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Abstract

Background. White matter hyperintensities (WMHs) are well known to affect post-stroke disability, mainly by cognitive impairment. Their impact on post-stroke balance and gait disorders is unclear.

Objectives. We aimed to test the hypothesis that WMHs would independently deteriorate post-stroke balance and gait recovery.

Methods. This study was performed in 210 individuals of the cohort Determinants of Balance Recovery After Stroke (DOBRAS), consecutively enrolled after a first-ever hemisphere stroke. Clinical data were systematically collected on day 30±3 (D30) post-stroke and at discharge from the rehabilitation ward. WMHs were searched on MRI, graded with the Fazekas scale, and dichotomized as no/mild (absence/sparse) or moderate/severe (confluent). The primary endpoint was the recovery of the single limb stance, assessed with the Postural Assessment Scale for Stroke (PASS). The secondary endpoint was the recovery of independent gait, assessed with the modified Fugl-Meyer Gait Assessment (mFMA). The adjusted hazard ratios (aHRs) of achievements of these endpoints by level of WMHs were estimated by using Cox models, accounting for other relevant clinical and imaging factors.

Results. Individuals with moderate/severe WMHs (n=86, 41%) had greater balance and gait disorders and were more often fallers than others (n=124, 59%). Overall, they had worse and slower recovery of single limb stance and independent gait (p<0.001). Moderate/severe WMHs was the most detrimental factor for recovery of balance (aHR 0.46, 95% confidence interval [CI] 0.32–0.68, p<0.001) and gait (0.51, 0.35–0.74, p<0.001), along with age, stroke severity, lesion volume and disrupted corticospinal tract. With cerebral infarct, endovascular treatments

had an independent positive effect, both on the recovery of balance (aHR 1.65, 95% CI 1.13–2.4, p=0.009) and gait (1.78, 1.24–2.55, p=0.002).

Conclusions. WMHs magnify balance and gait disorders after stroke and worsen their recovery. They should be better accounted for in post-stroke rehabilitation, especially to help establish a prognosis of mobility.

ClinicalTrials.gov registration: NCT03203109.

Key words. white matter hyperintensities, balance, gait, stroke recovery, single limb stance

Introduction

After a stroke, predicting the functional prognosis is of major importance. With mobility limitation as one of the most frequent complains [1] and one of the most severe causes of disability [1], patients and relatives ask about the prognosis of mobility and express their hope of a good recovery. Although recovering balance control is a prerequisite for an independent gait and a satisfactory mobility [2], the recovery of balance and gait disorders after stroke has been little modelled so far [2,3,4,5,6]. There is a pressing need to acquire specific and in-depth knowledge in this domain, both for establishing individual prognosis and improving clinical trials focused on mobility [2,4,7,8].

Several factors may affect balance and gait recovery after stoke: stroke volume [9] and severity [3], the disruption of the corticospinal tract (CST) [10], as well as the nature of clinical deficits [6,11,12]. Although highly suspected [13,14], the detrimental role of preexisting brain alterations related to small vessel disease remains to be established for balance and gait recovery, as it has been for the recovery of generally disability [13,15] and cognitive functions [16,17,18]. Small vessel disease alters the whole brain, thus especially deteriorating functions such as balance control, which involve numerous areas distributed in both hemispheres, the

cerebellum and the brain stem, interconnected in networks [19,20,21]. Overall, after a stroke, the reorganization of these networks supporting brain plasticity should be greatly altered by diffused brain alterations caused by small vessel disease. For example, the reorganization might alter the retuning of interhemispheric balance, involved in the sensorimotor recovery [22].

White matter hyperintensities (WMHs) constitute the most striking marker of small vessel disease [13,23], associated with worse balance and gait capacities in older people [24,25,26]. If any, WMHs may be sparse or confluent [13,27], which represents an indicator of severity, with greater and more diffuse whole brain alteration [13,27].

This study analyzed the effect of WMHs (dichotomized as no/mild or moderate/severe) on balance and gait recovery in a large cohort of individuals followed at the subacute phase after a first hemisphere stroke. The primary endpoint was the recovery of the single limb stance, a challenging task requiring an efficient postural control of the trunk and the four limbs that involves precise spatial representation and a coordinated sensori-motor control of body segments, thus the whole brain [28]. The second endpoint was independent gait, which involves a single limb stance. We used multivariate analyses dedicated to the follow-up to detect the possible effects of several other relevant clinical or imaging factors. We hypothesized that individuals with a stroke and preexisting confluent WMHs not only have greater balance disorders than others but also exhibit overall worse recovery of their balance abilities, especially the capacity to regain the single limb stance and to re-walk without a cane.

The reporting of the study follows the STROBE statement (checklist in Appendix A.1).

Methods

Study design

This was a monocentric observational study involving data from the cohort Determinants of Balance Recovery After Stroke [DOBRAS]; ClinicalTrials.gov: NCT03203109) with

participants comprehensively assessed in routine care in the rehabilitation ward [2]. For this study we used balance and gait data collected at 30 (±3) days after stroke (D30), then at discharge (within the last 3 days) in the neurorehabilitation ward. Assessments were performed by trained and multidisciplinary examiners, with blinding to other data and the study hypothesis. We also used demographic data and main clinical and imaging features. The sample size of the DOBRAS cohort was planned to conduct multivariate analyses focused on balance and gait recovery in a large series of individuals (≥ 200 observations), including multivariate (≥3 variables) Cox models performed in this study.

Ethical considerations and reporting

The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes) who validated the ClinicalTrials.gov registration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (*Commission nationale informatique et liberté*; CNIL-No.2014874-v1) and was performed in accordance with the Helsinki Declaration. According to French law, observational studies do not require approval by a national ethics committee, provided that participants have been informed of the specific research and are not opposed to use of their data. All eligible individuals were informed of the DOBRAS study (orally and in writing) and those who did not want to participate signed an opposition form.

Participants

From January 2012 to October 2019, we included 210 consecutive individuals (age 18 to 80 years), with a first-ever unilateral hemisphere stroke analyzed by MRI. Exclusion criteria were recurrent stroke, complications at the acute stage (malignant infarct, cerebral herniation, severe subarachnoid hemorrhage and hydrocephalus), dementia, previous disability interfering with

balance or vestibular disorders, and unstable medical condition or psychiatric problems jeopardizing data reliability (Fig. 1). These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination. Participants followed a personalized rehabilitation program, taking into account deficits and activity limitations, capacities to face intensive rehabilitation (fatigue or transitory medical problems), individual recovery, and the most appropriate guidelines. According to their abilities, participants had at least 2 physiotherapy and 1 occupational therapy sessions per day (each session lasting at least 30 min for a total daily time of sensori-motor rehabilitation over ≥1.5 hr per patient), plus sessions with a speech therapist, neuropsychologist, psychologist, or orthoptist if needed. The length of hospitalization of our participants was measured from stroke onset to discharge of the rehabilitation ward.

Risk factors related to WMHs

The categorical diagnosis of hypertension, diabetes, and dyslipidemia and information on consumption of tobacco and of alcohol were retrieved from hospital records for each participant. Thresholds were all those internationally recommended (details in Appendix A.1) [29].

Clinical assessments

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS), the most appropriate balance scale at the subacute stage after stroke [30,34]. The total score ranging from 0 to 36 (satisfactory balance) assesses balance abilities in daily life. The last 2 items assess single limb stance on paretic and non-paretic sides, which are independent of other items because of their difficulty [30]. According to the scoring of these items, an individual who is able to maintain a single limb stance for >5 sec (whatever the side) has a total PASS score >

32/36 [30], which we used as endpoint in this study. The 5-sec duration is the usual cutoff considered to indicate that this task is achieved [30,31]. The side of the single limb stance is almost always the non-paretic side in individuals with stroke [31].

Gait disorders were assessed with the modified Fugl-Meyer Assessment of gait (mFMA-gait), designed to classify post-stroke gait in 7 levels of mobility [32]. The mFMA-gait score ranges from 0 (no possibility to walk) to 6 (indicating a [quasi] normal gait) [35]. The 7 levels are as follows: 0, cannot walk at all; 1, can walk with the help of two persons; 2, can walk with the help of one person; 3, walk with the help of a walker, crutches or quadripod cane; 4, walk with the help of a simple cane or a crutch; 5; walk without any help but slowly or with lameness; 6, walk with normal speed for age. We used as the endpoint a score >4 indicating the ability to walk independently without a cane (or walker).

A fall was defined as an event that results in a person coming to rest inadvertently on the ground [33]. Falls during the rehabilitation ward (wherever the room and the time of occurrence) were monitored by the multidisciplinary team all during the rehabilitation stay. Any fall was declared on a specific hospital register and recorded in the patient's electronic file. The presence and number of falls were counted at the end of the stay. A faller was defined as a person who fell at least once.

Global disability was estimated with the modified Rankin Scale (mRS).

Clinical features of stroke comprised the initial stroke severity estimated by the US National Institutes of Health Stroke Scale (NIHSS) at 24 hr post-stroke (range 0-42, higher scores indicating greater stroke severity), stroke type (ischemic or hemorrhagic) and side (right or left hemisphere) as well as cortical or subcortical stroke location. Intravenous thrombolysis and/or thrombectomy were also considered for ischemic strokes.

Brain imaging

The presence of WMHs was sought on T2-FLAIR sequences from the first or second MRI (within the first 2 months after stroke) and graded with the Fazekas scale [27]. The scale simply grades WMHs in 4 levels: 0, no lesion; 1, focal lesions; 2, beginning lesions confluences; and 3, extended involvement with large confluent areas [32]. Two trained independent examiners (SD, CP), carefully examined the absence, presence, and severity of WMHs in the hemisphere spared by the stroke. If any, their differences of grading were resolved by consensus [23]. According to recommendations [15,34], we *a priori* planned to regroup grades 0 and 1 and grades 2 and 3. This approach takes into account the low frequency of grade 3 in individuals with a first hemisphere stroke and the fact that the difference between grades 0 and 1 may be tenuous. Its appropriateness was confirmed by our data.

Complementary analyses were performed to control for possible confounders, such as stroke volume and CST disruption, known to affect balance and gait disorders [9,10,35,36]. These imaging confounders were analyzed in the second MRI, with a reasonable interval that is recommended to avoid overestimating stroke volume [37]. Details about the machine and acquisition parameters are given in Appendix A.1. Lesion volume, determined as the percentage of hemisphere encroached on by the lesion (number of voxels for the lesion/number of voxels for the hemisphere *100) was measured by using MRIcron after a manual lesion delineation from axial slices acquired with T2-FLAIR sequences. All drawings involved 2 trained operators, the first from a panel of three (CL, SD, AC) and the second always the same and with blinding to behavioral data (CP). Any disagreements were resolved by consensus. Drawings were performed on axial slices of a T1-weighted MRI template from the Montreal Neurological Institute (https://www.mcgill.ca/bic/neuroinformatics/brain-atlases-human) normalized to Talairach's space. CST disruption was analyzed with the "Tractotron" tool of the BCBToolkit software (http://toolkit.bcblab.com/), which determines the disruption induced at

the level of a given lesion. Each participant's lesion was compared with an atlas of white matter tracts for each voxel. As suggested, we analyzed both the proportion and probability of the ipsilesional CST disrupted by the stroke [38]. The proportion corresponds to the number of damaged voxels in the CST divided by the total volume of this tract. The probability corresponds to the lesioned voxel with the highest percentage value. The CST was considered disrupted when an estimated proportion or probability was >50% [38].

For clarity reasons and length constraint, the effect of stroke location on balance and gait recovery was not analyzed in this study focused on the effects of WMHs as a marker of small vessel disease.

Statistical analysis

The two groups of WMH severity were compared with Mann-Whitney and chi-square tests. Effect sizes were calculated for significant factors by using the Z values of the Mann-Whitney test, $r=Z/\sqrt{n}$, and the X^2 of the chi-square test, $v=\sqrt{(X^2/n*\text{degree of freedom})}$. Values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both tests[39]. Factors found significant on univariate analysis were entered into a binary logistic regression to determine independent factors associated with moderate/severe WMHs. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated.

Cox proportional-hazard regression was used to determine factors independently associated with the achievement of the single limb stance and the achievement of the independent gait. We adopted this type of model because it determines independent factors involved in the recovery of these endpoints, taking into account individual timelines for this recovery (from D30 to discharge). Cases were censored as follows: recovery of single limb stance regardless of supporting lower limb with PASS score >32/36, recovery of independent gait with mFMA-gait score >4/6. We used backward Cox models to estimate the adjusted hazard ratios (aHRs)

of these endpoints (with 95% CIs). Two Cox models were run, for the recovery of balance (primary criteria) and gait, a primary model with relevant clinical factors (age, stroke severity and type, sex, BMI and endovascular treatments limited to infarcts), and a complementary model with imaging factors being potential confounders (stroke volume, CST disruption).

In addition, Kaplan-Meier survival tests were performed to compare the timeline of the achievement of single limb stance (and independent gait) between individuals with no/mild WMHs and those with moderate/severe WMHs. Differences between participants with no/mild and moderate/severe WMHs were compared by the log-rank test.

The relationships between balance and gait disorders (at D30 and discharge) were tested by linear regression. Continuous data are presented as median (Q1–Q3) and categorical data as number (percentage, %). Two-sided $p<0.05$ was considered statistically significant. Statistical analyses involved using SPSS 24.0 and Stata 15.1. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

The median age of the 210 participants was 67.3 years (57.4–72.7); 68 (32%) were females. In total, 172/210 (82%) had a brain infarct; 65 (38%) received thrombolysis and/or thrombectomy. The initial stroke severity was moderate to severe (median NIHSS on D1 12 [7–16]).

No data were missing for the primary analyses. Complementary analyses with stroke volume and CST disruption were conducted on the 182/210 observations of participants who had a second MRI (87%). To ensure the validity of the complementary cox model for imaging data, we analyzed the data sensitivity within the frame of the whole series. Sensitivity was high: 0.88 and 0.87 for the endpoints of single limb stance and independent gait, respectively. These results indicated that missing data for brain imaging were randomly distributed, inducing no bias.

Features of individuals with WMHs

A total of 44 (21%) participants did not show WMHs (grade 0); 166 (79%) presented WMHs graded as follows: grade 1, 80 (38%); 2, 71 (34%); and 3, 15 (7%). We constituted 2 groups: no/mild WMHs (n=124, 59%) and moderate/severe WMHs with confluent lesions (n=86, 41%). Characteristics are compared in Table 1. The latter group was older, more often female, more often hypertensive, and with more hematomas than the former group. When these 4 variables were analysed by binary logistic regression, sex did not remain significant, in contrast to hematoma (aOR 2.5, 95% CI 1.12–5.73, p=0.025), hypertension (2.17, 1.1–4.28, p=0.025), and age (1.08, 1.04–1.12, p<0.001). The 2 groups did not differ in brain imaging, including stroke volume or proportion/probability of CST disruption. Disability was greater with moderate/severe than no/mild WMHs, both at D30 and discharge. The length of hospitalization since stroke (acute/subacute neurological units, then neurorehabilitation ward) was longer in the moderate/severe than no/mild WMHs group.

Balance and gait disorders

Balance and gait scores were highly correlated, both at D30 (r=0.89, p<0.001) and at discharge (r=0.86, p<0.001), so balance capacity highly explained the information contained in gait capacity: 79% (95% CI 75–84, p<0.001) at D30 and 73% (67–79, p<0.001) at discharge. Balance and gait disorders were worse with moderate/severe than no/mild WMHs, both at D30 and discharge (Table 2).

Fallers more frequently had moderate/severe than no/mild WMHs (Table 2). The mean (SD) incidence of falls during rehabilitation was 0.6 (0.1) per person for 100 days with moderate/severe WMHs and 0.2 (0.1) per person for 100 days in others.

Balance recovery

In the first Cox model with clinical features (Table 3, upper part), moderate/severe WMHs had an independent detrimental role in balance recovery (aHR 0.46, 95% CI 0.32–0.68, p<0.001), along with age and initial NIHSS score. The aHR value of 0.46 meant that the chance to achieve the single limb stance (>5 sec) at discharge for individuals with moderate/severe WMHs was 0.46-fold that of individuals of the same age and stroke severity but with no/mild WMHs. Stroke type, sex, and BMI were not independently associated with poor balance recovery. This model limited to infarcts to include endovascular treatments (Appendix A.1) showed thrombolysis and/or thrombectomy with an independent beneficial effect on balance recovery (aHR 1.65, 95% CI 1.13–2.4, p=0.009). In the second model with imaging factors (Table 3, lower part), WMHs also played a primary detrimental role in balance recovery (aHR 0.46, 95% CI 0.31–0.67, p<0.001), along with disrupted ipsilesional CST and stroke volume. The aHR value of 0.46 meant that the chance to achieve the single limb stance (>5 sec) at discharge of individuals with moderate/severe WMHs was 0.46-fold that of individuals of the same lesion volume and CST disruption but with no/mild WMHs. The Kaplan-Meier survival test showed that the achievement of single limb stance was less frequent and delayed with moderate/severe than no/mild WMHs (Fig. 2A; X^2=19.2, p<0.001). The single limb stance was achieved with a median delay of 151 (66–196) days with moderate/severe WMHs and 70 (50–127) days for others. At discharge, 49% of participants with moderate/severe WMHs could not maintain the single limb stance for 5 sec versus 19% of those with no/mild WMHs (X^2=20.5, v=0.31, p<0.001).

Gait recovery

In the first Cox model with clinical features (Table 4, upper part), moderate/severe WMHs had an independent detrimental role in gait recovery (aHR 0.51, 95% CI 0.35–0.74, p<0.001), along

with age and initial NIHSS score. Stroke type, sex, and BMI were not independently associated with poor gait recovery. This model limited to infarcts to include endovascular treatments (Appendix A.1) showed that thrombolysis and/or thrombectomy had an independent beneficial effect on gait recovery (aHR 1.78, 95% CI 1.24–2.55, p=0.002). In the second model with imaging factors (Table 4, lower part), WMHs played a detrimental role in gait recovery (aHR 0.52, 95% CI 0.36–0.75, p=0.001), along with disrupted ipsilesional CST and stroke volume. The Kaplan-Meier survival test showed that the achievement of independent gait was less frequent and delayed with moderate/severe than no/mild WMHs (X^2=15.1, p<0.001) (Fig. 2B). Independent gait was achieved at a median delay of 130 (63–176) days with moderate/severe WMHs versus 69 (47–129) days with no/mild WMHs. At discharge, 43% of participants with moderate/severe WMHs could not regain independent gait versus 19% of those with no/mild WMHs (X^2=13.8, v=0.26, p<0.001).

Discussion

Our study confirms that gait disorders after stroke are more severe with confluent WMHs [14,40], reveals that this is due to balance disorders, and extends this finding to the risk of being a faller. Using multivariate Cox regression models and Kaplan-Meier survival tests to master possible confounding variables and rank independent effects, we confirm our hypothesis that WMHs independently alter the recovery of balance and gait, regardless of other clinical and imaging factors. The study goes even beyond our hypothesis, discovering that the presence of confluent WMHs plays a primary detrimental role on the recovery of endpoints such as the ability to maintain the single limb stance for 5 sec or the ability to walk without a cane, achieved roughly twice less frequently than for other patients of same age, stroke severity and volume, and disruption of CST. The single limb stance appears to be a key milestone, which should deserve more attention in balance and gait rehabilitation after stroke. These findings were

obtained in a large series of consecutive individuals admitted to rehabilitation after a first hemisphere stroke (n=210), with stroke severity (NIHSS, lesion volume, disability) comparable to that reported in the literature.

WMHs

Described 3 decades ago, under the terms leukoaraiosis and WMHs [27], altered brain white matter has become a major topic in gerontology and in vascular and neurological sciences. The literature is abundant and congruent about the detrimental effects of WMHs on cognitive functions [16,17,18]. However, the literature is more limited but still consensual about the detrimental effect of WMHs on mobility [24,25,26], most cohorts involving older people or people with neurodegenerative diseases [16,41].

WMHs and stroke share common risk factors [34,42], and WMHs increase the risk of stroke [15]. We found WMHs associated with usual demographic, cardiovascular and clinical factors (i.e., age, hypertension, and hemorrhagic stroke).

Balance disorders and their recovery after stroke

Balance ability refers to a dual control: for body orientation with respect to gravity and body stabilization with respect to the base of support [43]. Balance disorders combine both types of impairments [2], especially after stroke, and are globally assessed in daily life by the PASS, used in our study. We showed that individuals with moderate/severe WMHs have worse balance disorders than others at the subacute phase after stroke but did not analyse the specific effect of WMHs or body orientation with respect to gravity or body stabilization with respect to the base of support. This remains to be investigated.

Single limb stance is considered one of most challenging balance tests in the general population [43,44], a predictor of age-related decline [44] and also a milestone of satisfactory balance after

stroke [30,31]. For these reasons, the single limb stance would represent a particularly relevant aspect to investigate the impact of diffused brain alterations related to small vessel disease on balance recovery after stroke.

Using comprehensive multivariate analyses (Cox models), we showed that moderate/severe WMHs was one of the most detrimental factors affecting recovery of the single limb stance, whose achievement in individuals with confluent WMHs (grades 2 and 3) was twice less frequent than in individuals without or with sparse WMHs (grades 0 and 1), regardless of other clinical and imaging factors. We do not exclude that the preexistence of the WMHs might have affected the capacity of some individuals to balance on one leg before the stroke, particularly in the oldest participants. Although preexisting balance disorders was an exclusion criterion for this study, balance abilities had not been quantified before the stroke, which leads us to remain cautious with this assumption. However, several studies have indicated that abnormal single limb stance would be a marker of pathological cognitive and motor decline, a predictor of severe falls (with lesion) in older adults [44]. Given its simplicity, the single limb stance deserves wider utilization in medicine, to detect the consequence of general vascular risk factors on the brain.

Our study also underlines the detrimental effects of age, stroke severity, lesion volume, and disruption of CST, mainly taken into account in our models as possible confounders. There is a rich literature on the detrimental effect of CST disruption on the functional ability of upper and lower limbs after stroke [45], but the literature is more sparse on the effect of disrupted CST on post-stroke balance disorders [10]. Our study revealed that achieving the ability to maintain the single limb stance for 5 sec is greatly affected by an important disruption of CST. Age [4], stroke severity and lesion volume [9,36,46] are well-known factors affecting post-stroke balance abilities. Our study is one of the first to reveal the independent detrimental effect

of these factors on the recovery of balance after stroke, especially on the achievement of the single limb stance.

In our study, the probability to recover the ability to stand on one leg (for >5 sec) was 65% greater for individuals who underwent recanalization than others with a cerebral infarct but no endovascular treatment, regardless of other factors. This finding supports the view that individuals with confluent WMHs may be considered for endovascular treatments [47,48].

Gait disorders and their recovery after stroke

In our series of individuals examined at the subacute stage after stroke, gait ability was mainly linked to balance ability, so gait and balance were similarly affected by WMHs. WMHs predicted the recovery of an independent gait (walking without any assistance), considered an endpoint for recovery of satisfactory gait in the context of post-stroke rehabilitation. The single stance is the critical event of a gait without technical aid, requiring the ability to bear the body's weight on a single lower limb (alternatively non-paretic and paretic) and to master the control of a dynamic balance on this narrow base of support. This challenging task involves both hemispheres, which explains the detrimental role of moderate/severe WMHs on regaining independence of gait. This result was obtained with multivariate analyses, which again revealed the negative effect of age, stroke severity, lesion volume, and also marked disruption of the ipsilesional CST. These findings confirm previous results of studies of gait recovery after stroke, reporting the negative effect of age [3,5], stroke severity [3] and lesion volume [46]. The effect of disrupted CST on gait ability [35] has been more recently demonstrated. Of note, our study also showed a beneficial effect of endovascular therapy on gait recovery.

Falls

WMHs are a well-known determinant of falls in older people [24] and also a factor increasing the risk of falls after stroke [49]. We confirmed these findings, fallers being twice more frequent with moderate/severe than no/mild WMHs, which call for better fall prevention in stroke individuals showing moderate/severe WMHs. The analysis of brain imaging should be more systematic for assessing the individual risk of fall after stroke.

Impact of these results to the field

Predicting functional prognosis is of major importance after a stroke, and our study revealed that individuals with confluent WMHs had 2-fold less chance than others to recover an independent gait (without a cane), other things being equal, likely because of difficulty mastering the single limb stance [50]. Preexistence of severe comorbidity [3], stroke severity including severe weakness [12] and spatial neglect [19], together with the presence of a net lateropulsion [2] are the principle indicators of poor functional prognosis, jeopardizing the recovery of an efficient or even independent gait several months after the stroke. Our study reveals that whole brain alteration by small vessel disease is another major indicator raising fears of poor gait recovery, found the primary one in our study. The patient and the relatives must be informed, and solutions found to ensure, if possible by other ways, an independent mobility (wheelchair), with a house adapted as early as possible to prepare for discharge (to not inappropriately extend the length of stay). More positively, a reasonable short length of stay may be expected for individuals with no or sparse WMHs. An intact brain parenchyma outside the stroke should facilitate brain plasticity and recovery. We do not know whether a rigorous mastering of small-vessel disease risk factors might have a positive effect on long-term balance and gait recovery. With this hope at least for individuals with moderate forms, a systematic detection of WMHs after stroke is useful to treat the accessible risk factors. With a therapeutic

education leading to appropriate lifestyle modification [42], this should be a major challenge during the stay in the rehabilitation ward.

For research, our study suggests that stratifying trials of post-stroke balance and gait rehabilitation by level of WMH severity could be relevant. This stratification has been performed rarely, which might contribute to the high rate of negative trials in the field. MRI should be more systematically considered in this context. CST disruption is an important factor increasingly being taken into account to explain a poor recovery [45,51]. Our study suggests adding WMHs as another possible brain imaging biomarker of post-stroke recovery, at least for balance and gait.

Limitations

We used the Fazekas scale to quantify WMHs alterations, so we partly assessed MRI signs of small vessel disease and did not quantify WMHs in specific areas (periventricular or deep white matter) but rather hemisphere globally (side opposite the stroke). The Fazekas scale classifies individuals into 4 grades. Because of the limited number of individuals in grades 0 and 3, we merged grades 0 and 1 (no/mild WMHs) and grades 2 and 3 (moderate/severe WMHs). With this procedure that is frequently adopted [15,34], sample sizes were satisfactory in both groups (124 vs 86), ensuring clear and robust conclusions. However, the specific impact of grades 0 and 3 on balance and gait recovery remained unanswered. We do not frequently admit individuals >80 years old in our ward for rehabilitation after stroke, which explains why individuals of our series are among the youngest in the literature, with a relatively low prevalence of Fazekas grade 3. The ceiling effects of PASS and mFMA scores might be considered another limitation of the study. This is why we did not use scores but rather endpoints, analyzed with Cox regression models and Kaplan-Meier survival tests. The generalizability of our findings is limited to post-stroke rehabilitation [1,52]. In this context,

the results seem generalizable because participants had the usual demographic, cardiovascular and clinical factors associated with WMHs.

Conclusions

After stroke, WMHs alter balance and gait recovery and increase the number of fallers. These findings appeal for a systematic detection of WMHs in post-stroke rehabilitation, both in routine practice and research. In routine practice, knowing the existence and severity of WMHs should help establish the prognosis in terms of mobility recovery. For research, our study highlights the interest of a stratification by WMH grades for trials of balance and gait rehabilitation.

Conflict of interest. None declared.

Figure Legends

Figure 1. Flow of participants in the study.

Figure 2. Recovery of balance and gait. Time to achieve A) single limb stance (Postural Assessment Scale for Stroke score >32) and B) independent gait (modified Fugl-Meyer Assessment of Gait score >4) for 2 groups of white matter hyperintensities (WMHs).

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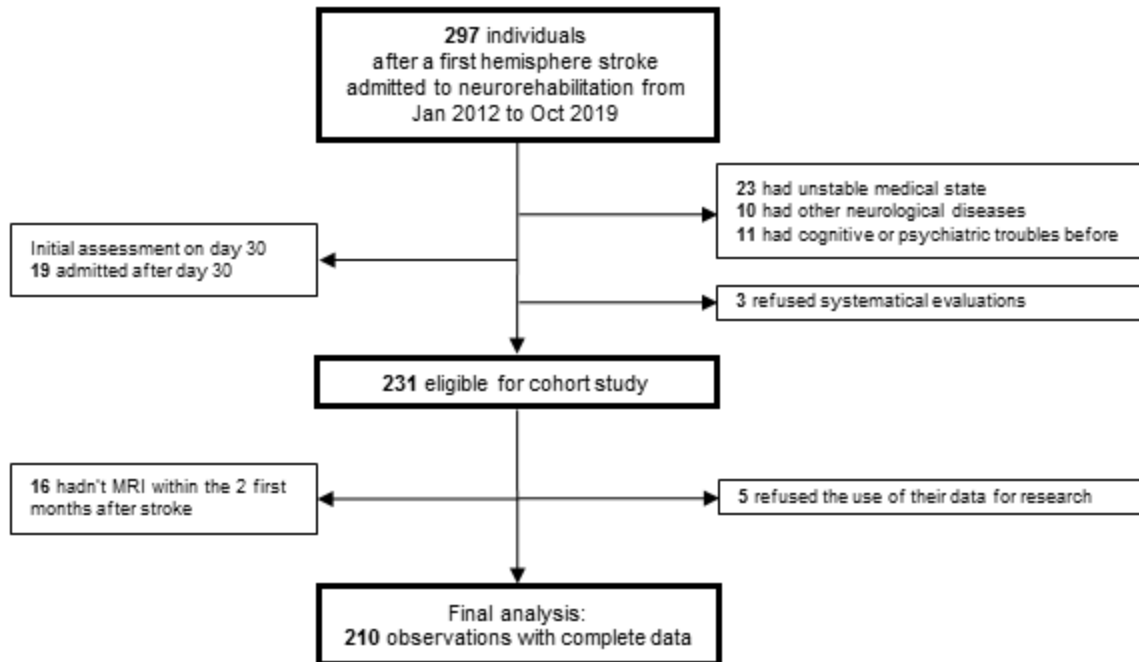
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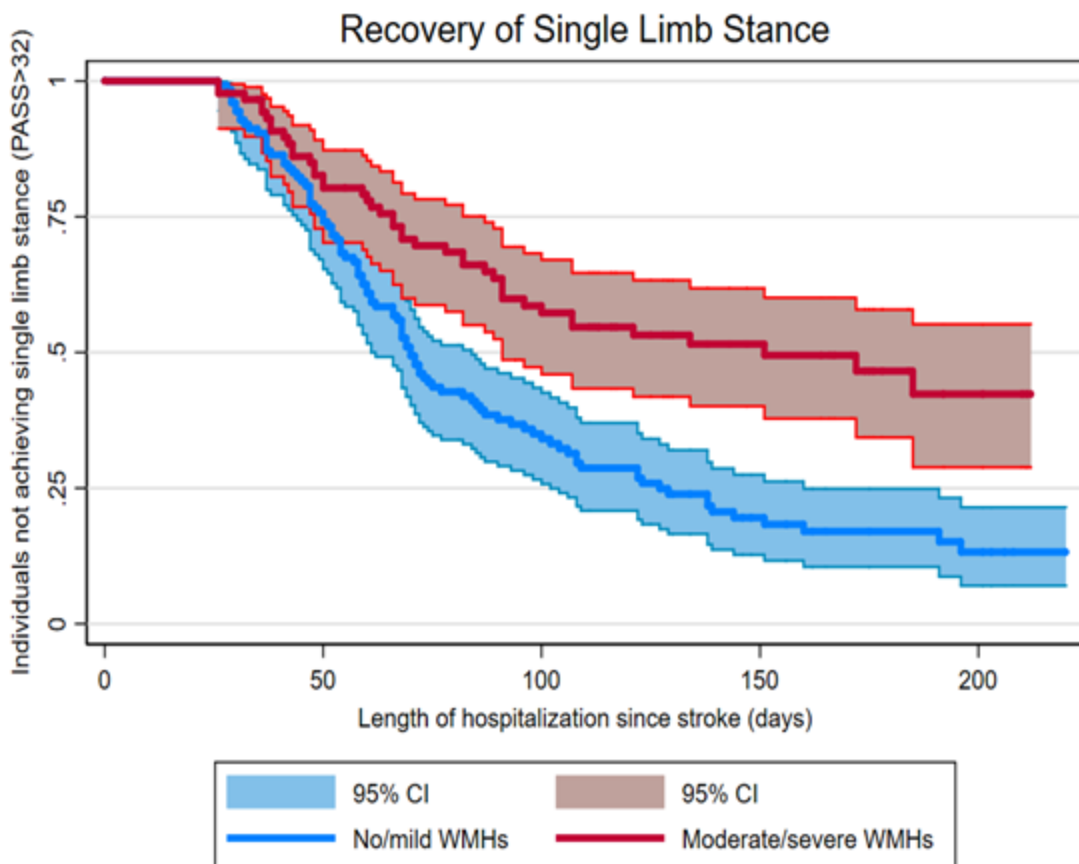
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                    ┌─────────────────────────────┐
                    │      297 individuals        │
                    │ after a first hemisphere    │
                    │ stroke admitted to          │
                    │ neurorehabilitation from    │
                    │    Jan 2012 to Oct 2019     │
                    └─────────────────────────────┘
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297 individuals
after a first hemisphere stroke
admitted to neurorehabilitation from
Jan 2012 to Oct 2019

23 had unstable medical state
10 had other neurological diseases
11 had cognitive or psychiatric troubles before

Initial assessment on day 30
19 admitted after day 30

3 refused systematical evaluations

231 eligible for cohort study

16 hadn't MRI within the 2 first months after stroke

5 refused the use of their data for research

Final analysis:
210 observations with complete data

A

Recovery of Single Limb Stance

Individuals not achieving single limb stance (PASS>32) vs. Length of hospitalization since stroke (days)

	95% CI		95% CI
	No/mild WMHs		Moderate/severe WMHs

B

Recovery of Independent Gait

Individuals not achieving independent gait (mFMA-gait>4) vs. Length of hospitalization since stroke (days)

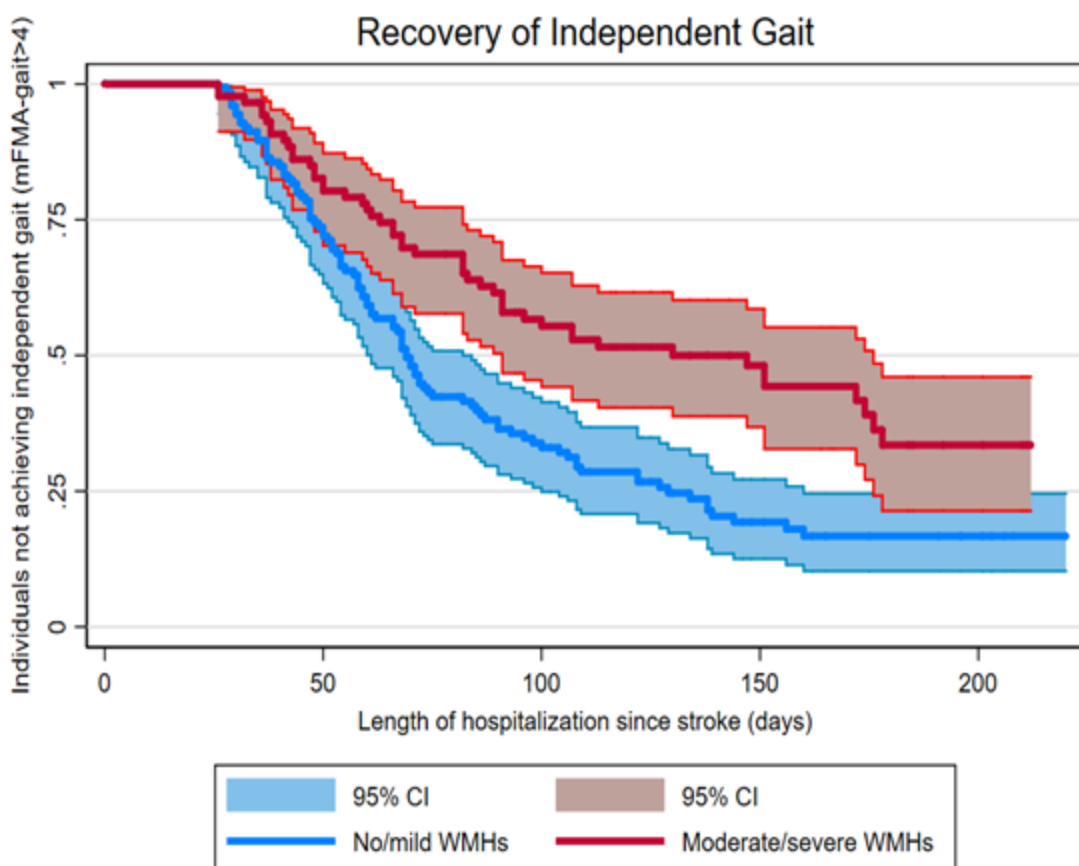|	95% CI		95% CI
	No/mild WMHs		Moderate/severe WMHs

Table 1. Demographic and clinical features of individuals with no/mild or moderate/severe white matter hyperintensities (WMHs).

	No/mild WMHs (n=124)	Moderate/severe WMHs (n=86)	P-value	Effect size
Demographics				
Age (years)	63.6 (53–69)	70.9 (66–74)	<0.001	r = -0.37
Sex, female (%)	32 (26)	36 (42)	0.014	v = 0.16
BMI (kg/m²)	24.5 (22–28)	26.2 (23–28)	0.134	
WMH risk factors				
Hypertension (%)	62 (50)	66 (77)	<0.001	v = 0.28
Diabetes (%)	21 (17)	22 (26)	0.127	
Dyslipidemia (%)	56 (45)	42 (49)	0.6	
Tobacco smoking (%)	77 (62)	44 (51)	0.115	
Alcohol drinking (%)	32 (26)	17 (20)	0.309	
Stroke features				
Stroke type: infarct (%)	108 (87)	64 (74)	0.019	v = 0.16
Thrombolysis and/or thrombectomy (%)	42 (39)	23 (36)	0.7	
Stroke side: right hemisphere (%)	56 (45)	39 (45)	0.979	
Stroke location (%):			0.284	
-Subcortical	34 (27)	30 (35)		
-Cortical	47 (38)	24 (28)		
-Subcortical+cortical	43 (35)	32 (37)		
Initial NIHSS score (0-42)	12 (7–16)	11 (7–16)	0.948	
*Imaging features				
*Delay of MRI (in rehabilitation) after stroke onset (days)	62 (59–74)	63 (58–76)	0.673	
*Lesion volume			0.497	
-in voxels	17,353 (3,781–40,600)	9,720 (2,061–38,202)		
-in %	2.3 (0–5)	1.3 (0–5)		
*Disrupted CST				
-Proportion > 50% (%)	62 (59)	48 (62)	0.654	
-Probability > 50% (%)	104 (99)	77 (100)	1	
Disability				
mRS on *D30* (0-6)	3 (2–3)	3 (3–4)	<0.001	r = -0.31
mRS *at Discharge* (0-6)	2 (1–2)	2 (2–3)	0.001	r = -0.3
#Length of hospitalization since stroke (days)	69 (48–111)	107 (61–166)	0.001	r = -0.23

Data are n (%) or median (Q1–Q3).

BMI, body mass index. NIHSS, US National Institutes of Health Stroke Scale. CST, corticospinal tract. D30, day 30. mRS, modified Ranking Scale. Effect sizes are given as "r" for the Mann-Whitney test and "v" for chi-square test. With p<0.05, effect sizes are given; values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney and chi-square tests.

*Imaging features were analyzed in 182 individuals with control MRI around day 60.

Duration from stroke onset to discharge from the rehabilitation ward.

Table 2. Balance and gait between groups with no/mild versus moderate/severe white matter hyperintensities (WMHs).

	No/mild WMHs (n=124)	Moderate/severe WMHs (n=86)	P-value	Effect size
D30				
Balance (PASS, 0-36)	33 (27–36)	29 (16–33)	<0.001	r = -0.28
Gait (mFMA-gait, 0-6)	5 (3–6)	3 (0–5)	<0.001	r = -0.26
Discharge				
Balance (PASS, 0-36)	35 (33–36)	33 (31–34)	<0.001	r = -0.36
Gait (mFMA-gait, 0-6)	5 (5–6)	5 (3–6)	0.013	r = -0.25
Fallers (%)	20 (16)	32 (36)	0.001	v = 0.23

Data are n (%) or median (Q1–Q3).

D30, day 30. PASS, Postural Assessment Scale for Stroke. mFMA-gait, modified Fugl-Meyer Assessment of gait.

Table 3. Multivariate Cox regression models* of factors associated with achieving single limb stance after stroke.

Variables	aHR	95% CI	P-value
Model 1 with clinical features (n = 210)			
WMHs (moderate/severe vs no/mild)	0.46	0.32–0.68	<0.001
Age (per year)	0.98	0.97–0.99	0.005
Initial NIHSS score (per point)	0.84	0.81–0.87	<0.001
Model 2 with imaging features (n =182)			
WMHs (moderate/severe vs no/mild)	0.46	0.31–0.67	<0.001
Lesion volume (per 1% of hemisphere)	0.94	0.91–0.98	0.003
Disrupted CST (proportion > 50% vs ≤ 50%)	0.59	0.4–0.89	0.01

WMHs, white matter hypertensities. NIHSS, US National Institutes of Health Stroke Scale. CST, corticospinal tract. aHR, adjusted hazard ratio. CI, confidence interval.

*Two models were tested. Model 1 involved clinical features of the 210 individuals with follow-up from day 30 post-stroke to discharge from the rehabilitation ward. Model 2 involved imaging features analyzed on MRI performed about 2 months after the stroke (182 individuals).

Table 4. **Multivariate Cox regression models* of factors associated with achieving independent gait after stroke.**

Variables	aHR	95% CI	P-value
Model 1 with clinical features (n, 210)			
WMHs (moderate/severe vs no/mild)	0.51	0.35–0.74	<0.001
Age (per year)	0.98	0.97–1	0.006
Initial NIHSS score (per point)	0.83	0.8–0.86	<0.001
Model 2 with imaging features (n =182)			
WMHs (moderate/severe vs no/mild)	0.52	0.36–0.75	0.001
Lesion volume (per 1% of hemisphere)	0.94	0.91–0.98	0.002
Disrupted CST (proportion > 50% vs ≤ 50%)	0.61	0.42–0.9	0.013

WMHs, white matter hypertensities. NIHSS, US National Institutes of Health Stroke Scale. CST, corticospinal tract. aHR, adjusted hazard ratio. CI, confidence interval.

*Two models were tested. Model 1 included clinical features of the 210 individuals with a follow-up from day 30 post-stroke to discharge from the rehabilitation ward. Model 2 included imaging features analyzed by MRI performed about 2 months after the stroke (182 individuals).