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A Retrospective Study of Progressive Gait Impairment in Alzheimer's Disease

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Abstract

Individuals with Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) have increased gait disturbances throughout disease progression. However, an understanding of gait impairment and progression in early versus late AD is lacking. Further, the longitudinal progression of gait impairment in AD as well as in those with MCI that transition to AD is lacking. Understanding gait pathology and progression of gait impairment is critical for implementation of strategies that could limit the high prevalence of gait related falls, mobility disability and decreased overall function. Further, better understanding of the gait impairment progression may provide insight into disease processes. As such, this retrospective study aimed to evaluate, via cross sectional and longitudinal analyses, the relationship between MCI and AD diagnosis and gait parameters. Cross-sectional findings

demonstrate significantly slower gait velocity and decreased step length as well as increased double limb support time and step length variability of both early and late AD when compared to MCI. For the longitudinal data the average time between gait assessment visits was 561 ± 267 days. The results demonstrate increasing gait impairment from intial gait assesement (visit 1) to a follow up gait assessment (visit 2) in both the early AD and late AD groups as well as significant decline in the gait profile from visit 1 to visit 2 in those with MCI that transitioned to having AD. These findings are important as they indicate an increasingly pathological gait profile among these populations suggesting need for early intervention.

Keywords
Gait; Alzheimer's disease; Mild cognitive impairment; disease progression

1. Introduction

Individuals with Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) have increased gait disturbances throughout disease progression [1-5]. When compared to healthy, aged matched peers, current evidence shows differences in spatiotemporal gait parameters, including decreased gait velocity and step length, and increased gait variability and double limb support times [2, 3] in both MCI and AD. These gait changes are more pronounced in AD compared to MCI and are affected concurrent to increasing cognitive impairment [1, 4, 5]. Some studies have shown that motor and, more specifically, gait impairments, may even precede cognitive impairment in MCI or AD, suggesting gait is useful for diagnosis and/or outcome analysis [2, 6, 7]. However, more work is needed on the longitudinal trajectory of gait decline, particularly in patients with early versus late AD as well as those patients that transition from an MCI to AD diagnosis.

Mild cognitive impairment is defined clinically as cognition that is "no longer normal relative to age expectations, but daily functions are not sufficiently disrupted to correlate with the diagnosis of dementia" [8]. Of those diagnosed with MCI, approximately 10-15% of people progress to a diagnosis of AD per year [8]. There is substantial literature and guidelines regarding the change in neuropsychological parameters for the transition from MCI to AD, however, there continues to be a high degree of variability in clinical diagnosis. Preliminary work has demonstrated gait dysfunction as a useful marker for risk of transitioning from MCI to AD and thus may aid in clinical decision making. For example, a pilot study by Gillain et al showed that people with MCI who eventually progressed to AD demonstrated a more impaired gait profile (as measured by gait speed and variability) while still classified as MCI, compared to the group with MCI that did not progress to AD [9].

In addition to potential insight into risk of transitioning from MCI to AD, increased understanding of the gait profile and the progression of gait pathology within AD sub groups is needed. For example, the gait profiles of those diagnosed with early onset AD (as defined by age, <65 years) versus those with late onset (≥65) is not adequately described. Better understanding of the gait profile and potential gait disturbance within these populations is important for multiple reasons. First, gait impairments, (e.g. slower gait speed and increased variability) are established marker of overall disability and increased fall risk [10, 11]. Thus, identification of impairment is critical for

intervention and preventive strategies. Secondly, gait speed is a proven and powerful predictor of several health-related outcomes (hospitalizations, morbidity and mortality) in healthy aging and patients populations and thus can serve as a marker of "overall" health [11-13].

This study aimed to evaluate, via cross sectional and longitudinal analyses, the relationship between MCI and AD diagnosis and gait parameters, specifically gait velocity, step length, step length variability, and double limb support. Based on the greater disease burden of AD, we first hypothesized that individuals with AD, both early and late, would have greater impairment in gait outcomes compared to MCI. In addition, based on the progressive nature of the disease, we hypothesized that all groups, except for those that remined MCI at a follow up gait evaluation (MCI-MCI), would demonstrate worsening gait parameters longitudinally. Lastly, we hypothesized that, despite significant differences in age, gait impairment would be similar between the early- and late-AD cohorts. This was hypothesized based on early evidence that early onset AD may be a separate, more severe entity with differential and more aggressive disease manifestation than late onset AD.

2. Materials and Methods

2.1 Population

Data for this retrospective study were collected at the Emory University Brain Health Center from September 2016 to April 2019. As part of standard care, individuals reporting for a clinical appointment underwent a gait assessment on an instrumented gait mat, detailed below. For patients to be evaluated on the instrumented gait mat they had to ambulate without physical assistance (assistive devices were permitted) and follow gait evaluation instructions. Inclusion criteria included for the presented analyses included diagnosis of MCI, early onset AD (<65 at age of diagnosis), or late onset AD. Exclusion criteria included those comorbid conditions affecting cognition or mobility such as cerebrovascular accident or other cerebrovascular disorder, seizure, traumatic brain injury, Parkinson's disease, mood disorders, hydrocephalus, concussion. Other types of dementia were also excluded from this study including vascular dementia, Lewy body dementia, and frontotemporal dementia. For the longitudinal analysis, only those that had two or more gait evaluations at least 6 months apart or greater were included. Gait parameters were linked to individual medical records to identify demographics and determine classification of cognitive impairment as MCI, early AD, or late AD. Review of the medical record was also done after a follow up gait evaluation to determine if those diagnosed with MCI at the initial visit remained stable (MCI-MCI) or transition from MCI at initial visit to AD at the follow up visit (MCI-AD). Thus, the group of interest included, 1) early-AD, 2) late-AD, 3) MCI-MCI and 4) MCI-AD. The diagnoses were provided by a board certified neurologist specializing in cognitive symptomology. Protocols were approved by the Emory University Brain Health Center and the Emory University Institutional Review Board.

2.2 Gait Measurements

The procedure for acquiring a gait evaluation within the cognitive neurology clinic has been described elsewhere [14]. Briefly, a demonstration and standard set of instructions were provided to each individual. Each individual performed one practice trial walking on the mat and two evaluation walks for a total of three walks on the mat. Participants started each trial standing behind a line of tape placed 1-meter from one end of the gait mat. Short rest breaks (5-10 seconds) were

provided between each walk. Verbal cues were provided to participants as necessary between each trial.

2.3 Gait Analysis

Temporal and spatial gait characteristics were calculated by the 20 ft. long × 4 ft. wide ProtoKinetics Zeno instrumented gait mat and associated software. The gait mat is an automatic gait analysis system based on the opening and closing of pressure sensitive switches as the individual walks across. Following a walk, gait data were processed for analysis unless the data was unusable due to footsteps outside the boundaries of the mat or pauses in ambulation. Once processed, selected gait parameters were generated by the gait mat software and exported. The following gait parameters were extracted from the gait mat software for analyses: gait velocity, step length mean and variability using standard deviation within trials, and total double limb support time mean.

2.4 Statistics

The data are presented as mean ± standard deviation or number (%) as appropriate. The baseline demographics and clinical features of patients with MCI-MCI, AD (early and late) as well as those that transitioned from MCI to AD (MCI-AD) were compared with ANOVA. For repeated measures, we used a linear mixed effects model. To measure the time effect, we entered the follow-up time (from initial visit to the follow-up visit) as the fixed effect in the model. The models were adjusted for age, sex and education level. To investigate the group difference and group*time interaction, we entered follow-up time and group as fixed effects and further adjusted for age, sex and education level. A Benjamini–Hochberg procedure was utilized to correction for multiple comparisons.

3. Results

Demographic information included age, sex, diagnosis and means for variables of interest are included in Table 1. The mean age at initial visit for the groups were: early AD (63.09 ± 5.92), late AD (79.51 ± 6.33), MCI-MCI (71.63 ± 8.99) and MCI-AD (75.13 ± 7.57) with most patients being female (54%). The Late AD group was significantly older than early AD, MCI-MCI and MCI-AD groups ($P < 0.05$). Conversely, the early AD group was statistically younger than all other groups ($P < 0.05$). There was no significant difference in age between the MCI-MCI group and the MCI-AD group.

Table 1 Initial visit demographics and cross sectional analyses for outcomes of interest.

	Mean ± Standard Deviation			
	Early AD	Late AD	MCI-MCI	MCI - AD
N	127	457	424	24
% Female	57	53	56	50
Age	63.09 ± 5.92*	79.51 ± 6.33#	71.63± 8.99$	75.13 ± 7.57&
Education (years)	13.71 ± 2.93	13.20 ± 2.32	12.2 ± 2.96	11.90 ± 2.01
Gait Velocity (cm/sec)	92.68 ± 22.21*	83.37 ± 24.94#	103.01 ± 22.48$	97.52 ± 23.08&
Step Length (cm)	55.23 ± 9.67*	49.18 ± 11.55#	58.77 ± 9.93$	56.01 ± 9.80&

Step Length Variability (cm)	3.49 ± 2.67*^	3.73 ± 2.47#	3.01 ± 1.73$	2.72 ± 1.06&
Double Limb Support (sec)	0.41 ± 0.13*^	0.44 ± 0.17#	0.38 ± 0.11$	0.34 ± 0.12&

AD = Alzheimer's disease; MCI = Mild cognitive impairment

*Significant difference between Late AD and Early AD; #Significant difference between Late AD and MCI-MCI; $Significant difference between Early AD and MCI-MCI; &Significant difference between Late AD and MCI-AD; ^Significant difference between Early AD and MCI-AD

3.1 Cross Sectional Analyses

At initial visit, when compared to the early AD group, the late AD patients had a slower gait velocity (83.37 ± 24.94 cm/sec vs. 92.68 ± 22.21 cm/sec, p = 0.001), a shorter step length (49.18 ± 11.55 cm vs. 55.23 ± 9.67 cm, p < 0.001) and increased double limb support time (0.44 ± 0.17 sec vs. 0.41 ± 0.13 sec, p < 0.001). When compared to the MCI-MCI group, the Late AD patients had a slower gait velocity (83.37 ± 24.94 cm/sec vs. 103.01 ± 22.48 cm/sec, p = 0.001), a shorter step length (49.18 ± 11.55 cm vs. 58.77 ± 9.93 cm, p < 0.001), increased double limb support time (0.44 ± 0.17 sec vs. 0.38 ± 0.11 sec, p < 0.001) and increase step length variability (3.73 ± 2.47 cm vs. 3.01 ± 1.73 cm, p < 0.001). When compared to the MCI-AD group, the late AD patients had a slower gait velocity (83.37 ± 24.94 cm/sec vs. 97.52 ± 23.08 cm/sec, p = 0.003), a shorter step length (49.18 ± 11.55 cm vs. 56.01 ± 9.80 cm, p < 0.001), increased double limb support time (0.44 ± 0.17 sec vs. 0.39 ± 0.12 sec, p < 0.001) and increase step length variability (3.73 ± 2.47 cm vs. 2.72 ± 1.06 cm, p < 0.001). At the initial visit, the early AD group showed increased step length variability and double limb support time when compared to both the MCI-MCI group and the MCI-AD group (P < 0.05). Of note, and in contrast to our hypothesis, the initial gait evaluation of the MCI-MCI group versus the initial gait evaluation of those with MCI that eventually transitioned to AD (MCI-AD) were not statistical difference on any outcome (Table 1).

3.2 Longitudinal Analyses

For the longitudinal data the average time between gait assessment at visit 1 and visit 2 was 561 ± 267 days. Across groups all gait outcomes significantly deteriorated from visit 1 to visit 2. For example, gait velocity at visit 1 averaged 98.02 ± 5.92 cm/sec and decreased to an average of 90.14 ± 8.54 cm/sec (p = 0.03) at visit 2. Similarly, step length decreased from 57.23 ± 3.19 cm to 53.02 ± 4.07 cm. Step length variability increased from 3.28 ± 0.06 cm to 3.78 ± 0.06 cm from the visit 1 to visit 2. Lastly, double limb support time increased from 0.39 ± 0.01 sec at visit 1 to 0.42 ± 0.03 sec at visit 2.

There were also significant group*time interactions in the mixed effects models. The early AD, late AD, and MCI-AD groups demonstrated deterioration in gait speed (P < 0.05; shown in figure 1) and step length (Table 2) between visit 1 and visit 2. The MCI-AD group also demonstrated increased step length variability from visit 1 to visit 2 (2.72 ± 1.06 cm to 3.30 ± 1.49 cm, p = 0.045). And, lastly, the late AD group demonstrated an increase in double limb support time across visits (0.39 ± 0.10 sec to 0.42 ± 0.11 sec, p = 0.018).

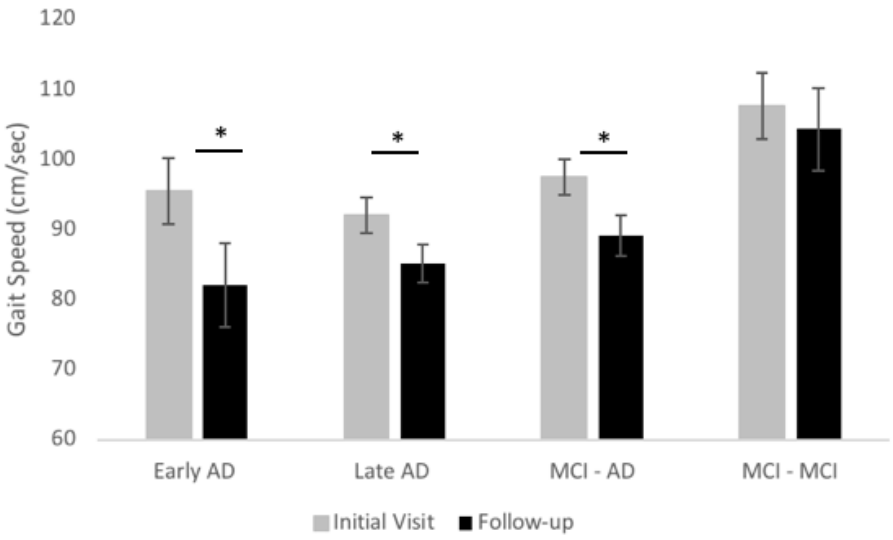

Figure 1 Change in gait speed from initial visit to follow up visit. * Indicates significant change from initial to follow up at $p < 0.05$.

Table 2 Mean and standard deviation for outcomes of interest from initial visit to follow up visit.

	Early AD	Late AD	MCI - MCI	MCI - AD
N =	19	70	61	24
Age at Initial Visit	62.37 ± 5.34	78.11 ± 6.98	72.80 ± 8.56	75.13 ± 7.57
Time between visits (days)	520 ± 259	559 ± 289	538 ± 292	630 ± 262
Gait Velocity (cm/sec)				
Initial	95.40 ± 20.34	91.59 ± 21.61	107.59 ± 19.82	97.52 ± 23.08
Follow Up	82.03 ± 26.11	85.10 ± 22.83	104.29 ± 22.48	89.15 ± 28.90
P value	**0.019**	**0.002**	0.102	**0.020**
Step Length (cm)				
Initial	58.76 ± 9.13	52.78 ± 10.21	61.37 ± 7.95	56.01 ± 9.80
Follow Up	50.93 ± 12.71	49.34 ± 10.78	59.88 ± 9.30	51.92 ± 13.27
P value	**<0.001**	**<0.001**	0.065	**0.005**
Step Length Variability (cm)				
Initial	4.11 ± 1.47	3.56 ± 1.44	2.75 ± 1.17	2.72 ± 1.06
Follow Up	4.88 ± 1.17	3.77 ± 1.83	3.16 ± 1.90	3.30 ± 1.49
P value	0.601	0.341	0.117	**0.045**
Double Limb Support (sec)				
Initial	0.42 ± 0.16	0.39 ± 0.10	0.36 ± 0.08	0.39 ± 0.12
Follow Up	0.48 ± 0.15	0.42 ± 0.11	0.38 ± 0.11	0.41 ± 0.13
P value	0.177	**0.018**	0.091	0.215

AD = Alzheimer's disease; MCI = Mild cognitive impairment. **Bold text indication significant change at p < 0.05 from initial visit to follow up visit.**

4. Discussion

The purpose of this study was to evaluate, via cross sectional and longitudinal analyses, the relationship between diagnosis and gait parameters in a large cohort of individuals MCI and AD. Similar to previous works, and in line with our hypothesis, our findings demonstrate significant gait impairment of both early and late AD when compared to MCI. For the longitudinal data, our results demonstrate increasing gait impairment from visit 1 to visit 2 in both the early AD and late AD groups (Figure 1). Lastly, our hypothesis of a differential gait profile at initial evaluation of those with MCI that transitioned to AD when compared to those that remained stable was not supported. However, our longitudinal analysis demonstrated significant decline in the gait profile from visit 1 to visit 2 in the MCI-AD group versus those that remained MCI (Figure 1).

The evaluation of gait has been increasingly utilized as a comprehensive measure of health in various aging and age-related disease populations. For example, gait has been repeatedly tied to significant health related outcomes including disability, falls, hospitalizations and mortality [11-13]. Specific to cognitive symptomology, a meta-analysis by Bahureska et al found a statistically significant difference in velocity, stride length, and stride time between those with MCI when compared to healthy controls [2]. Other studies have also found changes in velocity and gait variability are associated with diagnosis of MCI and faster cognitive decline in MCI [3, 15]. The GOOD Initiative, by Allali and colleagues [4], found that severity of cognitive impairment in MCI was related to the severity of worsening gait outcomes, with worsening cognitive symptomology being associated with a more severe gait impairment. Our work adds to these findings by demonstrating more severe gait impairment when comparing both early and late AD those patients with MCI.

Despite our hypothesis of a similar gait profile between early and late AD, we demonstrated that early AD had a higher functioning gait profile (greater gait velocity and step length as well as less double limb support time) when compared to late onset AD, with the exception of step length variability. This was hypothesis was made based on early evidence that early onset AD may be a separate, more severe entity with differential and more aggressive disease manifestation than late onset AD [16]. However, due to the fact gait speed is differentially impacted by age-related decreases in cardiovascular function it is possible that there would be greater impact on those with late onset AD, as late AD cohort was an average of 16 years older than the early AD cohort. The finding of no statistical difference in step length variability is interesting as studies have shown that increase step length variability is a better predictor of cognitive decline when compared to gait speed [17]. Thus, the step length variability in our early AD cohort may indeed support the idea of early onset AD being a separate, differential disease manifestation than late onset AD [16]. However, further research is needed.

Gait in the healthy population is primarily an automatic yet complex task, requiring coordination of multiple areas in the brain. These areas of the brain, including the prefrontal cortex, temporal lobe, and parietal lobe, are also active in higher level cognitive processing [15]. Beyond the neuroanatomical links, literature has shown that slower walking speeds and a greater decline in speed over time were at greater risk of developing dementia independent of changes in cognition [18]. There are multiple theories regarding the underlying mechanism behind motor impairment and dementia. Grande et al summarize two primary theories that lead to these dual cognitive and motor impairments: brain- driven hypothesis and body-driven hypothesis [15]. Brain-driven hypothesis suggesting that neurodegenerative and/or vascular pathology begins in the brain,

leading to impairments in gait and cognition [15]. The other, more indirect theory suggests that impairments in the cardiovascular, respiratory, and metabolic comorbidities affect multiple functions of the brain leading to impaired cognition and subsequent motor impairment [15]. While the mechanism of disease pathology is debated, it is clear cognition and motor impairments are closely interrelated.

An additional aim of this study was to investigate the potential of gait as a marker of disease progression and/or transitioning from MCI to AD. To date, accurately confirming a diagnosis is made post-mortem and/or with CSF examination including the evaluation of beta-amyloid deposition, pathologic tau, and neurodegeneration [19]. Adding to the variability, while many people with MCI ultimately transition to having AD, some do not [20, 21]. For this reason, current research is continually aiming to aid in the identification of additional biomarkers that may flag those at greatest risk of transitioning from MCI to AD. Our results showed regardless of remaining stable with MCI or transition to AD, the initial evaluation of gait showed a similar profile. However, those with MCI who transition to AD demonstrated a significant decrease gait speed, step length and step length variability from the initial gait evaluation to the follow up gait evaluation. Additional research is needed as to the time course of changes in gait and progression of the disease and to determine what qualifies as a marked or significant change in gait speed in the clinical environment.

We had suggested that gait dysfunction may be useful marker for risk of transitioning from MCI to AD and thus may aid in clinical decision making. While utilizing the gait profile as a diagnostic tool indicating potential of transitioning from MCI to AD was not supported by this work, its clinical relevance cannot be underestimated. Individuals with MCI (that transition to AD) or those with AD that exhibit decline in their gait profile (slower gait speed, for example) should be flagged for intervention as soon as possible for multiple reasons. First, change in gait speed is associated with an increased risk of falls in both community-dwelling elderly and people with cognitive impairment, suggesting need for physical therapy intervention to reduce fall risk [22-24]. As individuals with AD progress in the course of the disease, explicit learning decreases, requiring greater repetition of intervention for skill retention and new learning to take place [25]. It can be argued that physical therapy intervention for gait and balance will be most effective earlier in the course of the disease or even before transitioning to AD, to optimize therapy and functional carryover.

While we believe this study has important implication, it is not without limitations. The most evident is the small sample size of those that transitioned from MCI to AD. Given the nature of disease it is difficult to track a large subset of those with MCI that will subsequently transition to AD. While a diagnosis of MCI increases the risk of developing AD, there are currently no accurate means to identify those patients with MCI that will ultimately transition to AD. However, we believe our results highlight the need for further research aimed to determine if an aggressive decrease in gait function may be used to predict those that are at risk for progressing from MCI to AD. Patients with MCI can also be further divided into amnesic and non-amnesic types, which this study did not analyze. Future studies are needed to determine the differences in gait presentation between sub diagnoses of MCI. Lastly, there was also variability in follow up for participants included in the longitudinal analyses. We attempted to have the gait data collected each time the patient visited their providers, however this was not always possible. As such, not only were some patients missed at the follow up visit but there was variability in the time between initial gait evaluation and a follow up gait evaluation, as noted in Table 2. The variability in follow up time makes it difficult to determine timeline for increasing gait pathology and disease progression."

5. Conclusion

In conclusion, this study aligns with previous findings that people with AD, both early onset and late onset, have decreased gait velocity and step length mean when compared to MCI. This study also shows that people with late onset AD and early onset AD demonstrate significant decline in gait outcomes overtime. Similarly, those with MCI who transition to AD also show a significant change over time in gait function, while individuals with MCI who remain MCI at follow up have a gait pattern that remains more stable. These findings are important as they indicate an increasingly pathological gait profile among these populations suggesting need for early intervention.

Author Contributions

Kimberly Bader – Analysis and interpretation of data, drafting and final approval of intellectual content within manuscript. James J. Lah- Conception and design of the project, drafting and final approval of intellectual content within manuscript. Allan I. Levey- Conception and design of the project, drafting and final approval of intellectual content within manuscript. Greg J. Esper- Conception and design of the project, interpretation of data, drafting and final approval of intellectual content within manuscript. Whitney Wharton- Conception and design of the project, interpretation of data, drafting and final approval of intellectual content within manuscript. Joe R. Nocera -acquisition, analysis, or interpretation of data for the work, conception and design of the work, drafting and final approval of intellectual content within manuscript.

Competing Interests

The authors have no conflict of interest to report.

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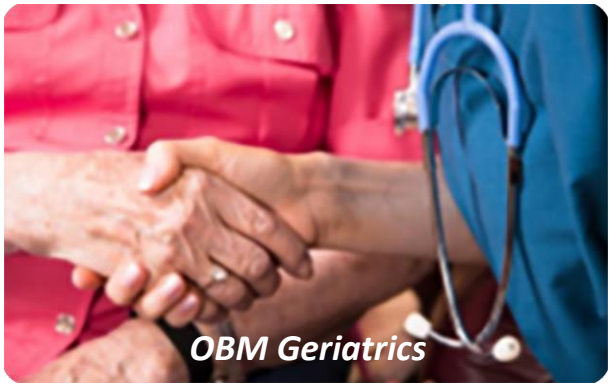

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