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Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease

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ABSTRACT

Objective: This prospective observational study investigates the role of CSF biomarkers in predicting progression of dopa-resistant gait impairments in Parkinson disease (PD) in the first 36 months from diagnosis.

Methods: Quantitative gait analysis was carried out longitudinally using an instrumented walkway (GAITRite) in 108 people with PD and 130 age-matched controls. A subgroup of 44 people with PD underwent lumbar puncture from which a battery of CSF biomarkers was measured: β-amyloid 1–42 and 1–40 (Aβ42 and Aβ40), total and phosphorylated tau protein (t-tau/p-tau$_{181}$), and α-synuclein (αSyn). Linear mixed models examined the association between CSF and dopa-resistant gait characteristics (defined as substantial progression despite optimal medication).

Results: Low baseline CSF Aβ42, and to a lesser extend Aβ40, predicted decline in gait characteristics in the first 3 years following diagnosis, independently explaining up to 12% of progression of step time variability (single task) and step length variability (dual-task). Interestingly, these findings were independent of age and cognition.

Conclusions: These findings implicate underlying amyloid pathology in neural networks involved in locomotor control. Results suggest that disturbed Aβ metabolism may be a biomarker for dopa-resistant gait impairments in early PD. Our findings raise interesting questions regarding therapeutic interventions such as compounds or molecules aimed at reducing amyloid burden to mitigate gait disturbance in early PD and potentially falls risk. Finally, progression of discrete gait characteristics suggests they may have potential as clinical biomarkers of pathology and disease progression. ***Neurology*® 2017;88:1501–1511**

GLOSSARY

αSyn = α-synuclein; **Aβ** = β-amyloid; **ICICLE** = Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation; **LEDD** = levodopa equivalent dose; **LP** = lumbar puncture; **MoCA** = Montreal Cognitive Assessment; **PD** = Parkinson disease; **PIGD** = postural instability and gait.

Parkinson disease (PD) is a common neurodegenerative disorder, second to Alzheimer disease.[1] Gait impairments are significant in very early disease, and even at this stage dominate as risk factors for falls.[2] While some aspects of gait are well-controlled by dopaminergic therapies in the early stages, resistance to levodopa makes clinical management challenging.

Recent work highlights the significant contribution of cholinergic disturbance to gait,[3,4] and recent trials targeting the cholinergic system have met with moderate success.[5] CSF proteins (e.g., β-amyloid [Aβ] 40 and Aβ42; total and p-tau$_{181}$), traditionally biomarkers of dementia and dementia risk,[6–9] have also been implicated in motor impairment, highlighting a role for pathologic protein accumulation other than Lewy body and PD-specific α-synuclein (αSyn). Cross-sectional studies in early and advanced PD show an association between CSF biomarkers and postural instability and gait (PIGD) phenotype.[10,11] However, lack of quantitative gait analysis

Supplemental data at Neurology.org

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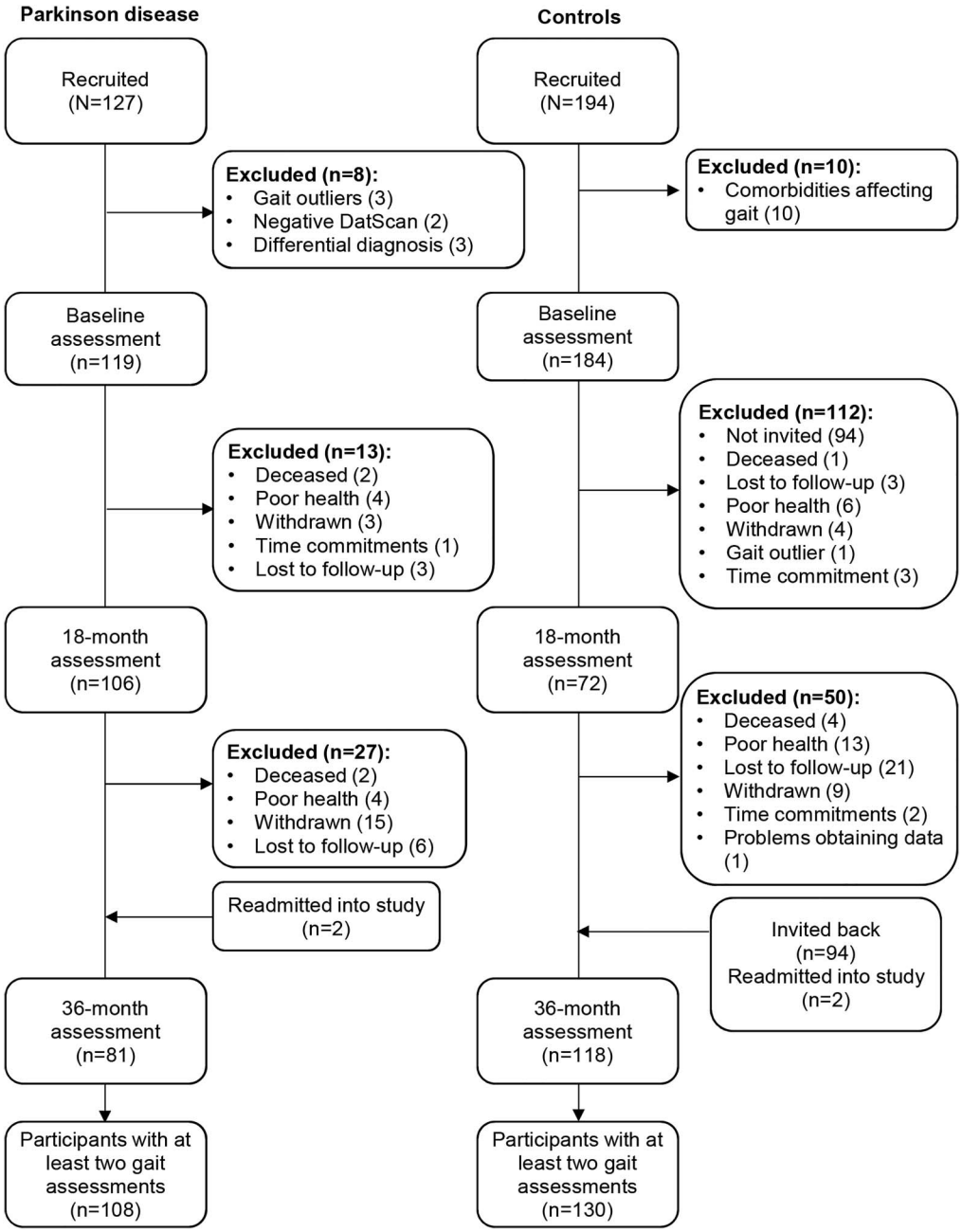
in these studies limits interpretation of findings. More importantly, longitudinal studies are lacking and urgently required in order to establish prediction.

The aims of this study were to investigate the role of CSF biomarkers to predict progression of dopa-resistant gait impairments in the first 36 months from diagnosis in PD. We were interested in the mechanisms underpinning dopa-resistant gait progression to provide an essential platform for future therapeutic interventions to mitigate gait disturbance and potential falls risk. Based on previous cross-sectional literature, we hypothesized that Aβ42 and p-tau$_{181}$ would predict progression in dopa-resistant gait characteristics.

METHODS

Participants. Participants were recruited into Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation (ICICLE)–GAIT a median of 5 months from diagnosis. This is a nested study within ICICLE-PD, an incident cohort study conducted between June 2009 and December 2011.

Figure 1 Participant flowchart



Flowchart of participants recruited and assessed as part of the ICICLE-Gait study.

A subset of the cohort was recruited into ICICLE-Gait at the same time (figure 1). Controls of a similar age and sex were recruited from community sources. The methods have been described in full in previous publications,[12–14] and are included as supplemental material at Neurology.org. Participants were tested "on" medication, which was defined as 1 hour after PD medication. Participants were evaluated at the Clinical Ageing Research Unit, Newcastle University, UK.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Newcastle and North Tyneside research and ethics committee and all participants gave informed consent.

Demographic and clinical measures. Clinical assessments included a standardized neurologic examination and the Movement Disorder Society–revised Unified Parkinson's Disease Rating Scale,[15] from which Hoehn & Yahr stage[16] and motor phenotype were calculated.[17] Levodopa equivalent dose (LEDD) scores were calculated according to established methods.[18] Global cognition was assessed using Montreal Cognitive Assessment (MoCA).[19]

Quantitative gait analysis and gait characteristics. Gait was assessed using a 7 meters long × 0.6 meters wide instrumented walkway (Platinum model GAITRite, software version 4.5, CIR Systems, Franklin, NJ). Participants were instructed to walk at their comfortable walking pace for 2 minutes around a 25-meter oval circuit under single and dual-task conditions. The dual-task protocol involved walking and memorizing digits, based on the Wechsler Forward Digit Span, which was used as the concurrent cognitive task.[20,21] Gait was repeatedly sampled as participants walked over the GAITRite mat (included in the 25-meter circuit) for a minimum of 5 passes (>40 steps per participant).[22] Gait was quantified according to an a priori model developed for older adults[23] and validated in PD[24] that describes 16 discrete gait characteristics.[25] We examined change in each gait characteristic over 36 months and characteristics that exhibited substantial change (despite optimal medication) were defined as dopa-resistant. Figure e-1 provides further details of the acquisition and processing of the gait data.

Quantification of CSF biomarkers. CSF biomarkers were measured using a robust protocol.[13] Lumbar puncture (LP) was performed on a subset of consenting participants using a standardized method as detailed previously.[13] All LPs were done between 8 and 10 AM after an overnight fast and while withholding PD medications. Samples were centrifuged within 15 minutes of collection at 2,000 *g* at 4°C for 10 minutes. The supernatant was divided into aliquots and frozen at −80°C, then analyzed for Aβ42 and Aβ40 using commercially available assays: Aβ42: Innotest TH β-amyloid (1–42), Fujirebio Inc./Innogenetics, Gent, Belgium; total and p-tau and Aβ40: hAmyloid β40, ELISA Aβ GmbH, Heidelberg, Germany.[12,13,26,27] Samples with artificial blood contamination (as assessed by visual inspection during LP, erythrocyte count >50/μL^3, or semiquantitative analysis of hemoglobin [using Hemastix, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany]) were excluded from analysis. No samples were excluded in the current analysis.

Statistical analysis. CSF biomarkers were selected for analysis on the basis of previous reports.[10,11] Dopa-resistant gait impairments were identified as follows: first, change per year for all (16) gait characteristics derived from single and dual task testing was assessed with a linear mixed-effects model (lme4 package, R statistical software version 3.2.2, Vienna, Austria).[28,29] Participants and time (from baseline assessment to subsequent testing sessions) were included as random effects and age at baseline and sex as fixed effects. We then examined between-group change in gait with group (control, PD) as a fixed effect. Rate of progression was determined in the total cohort (n = 108 PD and 130 controls) over 36 months (repeat assessments every 18 months from diagnosis) and then extracted for each individual for further analysis. Finally, bivariate correlations between change in LEDD and change in gait over 36 months for all CSF markers were conducted (data not shown), with significant relationships revealing dopa-resistant gait characteristics. These 3 steps validated the dopa-resistant classification; namely, substantial progression of gait impairment despite optimal medication; progression greater than controls; and no association between change in LEDD and gait over 36 months.

The second stage of analysis established whether CSF markers could predict progression in dopa-resistant gait characteristics using general linear modeling and controlling for age, global cognition (MoCA), and baseline gait. Preliminary data analysis suggested a potential interaction between baseline gait and CSF markers in predicting gait progression, and models were examined with and without this interaction. Baseline gait was dichotomized around the group median (to ensure balanced groups) for each variable.

Linearity of progression, normality, and homoscedasticity were inspected to ensure robustness of the fitted mixed and general linear models. There was moderate positive skewness in gait decline for step length and step time variability. Rerunning the models with log transformations did not affect findings; therefore the final models are presented using untransformed data to aid interpretation. A threshold of $p < 0.05$ was used to inform interpretation and 2-tailed 95% confidence intervals were calculated as interval estimates for rate of progression of gait impairment and its predictors in the general linear model.

RESULTS

Participant characteristics. Demographic and clinical data are shown in table 1. Of the 158 participants recruited to ICICLE-PD, 56 consented to LP and of these, 47 also consented to ICICLE-Gait. Participants without longitudinal assessment at each time point were excluded, leaving 44 participants for analysis. Participants were a median of 5 months postdiagnosis at baseline and 41 months at the 36-month follow-up assessment. They had mild disease with little difference between the subgroup who underwent CSF examination and the total PD cohort. There were no differences in global cognitive scores between the subgroup and total group of participants with PD. The UPDRS-III scores, PIGD phenotype, and mean LEDD dose were lower than the entire group, indicating less severe disease.

Gait progression in early PD. Gait outcomes were stable over 36 months for controls. For participants with PD, dopa-resistant gait characteristics (and % yearly progression rate) under single task conditions included variability of step time (4.5% per year), step length (5.7% per year), and step width (3.4% per year), and under dual-task conditions, variability of step length (5.7% per year) (table 2 for descriptive data and change depicted in absolute values). Progression of gait impairment was defined by an increase in variability (expressed as the SD). Increased dosage of levodopa (LEDD) over the 36 months was not related to

Table 1 Baseline demographic and clinical characteristics of participants included in longitudinal gait analysis

Characteristic	Control (n = 130)	PD (n = 108)	Group difference, *p* value	PD with CSF data (n = 44)
Age, y	69.5 (7.7)	66.9 (10.5)	0.073	66.9 (10.5)
Sex, F/M[a]	72/58	36/72	0.001[b]	16/28
Height, m	1.70 (0.09)	1.70 (0.08)	0.304	1.70 (0.08)
Body mass, kg	78.3 (14.9)	78.7 (15.1)	0.765	78.3 (15.5)
MoCA (control n = 73; PD = 103)	27 (2)	25 (4)	<0.001[c]	25 (4)
MMSE	29.2 (1.1)	28.7 (1.3)	<0.001[c]	28.8 (1.0)
NART	117 (8)	115 (11)	0.052	117 (12)
UPDRS-III	—	25.4 (10.4)	—	24.7 (10.0)
Hoehn & Yahr stage, n (%)				
I	—	28 (23)	—	10 (23)
II		70 (59)		25 (57)
III		21 (18)		9 (20)
Motor phenotype, n (%)				
PIGD	—	51 (47)	—	17 (39)
ID		10 (9)		6 (13)
TD		47 (44)		21 (48)
NFoG, n (%) who report FoG	—	11 (9)	—	3 (7)
LEDD, mg/d	—	176 (143)	—	145 (107)
t-Tau, pg/mL	—	—	—	139 (76)
p-Tau$_{181}$, pg/mL	—	—	—	48 (20)
Aβ42, pg/mL	—	—	—	958 (276)
Aβ40, pg/mL	—	—	—	10,532 (4,035)
Aβ40/Aβ42 ratio	—	—	—	11.2 (3.9)
α-Synuclein, pg/mL	—	—	—	86 (35)

Data presented as the group mean (SD) unless otherwise stated.
Abbreviations: Aβ = β-amyloid; FoG = freezing of gait; ID = indeterminate; LEDD = levodopa equivalent daily dose; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NART = National Adult Reading Test; NFoG = freezing of gait questionnaire; p-tau = phosphorylated tau; PD = Parkinson disease; PIGD = postural instability and gait difficulty; t-tau = total tau; TD = tremor dominant; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] Nonparametric comparison between groups.
[b] $p < 0.01$.
[c] $p < 0.001$.

progression of variability of step time (single-task $r = 0.015$, $p = 0.877$), or step length (single-task $r = -0.039$, $p = 0.687$; dual-task $r = 0.155$, $p = 0.108$), corroborating that these variables represented dopa-resistant progression. However, an increase in levodopa dosage was related to an increase in single-task step width variability ($r = 0.218$, $p = 0.023$), and was therefore not included in subsequent analysis.

Table 3 and figure 2 describe the relationship between baseline CSF and change in gait. Low baseline Aβ42 was an independent predictor of progression of step time variability (single task) in people with high baseline step time variability (above median: >16.7 ms). The overall model accounted for 48.5% of variance in progression of step time variability with Aβ42 independently accounting for 12.0%, independent of age and global cognition, which were not significant predictors. Aβ42 predicted progression of step length variability (dual-task) independent of baseline gait values, explaining 26.6% of the overall model variance and Aβ42 independently explaining 9.8%. Age and global cognition were not significant predictors in the model. In addition, we found that Aβ40 was a significant predictor of progression of step length variability (dual-task), with the full model explaining 22% of variance and Aβ40 alone explaining 11.1%. A significant interaction indicated a low baseline Aβ40 predicted progression in step length variability in participants with a high baseline step length variability (above median: $>2.36 \times 10^{-2}$ meters). There were no associations with total and p-tau$_{181}$, Aβ40/42, or αSyn.

Table 2 Baseline and change (Δ) of gait per year in 130 control participants and 108 people with Parkinson disease (PD)

		Controls		PD		
Domain	**Gait characteristic**	**Baseline**	**Δ per year**	**Baseline**	**Δ per year**	**Control vs PD, Δ per year**
Single task						
Pace	Step velocity, m/s	1.30 (1.26, 1.33)	−0.0054 (−0.0124, 0.0017)	1.11 (1.05, 1.18)[a]	−0.0099 (−0.0204, 0.0005)	−0.0044 (−0.0164, 0.0077)
	Step length, m	0.66 (0.65, 0.67)	−0.0048 (−0.0075, −0.0022)[b]	0.59 (0.56, 0.62)[a]	−0.0086 (−0.013, −0.0041)[b]	−0.0036 (−0.0085, 0.0013)
	Swing time SD, ms	13.8 (12.9, 14.7)	−0.156 (−0.377, 0.066)	16.9 (14.9, 19.0)[a]	0.594 (−0.058, 1.247)	0.733 (0.114, 1.352)[c]
Variability	Step time SD, ms	15.2 (14.2, 16.2)	−0.074 (−0.357, 0.21)	18.8 (16.7, 20.8)[a]	0.841 (0.192, 1.491)[d,e]	0.864 (0.225, 1.502)[e,g]
	Stance time SD, ms	18.5 (17.0, 19.9)	−0.19 (−0.612, 0.232)	23.2 (19.8, 26.5)[a]	0.818 (−0.094, 1.73)	1.004 (0.072, 1.936)[c]
	Step velocity SD, m/s	0.054 (0.051, 0.056)	−0.0004 (−0.0011, 0.0004)	0.054 (0.049, 0.059)	0.0009 (−0.0005, 0.0022)	0.0013 (−0.0001, 0.0027)
	Step length SD, m	0.019 (0.018, 0.020)	0.0004 (0.0002, 0.0007)[f]	0.021 (0.019, 0.023)[a]	0.0012 (0.0005, 0.0019)[b,e]	0.0008 (0.0002, 0.0014)[c,e]
Rhythm	Step time, ms	513 (504, 522)	−1.17 (−2.93, 0.58)	539 (525, 552)[c]	−2.56 (−4.71, −0.4)[d]	−1.37 (−4.14, 1.39)
	Swing time, ms	372 (366.2, 378)	−0.45 (−1.42, 0.53)	379 (369, 388)	−2.31 (−4.06, −0.55)[d]	−1.81 (−3.67, 0.05)
	Stance time, ms	654 (641, 668)	−1.78 (−4.58, 1.01)	699 (677, 722)[a]	−2.67 (−5.91, 0.57)	−0.74 (−5.07, 3.59)
Asymmetry	Step time asymmetry, ms	8.0 (6.1, 9.9)	0.61 (0.075, 1.144)[d]	17.3 (10.1, 24.5)[a]	0.114 (−1.34, 1.568)	−0.479 (−1.904, 0.946)
	Swing time asymmetry, ms	7.1 (5.3, 8.9)	0.082 (−0.342, 0.506)	13.7 (8.0, 19.5)[a]	−0.567 (−1.736, 0.602)	−0.712 (−1.802, 0.379)
	Stance time asymmetry, ms	6.9 (5.1, 8.7)	0.026 (−0.412, 0.464)	13.9 (8.2, 19.6)[a]	−0.428 (−1.646, 0.791)	−0.529 (−1.654, 0.597)
Postural control	Step length asymmetry, m	0.017 (0.013, 0.020)	0.0005 (−0.0003, 0.0013)	0.015 (0.009, 0.020)	0.0011 (−0.0005, 0.0027)	0.0007 (−0.001, 0.0023)
	Step width, m	0.082 (0.076, 0.087)	0.0004 (−0.0005, 0.0012)	0.082 (0.073, 0.092)	0.001 (−0.0003, 0.0022)	0.0006 (−0.0008, 0.0021)
	Step with SD, m	0.021 (0.020, 0.022)	0.0000 (−0.0003, 0.0002)	0.018 (0.016, 0.019)[a]	0.0006 (0, 0.0011)[d,e]	0.0006 (0.0001, 0.0012)[c,e]
Dual task						
Pace	Step velocity, m/s	1.22 (1.18, 1.26)	−0.0023 (−0.0091, 0.0046)	1.05 (0.98, 1.12)[a]	−0.0063 (−0.0165, 0.0039)	−0.0041 (−0.0159, 0.0077)
	Step length, m	0.68 (0.62, 0.65)	−0.0036 (−0.0061, −0.0011)[f]	0.57 (0.54, 0.60)[a]	−0.0072 (−0.0117, −0.0026)[f]	−0.0036 (−0.0084, 0.0012)
	Swing time SD, ms	15.4 (10.15, 20.7)	0.903 (−1.146, 2.953)	18.9 (16.6, 21.3)	1.657 (0.878, 2.436)[b]	0.4 (−2.052, 2.852)
Variability	Step time SD, ms	17.6 (14.8, 20.4)	−0.648 (−1.722, 0.426)	20.8 (18.2, 23.3)	0 (−1.08, 1.08)	0.576 (−0.917, 2.069)
	Stance time SD, ms	22.3 (20.4, 24.3)	−0.041 (−0.837, 0.754)	27.9 (23.7, 32.1)[a]	0.463 (−0.593, 1.518)	0.566 (−0.735, 1.867)
	Step velocity SD, m/s	0.060 (0.056, 0.064)	−0.001 (−0.0024, 0.0004)	0.055 (0.050, 0.060)	0.001 (−0.0005, 0.0025)	0.0019 (−0.0002, 0.004)
	Step length SD, m	0.020 (0.019, 0.0222)	0.0000 (−0.0004, 0.0003)	0.021 (0.019, 0.024)	0.0012 (0.0006, 0.0019)[b,e]	0.0013 (0.0006, 0.0020)[a,e]
Rhythm	Step time, ms	526 (515, 536)	−1.44 (−3.66, 0.78)	552 (537, 568)	−3.5 (−6.07, −0.93)[f]	−2.05 (−5.49, 1.39)
	Swing time, ms	376 (369, 382)	−0.67 (−1.88, 0.54)	382 (372, 393)	−2.59 (−4.58, −0.61)[f]	−1.91 (−4.1, 0.28)
	Stance time, ms	676 (660, 693)	−2.17 (−5.65, 1.3)	723 (697, 749)[g]	−4.28 (−8.19, −0.38)[d]	−2.02 (−7.34, 3.3)

Continued

Table 2 Continued

Domain	Gait characteristic	Controls		PD		
		Baseline	Δ per year	Baseline	Δ per year	Control vs PD, Δ per year
Asymmetry	Step time asymmetry, ms	7.9 (5.3, 10.5)	1.159 (0.364, 1.955)[f]	21.7 (14.0, 29.3)[a]	−1.169 (−2.775, 0.436)	−2.374 (−3.966, −0.782)[g]
	Swing time asymmetry, ms	7.2 (5.2, 9.3)	0.088 (−0.509, 0.685)	16.6 (11.1, 22.2)[a]	−0.918 (−2.139, 0.303)	−0.98 (−2.227, 0.267)
	Stance time asymmetry, ms	6.6 (4.5, 8.7)	0.321 (−0.304, 0.946)	17.0 (11.5, 22.4)[a]	−0.761 (−1.982, 0.461)	−1.05 (−2.319, 0.218)
Postural control	Step length asymmetry, m	0.018 (0.014, 0.021)	0.0007 (−0.0002, 0.0016)	0.017 (0.010, 0.024)	0.0004 (−0.0014, 0.0021)	−0.0003 (−0.0021, 0.0015)
	Step width, m	0.086 (0.080, 0.092)	−0.0003 (−0.0012, 0.0006)	0.083 (0.074, 0.093)	0.0013 (−0.0001, 0.0027)	0.0016 (0, 0.0032)
	Step with SD, m	0.028 (0.022, 0.024)	−0.0002 (−0.0006, 0.0001)	0.017 (0.015, 0.019)[a]	0.0006 (0, 0.0013)	0.0009 (0.0002, 0.0016)[c]

Data presented as group means (95% confidence intervals). Analysis controlled for age and sex.
[a] p Value of group comparison of both baseline gait and Δ over time: $p < 0.001$.
[b] p Value of Δ of gait over time within group: $p < 0.001$.
[c] p Value of group comparison of both baseline gait and Δ over time: $p < 0.05$.
[d] p Value of Δ of gait over time within group: $p < 0.05$.
[e] Gait characteristics where people with PD changed over time, and that change was different from control participants.
[f] p Value of Δ of gait over time within group: $p < 0.01$.
[g] p Value of group comparison of both baseline gait and Δ over time: $p < 0.01$.

Because previous reports highlight a relationship with motor phenotype (PIGD), we carried out additional analysis to see if PIGD phenotype predicted gait progression. While we saw a relationship at baseline, additional analysis of variance showed that gait progression did not differ between PIGD and TD motor phenotypes ($p = 0.407$).

DISCUSSION We report a study exploring the role of CSF biomarkers in the progression of gait impairment in early PD. We prioritized dopa-resistant gait characteristics because of the need to understand mechanisms explaining progression and identify potential therapeutic targets. Low baseline CSF Aβ42, and to a lesser extent Aβ40, predicted decline in gait characteristics in the first 3 years following diagnosis. The nature of the findings suggests a role for amyloid pathology. Our study included longitudinal evaluation in very early PD, the use of a robust model to inform (a priori) the selection of gait characteristics, and a broad battery of CSF proteins. The study was carried out in a community-based prospective incident cohort with robust case ascertainment and thus generalizes to idiopathic PD. Our findings are important for 2 key reasons. First, they point to potential mechanisms and novel targets for intervention to mitigate dopa-resistant gait disturbance (and by implication fall risk) at a very early stage of PD, and second, they identify discrete gait characteristics as potential clinical biomarkers for disease progression and therapeutic response.

Two previous studies have explored the relationship between CSF proteins and motor features, classified by motor phenotype. Lower values of Aβ42 and to a lesser extent Aβ40 were predictors independently explaining up to 12% of the variance in progression of dopa-resistant gait characteristics compared with CSF total and p-tau$_{181}$, Aβ40/42, and αSyn, which were not associated with gait progression. Our findings broadly concur with previous cross-sectional reports showing a relationship with amyloid (from CSF and PET imaging) and motor disturbance especially in the PIGD phenotype in early and advanced PD.[10,11,30] However, importantly, our findings highlight limitations of previous work and argue for a more selective investigation of gait impairment.

We found that motor phenotype is not a proxy for dopa-resistant gait impairments as it is not specific to dopa-resistant features or their progression, highlighting the limitations of cross-sectional study design and the use of motor phenotype. This is most likely explained by recent work that shows motor phenotype is unstable in early disease and individuals transition between phenotypes, questioning its longitudinal utility.[31] This study provides

Table 3 General linear models to predict change in gait using CSF (n = 44) of people with Parkinson disease

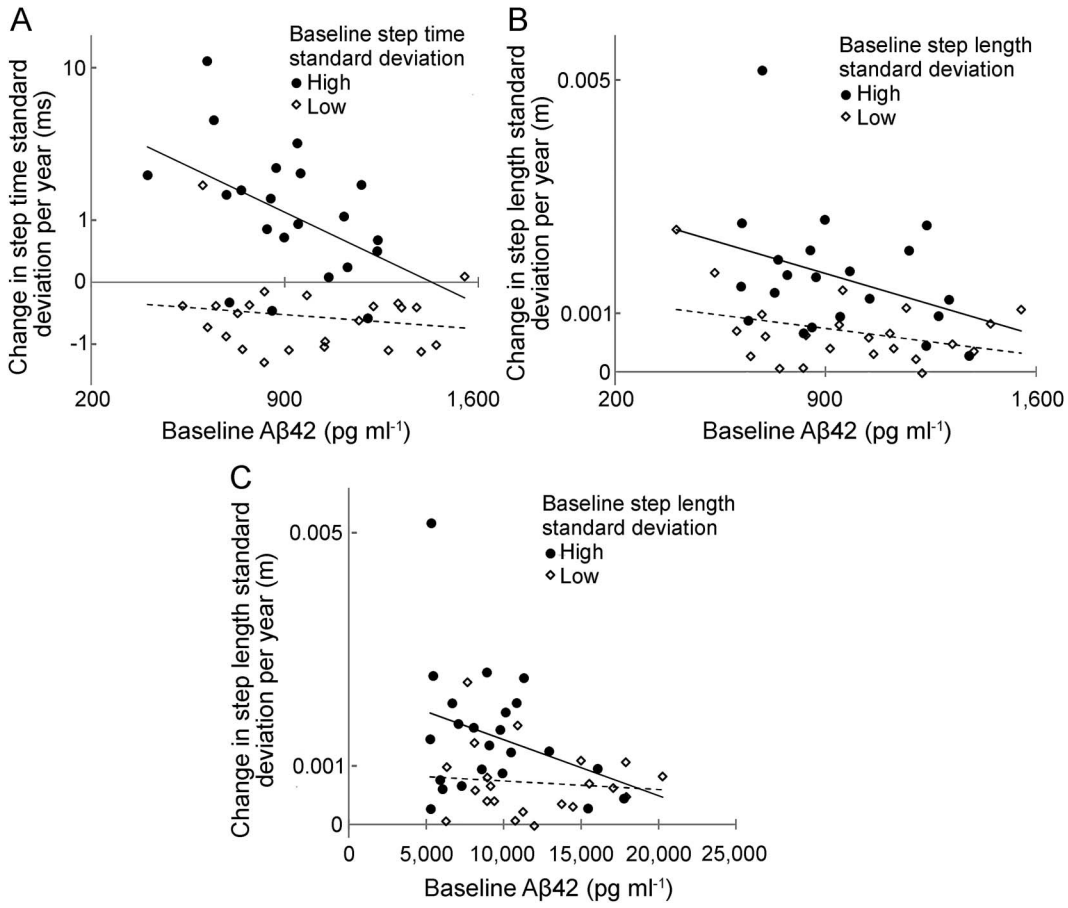
Dependent variable (R^2)	Predictor	Unstandardized estimates (95% CI)	p Value
Models including Aβ42			
Change in single-task step time SD, m/s (R^2_{adj} = 48.5%)			
	Intercept	3.441 (−2.825, 9.707)	0.273
	Age, y	−0.01 (−0.071, 0.051)	0.733
	MoCA (0–30)	−0.124 (−0.264, 0.015)	0.079
	Aβ42, pg/mL	-1.70×10^{-5} (-2.32×10^{-3}, 2.29×10^{-3})	0.988
	High baseline step time SD (>16.7 ms)	6.212 (2.267, 10.157)	0.003[a]
	Aβ42 (pg/mL) × high baseline step time SD (>16.7 ms)	-4.48×10^{-3} (-8.50×10^{-3}, -4.48×10^{-4})	0.030[a]
Change in dual-task step length SD, m/s (R^2_{adj} = 26.6%)			
	Intercept	1.37×10^{-3} (-1.54×10^{-3}, 4.28×10^{-3})	0.347
	Age, y	-8.16×10^{-6} (-3.84×10^{-5}, 2.20×10^{-5})	0.588
	MoCA (0–30)	-3.41×10^{-5} (-3.73×10^{-5}, 1.05×10^{-4})	0.340
	Aβ42, pg/mL	-1.07×10^{-6} (-2.04×10^{-6}, -1.01×10^{-7})	0.031[b]
	High baseline step length SD (>2.36×10^{-2})	9.70×10^{-4} (4.39×10^{-4}, 1.50×10^{-3})	0.001[c]
	Aβ42 (pg/mL) × high baseline step length SD (>2.36×10^{-2})	Not included in the final model	
Models including Aβ40			
Change in dual-task step length SD, m/s (R^2_{adj} = 22.0%)			
	Intercept	-1.72×10^{-4} (-3.259×10^{-3}, 2.91×10^{-3})	0.910
	Age, y	-6.29×10^{-6} (-2.65×10^{-5}, 3.91×10^{-5})	0.700
	MoCA (0–30)	2.04×10^{-5} (-4.71×10^{-5}, 8.78×10^{-5})	0.544
	Aβ40, pg/mL	-7.77×10^{-9} (-0.847×10^{-8}, 7.31×10^{-8})	0.847
	High baseline step length SD (>2.36×10^{-2})	2.34×10^{-3} (8.80×10^{-4}, 3.40×10^{-3})	0.002[a]
	Aβ40 (pg/mL) × baseline gait (>2.36×10^{-2})	-1.47×10^{-7} (-2.82×10^{-7}, -1.24×10^{-8})	0.033[b]

Data presented as group means (95% confidence intervals).
Abbreviations: Aβ = β-amyloid; CI = confidence interval; MoCA = Montreal Cognitive Assessment.
[a] $p < 0.01$.
[b] $p < 0.05$.
[c] $p < 0.001$.

evidence implicating amyloid in the pathogenesis of dopa-resistant gait characteristics in early PD, although direct causality is unknown.

Our findings highlight a possible role for disturbed amyloid metabolism in the neural networks involved in gait control. A number of explanations are possible to explain the mechanisms by which disturbed amyloid metabolism may exert an influence on gait. Lower values of Aβ42 and Aβ40 are generally considered to correlate with plaque formation in the brain.[7,32] Aβ plaque formation may exert a direct effect on synaptic function in the absence of tau[33] influencing the neural circuitry subserving dopa-resistant gait. Alternatively, it is possible that amyloid has a synergistic effect on other proteins such as tau or αSyn catalyzing protein misfolding,[34–36] leading to a more aggressive rate of progression in gait disturbance. However,

Figure 2 Correlation between baseline CSF and change in gait



Relationship between baseline CSF markers and change in gait in people with Parkinson disease.

contrary to our hypothesis, we did not see a relationship with total tau or p-tau$_{181}$. These findings, however, concur with other reports that tau per se is not a primary driver of pathogenesis in PD.[8] A combination of plaque formation, αSyn aggregation, and disturbance of neurotransmitter function (e.g., through synaptic rarefication via protein aggregation) is most likely to contribute to mechanisms underpinning gait progression. Age-related white matter burden may also contribute, although our results argue that for this cohort age was not a significant feature. Postmortem follow-up is required to confirm the precise mechanism. It appears that a combination of different pathologic influences mediate gait progression in a discrete manner in PD, emphasizing the need for a multimodal therapeutic approach.

We determined whether gait characteristics were dopa-resistant by modeling gait progression over 3 years from baseline, despite optimal medication. We also identified only those variables that showed significantly greater change compared to controls over the same time period to avoid confounding due to age-associated decline. Controls showed very little change in gait. Participants with PD exhibited significant decline in 3 gait characteristics over and above controls under single task (variability in step time, step length, and step width) and one under dual task (variability of step length). Variability of step time and step length were prominent, in accordance with earlier work. Step time variability in particular is a sensitive marker of incipient pathology.[37] Establishing the functional and structural correlates using multimodal brain imaging will help inform the neural basis of these findings. We were also able to discern those gait characteristics that were controlled by levodopa (not reported) (e.g., step length and asymmetry), highlighting specific positive benefits of levodopa medication in early stages.

The effect of single and dual task protocols on results is also worthy of comment. During single-task gait, participants are able to recruit additional attentional resources to maintain gait performance, in contrast to dual-task conditions, which preclude cognitive compensation by distracting attention. Our findings imply that dual task step length variability is mediated through motor circuits, whereas single task step time variability is more likely to be subserved by motor and cognitive networks, as

indicated by a (tentative) significant association between the MoCA and step time variability. Brain imaging with amyloid and tau in early PD will help clarify the topographic distribution of pathology driving these changes.

Our findings have interesting clinical implications. CSF Aβ42 is a validated in vivo marker of Aβ accumulation and is implicated in progression of dopa-resistant gait impairments in early PD. Early targeting of Aβ pathology has been proposed as a potential strategy to halt or prevent cognitive decline and dementia in PD.[8,9] Therapies to reduce accumulation of amyloid or target its production are under way. We argue that this may also offer the potential to target early gait impairments, and moreover, may provide a global strategy to concurrently target gait and cognitive impairment. Recently, amyloid deposition in the brain and decreased CSF amyloid have also been shown to predict falls in older adults at risk of dementia,[37] in support of this. Longer follow-up will determine the relationship with fall risk in our cohort.

Our data also suggest that selective gait characteristics may have a role to play in identifying early PD pathology and specific gait characteristics may be useful markers of progression in disease modification trials. Evidence that motor changes precede cognitive changes is common in older adults[38] and has fueled an interest in the role of gait as a clinical biomarker of cognitive decline.[6] The shared pathologic mechanisms of gait and cognitive decline support the potential of gait characteristics as clinical biomarkers of cognitive decline in PD[14,39] and work is under way investigating this.

Some study limitations should be acknowledged. The population was drawn from an incident PD cohort followed from diagnosis with repeat assessments every 18 months. While misdiagnosis may have contributed, this is unlikely to have had a major effect. Diagnosis followed a stringent process and the flowchart highlights revised diagnosis over the time course of the study, showing that the numbers are low. Dropout may also have confounded our analysis; however, this was low, suggesting it would not exert any undue influence. It is difficult to compare the absolute values of our CSF data with those of others due to the use of different assays across studies. Moreover, we did not have a control cohort with CSF. However, we were able to control for the effects of aging in our gait characteristics, only considering those that changed with respect to controls, and are therefore confident that our findings are PD-specific. Given the difficulty of obtaining CSF, this emphasizes the importance of clinically available biomarkers (such as high step time variability at diagnosis).

Our findings suggest that disturbed Aβ metabolism is a biomarker for dopa-resistant gait impairments in early PD. They also raise interesting questions with respect to therapeutic interventions such as compounds or molecules aimed at reducing amyloid burden to mitigate gait disturbance in early PD and by implication fall risk. Comprehensive reporting of gait characteristics was critical to this study and helped explain the heterogeneity of gait disturbance and therapeutic response. Moreover, selective progression of gait characteristics suggests they may have potential as clinical biomarkers of pathology and disease progression. Finally, the overlap in the pathologic substrates of gait and cognitive decline raises an interesting question as to whether a monotherapy may be able to concurrently target gait and cognitive dysfunction in the future.

AUTHOR CONTRIBUTIONS

Prof. Rochester: PI ICICLE-Gait; responsible for study concept and design, analysis and interpretation, drafted first manuscript. Dr. Galna: data analysis and interpretation, manuscript revision. Dr. Lord and Dr. Yarnall: interpretation and manuscript revision. R. Morris, Dr. Duncan, and Dr. Khoo: data acquisition and manuscript revision. Dr. Mollenhauer: manuscript revision and interpretation. Prof. Burn: PI on ICICLE-PD; manuscript revision.

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DISCLOSURE

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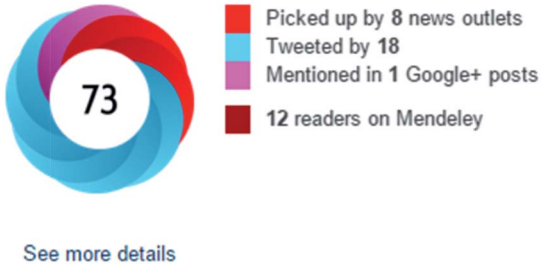

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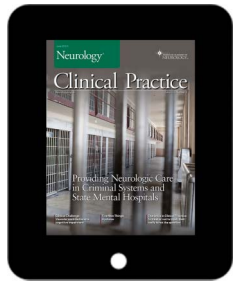

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Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease
Lynn Rochester, Brook Galna, Sue Lord, et al.
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WriteClick® Editor's Choice

Editors' Note: Commenting on "Long-term cortisol measures predict Alzheimer disease risk," Drs. Lattanzi and Silvestrini point out the interrelationships among cortisol dysregulation, insulin resistance, and blood pressure variability in Alzheimer disease (AD) and suggest that the authors study the association between cortisol exposure and the risk of non-AD dementias. Dr. Onofrj critiques "Mediodorsal nucleus and its multiple cognitive functions" because it omitted discussion of confabulations. He also shares a case he described with confabulations due to isolated bilateral lacunes of mediodorsal nuclei. Golden et al., authors of the study, agree and suggest a possible laterality to the role of the thalamus in the phenomenon of confabulations.

—Chafic Karam, MD, and Robert C. Griggs, MD

LETTER RE: LONG-TERM CORTISOL MEASURES PREDICT ALZHEIMER DISEASE RISK

Simona Lattanzi, Mauro Silvestrini, Ancona, Italy: We read with interest the article by Ennis et al.,[1] which found cortisol dysregulation to be related to an increased risk for Alzheimer disease (AD), and built on the unresolved question of whether systemic homeostasis primarily contributes to AD expression or represents an epiphenomenon of the underlying brain pathology. Additional considerations might provide useful insights toward a better and more comprehensive understanding of this issue. Within their pleiotropic effects, corticosteroids can greatly influence metabolic functions as well as blood pressure levels and fluctuations, all of which play key roles in dementia onset and course.[2] In the CNS, corticosteroid receptors are not uniformly localized and abnormal glucocorticoid signaling can result in cell type and site-specific differences.[3] Accordingly, it would be of great interest to address the interrelationships among cortisol dysregulation, insulin resistance, and blood pressure variability,[4] and to investigate the associations between cortisol exposure and the risk of non-AD dementias.[5]

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AUTHOR RESPONSE: LONG-TERM CORTISOL MEASURES PREDICT ALZHEIMER DISEASE RISK

Scott D. Moffat, Atlanta: I thank Drs. Lattanzi and Silvestrini for the thoughtful response to our article.[1] I fully agree with their suggested mechanisms of action by which cortisol may increase risk for AD. In our sample, we had very few non-AD dementias, which precluded a more comprehensive assessment of how cortisol dysregulation may affect risk for other dementias, though it is a fascinating question.

1. Ennis GE, An Y, Resnick SM, et al. Long-term cortisol measures predict Alzheimer disease risk. Neurology 2017; 88:371–378.

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LETTER RE: MEDIODORSAL NUCLEUS AND ITS MULTIPLE COGNITIVE FUNCTIONS

Marco Onofrj, Chieti, Italy: The review on mediodorsal (thalamic) nucleus by Golden et al.[1] omitted referencing relevant information. Mediodorsal nucleus was the focus of a historic debate on the origin of confabulations in Korsakoff syndrome,[2–4] which is characterized by confabulations (beyond amnesia) only if mediodorsal nuclei are involved.[2–4] Clinical findings observed in isolated lacunes of mediodorsal nuclei could elucidate the point, yet isolated lacunes, like the one described in the representative case,[1] are extraordinarily rare.

I recently described one case with confabulations due to isolated bilateral and symmetric lacunes of

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mediodorsal nuclei where connectivity could also be studied.[5] In this report,[5] the possible role of projections to medial prefrontal cortex, node of the anterior default mode network associated with self-referential narrative, was underlined (same as in the review by Golden et al.). The omission of considering confabulations in the review may be due to the fact that the representative case described did not have confabulations.[1] However, the patient's lesions were only in the left mediodorsal nucleus,[1] while from analysis of my patient and discussion of the only 5 documented cases, a key role emerged for the right mediodorsal nuclei (or bilaterality) in the genesis of thalamic confabulations.[5]

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AUTHOR RESPONSE: MEDIODORSAL NUCLEUS AND ITS MULTIPLE COGNITIVE FUNCTIONS

Erin C. Golden, Jonathan Graff-Radford, David T. Jones, Eduardo E. Benarroch, Rochester, MN: We thank Dr. Onofrj for the comments on our review,[1] and for highlighting past literature that suggested the mediodorsal nucleus of the thalamus may also be involved in the development of confabulations in addition to the clinical features described in our case of an isolated left-sided lesion. Indeed, Dr. Onofrj's group's recent clinical case of bilateral lesions of the mediodorsal thalamic nuclei and the associated imaging data lend further support to this concept. Their study and case series would interestingly suggest a possible laterality to the role of the thalamus in the phenomenon of confabulations and provide valuable groundwork for future study in this area.

1. Golden EC, Graff-Radford J, Jones DT, Benarroch EE. Mediodorsal nucleus and its multiple cognitive functions. Neurology 2016;87:2161–2168.

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CORRECTIONS

Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT)

In the article "Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT)" by J. Bernhardt et al.,[1] there was an error in the Creative Commons (CC) license statement. The article, funded by NIHR, should have published with a CC-BY license rather than a CC BY-NC-ND license. An article with the corrected license statement was republished on June 5, 2017. The authors regret the error.

REFERENCE

1. Bernhardt J, Churilov L, Ellery F, et al. Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). Neurology 2016;86:2138–2145.

Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease

The article "Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease" by L. Rochester et al.,[1] funded by Parkinson's UK (COAF Partnership), should have published with the Creative Commons Attribution License (CC BY). The article with the corrected license statement was republished on June 3, 2017. The authors regret the error.

REFERENCE

1. Rochester L, Galna B, Lod S, et al. Decrease in Aβ42 predicts dopa-resistant gait progression in early Parkinson disease. Neurology 2017;88:1501–1511.

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