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ARTICLE

Balance impairment does not necessarily coexist with gait apraxia in mild and moderate Alzheimer's disease

Comprometimento do equilíbrio e apraxia da marcha não necessariamente coexistem na doença de Alzheimer leve e moderada

Fernando Vieira Pereira, Fabricio Ferreira de Oliveira, Rodrigo Rizek Schultz, Paulo Henrique Ferreira Bertolucci

ABSTRACT

Currently, there are no studies reporting how much balance impairment coexists with gait apraxia in mild and moderate Alzheimer's disease (AD). **Objectives:** To assess correlations among gait apraxia, balance impairment and cognitive performance in mild (AD1, n = 30) and moderate (AD2, n = 30) AD. **Method:** The following evaluations were undertaken: gait apraxia (Assessment Walking Skills); balance performance (Berg Balance Scale); Clinical Dementia Rating and Mini-mental State Examination (MMSE). **Results:** While disregarding AD subgroups, Berg Balance Scale and the MMSE correlated significantly with Assessment Walking Skills and 23% of all subjects scored below its cut-off. After stratification, Berg Balance Scale correlated significantly with Assessment Walking Skills in both AD subgroups, and with the MMSE only in AD1. **Conclusions:** Balance impairment does not necessarily coexist with gait apraxia. Gait apraxia is more prevalent in moderate AD when compared with mild AD.

Keywords: Alzheimer disease; gait; apraxias; postural balance.

RESUMO

Apraxia da marcha e desequilíbrio são condições subinvestigadas na doença de Alzheimer (DA) leve e moderada. **Objetivo:** Verificar a correlação da apraxia da marcha com desequilíbrio e cognição em 30 idosos com DA leve (DA1) e 30 idosos com DA moderada (DA2). **Método:** Foram feitas as seguintes avaliações: apraxia da marcha (Assessment Walking Skills); equilíbrio (Berg Balance Scale); Clinical Dementia Rating e Mini-exame do estado mental – MEEM. **Resultados:** Desconsiderando-se os grupos, Berg Balance Scale e MEEM correlacionaram-se significativamente com a Assessment Walking Skills, enquanto 23% dos participantes pontuaram abaixo da note de corte da mesma. Considerando-se os grupos, Berg Balance Scale correlacionou-se significativamente com a Assessment Walking Skills em ambos os grupos, embora o MEEM o tenha feito apenas em DA1. **Conclusões:** Desequilíbrio e apraxia da marcha não necessariamente coexistem com apraxia da marcha. Prevalência de apraxia da marcha foi maior na DA moderada do que na DA leve.

Palavras-chave: doença de Alzheimer; marcha; apraxias; equilíbrio postural.

Earlier studies suggested that frontal and parietal cortices, basal nuclei and/or neural pathways among them (white matter lesions) underlie apraxia disorders[1,2]. The mesial frontal lobes[3] and the supplementary motor area[4] have already been linked to gait apraxia (GA), despite the need for more research to include other potential neuroanatomic sites.

In the literature, GA is considered a frontal gait disorder as well as a high level gait disorder[5]. Importantly, GA is commonly described as the most complex and less understood gait disorder among the high level gait disorders. For example, Elble[6] reported that GA relies over controversial concepts and contributes to make the high level gait disorders even more complex. Zadikoff and Lang[7] went further by suggesting that GA is more likely to be a misnomer than a real clinical entity.

Della-Sala et al.[8] investigated GA in patients with mild and moderate Alzheimer's disease (AD) by elaborating and validating a scale called "Assessment Walking Skills" (AWS). In their results, the authors not only verified that 40% of their sample (n = 60) performed below the cut-off of AWS (< 38), but they also reported that both dementia severity (r = 0.53) and upper limb apraxia (r = 0.50) had significant correlations

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with AWS ($p < 0.01$). To our knowledge, AWS is the only quantitative gait apraxia test available in the literature.

In addition, it is pretty hard to talk about gait without mentioning balance, which can be summarized as the ability to maintain the body's center of mass over its base of support, no matter the condition (static or dynamic)[9]. In summary, preserved balance performance is a precondition for successful gait performance.

Previous studies suggested that impaired balance performance is more evident in AD individuals when compared with controls[10] and declines according to the dementia stage[11]. Similar results were reported by Kato-Narita et al.[12] when the Berg Balance Scale (BBS) was employed to measure balance performance in mild and moderate AD. In their results, the authors reported that BBS correlated with disease severity but not with history of falls or functional decline.

Taking prior studies into consideration, this investigation aimed to answer the following question: "How much do impaired balance performance and GA correlate with each other in mild and moderate AD?" Moreover, two other objectives were outlined: to check whether cognitive performance correlates with GA; and to compare three independent scales, mini-mental examination (MMSE), BBS and AWS between patients with mild and moderate AD.

Here we emphasize that this investigation did not intend to disentangle or validate the GA terminology ***per se***, but rather its presence in mild and moderate AD. For more details about GA and its history we suggest the reference by Elble[6].

METHOD

Participants

Subjects with mild (AD1 subgroup) and moderate (AD2 subgroup) AD were recruited from the Behavioral Neurology Section of our university hospital. All the patients with AD who were included in this investigation already had a diagnosis of probable AD, which was confirmed by way of the Consortium to Establish a Registry for Alzheimer's Disease[13], and all subjects were treated with cholinesterase inhibitors. This study was approved by the Ethics Committee of our university hospital. Every participant and/or his legal representative signed an informed consent form.

Inclusion criteria for AD subgroups were: one year or more of probable AD diagnosis; balance-related complaints confirmed by both the caregiver and the patient; and preserved comprehension of verbal commands. Exclusion criteria were: use of gait auxiliary devices; clinical Parkinsonian signs; and positive report for vestibular symptoms, peripheral neuropathies, severe rheumatic disorders, limited visual acuity and orthostatic hypotension-related symptoms.

Subgroup characteristics

Mini-mental State Examination[14] and Clinical Dementia Rating (CDR)[15] scales were employed to allocate patients into AD1 or AD2 subgroups. AD1: CDR = 1.0 and MMSE scores between 19 and 25; AD2: CDR = 2.0 and MMSE scores between 12 and 18. It is important to highlight that CDR, and not MMSE, was employed to consider each patient as mild or moderate AD. MMSE cut-off scores described above were added only to avoid ceiling and floor effects, since CDR is not affected by education and previous reports have already identified significant correlations between their scores[16,17].

GA assessment

Assessment Walking Skills is a binary (one/zero) qualitative scale for gait apraxia divided into two parts: the first part evaluates trunk praxis while walking and has 22 items; the second part evaluates lower limbs praxis while walking and has 20 items. Each item must be scored as zero (incorrect answer) or one (correct answer). Minimal and maximal scores range from zero to 42 points. The cut-off score was set at 38 points. Employment of the AWS scale followed the guidelines published by Della-Sala et al.[8].

Balance assessment

The Berg Balance Scale[18,19] evaluates both static and dynamic balance performance while standing and walking. The BBS has excellent reliability and good correlation with other balance assessment instruments such as the Tinetti scale ($r = 0.91$) and the Timed Up and Go Test ($r = 0.76$)[20]. The BBS has 14 items with scores ranging from 0 to 4 each (best condition = 56). Scores between 53–46 mean low to moderate risk of falls, between 45–20 mean high risk of falls, and scores < 20 mean wheelchair bound users and/or recurrent fallers[21]. Since measurement of risk of falls was not the objective of this research, BBS cut-off scores were not employed to verify the level of agreement with the AWS scale.

Data analysis

All the statistical analysis was undertaken with the SPSS software. Two samples t-test was employed for paired comparisons. Pearson correlation coefficients (PCC) and linear regression analysis (R^2) were calculated to quantify the strength and evaluate the level of agreement among AWS, the BBS and the MMSE in both AD subgroups, despite the fact that different AD subgroups were not considered to verify correlations between the MMSE and the BBS with AWS in the overall analysis. Regression analysis modeling was adjusted for age and gender when necessary. All the comparison tests were two-tailed and the p-value for statistical significance was set at ≤ 0.05.

RESULTS

Overall analysis

A total of 30 mild AD (AD1 subgroup) and 30 moderate AD (AD2 subgroup) subjects were recruited. Regarding AWS, 14 (23.3%) patients with AD (13.3% from AD1 and 33.3% from AD2) scored below the cut-off of AWS (< 38). When patients with AD were considered as a whole (no subgroups), the BBS reached the most significant correlation with AWS (PCC = 0.628, R^2 = 0.395, p < 0.001). Once the MMSE was added to the model (multiple linear regression), the correlation became less significant (p = 0.002), despite the fact that both PCC and regression increased in 0.072 (PCC = 0.700) and 0.095 (R^2 = 0.489), respectively. Importantly, age and gender did not significantly influence this correlation when utilized as controlling variables. A scatterplot (matrix) with regression values among AWS, the BBS and the MMSE was built for better visualization of the data above (Figure 1).

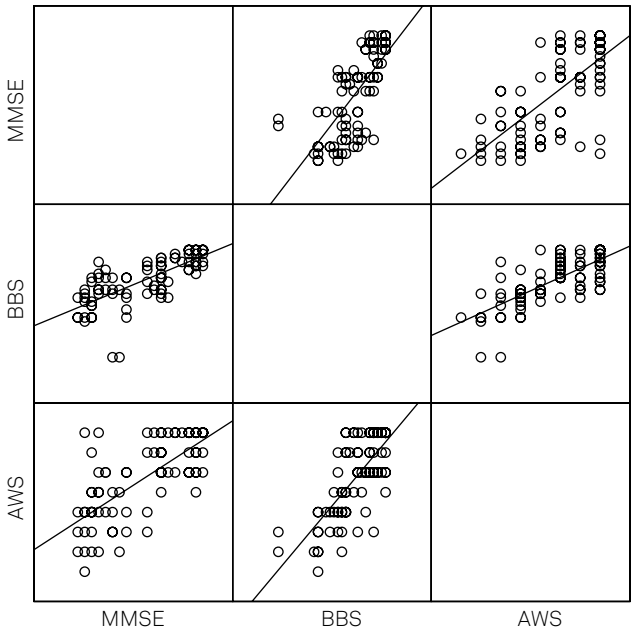
Subgroup analysis

Table 1 shows demographic and score results from both AD subgroups, as well as the comparative analysis between them**.** Age and gender were not significantly different between the AD subgroups. AWS and the BBS correlated significantly in both AD1 (PCC = 0.524, R^2 = 0.274, p = 0.003) and AD2 (PCC = 0.632, R^2 = 0.399, p < 0.001) subgroups. Regarding the MMSE, we observed that it correlated significantly with AWS in AD1 (PCC = 0.623, R^2 = 0.388, p < 0.001) but not in AD2 (PCC = 0.217, R^2 = 0.047, p = 0.249). Furthermore, both BBS and MMSE correlations with AWS throughout AD subgroups were not influenced by age or gender when employed as controlled variables. See Figure 2 for better visualization of the data above.

AWS-subgroup analysis

Here we aimed to analyze potential significant differences regarding age, gender, MMSE and BBS scores between patients with AD who scored above (ADabove: AWS ≥ 38, n = 46) and below the cut-off of AWS (ADbelow: AWS < 38, n = 14). In ADabove, the BBS (PCC = 0.521, R^2 = 0.271, p < 0.001) and the MMSE (PCC = 0.514, R^2 = 0.264, p < 0.001) correlated significantly with AWS. In relation to ADbelow, the BBS and the MMSE did not have significant correlations. More details about this comparison are shown in Table 2 and in Figures 3 and 4.

In addition, we also compared the 14 AD patients (4 from AD1 and 10 from AD2) who scored below the cut-off of AWS.



BBS;MMSE: R^2 Linear = 0.538
AWS;BBS: R^2 Linear = 0.538
MMSE;BBS: R^2 Linear = 0.538
BBS;AWS: R^2 Linear = 0.538
MMSE;AWS: R^2 Linear = 0.499
AWS;MMSE: R^2 Linear = 0.499

Figure 1. Simple linear regressions regarding assessment walking skills (AWS), Berg balance scale (BBS) and mini-mental state examination (MMSE) for all participants.

Table 1. Demographic and clinical comparisons between mild Alzheimer's disease (AD1) and moderate Alzheimer's disease (AD2) subgroups.

Variables	Subgroup	n	Mean	SD	95%CI		p-value
					Lower	Upper	
Age	AD1	30	71.3	5.1	69.4	73.2	0.351
	AD2	30	72.87	7.551	70.05	75.69	
Gender	AD1	30	F = 17 / M = 13	0.504	1.25	1.62	0.799
	AD2	30	F = 16 / M = 14	0.507	1.28	1.66	
MMSE	AD1	30	22.27	2.318	21.4	23.13	< 0.001
	AD2	30	14.4	1.522	13.83	14.97	
BBS	AD1	30	47.3	5.107	45.39	49.21	0.016
	AD2	30	44.07	5.003	42.2	45.93	
AWS	AD1	30	39.77	1.716	39.13	40.41	0.001
	AD2	30	38.2	1.73	37.55	38.85	

SD: standard deviation; 95%CI: confidence interval of the mean. MMSE: mini-mental state examination; BBS: Berg balance scale; AWS: assessment walking skills; F: female; M: male.

More details about these 14 individuals are shown in Table 3. In this scenario, the correlation between the BBS and the MMSE was not significant for both AD1 and AD2 subgroups ($p > 0.05$) even after age and gender adjustments.

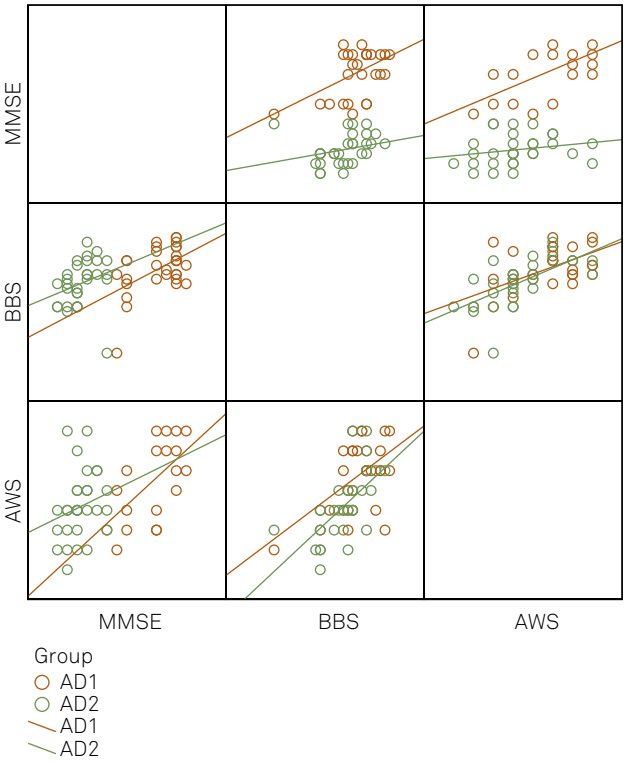


Figure 2. Simple linear regressions regarding assessment walking skills (AWS), Berg balance scale (BBS) and mini-mental state examination (MMSE) for mild Alzheimer's disease (AD1) and moderate Alzheimer's disease (AD2) subgroups.

DISCUSSION

Provided by Della-Sala et al.[8] since prevalence of GA tends to be higher in moderate than in mild AD.

When patients with AD were stratified into ADabove and ADbelow the cut-off of AWS, it was possible to verify that both the BBS and the MMSE had significant correlations in the ADabove subgroup only. Similar results were confirmed by verifying AWS correlations with the BBS and the MMSE between AD1 AND AD2 individuasl who scored below the cut-off of AWS. In this scenario, the BBS and the MMSE did not correlate in both subgroups. One possible explanation about these conflicting data might be related to the small sample of individuals (4 from AD1 and 10 from AD2) who scored below the cut-off of AWS.

It is hard to evaluate apraxic disorders because they are usually exclusion diagnoses[22]. In relation to GA, we conducted a similar approach to earlier studies, since simpler explanations should be considered first in AD individuals with walking difficulties. In this investigation, the CDR was employed to stratify patients with AD into subgroups of mild and moderate AD. Ranges of MMSE scores were used as a secondary tool to make sure the cognitive performance was in agreement with the classification provided by the CDR scale. It is important to note that this methodology did not limit our statistical analysis, since MMSE correlations with AWS and the BBS were verified either by considering two AD subgroups or by putting them together (no subgroups). This analysis is available in Figures 1, 2 and 3.

Earlier studies had demonstrated significant correlations between gait and cognitive decline in AD[23,24]. However, confirmation of frontal involvement in these patients might demand neuroimaging and a more comprehensive cognitive assessment to investigate every single domain related to these brain regions. Behavioral symptoms might also be correlated with gait in the same way that they are correlated with cognitive and functional decline in AD[25], which would be an interesting idea for future studies.

In summary, we can say that 23% of patients with AD (10 from the AD2 subgroup) with balance related complaints

Table 2. Comparisons between subject subgroups regarding gait apraxia.

Variables	Gait apraxia subgroup	n	Mean	SD	p-value
Age	No gait apraxia	46	71.43	5.443	0.284
	Gait apraxia	14	74.21	8.894	
Gender	No gait apraxia	46	F = 7 / M = 7	0.501	0.682
	Gait apraxia	14	F = 26 / M = 20	0.519	
MMSE	No gait apraxia	46	19.11	4.418	0.007
	Gait apraxia	14	15.79	3.446	
BBS	No gait apraxia	46	47.22	3.681	0.003
	Gait apraxia	14	40.64	6.594	
AWS	No gait apraxia	46	39.74	1.421	< 0.001
	Gait apraxia	14	36.5	0.65	

SD: standard deviation; MMSE: mini-mental state examination; BBS: Berg balance scale; AWS: assessment walking skills; F: female; M: male.

scored below the cut-off of AWS. In other words, 77% of patients with AD with balance related complaints did not have GA according to AWS. These numbers are nearly half of those reported by Della-Sala et al.[8] when 40% of patients with AD scored below the cut-off of AWS. In relation to that, it is necessary to highlight that whilst they included patients with AD with gait difficulties, this investigation included patients with AD with balance-related complaints only. Despite those findings, a common thread is that our results match those In this investigation, the main contradictory result was that MMSE and AWS scores correlated significantly in AD1 but not in AD2. In this scenario, there are two possible explanations: the least reasonable one is that cognitive performance does not correlate with GA; and the most reasonable one is that a deeper cognitive evaluation should be considered since the MMSE is a cognitive screening tool and has its own limitations. Despite this caveat, the MMSE correlated significantly with AWS once patients with AD were separated between those above and below the cut-off of AWS. A possible interpretation for that is that the correlation of the MMSE with AWS would be useful to differentiate patients with AD under higher risk for GA but useless if employed to estimate GA risk for different disease severity stages (mild and moderate).Another possible limitation regards both the BBS and AWS. The BBS is a functional balance assessment tool and so was not designed to distinguish among

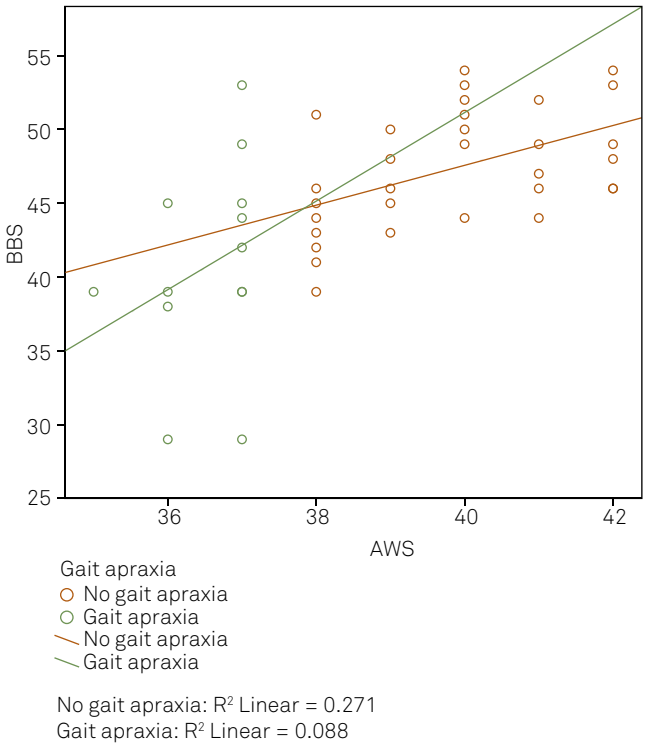


Figure 3. Simple linear regression between assessment walking skills (AWS) and the Berg balance scale (BBS) for mild Alzheimer's disease (AD1) and moderate Alzheimer's disease (AD2) subjects scoring above and below the cut-off of AWS.

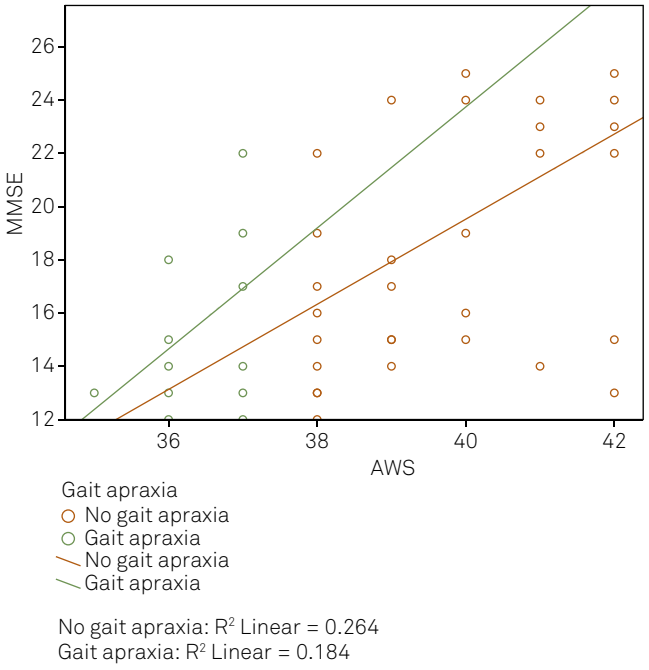


Figure 4. Simple linear regression between assessment walking skills (AWS) and the mini-mental state examination (MMSE) for mild Alzheimer's disease (AD1) and moderate Alzheimer's disease (AD2) subjects scoring above and below the cut-off of AWS.

Table 3. Comparisons between mild Alzheimer's disease (AD1) and moderate Alzheimer's disease (AD2) subjects who scored below the cut-off of assessment walking skills (AWS).

Variables	Subgroup	n	Mean	SD	t-test
Age	AD1	4	68.75	3.5	0.049
	AD2	10	76.4	9.571	
Gender	AD1	4	F = 2 / M = 2	0.577	0.99
	AD2	10	F = 5 / M = 5	0.527	
MMSE	AD1	4	20.25	2.062	0.003
	AD2	10	14	1.826	
BBS	AD1	4	41.5	10.116	0.834
	AD2	10	40.3	5.314	
AWS	AD1	4	36.75	0.5	0.325
	AD2	10	36.4	0.699	

SD: standard deviation; MMSE: mini-mental state examination; BBS: Berg balance scale; F: female; M: male.

different types of balance impairments. However, this is not a limitation of the BBS only since most functional balance assessment scales assess risk of falls and/or functional limitations but do not help to elucidate their etiology[26]. In a certain way, we have the same for AWS since it does not provide the underlying cause for GA. Finally, the small sample size precludes deeper assumptions regarding gait apraxia in these patients.

By intending to avoid comments like "apraxia of gait is another term that perhaps is a misnomer[7]", we propose a GA rating scale (e.g. mild, moderate and severe). A similar approach was also proposed by Elble[6]. Yet, future GA-related studies should consider running a factorial statistical analysis for AWS, since it has 42 items and its completion is time consuming.

In conclusion, impaired balance performance does not necessarily coexist with GA. Prevalence of GA tends to be higher in moderate AD when compared with mild AD, despite the fact that the MMSE correlated with AWS only in mild AD. The BBS and the MMSE correlated significantly with AWS when no subgroups were considered.

In the AWS-subgroup (AD1 and AD2 individuals below the cut-off of AWS), neither the BBS nor the MMSE reached significant correlations with AWS. Moreover, an important limitation of this study resides on the fact that the sample size of these subgroups was insufficient to provide more solid comparisons between: AD1above X AD1below; and AD2above X AD2below.

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