Higher level gait disorders in subcortical chronic vascular encephalopathy: a single photon emission computed tomography study

CHIARA CARBONCINI
Azienda Ospedaliera Universitaria pisana–Neurosciences, via Roma, 67 Pisa 56126, Italy

Address correspondence to: Chiara Carboncini. Tel: (+39) 050995581; Fax: (+39) 050995724.
Email: m.carboncini@ao-pisa.toscana.it

Abstract

Background: the so-called higher level gait disorders include several types of gait disorders in which there are no major modifications in strength, tone, sensitivity, coordination and balance. Brain activation sites related to walking have been investigated using SPECT in humans. The aim of the study was to investigate brain activation during walking in subjects with high-level gait disorders due to chronic subcortical vascular encephalopathy.

Subjects: twelve patients with a chronic vascular encephalopathy were enrolled in the study. Seven subjects had apraxic gait while in the other five the gait was normal. All patients had undergone a recent cerebral magnetic resonance that revealed diffused chronic ischemic lesions within the white matter.

Methods: all 12 patients underwent a regional cerebral blood flow (rCBF) brain SPECT study with $^{99m}$Tc-Bicisate on two separate days and under two different conditions: at rest (baseline) and while walking (functional).

Results: the rCBF increase induced by the treadmill test (functional–baseline), bilaterally in the medial frontal gyrus and in the anterior lobes of the cerebellum, resulted significantly ($P < 0.001$) lower in patients with gait apraxia versus those without it.

Conclusions: this study of the brain with SPECT records the areas of perfusion deficit that appear in apraxic subjects when they walk, compared with the recordings obtained with the same investigation performed at rest.

Keywords: higher level gait disorders, cerebrovascular disease, SPECT, elderly

Introduction

The so-called higher level gait disorders [1] include several types of gait disorders in which there are no major modifications in strength, tone, sensitivity, coordination and balance.

The clinical features are flexed posture, shortened stride, increased base for support, hesitation and difficulty in starting to walk, postural instability, but no difficulty in performing isolated steps [2].

There are different terms for these alterations in gait: atherosclerotic parkinsonism [3], gait apraxia [4], vascular pseudo-parkinsonism [5] and parkinsonism in the legs [6].

Subcortical vasculopathy is the most frequent cause of apraxic gait.

From an epidemiological point of view, chronic subcortical vascular encephalopathy is the second neurological cause of altered gait in the elderly after Parkinson’s disease [7].

The kinematic characteristics of apraxic gait are superimposable to those of the typical gait seen in subjects with Parkinson’s disease, to the extent that the functional alterations under the two conditions may be considered similar.

One of the most suitable tools for studying brain activity changes induced by gait is regional cerebral blood flow (rCBF) SPECT; radiotracers can be administered during a task performance, such as walking, and their brain distribution is proportional to the rCBF at that moment. Moreover, the radiotracer distribution within the brain does not change over time even when the subject stops walking, and SPECT acquisition can be obtained afterwards.

Brain activation sites related to walking have been investigated using SPECT in humans. Fukuyama et al. [8] evaluated changes in brain activities during walking using SPECT, which enables scanning the performance at rest, immediately after walking, to indicate the rCBF at the time of injection. Activation of the supplementary motor area (SMA), medial primary sensorimotor area, striatum, cerebellar vermis and visual cortex in normal young adults was observed. Subsequently, they reported activation sites during walking in the medial frontoparietal cortex, dorsal brainstem, basal...
ganglia and cerebellum in normal elderly subjects. The activated medial frontoparietal cortex formed a large cluster including the SMA, lateral premotor areas, medial primary sensorimotor areas, anterior cingulate cortex and superior parietal cortex.

The aim of the study was to investigate brain activation during walking in subjects with high-level gait disorders due to chronic subcortical vascular encephalopathy. Moreover, since vascular apraxic gait is very similar to the Parkinson gait, the initial theory surmised was that the areas of hypoperfusion might be the same.

### Patients

Twelve patients with chronic vascular encephalopathy (six males and six females) were enrolled in the study. Seven subjects (four males, three females; mean age 78.1 ± 8.9) had apraxic gait while in the other five (two males and three females; mean age 77.6 ± 3.2) the gait was normal. All the asymptomatic subjects had various degrees of chronic subcortical ischaemic vascular encephalopathy, which was detected by chance; a neuroradiological examination had been performed for other ongoing conditions (a frigore facial paralysis in three subjects; facial idiopathic hemispasm in two subjects).

All subjects were scored against the Tinetti scale [9]. This scale permits assessment of balance and certain features of gait, such as difficulty in starting to walk, the length, symmetry and progression of the steps and the direction taken when walking. The clinical characteristics and the scores achieved by the subjects studied against the Tinetti scale are given in Table 1.

All patients had undergone a recent (within 1 month) cerebral magnetic resonance (MRI), which revealed diffused chronic ischaemic lesions within the white and grey matter. Ischaemic lesions were detected also in the thalamus (n = 1) and cerebellum (n = 2) (Table 1).

### Methods

All 12 patients underwent an rCBF brain SPECT study with $^{99m}$Tc-Bicisate (ECD, Neurolute Bristol Meyers Squibb, 740 MBq) on two separate days and under two different conditions: at rest (baseline) and while walking (functional). In six subjects, the baseline was obtained before the functional study, while the sequence was inverted in the other six subjects. In the baseline study, the radiotracer was injected during the resting condition, in a quiet room with minimal sensory stimulation. In the functional study, ECD was administered during walking, as follows: patients were invited to walk for 8 min on a treadmill at a speed of 1 km/h, after a brief period of training. After the first 4 min of walking, ECD was injected using a previously set up I.V. line while patients continued to walk at the same speed for the remaining 4 min in order to obtain complete distribution of the radiotracer within the brain. The rapid brain uptake of ECD allowed acquisition of the distribution of rCBF directly related to the functional test.

Scans were performed with a dual head gamma camera (Optima NT, ELGEMS, Milwaukee, USA) equipped with low energy, high-resolution collimators. Raw data were collected in a $128 \times 128$ matrix (3 mm pixel size) for 128...
projections over a 360° circular orbit for each detector, with an acquisition time of 15 s for each step. Energy setting was centred on the 140 keV peak of $^{99m}$Tc, with a 20% window. Images were reconstructed with filtered back projection using a Butterworth pre-filter and uniform attenuation correction. After reconstruction, images were reoriented along the anterior commissure-posterior commissural line. Reconstructed DICOM 3.0 axial slices were exported to a Windows-based personal computer (Microsoft, Redmond, WA, USA) and converted to the analyse format using MRIcro (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html).

**Image processing and statistical comparison**

Statistical parametric mapping (SPM) was used for SPECT data analysis. Image processing was performed using MATLAB 6.5 (The MathWorks, Inc., Natick, MA, USA) and SPM99 (Institute of Neurology, University College of London, UK). Baseline axial data of each patient were realigned to functional ones and both studies were spatially normalized to the SPECT CBF template in the standard stereotactic space according to the Montreal Neurological Institute (http://www.bic.mni.mcgill.ca), which approximates the space defined by Talairach and Tournois [10]. Normalized images were smoothed prior to statistical analysis with a 12 mm full height at half maximum isotropic Gaussian kernel in order to improve signal noise ratio.

SPM analysis tested the differences of the effect of the functional test on rCBF between the two groups of patients (with and without gait disorder). A statistical design, multigroups—conditions and covariates, was used for the analysis. Differences in baseline rCBF pattern between the two groups of patients (unpaired t-test) were also performed. Statistical significance was taken at $P < 0.001$, uncorrected for multiple comparisons.

**Results**

No significant age differences were present between the group of patient with gait disorders and those without symptoms. The score of the Tinetti scale resulted significantly reduced ($P < 0.0002$) in patients with gait apraxia ($5.3 \pm 2.3$ vs. $11.4 \pm 0.9$).

No significant differences were found in baseline rCBF between the group of patients with gait disorders and those without symptoms.

The rCBF increase induced by the treadmill test (functional–baseline) in the medial frontal gyrus bilaterally and in the anterior lobes of the cerebellum resulted significantly ($P < 0.001$) lower in patients with gait apraxia versus those without it. Figure 1 shows the results and the statistical design of the SPM analysis. Figure 2 shows the same areas co-registered to a MRI T1-weighed template.

Table 2 reports the brain areas with stereotactic coordinates with significant activation induced by walking in asymptomatic patients, but which is lacking in those with gait apraxia (see supplementary data available on Age and Ageing online).

Figure 3 reports the percentage increase of rCBF in patients with and without gait apraxia, obtained by performing VOI (volume of interest) measurements within cerebellum and frontal area clusters of voxels, which, on SPM analysis, did not significantly activate in the patients with gait apraxia versus those without it (see Appendix 2 in supplementary data available on Age and Ageing online).
Figure 2. Areas of activation co-registered to a MRI T1-weighted template. On the left, coronal, sagittal and axial slices with activation of the left and right medial frontal gyrus; on the right, areas of activation within the cerebellum (anterior lobes). In the coronal slices, the right side of the images corresponds to the right side of the brain.

No statistically significant difference between the rCBF changes in the two groups was found using the patients’ age as a covariate.

Discussion

Walking necessitates the production of a basic locomotorial rhythm that determines the pattern of muscular activation, control of the body during motion and adjustment to the environmental requirements [11]. A central pattern generator provides the motor signals that elicit these complex sequences in mammals.

Although similar in some respects to that of quadrupeds, human gait has certain peculiarities. For instance, the existence of central pattern generators in humans is still a question for debate; evidence of their existence is noted in newborns, who do ‘stepping’ movements if they are held erect over a flat surface immediately after birth [12, 13]. Nevertheless, persons with full spinal damage are unable to walk, contrary to cats [14, 15]. In fact, spontaneous rhythmic and alternating activity of the flexor–extensor muscles in the legs of adults with spinal damage is rare [15]. These data suggest that, contrary to what happens in cats, the activation of brainstem and spinal structures in humans depends more on cortical and subcortical inputs. This is supported by various data. First of all, recent studies on transcranial magnetic stimulation have demonstrated that the cortex exerts fine control of the ankle muscles during the swing stage of a step [16]; secondly, these
cortical areas are strictly involved in the activity of dorsiflexor muscles in the ankle during both walking and voluntary contraction [17], suggesting that the biomechanical requirements of biped gait have encephalized motor control in human gait [16, 17]. Moreover, Nutt and colleagues [18] reported that patients with damage in pre-motor areas have difficulty in starting and continuing walking, changing their direction and going through narrow spaces. In addition, neurophysiological and biomechanical studies on walking performed in healthy subjects [19, 20] and in subjects with damaged SMA suggest that the SMA is involved in the motor preparation and planning of tasks such as starting and finishing walking.

The rhythmic progression of steps is controlled by SMA function [18]. Phillips et al. [21] suggest that this area has a role in the choice of the set of instructions required for preparing sub-coordinated movements, the input of which is then conveyed to the primary motor cortex. SMA lesions are the cause of serious hypokinetic [22] and apraxic gait [23].

The basic theory regarding this symptomatology in subjects with subcortical vasculopathy is that it is connected with variations in brain perfusion. The presence of diffused subcortical ischaemia (disease of the small vessels,Binswanger’s disease) produces a disconnection between the basal ganglia and the cortex [2]. The selective involvement of the legs appears to be attributable to the fact that the projection of the legs from the peri-ventricular area to the frontal horn is more superficial than that of the arms.

Liston [1] hypothesizes three main types of higher level gait disorders based on presumptive sites of anatomical damage: ignition apraxia, equilibrium apraxia and mixed gait apraxia, postulating that the first condition is caused by ischaemia/disconnection between basal ganglia and the SMA. This theory is supported in studies by Meyer et al. [5], Hennerici et al. [24] and Chang et al. [3]. The second condition is caused by ischaemia/disconnection between sensitive areas and pre-motor areas [25]. A combination of the previous two conditions causes mixed gait apraxia. Using SPECT with $[^{99mTc}]$ HMPAO, Hanakawa et al. [26] compared brain activation between normal subjects and patients with Parkinson’s disease while walking on a treadmill. Under-activation in the left medial frontal area, right precuneus and left cerebellar hemisphere and over-activity in the left temporal cortex, right insula, left cingulate cortex and cerebellar vermis were observed in Parkinson patients. The under-activation of the medial frontal area corresponded to the rostral portion of the SMA, suggesting that impairment of the basal ganglia-thalamus-SMA loop may be involved in gait disturbance in Parkinson’s disease.

Hypoperfusion in the SMA was observed in subjects with apraxic gait in this study, as well. This event might be the result of a disconnection of the basal-secondary motor area nuclei, due to the vascular damage. This is confirmed by the poor response to dopaminergic drugs of a typical feature of apraxic gait that is also seen in the Parkinson gait, that is, freezing. This freezing in a subject with Parkinson’s disease can be treated successfully, both with dopaminergic drugs and with deep stimulation of the subthalamus. In contrast, dopaminergic drugs in subjects with apraxic gait due to chronic subcortical vascular encephalopathy produce poor results, even though some authors [27] report of an improvement in motor performance after the administration of amantadine even in subjects with apraxia.

As far as the hypoperfusion of the anterior cerebellar lobules is concerned, seen in the apraxic subjects in this study (and reported in Parkinson patients [26]), this appears to be connected with the loss of frontal ‘swing’ in subjects with Parkinson’s disease because of their inability to shift their centre of gravity to one leg, and is responsible for their small shuffling steps. These similarities with apraxic gait kinematics suggest that the subject with apraxia might also be unable to shift the centre of gravity onto one leg. Furthermore, since the roof nuclei are considered the site of cerebellar locomotor centres [28], their malfunction might produce alterations in gait.

To conclude, this study of the brain with SPECT records the cerebral areas of deficit that appear in apraxic subjects when they walk; when compared with the same investigation performed at rest [29], the altered perfusion seen in subjects with Parkinson’s disease is almost superimposable to that seen in subjects with apraxic gait, thus justifying the theory that the alterations in gait are similar under the two conditions.

Key points

- Higher level gait disorders are a common gait alteration in older people.
- This gait disorder can occur in cerebrovascular disease of small vessels (leukoaraiosis).
- The perfusional functional cerebral SPECT demonstrates the hypoperfused areas during gait in subjects with higher level gait disorders.
- Hypoperfusion during gait of the SMA and cerebellum, documented in this study, could explain the typical alterations in subjects with higher level gait disorders.

Conflict of interest

None

Ethical approval

All patients gave their informed consent to the experimental procedure, which had been approved previously by the Ethics Committee of the University of Pisa.

Supplementary data

Supplementary data are available at Age and Ageing online.
C. Carboncini

References


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