Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review

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Cover Title: Review: white matter lesions and fall risk

Number of Tables and figures: ***1 in total***

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Key Words: white matter lesions, magnetic resonance imaging (MRI), brain, aged and accidental falls, physical function, gait

Manuscript word count: 4389

Abstract

Background and Purpose

White matter lesions (WMLs) are common findings on neuroimaging in older people. This review systematically evaluates the published literature on the associations between WMLs and balance, gait, mobility and falls in older people.

Methods

Studies were identified with searches of the Medline databases. Papers reporting associations between WMLs and balance, gait, mobility and falls in older people in cross-sectional and longitudinal studies were included.

Results

Thirty one papers reporting data from 19 studies met the inclusion criteria. There were consistent findings from both cross-sectional and longitudinal studies indicating greater WML volumes are associated with impaired balance, slower gait and reduced mobility. Most studies addressing regional WML distributions have reported that WMHs in the frontal lobe and periventricular regions show the strongest relationships with balance, gait and mobility impairments. In relation to falls, a threshold effect was apparent, in that only those with severe WML volumes were found to be at increased risk of falling.

Conclusions

The findings of this systematic review indicate that WMLs are common and are significantly associated with impaired balance, gait, mobility and falls in older people. In many studies, however, impaired mobility and increased fall risk are only evident in people who have the most severe degree of WMLs.

Introduction

Over one third of older people suffer one or more falls per year, with about half of these resulting in injuries[1]. Among older people, falls account for 14% of emergency admissions and are the leading cause of the injury-related deaths[1]. Falls can also result in disability, loss of mobility, reduced quality of life and fear of falling[1, 2].

With the advent of computed tomography (CT) and magnetic resonance imaging (MRI), presence of white matter lesions (WMLs) or leukoaraiosis[3], have been used as a measure of central nervous system abnormality that may contribute to increased fall risk through functional deterioration in balance and gait[4, 5]. WMLs are seen as hypo-intense signals on CT and hyper-intense signals on T2 weighted and FLAIR sequence MRI. Although the aetiology of WMLs is not fully understood, there is increasing evidence that chronic cerebral ischemia due to microvascular disease play a central role in the pathogenesis of WMLs[6].

Several studies have now reported that WMLs are associated with balance, gait and mobility impairments. However, the findings have not been consistent, mainly due to differences in methodologies. The extent to which WMLs influence physical functioning and fall risk also needs clarification. Moreover, the importance of WMLs in specific brain regions with respect to influencing balance and gait is controversial. This article reviews the cross-sectional and longitudinal studies that have examined the relationships between WMLs and balance, gait, mobility and falls in older people, and discusses whether there is sufficient evidence to conclude that WMLs contribute to fall risk in older people.

Materials and Methods

We searched MEDLINE (1985 to December, 2010) using the search terms for WMLs and balance, gait and falls (Supplemental table 1.1). Two investigators (JZ and KD) independently screened all titles and abstracts to identify potentially relevant articles. All discrepancies were resolved by a third examiner (SL or JC) to reach a consensus. For all potentially relevant articles, full-text articles were retrieved, and data were extracted from the articles if they met the following criteria: (1) the primary objective of the study was to examine the impact of WMLs on balance, gait, mobility or falls in older people, (2) the assessment methods for WMLs, and balance or gait or mobility or falls were described, (3) structural MRI or computed tomography (CT) were used as imaging tools, and (4) the mean age of the participants in the study was 60 years or over. Case reports, reviews and studies that examined WMLs resulting from discrete pathologies such as multiple sclerosis, hydrocephalus and Parkinson's disease, or from substance abuse were excluded. Studies were also excluded if the study populations predominantly comprised people with cognitive impairment , Alzheimer's disease or other dementias.

Results

Search Results

The Medline search identified 145 papers; 57 of which were potentially relevant for the review, and 27 met the inclusion criteria (see supplemental figure 2.1). Three additional papers[7-9] were recommended by experts in this field and one article was retrieved from the bibliographies of the full text articles[10]. A total of 31 papers reporting data from 19 studies were subsequently included in the literature review. The modified version of the Quality Assessment of Diagnostic Accuracy Studies (QADAS) was used to grade the quality of the included studies[11]. This tool comprises 8 questions answered as yes, no or unclear. Thirteen papers scored the maximum score on the QADAS (supplemental tables 1.2 and 1.3). We extracted data from the included articles and classified the findings into four categories with respect to the associations between WMLs and (a) balance control, (b) gait and stepping, (c) mobility and (d) falls. Table 1 summarises the main results (See also supplemental tables 1.4 – 1.7 for the study design, assessment methods and more detailed findings).

(INSERT TABLE 1 HERE)

Relationship between WMLs and Balance Control

Seven cross-sectional studies have assessed the relationship between WMLs and measures of balance control (Supplemental table 1.4). With one exception[33], these studies[7, 9, 14, 18, 20, 25, 29] report an association between greater WML volumes and reduced balance control in older people. Of particular interest is the finding from the LADIS study[14], in which impaired balance was associated with deep frontal WMLs, but not with WMLs in the parietal and periventricular regions, despite a considerable prevalence of WMLs in all regions. The LADIS study also reported a threshold effect, in that only those with the most severe degree of WMLs could not perform the single leg stance test, a finding that was independent of other risk factors known to affect balance control. One study suggested that the association between WMLs and balance might be moderated by gender and reported a significant association between WMLs and single leg stance in men only[29].

Relationship between WMLs and Gait and Stepping

Twelve cross-sectional[7-9, 12, 13, 15, 18, 20-23, 25-27, 33] and six longitudinal studies[23, 24, 28, 34, 36, 37] have investigated the relationship between WMLs and gait, and one study has investigated the association between WMLs and voluntary stepping speed[16](Supplemental table 1.5). Greater volumes of WMLs, especially in the periventricular regions, were associated with decreased gait speed, shorter step length, increased double support time and slowed gait initiation in cross-sectional studies[8, 16, 21-23, 25]. Two large longitudinal studies with follow-up periods of 8 and 13 years respectively found that individuals with severe periventricular WMLs show a more progressive decline in walking speed[23, 24]. Four cross-sectional[7, 18, 23, 25] and two longitudinal studies[23, 24] have also reported non-significant associations between deep WMLs and gait performance, supporting the notion of different functional consequences of periventricular and deep WMLs. Findings of a threshold effect with only the most severe degree of WMLs having a significant impact on gait are reported in three studies[15, 21, 23]. The contradictory results of the association of WMLs and gait impairment from two studies may be attributed to sample selection factors. One study selected younger participants (average age 65 years) without a history of recurrent falls, therefore people with the most severe lesions and gait abnormalities were likely excluded from the study [7] . The second study showed a significant relationship between greater volumes of WMLs and mobility impairments, but not with gait impairment, which could possibly be attributed to the small sample size (28 participants)[33].

Relationship between WMLs and Mobility

Nine cross-sectional[8-10, 13, 15, 17, 19, 23, 30, 32, 33, 38] and five longitudinal studies[28, 31, 34, 35, 37] have assessed the relationship between WMLs and mobility (Supplemental table 1.6). All studies found an association between mobility impairment and overall increased WML volumes as well as increased regional WML volumes in periventricular, frontal, parietal-occipital and frontal periventricular areas[8, 13, 17, 23, 32]. Two studies also reported a threshold effect of WMLs on mobility[7, 16] with larger volumes of WMLs at baseline found to predict greater declines in mobility over time in longitudinal studies[28, 34, 35, 37]. Finally, it has been reported that a significant increase in WML volumes occurs more frequently in mobility impaired people compared with people without such impairment [31].

Relationship between WMLs and Falls

Eight studies have investigated the association between WMLs and falls, of which seven reported that fallers have greater WML volumes compared with non-fallers[14, 20, 21, 30, 35, 37, 38](Supplemental table 1.7). These studies have varied in a number of parameters (retrospective or prospective recording of falls, fall definitions, study sample sizes, measures of WMLs and statistical analysis) making it difficult to collate and summarize the findings. The strongest evidence for an association between WMLs and falls comes from two recent prospective studies conducted in large community-dwelling samples. In a 12-month prospective study of 294 older community-dwelling people[21], the risk of falls was doubled in people with WML volumes in the highest quintile of distribution compared to those in the lowest quintile. In another prospective study of 820 community-dwelling older people, a significant association between WMLs and fall-related hip fractures was reported in participants younger than 80 years[30]. Only one study has investigated the location of WMLs in relation to falls, and found that the presence of frontal periventricular WMLs was the best regional predictor of fall risk[14].

Discussion

Despite considerable methodological differences between studies, a number of consistent findings emerge. WMLs are common and the progression of WMLs is strongly dependent on baseline lesion volume [24, 35, 39-42] and presence of vascular risk factors[7, 15, 23, 39, 41, 42]. There is consistent evidence of an association between higher volumes of WMLs and balance, gait and mobility impairments. Many studies support the notion of a nonlinear relationship between WMLs and fall risk with the clinical manifestations only evident in people who have the most severe degree of WMLs [21,30] Some studies have distinguished deep from periventricular WMLs in relation to physical performance and have reported that periventricular and fronto- parietal WMLs are more strongly associated with physical function impairments than WMLs in other regions [7, 8, 14, 15, 17, 18, 23, 25, 32]. However, such distinctions need further corroboration as it has been suggested that categorization of WMLs as periventricular or deep may be arbitrary and merely a reflection of total WML volume.[11]

Mechanisms to explain relationships between WMLs and fall risk

Several potential mechanisms may underlie the association between WMLs and fall risk. Firstly, the integrity of the neural network within the brain (i.e. the corticostriate fibers or thalamostriatal fibers[16, 43]) and the long descending motor fibers (i.e. corticospinal fibers) are crucial in lower extremity motor control[34], especially in relation to the selection and initiation of movement, direction of movement, and speed and duration of movement. Secondly, disruption in the frontal-subcortical circuits that interconnect various cortical areas is likely to compromise cognitive performance [43]. It has also been suggested that the relationship between WMHs and impaired physical performance is mediated by the effect of WMHs on executive function[44-46]. For example, it has been found that WMLs in frontal regions have a stronger association with postural control compared to other regions[7, 14, 47]. The frontal lobe is involved in a variety of cognitive processes including executive function[48], which has previously been proposed to play a central role in the cognitive control of postural control[49, 50] and fall risk[51], especially in older people. Thirdly, vascular risk factors are acknowledged risk factors for both WMLs and impaired physical performance. Even so, the associations between WMLs and impaired physical performance reported in several studies remained significant after controlling for vascular risk factors such as heart disease, hypertension, diabetes, homocysteine levels and physical activity[15, 21, 23, 28, 29] . This suggests that vascular risk factors explain only a small component of the variance in the relationship between WMLs and physical performance.

Limitations

Studies included in this review showed a substantial variation with respect to the rating scales of both WMLs and measures of physical performance and falls. It is important to acknowledge that visual rating scales on non-contrast low resolution MRI or CT are less sensitive in detecting small WMLs than automated volumetric measures of WMLs on high resolution MRI [52, 53]. However, these techniques are equally sensitive in detecting large lesions [54] and given the threshold effect of WMLs on fall risk, were not excluded from this review. Lacunar infarcts have also been reported to be associated with small vessel disease and physical deficits[27,23, 55]. However, the lack of consistency regarding the analyses of lacunar infarcts across the studies made it too difficult to synthesize the findings on the effects of lacunar infarcts on fall risk.

Implications for future research

This review shows there is a consistent relationship between WMLs and functional performance. However, the exact nature of the involvement of WMLs in gait and balance still requires elucidation, especially in relation to the size and location of the lesions in the brain. Large longitudinal studies in community-dwelling older people are required to understand the impact of WML progression on physical function and fall risk. Automated quantification of WML progression, sensitive assessments of balance and gait, precise measurement of falls prospectively, and a clearly defined measure of vascular risk should be considered in the design of future studies.

Further research is also required to better understand the causal mechanisms that underpin the reported association between increasing volumes of WMLs and impairments in physical performance. It is likely that there are a number of mediating factors contributing to the relationship, including well known vascular risk factors such as hypertension. Treatment of known vascular risk factors has been shown to reduce the incidence and severity of cerebrovascular disease, but it is not a recognized approach to falls prevention, with no clinical trials showing that vascular risk reduction can lead to a reduction in falls. It would be reasonable to hypothesize that addressing vascular risk factors may have an impact on both the presence and progression of gait and mobility impairments and ultimately on the risk of falls and fall related injury in older people. The severity, rather than the absence or presence of WMLs, could be evaluated in clinical practice and it is possible that in the future the volume of WMLs may contribute to a model for prediction of falls as well as a marker for potentially targeted interventions to prevent falls.

Disclosures

None.

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Tables

Table 1. Summary of Included Studies Examining the Effect of White Matter Lesions on the Physical Fall Risk Factors and Falls in Older People

Study	Outcome Measures			
	Balance	Gait and Stepping	Mobility	Falls
Cross-sectional studies				
Murray,2010[12]	--	S(X)	--	--
Novak,2009[7]	S(X)	NS	--	--
Wakefield,2010[13];and Moscufo,2009[8]	--	S(X)	S(X)	--
Blahak,2009[14];and Baezner,2008[15] *	S(X)	S(X)	S(X)	S(X)
Sparto,2008[16]	--	S(X)	--	--
Onen,2004[17]	--	--	S(X)	--
Starr,2003[18]	S(X)	S(X)	--	--
Guo,2000[19]	--	--	S(X)	--
Briley,1997[10]	--	--	S(X)	--
Masdeu,1989[20]	S(X)	S(X)	--	S(X)
Longitudinal studies				
Srikanth, 2010 and 2008[21, 22] *	--	S(X)	--	S(L)
Soumare,2009[23]*	--	S(L)	S(X)	--
Silbert,2008[24]; and Camicioli,1999[25] *	S(X)	S(L)	--	--
Rosano,2007[26], 2006[27] and 2005[28];Tell,1998[29]; and Longstreth, 1996[9]*	S(X)	S(L)	S(L)	--
Corti,2007[30] *	--	--	S(X)	S(L)
Wolfson,2005[31]; Benson,2002[32]; and Guttmann,2000[33]	NS	NS	S(L)	--
Baloh, 2003[34];and Whitman, 2001[35]	--	S(L)	S(L)	S(L)
Baezner, 2000[36]	--	S(L)	--	--
Kerber,1998[37] and Baloh,1995[38]	--	S(L)	S(L)	S(L)

S(X), indicates significant association with WMLs found in the cross-sectional study; S(L), indicates significant association with WMLs found in the longitudinal study; NS, indicates non-significant association with WMLs found; --, no data reported. * studies with higher quality designs [11]