gain to the left +/-SD	88.0+/-4.4	82.4+/-7.4	85.3+/-8.2	80.8+/-13.7	0.131
Mean pursuit gain to the right +/-SD	86.5+/-7.9	81.8+/-7.9	88.6+/-4.2	84.5+/-7.7	0.059
Mean pursuit gain down +/-SD	83.4+/-12.4	80.1+/-8.2	81.1+/-12.3	73.8+/-12.9	0.106
Mean pursuit gain up +/-SD	85.6+/-6.8	79-6+/-8.0	83.5+/-8.7	74.2+/-8.5	**0.005**[b]
Mean saccade latency to the left +/- SD	259.6+/-57.8	270.9+/-65.2	262.0+/-25.4	318.6+/-76.3	0.121
Mean saccade velocity to the left +/- SD	434.7+/-66.3	271.9+/-89.6	424.0+/-55.3	423.5+/-72.3	**<0.001**[c]
Mean saccade gain to the left +/- SD	92.0+/-6.1	81.8+/-18.7	90.2+/-4.0	85.4+/-7.6	0.068
Mean saccade latency to the right +/- SD	250.5+/-44.8	252.7+/-58.9	261.1+/-42.2	316.8+/-62.8	**0.041**[d]
Mean saccade velocity to the right +/- SD	422.0+/-52.7	269.2+/-89.3	420.0+/-58.3	392.1+/-112.6	<**0.001**[e]
Mean saccade gain to the right +/- SD	87.6+/-7.0	78.9+/-17.1	88.0+/-4.4	74.1+/-22.5	0.130
Mean saccade latency down +/- SD	295.5+/-73.0	347.0+/-95.0	290.9+/-57.7	349.2+/-47.0	0.128
Mean saccade velocity down +/- SD	420.4+/-114.0	185.1+/-107.6	438.9+/-65.6	450.4+/-129.5	**<0.001**[f]
Mean saccade gain down +/- SD	87.1+/-10.6	57.1+/-26.3	86.6+/-9.4	80.3+/-14.5	**<0.001**[g]
Mean saccade latency up +/- SD	268.0+/-55.5	338.8+/-77.5	269.1+/-48.5	347.4+/-69.1	**0.005**[h]
Mean saccade velocity up +/- SD	386.4+/-99.4	179.8+/-106.2	393.2+/-68.3	371.8+/-131.3	**<0.001**[i]
Mean saccade gain up +/- SD	76.1+/-10.2	59.0+/-23.4	69.3+/-18.0	62.7+/-18.3	0.122

Mean VHIT gain to the left +/- SD	0.8+/-0.2 n=12	0.8+/-0.1 n=17	0.9+/-0.1	0.9+/-0.1 n=7	0.732
Mean VHIT gain to the right +/- SD	0.9+/-0.1 n=12	0.9+/-0.1 n=17	0.8+/-0.1	0.9+/-0.1 n=7	0.372
GEN, number of patients (%)	0 (0)	2 (11.1)	3 (37.5)	1 (11.1) n=9	0.081
HSN, number of patients (%)	9 (75) n=12	12 (70.6) n=17	7 (87.5)	5 (83.3) n=6	0.790
VN, number of patients (%)	11 (91.7) n=12	16 (94.1) n=17	5 (83.3) n=6	6 (100) n=6	0.725
PN, number of patients (%)	11 (78.6)	12 (70.6) n=17	8 (100)	6 (100) n=6	**0.039**[j]

PD, Parkinson's Disease; PSP, Progressive Supranuclear Palsy; MSA, Multiple System Atrophy; CBS, Corticobasal Syndrome; SWJ, Square wave jerks; VHIT, Video-head impulse test; GEN, Gaze-evoked nystagmus; HSN, Head-shaking nystagmus; VN, Vibration nystagmus; PN, Positional nystagmus

[a]PD vs. PSP, p=0.049

[b]PD vs. CBS, p=0.006

[c]PD vs. PSP, p<0.001; PSP vs. MSA, p=0.002; PSP vs. CBS, p=0.003

[d]PSP vs. CBS, p=0.038

[e]PD vs. PSP, p<0.001; PSP vs. MSA, p<0.001

[f]PD vs. PSP, p<0.001; PSP vs. MSA, p<0.001; PSP vs. CBS, p<0.001

[g]PD vs. PSP, p<0.001

[h]PD vs. CBS, p=0.042

[i]PD vs. PSP, p<0.001; PSP vs. MSA, p<0.001; PSP vs. CBS, p=0.002

[j]PSP, p=0.003

A p<0.041 was considered significant, after Benjamini-Hochberg correction for multiple comparisons, using a false discovery rate (FDR) of 10%

Table 3. Positional nystagmus.

	PD n=11	PSP n=12	MSA n=8	CBS n=6
Nystagmus waveform				
Persistent, number (%)	7 (63.6)	8 (66.7)	8 (100)	5 (83.3)
Paroxysmal, number (%)	1 (9.1)	0 (0)	0 (0)	0 (0)
Mixed, number (%)	3 (27.3)	4 (33.3)	0 (0)	1 (16.7)
Nystagmus direction				
Downbeat, number (%)	9 (81.8)	2 (16.6)	4 (50)	2 (33.3)
Apogeotropic, number (%)	0 (0)	6 (50.0)	5 (62.5)	4 (66.6)
Geotropic, number (%)	4 (36.3)	2 (16.6)	0 (0)	0 (0)
Horizontal, direction-fixed, number (%)	3 (27.2)	3 (25.0)	1 (12.5)	2 (33.3)

PD, Parkinson's Disease; PSP, Progressive Supranuclear Palsy; MSA, Multiple System Atrophy; CBS, Corticobasal Syndrome

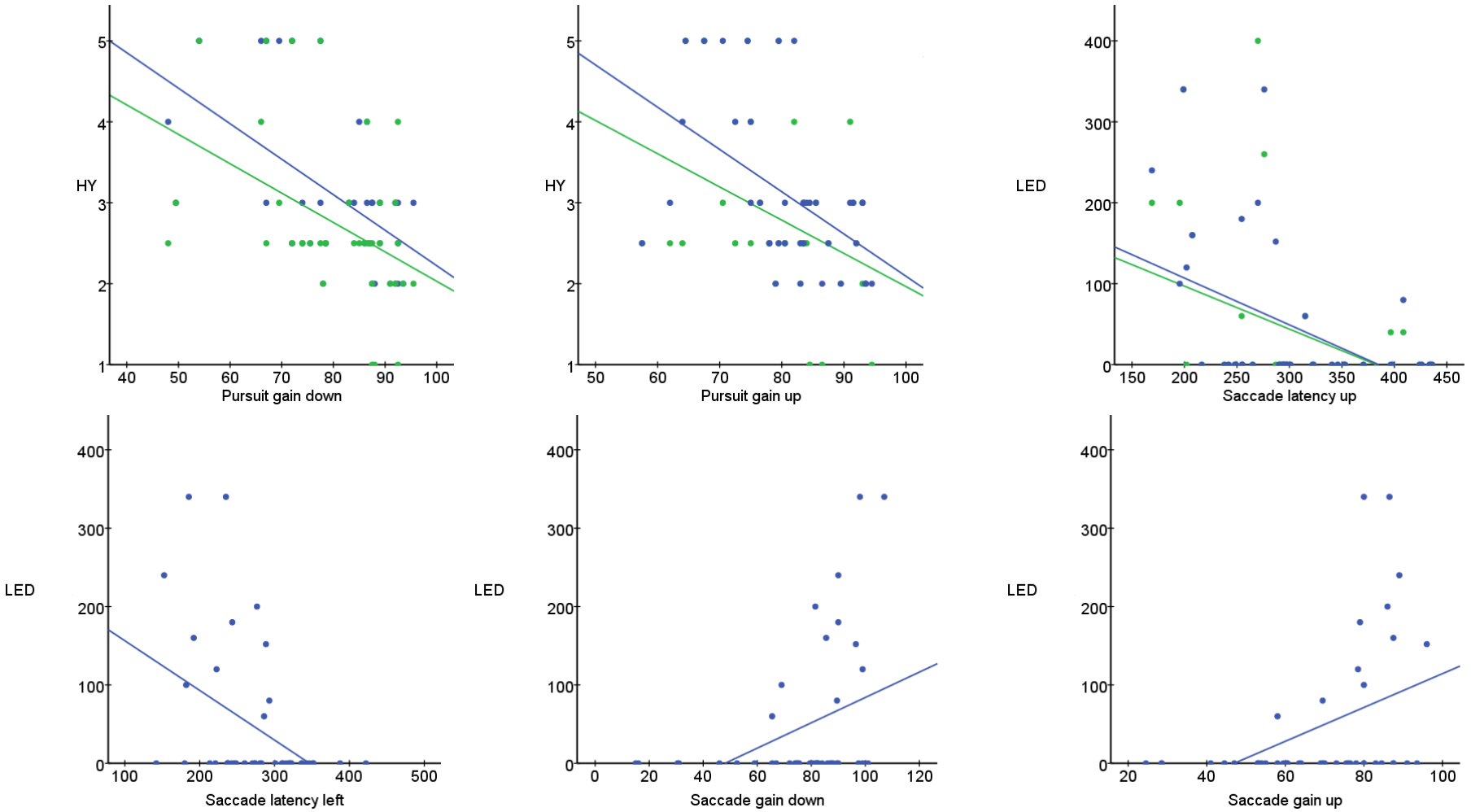

Figure 1. Correlation analysis. A p<0.005 was considered significant, after Benjamini-Hochberg correction for multiple comparisons, using a false discovery rate (FDR) of 10% (see Text for details). HY, Hohen & Yahr; LED, Levodopa equivalent dosage

Table 4. Regression analysis.

HY at baseline	B	SE	t	p value	CI 95%		Adjusted R2
Diagnosis	0.379	0.120	3.166	**0.003**	0.137	0.621	0.307
Pursuit gain down	-0.027	0.015	-1.766	0.085	-0.058	0.004	
Pursuit gain up	0.004	0.021	0.182	0.856	-0.038	0.046	
HY at 1 year	**B**	**SE**	**t**	**p value**	**CI 95%**		**Adjusted R2**
Diagnosis	0.279	0.127	2.193	**0.035**	0.021	0.537	0.351
Pursuit gain down	-0.032	0.016	-2.051	**0.048**	-0.064	0.000	
Pursuit gain up	-0.008	0.021	-0.355	0.725	-0.051	0.036	
LED at baseline	**B**	**SE**	**t**	**p value**	**CI 95%**		**Adjusted R2**
Diagnosis	-36.853	13.514	-2.727	**0.009**	-64.125	-9.581	0.278
Saccade latency up	-0.502	0.210	-2.395	**0.021**	-0.926	-0.079	
LED at 1 year	**B**	**SE**	**t**	**p value**	**CI 95%**		**Adjusted R2**
Diagnosis	-25.925	10.673	-2.429	**0.020**	-47.550	-4.300	0.397
Saccade latency up	0.064	0.227	0.284	0.778	-0.396	0.525	
Saccade latency to the left	-0.694	0.256	-2.709	**0.010**	-1.213	-0.175	
Saccade gain down	2.093	0.744	2.812	**0.008**	0.585	3.602	
Saccade gain up	-0.203	0.839	-0.241	0.811	-1.903	1.498	

A p<0.047 was considered significant, after Benjamini-Hochberg correction for multiple comparisons, using a false discovery rate (FDR) of 10%. HY, Hohen & Yahr; LED, Levodopa equivalent dosage

DISCUSSION

In the current study we found distinctive ocular motor features in several parkinsonian syndromes and important correlations between these and motor and medication status. While the findings of ocular fixation instability and overall slowed and hypometric saccades particularly along the vertical plane in PSP, and low gain pursuit and prolonged saccadic latency in CBS importantly support previous work on eye movements in parkinsonian syndromes, the evidence of lower prevalence of positional nystagmus in PSP, together with the significant correlation between vertical pursuit and saccades disturbance and motor (i.e., HY score) and medication (i.e., LED) status at the time of ocular motor assessment and one year later are unique and deserve further consideration.

Central positional nystagmus (CPN) indicates the presence of nystagmus induced by a change in head position, caused by cerebellar nodulus, uvula and/or tonsil dysfunction [30]. In PS, CPN has been mostly described in MSA, often presenting as downbeat nystagmus in head hanging position [30,31]. Importantly, CPN may constitute a helpful feature in differentiating PD from MSA patients, since CPN is far less common in the former condition [30]. Our data extends these findings by showing a lower prevalence of positional nystagmus in PSP patients, when comparing with other PS. This finding might reflect the relative sparing of cerebellum in most PSP autopsy cases [32]. Additionally, we believe that a major loss of the vertical and horizontal saccadic burst neurons in PSP not only impairs voluntary saccades, turning them progressively slower and hypometric, but also potentially affects rapid saccadic phases of nystagmus, abating several forms of nystagmus, including positional nystagmus in dark as in our series. In MSA and CBS on the other hand, all patients showed some form of positional nystagmus in dark. Interestingly, cerebellar vermal atrophy and its putative role in the cognitive deficit observed in CBS has been recently demonstrated, and therefore, detecting positional nystagmus in dark might be an additional way for putting in evidence cerebellar vermal impairment in CBS [33]. Of note, positional nystagmus in our series was very mild, and thus, at least in some patients, might not necessarily reflect full blown CPN but rather physiological nystagmus in dark [34].

The gain of downward pursuit was an independent predictor of motor disability (HY score) in all PS, specifically at 1 year after eye movement assessment. Since ocular pursuit pathways are widely distributed throughout the central nervous system, is not surprising that pursuit is most often damaged in CNS disease, making it a highly sensitive albeit unspecific marker of CNS dysfunction [7]. Indeed, vertical pursuit impairment, more often than that of its

horizontal counterpart, has been shown to constitute a useful marker of CNS dysfunction in several non-related disorders, such as traumatic brain injury or children with developmental coordination disorder [35,36]. Such directional asymmetry in ocular pursuit in CNS patients is probably the result of pursuit directional asymmetries already present in normal individuals. Specifically, downward pursuit shows higher gain than upward pursuit in healthy individuals [37]. Thus, it is plausible than when CNS dysfunction is present, downward pursuit impairment not only is more sensitive for its presence, but might also better correlate with PS motor disability and clinical progression than upward pursuit impairment, since the latter parameter shows relative lower gain *ab initio*, even in normals. The strict correlation with HY scale, but not UPDRS, might be due to the greater influence of motor state (on versus off state) during assessment in the latter scale, making UPDRS score more prone to variation over time [38].

Latency of upward and leftward saccades and gain of downward saccades, and PS subtype constituted independent predictors of dopaminergic agonists LED at the time of eye movement assessment or 1 year later. Dopaminergic effects on eye movements have been mostly investigated in PD patients and almost exclusively for levodopa and not dopaminergic agonists. Here, some studies showed no effect of dopamine treatment, whereas others reported small beneficial effects on latency, gain or amplitude [39]. Overall, levodopa and dopamine agonists seem to shorten the latency
of voluntary saccades while prolonging the latency of more reflexive saccades, although all of these effects are relatively small [39]. Indeed, in our study, higher intake of dopaminergic agonists correlated with faster saccade latencies in all PS subtypes, which could point to a beneficial effect of these drugs on saccade latency and gain. However, we believe that our findings merely reflected physicians' choice in our sample, who generally tended to avoid the use of dopaminergic agonists or use them modestly in atypical parkinsonism (e.g., PSP, MSA and CBS), due to its inefficacy and in a minority of case, their side effects [19]. And significant greater latency and smaller gain of saccades were seen in CBS and PSP groups. Thus, latency and gain correlations with dopaminergic agonists use in our work most probably flagged the presence of atypical parkinsonism in our sample and might not reflect a medication effect.

There are several important limitations in our work. First, its retrospective nature, which led to a significant amount of missing data in certain variables (e.g., MoCA and MMSE assessments), precluding further analysis or making it less robust. Secondly, the small number of patients in each group, which made our data less robust. Efforts were nevertheless made to improve our analysis, by using a non-parametric approach and

correcting for multiple comparisons. Thirdly, we did not balance saccade amplitude between right and left direction in our paradigm. Still, all groups underwent the same built-in randomized saccadic protocol.

CONCLUSION

In our study, fixation, pursuit and saccade abnormalities abled us to clearly different between PD, PSP, MSA and CBS, stressing the utility of detailed ocular motor assessment in PS. As previously shown, such assessment was less helpful in differentiating MSA from PD, when performed exclusively in upright position [40]. Adding vestibular assessment and including positional testing in paradigms further helped to differentiate PS subtypes, but PD and MSA differentiation still remained unclear. Vertical pursuit seems to be a helpful predictor of PS disability, regardless of PS subtype. Potential correlations between dopaminergic agonists and eye movement data should be carefully interpreted since these might simply reflect overall clinician's therapeutic strategy in avoiding the use of dopaminergic agonists in atypical parkinsonism.

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