Chapter 11

Gait Pathway in Subcortical Vascular Dementia and in Alzheimer's Disease

Rita Moretti, Arianna Sartori, Beatrice Baso and Silvia Gazzin

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/59834

1. Introduction

Gait impairment, worse equilibrium scores and falls are associated with leukoaraiosis, as widely recognised [1-6]. In Binswanger's disease with a severe leukoaraiosis gait disorders are clearly evident while patients with mild periventricular changes may present subclinical forms of gait disorders, as proposed by some authors (see data in [7]).

Gait disorders in the elderly are particularly relevant, since they can influence the loss of functional independence and death [8]. As anticipated, cerebral small vessel disease (both white matter lesions and lacunar infarcts) correlates with gait parameters: stride length and a lower gait velocity [8]. Most importantly, subcortical vascular lesions seem to increase the possibility of falls, even if clear evidences are still lacking [9-11].

Walking difficulties in Alzheimer's disease are well described [12]: patients show slow and irregular steps, difficulties in turning and avoiding obstacles [13, 14]. These disturbances have been described also in patients free from extrapyramidal, ataxic, paretic signs, and clinically relevant musculoskeletal impairments [12, 14]. Moreover, Alzheimer's disease patients have a worse balance [12, 14, 15] and a higher risk of falls compared with matched controls [16, 17]. The prevalence of gait abnormalities varies widely across the studies (from 8.7% [18] to over 90% [19]); this can be explained because of different inclusion criteria and/or assessment procedures.

These observations have been confirmed by studies demonstrating that patients with Alzheimer's disease walk more slowly compared to healthy controls [12] and these gait problems have been interpreted as manifestations of the extrapyramidal deficits (well-known to affect

12–28% of Alzheimer patients), or as side effects of drug treatment (e.g. neuroleptic agents) [20]. Since a overt walking problems and trunk movement alterations can be seen also in absence of extrapyramidal signs, it has been proposed that some Alzheimer's disease patients may present "frontal gait disorder", a syndrome coterminous with gait apraxia [21, 15]. The lack of a standardised instrument to assess gait has been implicated as a possible cause for the low frequency of reports on the topic.

Since the walking assessment cannot discriminate between walking disorders caused by gait apraxia and other neurological causes of walking difficulty, there has been the necessity to exclude alternative causes of walking abnormalities in Alzheimer's disease (overt extrapyramidal impairments or other concurrent neurological diseases); in order to assess gait capacity, a new test has been proposed and a large proportion of the sample (40%) scored below cut off, even if the percentage of severely impaired was smaller. Although the possibility of right–left confusion, working memory deficits, and problems with verbal comprehension was minimised by demonstrating the items, the complexity of some of them might have contributed to inflating the proportion of patients performing poorly. Even though, the presence of associated vascular pathology in a few patients also cannot account for the outcome. Neuroradiological signs of white matter changes were reported in three of the 24 patients (22.5%) in the Della Sala *et al.*'s study [12], who scored below cut off in the assessment of walking skills.

Therefore, in a well-defined population suffering from subcortical vascular dementia and Alzheimer's disease (standing from a neurological, clinical, and radiological criteria), we tried to explore gait, balance and equilibrium alterations, and a behavioral complex symptom, such as apathy, even considering precipitant factors, such as concomitant pathologies and consequent therapies. We now present an extension of the work, with a speculation on what we observed for a two-year follow-up.

2. Subjects and methods

2.1. Patients

From June 1st 2010 to June 1st 2013, 155 patients diagnosed with Alzheimer's disease (AD), according to NINDCS-ADRDA criteria [22], and 673 patients with subcortical vascular dementia (according the NINDS-AIREN criteria for probable VaD [23]) (age 65–94 years) have been examined in Cognitive Disorder Unit Evaluation of the University of Trieste and enrolled in the present study.

The inclusion criteria were a Mini-Mental State Examination (MMSE) scores of at least 14 and satisfying the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for dementia. As far as neuroimaging is concerned, subcortical VaD (sVAD) was diagnosed when the CT/MRI scan showed moderate to severe ischemic white matter changes [24] and at least one lacunar infarct. In order to be enrolled into the study, Alzheimer's subjects had to show on brain MRI the classical pattern of atrophy of AD (hippocampal

http://dx.doi.org/10.5772/59834

atrophy) and display hypoperfusion in temporoparietal and precuneus regions (AD) on HMPAO-SPECT. The neurologist (RM) assessed independently, after the radiologist's opinion, brain CT and/or MRI images and all the diagnoses have been confirmed after a long term clinical follow-up (12 and 36 months).

Exclusion criteria were: normal pressure hydrocephalus, diagnoses of major stroke or brain haemorrhage, previous brain tumours, white matter lesions due to specific aetiologies (e.g. multiple sclerosis, vasculitis, brain irradiation, and genetic forms of vascular dementia such as CADASIL or CARASIL). Finally, also major psychiatric illness (e.g.. schizophrenia, bipolar disorders, psychosis, compulsive-obsessive disorders, etc) or central nervous system disorders and alcoholism were excluded. Also absence of an informed caregiver, unavailability of neuroradiological examination, and/or the use of psychotropic drugs within two months prior to the clinical assessment implied patient's exclusion from the study. According to these exclusion criteria, 27 AD patients and 70 sVAD patients were excluded. We did not consider a discriminant/exclusion criteria depression, referring to different studies (such as [25]), according to the potential correlation to vascular dementia predisposing factor.

2.2. Study design

This was a prospective cohort study, designed to investigate behavioural alterations, and in particular apathy of a AD and of a sVAD population. Study subjects underwent the following evaluations. The standardized baseline assessment implied a detailed history, physical examination (pulse rate and rhythm, blood pressure, heart size and sounds, peripheral pulses, retinal vessel and carotid artery evaluation), EKG, chest X-ray, laboratory tests and psychiatric evaluation. All patients were followed with neurological examinations scheduled every four months, while the complete neuropsychological examination was conducted at baseline and at 36 months. We conducted the study in accordance with the Declaration of Helsinki and with the Ethics Guidelines of the Institute.

2.3. Outcome measures

All patients were studied, with complete neurological and neuropsychological examinations. Main outcomes of the study were: global performance, which was assessed using the Mini Mental State Examination [26], Frontal Assessment Battery (FAB) [27]; global behavioral symptoms, assessed by the Neuro Psychiatric Inventory, NPI [28]; the caregiver stress, assessed by the Relative Stress Scale, RSS [29]. In addition to these main outcome measures, the Clinical Insight Rating Scale (CIR) [30] (which provides a measure of its four comprising items – awareness, cognitive deficit, disease progression and functional deficit) was performed. The Barthel index (BI) [31] and the Instrumental activity of Daily living (IADL) [32] have been used to assess functional activities and complex activities of daily living, respectively. Mobility problems were evaluated by the Tinetti scale for equilibrium/balance and gait [33]: in particular, a semiquantitative assessment was used, consisting of the modified Tinetti test with 17 items, 9 for body balance (0-16), 8 for gait (0-12). Patients were registered for their medical intake.

3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0). Wilcoxon Signed Ranks test was used to analyze the Within-group changes, from baseline to 24 months, of the overall scores for each efficacy variable.

Behavioral outcome measures, cognition, Tinetti scale, global, balance and equilibrium, and BI correlations were analyzed applying the Spearman's rank correlation analyses.

4. Results

The study subjects were 128 AD patients and 603 sVAD patients. All the patients could be fully studied (mean age 72.3 ± 7.3 years, range= 62-94 years). 1 AD patient and 5 sVAD patients died during the two-year follow-up. As anticipated, the diagnosis based on clinical history, neuropsychological assessment and neuroimaging was reinforced by subsequent follow-up in all cases.

All the selected patients underwent neuroimaging: 128 AD patients did MRI studies; 603 sVAD patients did CT scans; moreover, 201 of the latter completed the diagnostic pathway with MRI images, in case of not adequate imaging acquisition or not convincing data. Therefore, the patients who did CT/MRI were homogeneously recruited and no demographical/social/cultural/clinical difference distinguished from each other.

A neurologist (RM) revised all the imaging, employing the Blennow *et al.* [34] scale for CT scans and the Scheltens *et al.* [35] scale for MRI imaging in sVAD patients and Wahlund *et al.* [36], Kantarci *et al.* [37] and den Heijer *et al.* [38] criteria for AD MRI imaging. There was 95.8% inter-rater agreement for the independent assessment of the scans (kappa=0.8).

Patients were allowed to continue any previous therapy (e.g. antihypertensive, antidyslipidemic, antidiabetic drugs). During the follow-up, the patients were prescribed neuroleptics and/or benzodiazepines.

A synopsis of the cognitive performances obtained by the two groups has been reported in Table 1-2-3-4.

Baseline	**sVAD**	**AD**	**P value (between groups)**
MMSE	25.8 (2.4)	19.9 (1.9)	<0.01
Arithmetic calculations (WAIS) §	6.3 (1.6)	8.6 (1.2)	<0.05
Digit span forward (WAIS)	5.8 (1.5)	5.1 (0.6)	<0.05
Digit span backward (WAIS)	4.4 (2.5)	2.6 (0.8)	<0.05
FAB total score	9.2 (2.1)	11.8 (1.2)	<0.05

Table 1. Cognitive synoptical results obtained by the two groups studied. Values are mean (SD); ns = not significant. § number of mistakes.

http://dx.doi.org/10.5772/59834

24-month follow-up	sVAD within group (24 months vs baseline)	AD within group (24 months vs baseline)	P value (between groups)
MMSE	20.2 (2.2) (-5.2 (.0.3); p<0.01)	15.1 (1.7) (-4.85 (0.2); p<0.01)	<0.01
Arithmetic calculations (WAIS) §	5.4 (1.1) (-0.9 (0.5); ns)	3.4 (1.7) (-5.2 (0.5); p<0.01)	<0.05
Digit span forward (WAIS)	4.1 (1.4) (-1.7 (0.1); p<0.05)	3.2 (0.2) (-1.9 (0.4); p<0.05)	<0.05
Digit span backward (WAIS)	3.6 (0.3) (-0.8 (2.2); ns)	1.9 (0.1) (-0.5 (0.7); p<0.05)	<0.01
FAB total score	4.7 (1.5) (-4.5 (0.6); p<0.01)	7.5 (0.2) (-3.3 (1.0); p<0.05)	<0.01

Table 2. Cognitive synoptical results obtained by the two groups studied, at 12 months. Values are mean (SD); ns = not significant. § Number of mistakes. In brackets, in each column, comparison within group, 24 months *vs* baseline, reported as mean, SD, and p.

Tests	Baseline sVAD	Baseline AD
Barthel Index	87.41 ± 11.3	92.14 ± 0.11
Instrumental Activity of Daily Living	6.8 ± 0.34	5.84 ± 1.3

Table 3. TESTs results in the patients observed during follow-up.

Tests at 24 months	sVAD	AD	Between groups (sVAD vs AD)
Barthel Index	-25.17± 3.4 p<0.01	-13.57 ± 3.4 p<0.05	p<0.01
Instrumental Activity of Daily Living	-1.7 ± 0.3 p<0.05	-3.4 ± 3.4 p<0.01	p<0.01

Table 4. Results at 24 months: a comparison over baseline.

In summary, there are some important cognitive differences in the two groups: AD patients did worse in MMSE, in arithmetic calculation and in digit tasks of WAIS, IADL; sVAD patients did generally worse in FAB tests, Barthel Index.

From the behavioral perspective (Table 5-6), at baseline, the AD group had a worse score of NPI and BEHAVE-AD, and their caregivers did have a heavier stress (RSS). On the contrary, sVAD patients, at baseline did feel much more depressed (as stated by NPI partial scores, not purposely evaluated in this topic) and did have a better insight in their situation. After 24 months, AD patients showed higher NPI and Behave scores; sVAD patients did show more

insight. Surprisingly, the stress levels of the caregivers were not significantly different in the two groups. sVAD patients did manifest more overt apathy, which increase during follow-up and remained a major key point in behavior disturbances of these patients.

Moreover, there was a dramatic decrease, either in gait and equilibrium control, either in the combined synoptical measure (of total score) in both groups, with sVAD patients showing a constantly worse performance, compared to AD patients (Table 7-8).

baseline	sVAD	AD	P value
RSS	24.7 (8.7)	36.1 (8.5)	(p<0.01)
NPI	16.9 (0.3)	24.4 (5.2)	(p<0.01)
CIR	3 (0.2)	2 (0.5)	(p<0.05)

Table 5. Behavioral synoptical results. Values are mean (SD); ns = not significant.

24-month follow-up	sVAD	AD	P value
RSS	47.5 (1.3) (+22.8 (5.9), <0.01)	45.2 (2.1) (+9.1 (6.8), <0.05)	ns
NPI	34.1 (0.8) (+17.2 (0.5), <0.01)	56.3 (4.5) (+31.9 (1.1), <0.01)	(p<0.01)
CIR	2.2 (0.3) (-0.8 (0.1), ns)	1.0 (0.3) (-1.0 (0.3), <0.05)	(p<0.01)

Table 6. Behavioral synoptical results. Values are mean (SD); ns = not significant; in brackets, in each column, comparison within group, 24 months *vs* baseline, reported as mean, SD, and p.

Tests	sVAD	AD	P value
TINETTI equilibrium	10.1 ± 0.1	14.3 ± 1.1	<0.001
TINETTI gait	10.2 ± 1.1	11.4 ± 0.3	<0.05
TINETTI tot. score	20.3 ± 1.2	25.7 ± 1.4	<0.001

Table 7. Gait TESTs results in the patients observed at baseline.

Tests at 24 months	Over baseline sVAD	Over baseline AD	Between groups (sVAD vs AD)
TINETTI equilibrium	-5 ± 0.6 p<0.01	-3.4 ± 0.6 p<0.01	P<0.001
TINETTI gait	-7.9 ± 1.1 p<0.01	-3.1± 1.1 p<0.01	P<0.001
TINETTI tot. score	-12.9 ± 0.2 p<0.01	-6.5 ± 0.2 p<0.01	P<0.001

Table 8. Results at 24 months: a comparison over baseline at 24 months.

http://dx.doi.org/10.5772/59834

Spearman's rank correlation analyses indicated that there was a significant correlation between Gait scores (total and separately, gait and equilibrium) and FAB scores (**total Tinetti score/ FAB**: r=0.81, $p < 0.05$ baseline; r=0.83, $p < 0.01$ over 24 months); **gait Tinetti score/FAB:** r=0.82, $p < 0.01$ over baseline; r=0.87, $p < 0.01$ over 24 months); **equilibrium Tinetti score/FAB:** r=0.81, $p < 0.05$ over baseline; r=0.83, $p < 0.01$ over 24 months) in sVAD.

Spearman's rank correlation analyses indicated that there was a significant correlation between Tinetti total, and equilibrium and gait score and BI over baseline, and 24 months (**total Tinetti score/BI**: r=0.81, $p < 0.05$ over baseline; r=0.89, $p < 0.01$ over 24 months); **gait Tinetti score/BI:** r=0.82, $p < 0.01$ over baseline; r=0.89, $p < 0.01$ over 24 months; **equilibrium Tinetti score/BI:** r=0.84, $p < 0.01$ over baseline; r=0.89, $p < 0.01$ over 24 months) in sVAD.

Furthermore, we have found a correlation between Tinetti equilibrium score and NPI over 24, months (equilibrium Tinetti/NPI: r=0.78, p<0.05 in sVAD; r=0.87, p<0.01 in AD), and Tinetti gait score and NPI over 24 months (**gait Tinetti /NPI**: r= 0.78, p<0.05 in sVAD; r=0.86, p<0.01 in AD), and Tinetti total score and NPI over 24 months (**Tinetti total score/NPI**: r= 0.78, p<0.05, in sVAD; r= 0.93, p<0.01 in AD).

Spearman's rank correlation analyses indicated that there was a significant correlation between Gait scores (total scores and separately, gait and equilibrium) and MMSE (**total Tinetti score/ MMSE**: r=0.81, $p < 0.05$ over 24 months in AD).

Surprisingly, we have found only a correlation between benzodiazepines intake and Tinetti equilibrium score at 24 months (respectively r=0.77, p<0.05 in sVAD; r=0.84, p<0.01 in AD).

We distinguished typical from atypical neuroleptic intake (Table 9). Moreover, since quetiapine, as an atypical neuroleptic, has a lower dopamine affinity compared to olanzapine, we considered separately the compounds, concluding as follows:

- Typical neuroleptics: a significant correlation between haloperidol intake and Tinetti equilibrium score at baseline and at 24 months (respectively: r=0.61, p<0.05, at baseline and r=0.81, p<0.01 in AD patients; r=0.72, p<0.05 at 24 months in sVAD); between haloperidol intake and Tinetti total score at baseline and 24 months (respectively: r=0.81, p<0.01 and r=0.86, p<0.01 in AD; only at 24 months r=0.71, p<0.01 in sVAD); not significant correlation between promazine chloridate intake and Tinetti sub-scores at baseline and at 24 months in AD; we have found a positive correlation between the equilibrium score of Tinetti test and promazine intake at 24 months in sVAD, not in AD group (r=0.74, p<0.05).
- Atypical neuroleptics: we have found a significant correlation between olanzapine intake and Tinetti equilibrium score at 24 months in AD groups (none of sVAD took olanzapine in our study) (r=0.74, p<0.05) and between olanzapine intake and Tinetti total score at 24 months (r=0.71, p<0.05); we have found a positive correlation between the equilibrium score of Tinetti test and quetiapine intake at 24 months (respectively: r=0.79, p<0.05 in AD group; r=0.82, p<0.01 in sVAD). The mean dose of olanzapine remained stable during the 24-month follow-up (5.2-5.4 mg/day); on the contrary, quetiapine dosage increased up to 24-month follow-up (56.3-89.6 mg/day).

Drug utilization	Baseline sVAD	24 months sVAD	Baseline AD	24 months sVAD
Benzodiazepines	144 patients	289 patients	298 patients	304 patients
lorazepam, mean (±SD) dose	1.27± 0.3 mg/day	2.56 ± 0.65 mg/day	3.94 ± 1.5 mg/day	4.56 ± 1.65 mg/day
delorazepam, mean (±SD) dose	1.21 ± 0.8 mg/day	2.61 ± 1.29 mg/day	3.1 ± 1.54 mg/day	4.1 ± 1.89 mg/day
bromazepam, mean (±SD) dose	2.11 ± 1.1 mg/day	3.41 ± 0.8 mg/day	4.6 ± 1.4 mg/day	5.41 ± 1.8 mg/day
Typical neuroleptics	88 patients	356 patients	88 patients	127 patients
haloperidol, mean (±SD) dose	1.56 ± 0.54 mg/day	2.34 ± 0.67 mg/day	2.87 ± 1.54 mg/day	3.56 ± 0.54 mg/day
promazine chloridrate, mean (±SD) dose	53.12 ± 12.23 mg/day	59.12 ± 16.91 mg/day	63.12 ± 7.2 mg/day	67.12 ± 1.56 mg/day
Atypical neuroleptics	4 patients	23 patients	63 patients	83 patients
olanzapine, mean (±SD) dose	0.0 ± 0 mg/day	0 ± 0 mg/day	5.6 ± 1.6 mg/day	5.9 ± 2.94 mg/day
quetiapine, mean (±SD) dose	37.5 ± 5.21 mg/day	56.9 ± 3.5 mg/day	66.8 ± 3.5 mg/day	89.9 ± 3.5 mg/day

Table 9. A synopsis of the CNS drugs employed by the patients.

5. Discussion

Walking is a complex mechanism, based on motor control, step rhythm, muscular activation and dys-activation, motor adjustment, attention, perception and so on. Spinal and brainstem activation, which seems to be fundamental for quadrupeds, is not so dominant in humans, where gait depends more on cortical and subcortical inputs [39].

The motor cortex, represented by distinct areas in the frontal lobes, receives a variety of inputs: sensory areas, motor control structures, and modulatory pathways including the thalamus and basal ganglia (BG). Movement planning and performance are strictly dependent from this cluster of architectonically distinct frontal fields [40]. In particular, SMA activates immediately before gait ignition in normal walking, suggesting a preparatory activity for each sub-component of a movement sequence [41]. It has been suggested that this activity may reflect sub-movement program selection, subsequently sent to the M1. On the other hand, BG generate a phasic activity, which switches off SMA output and which is probably involved in providing a non-specific cue both to trigger the sub-movement and to instruct the SMA to prepare for the next, finally generating an "automatic" movement sequence [42, 7]. In conclusion, internal cues give rise to automatic movement sequences, as a result of the cooperation of BG and SMA [7].

Gait control and in particular gait variability are deeply influenced by BG compensatory activity [43]. Rosano and colleagues reported that subclinical brain vascular abnormalities (WM infarcts and hyperintensities in MRI) were more frequent and severe in patients with a greater variability of step length, independently from age, gender, and cognitive function [43]. Moreover, older people and patients with leukoaraiosis show higher-level gait alterations, supporting the previous observations [39]. These data have been clinically confirmed by other works by the LADIS group [11], by Srikanth *et al.* [44] and by Masdeu and Wolfson [45].

http://dx.doi.org/10.5772/59834

Though, there are quite real differences among the few other studies on this point. It has been established by Della Sala *et al.* [12] that even AD, in a sizeable proportion (40% of their population) scored as having gait alteration. Though, it must be pointed out that the presence of associated vascular pathology, declared by the writers themselves is a not indifferent proportion (22.5%), even if they asserted that this could not account for the outcome. The Authors declared that their patients showed the gait apraxia phenomenon, referring to deficits of a relatively unitary function, with the reference to a theoretical model. Within the dichotomy, proposed by Benke [46], between a conceptual system of motor acts and a system which controls sensorimotor and spatial-temporal features of movement, gait apraxia would arise from the impairment of the latter system. Gait apraxia suggested Della Sala *et al.* [12] should also be distinguished from ideomotor apraxia, which hampers individual movements and meaningless gestures. What we observed in our study was the dramatically significant overcome of gait disturbances, either considering balance, either gait by itself, in pure sVAD rather than in pure AD pathology. Gait imbalance in AD relates with progressive and dramatic worsening of global cognitive functions (MMSE), with behavioural deterioration (NPI) and with consequent drugs intake.

On the contrary gait and balance in sVAD is a very precocious symptom, which relates, from the very beginning with frontal executive functions (FAB) and Barthel Index (BI) (Table 10).

Gait disturbances	**sVAD**	**AD**
Characteristics	Peculiar	Unspecific
	Early	Late
	Frequent	Less frequent
Relate to	Frontal executive functions (FAB)	Global cognitive functions (MMSE)
	Barthel Index (BI)	Behavioral performance (NPI)
		Drugs intake

Table 10. Summary: characteristics of gait disturbances in sVAD and AD patients.

Insofar, we hypothesize that even though gait apraxia is one of the symptoms declared in AD, affecting highly routinized synergistic actions, it relates to AD cognitive worsening. On the contrary, it is a key, precocious and very peculiar aspect of sVAD. Therefore, considering this point, it can be found a good explanation of the phenomenon, in Liston *et al.* [7] work; they suggested that microvascular alteration affecting the SMA, its connections in the periventricular WM, or the BG can cause a higher-level gait disorders (HLGDs), a hypothesis that seems to agree with the concept of gait apraxia caused by any mesial frontal lesion (SMA anatomical location) purposed by Meyer [47]. A further clinical confirmation is provided by current evidence of gait abnormities in early vascular dementia, in particular when WM alterations affect strategic pathways (linking the BG to the ventro-lateral nucleus of the thalamus and to the SMA and frontal areas) [48, 49]; these critical locations compromise the timing cues from the BG; the analogy to PD disconnections may suggest similar gait abnormalities. It is well known and widely accepted that leukoaraiosis is associated with gait impairment, falls, and worse equilibrium scores [1, 3-6, 8, 50]. Some authors suggest a spectrum of severity in gait

disorders associated with WM abnormalities: on one side, severe gait disorder observed in Binswanger's disease with massive leukoaraiosis [7], on the other subclinical forms of gait disorders can occur in patients with mild periventricular changes.

However, it has been demonstrated that many patients with vascular-HLGDs present with disequilibrium as primary complaint rather than timing and movement ignition problems [4, 51, 7]. To explain this phenomenon it has been purposed that an alteration of the sensory/PMA pathways, compromising the contribute to sub-movements initiation and control of sensory input (proprioceptive, auditory, vestibular and visual information), may represent their primary disorder [7]. The preservation of BG/SMA pathways guarantees the generation of automatic, internally cued movements,

A clear point should be made in our study to the extremely strict exclusion criteria in AD and in sVAD recruitment, basically founded on clinical signs and neuroimaging world-wide accepted criteria. For example, in order to eliminate any confounding, we excluded patients with brainstem lesions, which ischemic lesions could cause specific gait and equilibrium abnormalities. Similarly, we considered also concurrent medications and co-morbidities, in order to ensure that the gait and balance alterations observed should be considered as an exclusive result of subcortical WM widespread damage. During the follow-up, a general worsening, decrease of behavioural control, and consequent pharmacologic intake (neuroleptics and benzodiazepines) stressed but did not cause directly the described gait abnormalities. In conclusion, it might be stated that subcortical lesions cause "per se" the interruption of long loop reflexes of deep white motor tracts and descending motor fibers arising from medial cortical areas (see data and literature in: Guerini *et al.* [10], Moretti *et al.* [52]), translating in gait alteration and imbalance. Moreover, subcortical vascular lesions involve fibres connecting frontal cortex and subcortical structures, which are responsible for motivation, executive function, planning and attention too (see in particular frontal eye fields). It has been suggested (see data and Literature in Moretti *et al.* [52]) that the basal ganglia maintains cortically selected motor set in the supplementary motor area and provides internal cues to the supplementary motor area in order to enable each sub movement to be correctly linked together [53-56].

Author details

Rita Moretti[1*], Arianna Sartori[2], Beatrice Baso[2] and Silvia Gazzin[3]

*Address all correspondence to: moretti@univ.trieste.it

1 Clinica Neurologica, Responsabile Ambulatorio Complicanze Internistiche Cerebrali, Dipartimento Universitario Clinico di Scienze Mediche, Chirurgiche e della Salute, Università degli Studi di Trieste, Italy

2 Clinica Neurologica, Dipartimento Universitario Clinico di Scienze Mediche, Chirurgiche e della Salute, Università degli Studi di Trieste, Italy

3 Area Science Park, FIF, Basovizza, Ospedale di Cattinara, Trieste, Italy

http://dx.doi.org/10.5772/59834

References

[1] Steingert A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in subjects with diffuse white matter lucencies on computed tomographic scan (leuko-araiosis). Arch Neurol. 1987;44(1):32–5.

[2] Junqué C, Pujol J, Vendrell P, et al. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. Arch Neurol. 1990;47(2):151–6.

[3] Masdeu JC, Wolfson L, Lantos G, et al. Brain white matter changes in the elderly prone to falling. Arch Neurol. 1989;46 (12):1292–6.

[4] Baloh RW, Yue Q, Socotch TM, et al. White matter lesions and disequilibrium in older people. I. Case-control comparison. Arch Neurol. 1995;52(10):970–4.

[5] Mirsen TR, Lee DH, Wong CJ et al. Clinical correlates of white-matter changes on magnetic resonance imaging scans of the brain. Arch Neurol. 1991;48(10):1015–21.

[6] Inzitari D, Cadelo M, Marranci ML, et al. Vascular deaths in elderly neurological patients with leukoaraiosis. J Neurol Neurosurg Psychiatry 1997;62(2):177–81.

[7] Liston R, Mickelborough J, Bene J, et al. A new classification of higher level gait disorders in patients with cerebral multi-infarct states. Age Ageing. 2003;32(3):252–8.

[8] de Laat KF, van Norden AG, Gons RA, et al. Gait in elderly with cerebral small vessel disease. Stroke. 2010;41(8):1652-8.

[9] Guttmann CR, Benson R, Warfield SK, et al. White matter abnormalities in mobility impaired older persons. Neurology. 2000; 54(6):1277-83.

[10] Guerini F, Frisoni GB, Marrè A, et al. Subcortical vascular lesions predict falls at 12 months in elderly aptients discharged from a rehabilitation ward. Arch Phys Med Rehabil. 2008;89(8):1522-7.

[11] Baezner H, Blahak C, Poggesi A, et al. Association of gait and balance disorders with age-related white matter changes. Neurology. 2008;70(12):935-42.

[12] Della Sala S, Spinnler H, Venneri A. Walking difficulties in patients with Alzheimer's disease might originate from gait apraxia. J Neurol Neurosurg Psychiatry 2004;75(2): 196-201.

[13] Ala TA, Frey WH. Validation of the NINCDS-ADRDA criteria regarding gait in the clinical diagnosis of Alzheimer disease. A clinicopathologic study. Alzheimer Dis Assoc Disord. 1995;9(3):152–9.

[14] Alexander NB, Mollo JM, Giordani B, et al. Maintenance of balance, gait patterns, and obstacle clearance in Alzheimer's disease. Neurology. 1995;45(5):908–14.

[15] Visser H. Gait and balance in senile dementia of Alzheimer's type. Age Ageing. 1983;12(4):296–301.

[16] Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. JAMA.1987;257(11):1492–5.

[17] van Dijk PT, Meulenberg OG, van de Sande HJ, et al. Falls in dementia patients. Gerontologist. 1993;33(2):200–4.

[18] Koller WC, Wilson RS, Glatt SL, et al. Motor signs are infrequent in dementia of the Alzheimer type. Ann Neurol. 1984;16(4):514–16.

[19] Fransenn EH, Kluger A, Torossian CL, et al. The neurologic syndrome of severe Alzheimer's disease. Relationship to functional decline. Arch Neurol 1993;50:1029–39.

[20] Burns A, Jacoby R, Levy R. Neurological signs in Alzheimer's disease. Age Ageing. 1991;20(1):45–51.

[21] Kurlan R, Richard IH, Papka M, et al. Movement disorders in Alzheimer's disease: More rigidity of definition is needed. Mov Disord 2000;15(1):24–9.

[22] McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 34(7): 939–44.

[23] Román GC, Tatemichi TK, Erkinjuntti T et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43(2):250- 60.

[24] Erkinjuntti T. Vascular dementia: challenge of clinical diagnosis. Int Psychogeriatr. 1997;9:77–83.

[25] Bus BA, Marijnissen RM, Holewjin S, et al. Depressive symptom clusters are differentialy associated with atherosclerotic disease. Psychol Med. 2011;41(7):1419-28.

[26] Folstein MF, Folstein SE, McHugh PR. "Mini-Mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3): 189–98.

[27] Dubois B, Slachevsky A, Litvan I, et al. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000;55(11):1621-6.

[28] Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–14.

[29] Greene JG, Smith R, Gardiner M, et al. Measuring behavioural disturbance of elderly demented in patients in the community and its effects on relatives: a factor analytic study. Age Ageing. 1982;11(2):121–6.

[30] Ott BR, Lafleche G, Whelihan WM, et al. Impaired awareness of deficits in Alzheimer Disease. Alzheimer Dis Assoc Disord. 1996;10(2):68-76.

[31] Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J. 1965;14:61-65.

[32] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.

[33] Tinetti ME. Performance-oriented assessment of mobilty problems in elderly patients. J Am Ger Soc. 1986;34(2):119-26.

[34] Blennow K, Wallin A, Uhlemann C, et al. White-matter lesions on CT in Alzheimer patients: relation to clinical symptomatology and vascular factors. Acta Neurol Scand. 1991;83(3):187-93.

[35] Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci. 1993;114(1): 7-12.

[36] Wahlund LO, Almkvist O, Blennow K, et al. Evidence-based evaluation of magnetic resonance imaging as a diagnostic tool in dementia workup. Top Magn Reson Imaging. 2005;16(6):427-37.

[37] Kantarci K, Jack CR Jr. Neuroimaging in Alzheimer disease: an evidence-based review. Neuroimaging Clin N Am. 2003;13(2):197-209.

[38] den Heijer T, Geerlings M, Hoebeek F, et al. Use of hippocampal and amygdalar volumes on MRI to predict dementia in cognitively intact elderly. Arch Gen Psychiatry 2006;63(1):57-62.

[39] Carboncini MC, Volterrani D, Bonfiglio L, et al. Higher level gait disorders in subcortical chronic vascular encephalopathy: a single photon emission computed tomography study. Age Ageing. 2009;38(3):302-7.

[40] Donoghue JP, Sanes JN. Motor areas of the motor cortex. J Clin Neurophysiol. 1994;11(4):382-96.

[41] Georgiou N, Iansek R, Bradshaw JL, et al. An evaluation of the role of internal cues in the pathogenesis of parkinsonian hypokinesia. Brain. 1993;116(Pt 6):1575–87.

[42] Phillips JG, Martin KE, Bradshaw JL, et al. Could bradykinesia in Parkinson's disease simply be overcompensation? J Neurol. 1994;241(7):439–47.

[43] Rosano C, Brach J, Studenski S, et al. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. Neuroepidemiology. 2007;29(3-4):193-200.

[44] Srikanth V, Beare R, Blizzard L, et al. Cerebral white matter lesions, gait and risk of incident falls: a prospective population based study. Stroke. 2009;40(1):175-80.

[45] Masdeu JC, Wolfson L. White matter lesions predispose to falls in older people. Stroke. 2009;40(9):e546.

[46] Benke T. Two forms of apraxia in Alzheimer's disease. Cortex. 1993; 29(4):715-29.

[47] Meyer JS, Barron DW. Apraxia of gait: a clinico-physiological study. Brain.1960;83(2): 261–84.

[48] Hennerici MG, Oster M, Cohen S, et al. Are gait disturbances and white matter degeneration early indicators of vascular dementia? Dementia. 1994;5(3-4):197–202.

[49] Moretti R, Torre P, Antonello RM, et al. The on-freezing phenomenon: cognitive and behavioural aspects. Parkinsons Dis. 2011; Article id:746303;1-7.

[50] Junque C, Pujol J, Vendrell P et al. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. Arch Neurol. 1990;47(2):151–6.

[51] Waite LM, Broe GA, Creasey H, et al. Neurological signs, aging, and the neurodegenerative syndromes. Arch Neurol. 1996;53(6):498–502.

[52] Moretti R, Torre P, Antonello RMA. Basal ganglia: functional and organic roles in behavior and cognition. Nova Science Publishers Inc, New York; 2009.

[53] Iansek R, Bradshaw JL, Phillips JG, et al. Interaction of the basal ganglia and supplementary motor area in the elaboration of movement. In: Glencross DJ, Piek JP (ed.) Motor control and sensorimotor integration. Amsterdam: Elsevier Science; 1995. p37–59.

[54] Lee AC, Harris JP. Problems with perception of space in Parkinson's disease: a questionnaire study. Neuro-Ophthalmology 1999;22(1):1-15.

[55] Almeida QJ, Frank JS, Roy EA, et al. An evaluation of sensorimotor integration during locomotion toward a target in Parkinson's disease. Neuroscience. 2005;134(1): 283-93.

[56] Gurvich C, Georgiou-Karistianis N, Fitzgerald PB, et al. Inhibitory control and spatial working memory in Parkinson's disease. Mov Disord 2007;22(10):1444-50.