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EDITORIAL

Are falls a manifestation of brain failure? Revisited 40 years later

Keywords: older adults, falls, gait, cerebral small vessel disease, neuroimaging

Key Points

- Editorial to accompany: Gait and falls in cerebral small vessel disease: a systematic review and meta-analysis [5].
- Vascular brain burden, evaluated as white matter hyperintensities (WMH), is associated with gait disorders and falls in older adults.
- Intensive hypertension management can reverse WMH, opening an opportunity for preventing 'brain failure' in older adults.
- Gait disorders and falls in older adults may be prevented by treating covert cerebrovascular disease and hypertension.

More than four decades ago, Professor Bernard Isaacs postulated in this journal that to attribute falls in older individuals only to muscular-articular and sensory impairments and their effect on gait and balance was overly simplistic [1]. Rather, a failure of our sophisticated system of brain motor control plays a capital role in triggering falls [2].

Since his seminal article, clinical and research evidence have established that brain motor control of gait arises from specific cortical and subcortical brain areas and networks that share complex cognitive functions, such as executive function (Figure 1). Due to their particular watershed vascularisation (border-zone regions in the brain supplied by the major cerebral arteries where blood supply is decreased), these shared brain networks are highly susceptible to microvascular ischemia and the effects of hypertension that, when damaged, may lead to both gait impairments and falls and to severe cognitive decline [3]. Thus, white matter hyperintensities (WMH) may impair gait performance directly, by disrupting motor-related networks, or indirectly, by disrupting networks responsible for executive function that is fundamental for high-attentional motor control of gait [3].

The LADIS cohort study was one of the first to establish that covert cerebral small vessel disease (CSVD), expressed as WMH, is associated with gait impairments, falls and future disability [4]. In this issue of the *Age and Ageing* journal, Smith et al. present a systematic review and meta-analysis (SR & MA) that confirms this finding and adds evidence that other expressions of CSVD, including lacunar infarcts, cerebral microbleeds and enlarged perivascular spaces, are likewise associated with gait impairments, mainly slowing gait speed and falls [5]. Importantly, this SR & MA shows longitudinal associations between CSVD and further gait speed decline and falls, suggesting a causal role.

WMH are highly prevalent in older adults, rising from about 5% for people aged 50 years to nearly 100% for people aged 90 years [6]. They are seen in brain MRI T2-weighted sequences and are supposed to represent CSVD, which are thought to result from ischaemia due to occlusive lesions of deep penetrating arteries, a phenomenon strongly associated with hypertension. However, the occurrence of WMH throughout the whole brain militates against ischemia being their sole cause, and other mechanisms such blood–brain barrier dysfunction due to degradation of tight junctions, brain venular stasis, endothelial dysfunction and chronic low grade of systemic/brain inflammation have been proposed [7, 8]. Interestingly, hypertension per se can cause endothelial dysfunction, blood–brain barrier dysfunction, and trigger low-grade systemic and vascular inflammation, as well as activation of microglia, which are also associated with CSVD [9].

Large cohort studies, including the Cardiovascular Health Study, the Mobilize Boston Study and the Gait and Brain Study, have shown that presence of WMH and their specific brain anatomic locations are associated with hypertension and with slowing gait, greater dual-task cost on gait, and falls [10, 11, 12]. As Smith et al. acknowledge, methodological differences in the original publications restricted their meta-analysis to just WMH volume. Future meta-analyses should address WMH anatomical locations and their association with gait impairments and fall risk. The integrity of white matter tracts seems to deteriorate early, before manifesting as WMH, as diffusion tensor imaging studies have shown that low white matter integrity in the corpus callosum, forceps minor and the left inferior fronto-occipital fasciculus were significantly associated with gait impairment and future falls in a small sample of older adults with mild cognitive impairment [13].

Besides CSVD, other potential brain changes and mechanisms underlying the causes of gait decline and increased falls have been described, including brain atrophy of selected cortical and subcortical areas, amyloid-β deposition burden,

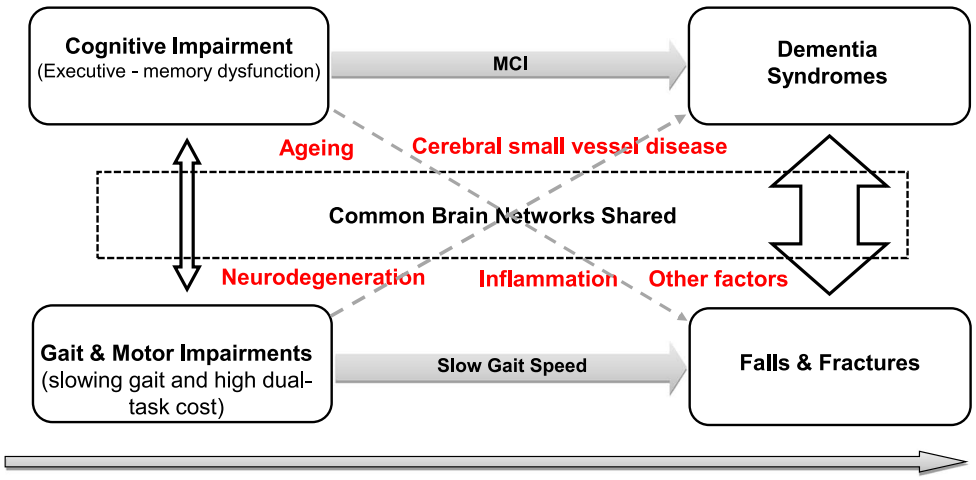

Figure 1. Cognitive function and gait performance decline with ageing, and may lead to dementia and falls (gray lines). Low cognition not only predicts dementia, but also mobility decline and falls, whereas mobility decline and slow gait predict cognitive deterioration and progression to dementia (dotted lines). These simultaneous declines may occur due to burden in shared common brain networks. Factors and diseases damaging brain areas and brain network integrity, which are important for maintaining gait and cognition, are shown in red. From Montero-Odasso et al. [3].

and accentuated depletion of neurotransmitters [14–19, 20]. The close proximity of frontal subcortical networks that control both motor and cognitive functions may explain why frontal atrophy and WMH may simultaneously cause dysfunction involving memory, executive function, gait and balance in older adults. Future research should address the relative contribution of CSVD in gait decline and falls compared with regional brain atrophy and/or brain amyloid-ß deposition.

The authors' findings also support treating manageable vascular risk factors and hypertension, especially when they represent early manifestations of brain damage, as such interventions have the potential to be a complementary method to prevent the loss of mobility and falls in older adults. The fact that three well-conducted clinical trials (SPRINT-MIND, PRoFESS and SCOPE) have shown that intensive antihypertensive treatment resulted in significantly less progression of WMH [21] suggests that antihypertensive treatments may also prevent or delay mobility decline and falls associated with impairments in gait and motor control. However, fluctuations of blood pressure and acute hypotension that can happen with intensive treatment can harm the brain. Therefore, those who might benefit the most, such as older adults with multimorbidity or frailty, should be carefully selected to avoid harm.

In summary, This SR & MA present high-quality evidence to support the hypothesis [15] that WMH burden is associated with gait disorders in the course of ageing and future falls. Although important details require further study, our collective research findings, reinforced and enriched by the current study, strongly suggest that microvascular ischemic changes affecting our most complex organ, the brain, and contribute to the mobility decline associated with ageing. This could give rise to new strategies for the prevention of gait disorders and falls in older adults based on the management of cerebrovascular risk factors and hypertension to prevent 'brain failure'.

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