NeuroImage 49 (2010) 1659–1666

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Gait disturbance associated with white matter changes: A gait analysis and blood flow study

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ARTICLE INFO

Article history:
Received 9 July 2009
Revised 1 September 2009
Accepted 14 September 2009
Available online 19 September 2009

Keywords:
Age-related white matter changes
Vascular parkinsonism
Cerebrovascular
Gait disorder
SPECT
Gait analysis

ABSTRACT

To clarify the mechanisms underlying gait disturbance secondary to age-related white matter changes (ARWMC), cerebral perfusion was investigated during treadmill walking. Twenty subjects with extensive hyperintensities in the periventricular and deep white matter on T_2-weighted magnetic resonance images (MRI) were recruited. The ARWMC subjects were classified into gait-disturbed (GD) and non-GD groups according to clinical criteria. All the subjects underwent gait analyses and cerebral perfusion measurements during both gait and rest by using single photon emission computed tomography. The GD group showed greater double support time/phase and stride width, and slower walking velocity, than the non-GD group. In an analysis of pooled data from all the subjects, gait-induced increases in cerebral perfusion were observed in the supplementary motor areas (SMA), lateral premotor cortex (PMC), primary motor and somatosensory areas, visual areas, basal ganglia and cerebellum. A between-group comparison of gait-induced perfusion changes showed relative underactivation of the SMA, thalamus and basal ganglia, together with relative overactivation of the PMC, in the GD group compared with the non-GD group. In a separate correlation analysis including all the subjects, as the double support phase was longer (that was, gait disturbance was more severe), the gait-induced perfusion changes were proportionally reduced in the SMA, visual cortex, and thalamus. The present study suggests that abnormalities in the basal ganglia–thalamo–cortical loops partly explain gait disturbance observed in a subset of subjects with ARWMC.

Introduction

Age-related white matter changes (ARWMC) have been proposed to describe the neuroradiological state of extensive white matter lesions (WML) in elderly people (de Leeuw et al., 2001; Hachinski et al., 1987; Inzitari et al., 2007). People with severe ARWMC may present with dementia (Jellinger, 2005) or gait disturbance (GD) characterized by impairment of locomotion, equilibrium and gait ignition (Baezner and Hennerici, 2005). Computerized gait analysis may reveal short steps, decreased gait speed and cadence (steps/min) and long double support time, even in the early stages of the disease (Bazner et al., 2000; Ebersbach et al., 1999; Rosano et al., 2006).

A subset of people with ARWMC manifesting gait disturbance are sometimes said to have lower-body parkinsonism (Thompson and Marsden, 1987). However, there are similarities and differences in the manifestation of gait disturbance between individuals with ARWMC and those with idiopathic Parkinson's disease (PD). Gait disturbance is characterized by slow walking speed, start hesitation, short steps, and freezing in both groups. A major difference is the stride width, which is typically much wider in subjects with ARWMC than in PD patients (Jankovic et al., 2001).

Measurements of cerebral perfusion with single photon emission computed tomography (SPECT) have revealed abnormality of the basal ganglia (BG)–thalamo–supplementary motor area (SMA) loop as a mechanism underlying the gait disturbance in PD (Hanakawa, 2006). In the present study, the same method was used to examine brain activity during treadmill walking in ARWMC subjects with various degrees of gait disturbance. Brain activity was analyzed in reference to objective measures of gait disturbance from gait analyses. Considering the overlapping phenomena in gait disturbance between

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doi:10.1016/j.neuroimage.2009.09.023

ARWMC and PD, it was hypothesized that the BG–thalamo–SMA loop was, at least in part, responsible for the gait disturbance in individuals with ARWMC (Rektor et al., 2006).

Materials and Methods

Subjects

Twenty subjects with ARWMC were enrolled at our Neurology Clinic. The inclusion criteria were (1) age range between 65 and 84 years old and (2) both irregular periventricular hyperintensity extending into the deep white matter (Fazekas' PVH 3) and confluent hyperintensity in the deep white matter (Fazekas' DWMH 3), diffusely involving at least the bilateral frontal subcortical areas and not confined to a single vascular territory, on T_2-weighted MRI (Fazekas et al., 1987). The exclusion criteria were (1) a history of acute stroke in the previous 3 months, (2) lumbago or pain in the knee, (3) surgery of the knee or vertebrae in the previous 6 months, (4) severe ventricular dilatation or narrowing of the cerebrospinal fluid space in the superior convexity area on MRIs, indicating idiopathic normal pressure hydrocephalus (NPH), (5) severe brain atrophy (6) cortical infarction on MRIs, (7) major vessel occlusion or stenosis more than 50% on MR angiography, (8) response to anti-Parkinsonian medication, (9) severe orthostatic hypotension revealed by the Shellong postural test, (10) symptomatic osteoarthritis of the hip or other joints, and (11) severe gait disturbance precluding gait analyses. Most subjects ($n=16$) underwent MRI scans during assessment of headache or vertigo, or as a part of extensive medical check-up. The others ($n=4$) did so for follow-up of old lacunar infarctions or small hemorrhages. Although in none of them gait disturbance was their chief complaint at the first visit, some complained of gait disturbance after full neurological assessment at the first visit or after a few visits. All the subjects included in the present study underwent neurological examinations, and none of the subjects had sensory ataxia or peripheral neuropathy. The research protocol was approved by the local ethics committee, and written informed consent was obtained from each patient.

Gait analysis and patient classification

The subjects completed a Falls and Gait Questionnaire (FGQ) including the Freezing of Gait Questionnaire to assess episodic difficulty in walking (Giladi et al., 2000). They also underwent a two-step gait assessment procedure. First, speed and cadence were measured while the subjects were walking naturally on a 10-m walkway for three times. All the subjects were instructed to walk with their preferred pace at which they normally do in their daily life. Three board-certified neurologists, all of whom were blind to the patients' profiles, reviewed videos taken during the 10-m walking test and rated gait disturbance, especially paying attention to stride length, shuffling, stride width, disequilibrium, and freezing (Baezner and Hennerici, 2005). Based on this clinical evaluation, the 20 ARWMC subjects were classified into those with a mild-to-moderate degree of gait disturbance (GD group, 11 subjects) and those with normal gait or a subclinical degree of gait disturbance (non-GD group, 9 subjects). An inter-rater reliability analysis using the weighted kappa statistic was performed to determine consistency among the raters. The kappa values were 0.898 between the raters 1 and 2 or 3 and 1.00 between raters 2 and 3. Kappa values between 0.81 and 1.00 indicate almost perfect agreement (Altman, 1999; Landis and Koch, 1977). There were no significant differences in age ($P=0.221$), sex ($P=0.178$), and height ($P=0.859$) between the two groups (t-test). Note that the non-GD group included subjects with a minimal degree of gait disturbance, which could be detected by a computerized gait analysis.

Second, the subjects were assessed with a three-dimensional (3D) locomotion analysis machinery (GATAL-ITS-60, Sumitomo Metal Inc., Osaka, Japan) equipped with two force plates and foot switches (9090S, Bertec Inc., OH) located on an 8-m walkway with 90-cm width. Stride length, stride width (SW), gait cycle (GC), and the ratios of double support time per GC (DST/GC) were measured. These gait parameters were compared between the two groups (t-test), and correlations among these parameters were checked (Pearson's test).

Assessment of clinical backgrounds

Major risk factors of cerebrovascular disease (hypertension, hyperlipidemia and diabetes mellitus) were analyzed. The prevalence of these risk factors was compared with a chi-square test between the GD and non-GD groups; however, caution must be used in the statistical interpretation of the results because of the relatively small number of subjects for this type of analysis. For the assessment of cognitive status, the minimental state examination (MMSE) scores were obtained. The MMSE scores were not intended to be used for precise evaluation of cognitive impairment as our focus was gait impairment. T_1-, T_2-, and T_2*-weighted MRIs from a 1.5-Tesla scanner were reviewed by two board-certified neurologists to confirm consistency with the inclusion and exclusion criteria and to check for the existence of lacunar infarctions or microbleeds (Mbs) in the BG or thalamus.

Task conditions

Cerebral perfusion was measured during rest and walk conditions. In the rest condition, the patients stayed still in a supine position for 5 min. During the rest condition, the subjects were instructed to open their eyes and to look at the white ceiling in the room. In the walk condition, the subjects walked on a treadmill moving at a steady speed of ~0.2 m/s for 5 min. The treadmill speed was adopted from our previous studies (Hanakawa et al., 1999a,b), so that all subjects could walk without difficulty after a short practice. They were instructed to walk with their preferred stride length to keep to the walking speed. During the walking task, the subjects walked with their bare feet on the nonslippery, artificial rubber floor of the treadmill and were allowed to hold the side-bars of the treadmill gently for safety.

Every possible effort was made to match the elementary perceptual aspects between the conditions. The brightness of the room was adjusted similarly between the conditions. To control visual inputs between the task conditions, they were asked to keep watching a white wall in front of them during the walk condition, so that visual information from the moving treadmill was not available. No other visual or auditory cues were given during the walking task. In the walk condition, gait performance of each subject was recorded with a digital video camera for subsequent review, and stride length and mean cadence were calculated.

Image acquisition

^{99m}Tc-ethyl cysteinate dimer (ECD) was employed as a blood flow tracer. Similar to ^{99m}Tc-hexamethyl propylene amine oxime (HMPAO) that has been used for previous gait activation SPECT studies, ^{99m}Tc-ECD distributes rapidly in the brain in proportion to blood flow after administration and remains stable for a long period of time. This characteristic makes this tracer suitable for measuring cerebral blood flow with a split-dose tracer injection method (Audenaert et al., 2001).

The subjects underwent two consecutive SPECT scans, one for each condition. The order of the task conditions was counterbalanced across subjects to reduce the order effects. When the walk condition was studied first, the procedures were as follows. After treadmill walking reached a steady state, 300 MBq of ^{99m}Tc-ECD was administered through a venous line fixed onto the subject's left forearm while the