Complex distal movement in cortical-basal ganglionic degeneration. A functional evaluation

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Summary

We evaluated cortical activation during simple and complex learned movements in five patients diagnosed with cortical-basal ganglionic degeneration. Since the parietal area is one of the areas most involved in this degenerative pathology, we focused on the possible role of the parietal lobe, in learning and executing simple and complex motor sequences. We also attempted to describe the role of the parietal area in spatial and visual control, which is necessary to define and optimise movement execution in daily living. We discuss the results of our evaluation, and give an overview of the literature on the topic.

KEY WORDS: Apraxia, cortical-basal degeneration, f-MRI, magnetic resonance, movement, parietal lobe.

Introduction

A clinical syndrome of asymmetric parkinsonism associated with cortical abnormalities and a peculiar pathological picture was labelled cortical-basal ganglionic degeneration (CBGD) (1,2). The most common signs and symptoms were, in descending order: limb rigidity (100%), limb apraxia (91%), gait difficulties (89%), focal reflex myoclonus (88%), eye movement abnormalities (78%), limb dystonia (77%), pyramidal signs (73%), dysarthria (62%), cortical sensory abnormalities (55%), and the alien limb phenomenon (55%). Tremor, frontal lobe reflexes, and cognitive impairments were considered less common. However, a recent evaluation of Canadian Brain Tissue Bank cases (3,4) suggests that dementia may be the most common presenting feature, rather than the better recognised perceptual-motor syndrome just outlined. Contradictory results are, in fact, very probable in the diagnostic dilemma evoked by CBGD. It is, for example, a well known, but highly inexplicable fact that one third of the patients had symptoms starting on the right and two thirds on the left. The disease is steadily progressive, with a mean survival of 6-7 years.

Neuropathologically (5,6), circumscribed parietal or frontoparietal lobar atrophy may be present. Severe neuronal loss and intense astrogliosis are evident in the cortex; spongiosis, swollen and achromatic neurons (ballooned cells or pale bodies), neuropil threads, and neurofibrillary tangles can also be found. Ballooned cells can be detected in the neocortex; basophilic argyrophilia and tau-positive inclusions are found in the neurons of the substantia nigra and subthalamus nucleus, striatum and pallidum and even along the dentate-rubro-thalamic tracts (7-9).

From a pathological perspective, too, data are rather uncertain. Most CBGD cases present with the characteristic ballooned neurons, and tau-positive neuronal and glial inclusions are not infrequent, while other cases are difficult to classify due to the presence of overlapping neuropathological features of Alzheimer’s disease, progressive supranuclear palsy, Parkinson’s disease and pure hippocampal sclerosis (10). In this context, the presence of apraxia is almost the only certainty in CBGD. Apraxia can be defined as the inability to perform coordinated motor activities, in the absence of weakness, comprehension deficits, or adventitious movements. An apraxia study focusing on the less involved limb in ten patients with CBGD showed that seven had ideomotor apraxia and none had buccofacial apraxia (11). Four of the seven patients who manifested ideomotor apraxia had intact gestural comprehension so their apraxia was considered to be of a “frontal type”; the other three had more severe apraxia, with ideational deficits as well as difficulties with gestural comprehension. There appear to be no data evaluating movement organisation in CBGD: therefore, starting from this perspective, we studied five patients with CBGD, in an attempt to highlight the disruption of fine distal movement execution, not only from a clinical point of view but also, by means of functional magnetic resonance imaging (f-MRI), documenting it through a dynamic study.

Presentation of the cases

During the period 1st January 1997 - 1st January 2001, five patients (two males and three females) came to our
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attention. Their mean age was 66.6 years (± 7.6) and all were right-handed (giving an average Briggs and Nebes test score of +22.56) (12). The past history of all the five patients was completely negative for cerebrovascular disease, hypertension and metabolic disorders. Their most common complaint was the relatively recent development of an asymmetric akinetic syndrome affecting, in all five of them, their left upper limb. They also showed bradykinesia, alien limb syndrome (in two subjects, one male and one female), slurred speech and gait difficulty. Only two of the subjects showed action tremor and one of them supranuclear gaze palsy.

At presentation, the neurological examination demonstrated plastic, asymmetric rigidity, complicated by uneven resistance of the limbs to passive movement (Gegenhalten). All the patients showed a left hand apraxia, left astereognosis and left tactile extinction. As mentioned above, alien limb was observed in two of them. A positive response to L-dopa administration was excluded and no autonomic disturbances were detected.

As stated, only one patient showed supranuclear palsy, affecting both vertical and horizontal gaze. However, all the patients underwent a complete ocularmotor evaluation: in general, we found normal saccadic velocity (considering anti-saccades, reflexive saccades and voluntary saccades) with increased latency of saccades (especially of voluntary saccades) and preservation of pursuit and optokinetic nystagmus. The symptoms pre-dated admission by an average of 8.4±2.83 months.

From a cognitive perspective, intelligence performances were within normal range (106±4.5) as shown by the average score obtained in the Raven Standard Progressive Matrices (13); the patients recognised right/left personal and extrapersonal hemispace, and no signs of tactile agnosia or of buccofacial apraxia were found (14).

The average Wechsler Adult Intelligence Scale (WAIS) (15) results demonstrated a mild general tendency to global deterioration (12.4%±4.7%). Calculations, morphological and semantic aspects of linguistic performances, and attention appeared normal. The patients could speak and to ignore the left hemispace and slight impairment in its realisation. The patients performed the Proverb Interpretation Test (20) in a rather approximate, practical and simplified manner. None of the subjects could produce pantomimes to the verbal command of the examiner, while they were slightly better at imitating pantomimes performed to them: all of them showed signs of ideomotor apraxia with the left, affected hand. On the contrary, when given a prop to use, their performance with the left hand was virtually normal, though the movements were awkward and slightly clumsy. In other words, while they had the right idea, the movement was not right, therefore they showed clear signs of ideomotor and not of ideational apraxia of the left hand. Using the right hand they executed quite well all the orders given. They performed the Repetitive Graphomotor Sequences (21) quite well with their right hand. The left hand, in all cases, produced only awkward and clumsy signs with modest perseverative tendency. They all performed badly on the Clock Test (22), not completing, with the right hand, the hour sequences requested by the examiner (mean score 5.6±1.76). While all the patients showed moderate awareness of their general situation, especially of their motion disruption, they were not particularly worried about their cognitive deficiency.

All the patients underwent a brain MRI, performed using a 1.5 T magnet. The examination showed severe, asymmetric pericentral cortical atrophy, mainly located in the perihippocampal gyri, and in particular in the postrolandic cortex. Subtle MRI T2 hyperintense lesions in the primary motor cortex, compatible with underlying gliosis, were associated with mild atrophy of the basal ganglia, and in only one case, we found clear hypointensity in the lenticular nuclei, a feature reported by other authors (23-25).

The patients also underwent a 99-mTc-ECD-SPECT, which showed clear right-posterior parietal hypoperfusion, with a concomitant discrete lower perfusion of the right temporal cortex and frontal homolateral region. A dyshomogeneous hypoperfusion could also be seen in the left parietal and temporal regions. During the observation period, patients were invited to undergo three or four training sessions daily, in order to practice and to perform better a finger opposition task, first with the left (affected) and then with the right (healthy) hand. The subjects had to touch all four fingers with the thumb, with beginning thumb/index finger contact and proceeding to the small finger in a 2, 3, 4, 5 sequence which would then be repeated, again starting with contact between the thumb and index finger. Then, they were asked to execute a complex alternating sequence, first with the left (affected) and then with the right (healthy) hand. Subjects had to touch the fingers in a specific sequence: 1-2, 1-4, 1-3 and 1-5.

After one week of training, the subjects underwent f-MRI.

The total acquisition time was equally divided into three motor task periods, separated by three rest periods. Seven images per period were collected, so in each acquisition a total of 42 images were collected. Images were oriented transversally. The GRE studies were performed using a standard 1.5 T imager (Gyrosan S15-ACS II, Philips Medical System, Best, The Netherlands). The maximum gradient strength was 10mT/m. A standard quadrature birdcage headcoil was used as the receiver coil, and the body coil was used for excitation. The major parameters of the 2D gradient-echo MR pulse sequence were the following: TR=60 ms, TE=40ms, flip angle=25, FOV=160x144 mm², slice thickness=4 mm, scan matrix=128x128. The T1 contrast enhancement option was activated (26). An MR angiography acquisition was performed for each T1-GRE f-MRI acquisition. The major parameters of the angiographic sequence were the following: TR=shortest, flip angle=20, FOV=the
same as the T1-GRE, slice thickness=1 mm, scan matrix=256x256, slices=12, slice thickness=1 mm, phase contrast technique. Image analysis was performed using a program developed in IDL environment (Interactive Data Language, Research System Inc., USA). The basic analysis consisted of the calculation of the correlation coefficient between the time-intensity behaviour of each pixel and a square wave model function. In order to exclude transient haemodynamic responses, 5 images per block (from the 3rd to the 7th of each block) were included in the analysis. By applying a correlation analysis (p<0.001) and a cluster filtering (at least 5 pixels) a raw activation map was obtained. The raw map was affected by flow artefacts; to eliminate these artefacts, activation map and MR angiography were compared and activation clusters related to vessels were rejected. Whole-head, high-resolution, T1-weighted images were then acquired to be used as an anatomical reference for transformations into the Talairach space (27).

We were able to demonstrate that during a simple motor task involving the right hand (Fig. 1A) there is a good activation of the left rolandic cortex, associated with discrete activation of the supplementary motor area (SMA) and of the parietal regions, as well as discrete activation of the right prefrontal region. On the contrary, during a simple finger opposition task executed with the left (affected) hand (Fig. 1B), clear hypo-activation of the right and left perirolandic cortex was found, associated with clear hypo-activation of the contralateral SMA and, obviously, of the affected parietal region. During complex sequence execution by the right hand (Fig. 1C), an obvious bilateral activation of rolandic areas, of the parietal areas, of the SMA, and of the left frontal region could be seen, whereas when the sequence was executed by the left hand (Fig. 1D), the observed activation was limited to the bilateral rolandic region, the SMA, and very modest activation of the parietal regions.

Fig. 1 - A. f-MRI normal cortical activation during simple motor sequence executed with the right hand; B. f-MRI defective cortical activation during simple motor sequence executed with the left (affected) hand; C. f-MRI normal cortical activation during complex motor sequence executed with the right hand; D. f-MRI altered cortical activation during simple motor sequence executed with the left (affected) hand.
Discussion

As far as the cortical organisation of fine learned motor movements is concerned, the evidence from these five additional CBGD cases, studied with f-MRI, lends positive support to the hypothesis we developed on the basis of a single case (28), namely that visuospatial disruption, the principal consequence of parietal damage, leads to alteration of fine, sequential, learned movement and that this might be explained by complex disruption of cortical activation. Further, these evaluations suggest wider possible explanations of what was initially observed.

Patients with CBGD, showing clear signs of ideomotor, but not of ideational apraxia, were instructed and trained to perform different motor sequences: a simple one (sequential finger opposition task), and a complex one (alternate opposition task). Despite being apraxic, the patients were nevertheless able to learn complex movements too. In effect, movements with the left (affected) hand were slightly awkward and clumsy, especially when compared to those executed with the right hand, but the patients responded to the training quite well. A constant finding in all the patients was the absolute necessity to control, through visual input, sequential movement when this was performed with the left hand, whereas the movement was performed quite easily and without support when executed with the right hand. Moreover, while a differential, intercurrent and involuntary stimulus was found to distract them from the execution with the left hand, the same stimulus had almost no effect on the execution of the sequential movement with the right hand. When they underwent f-MRI, the patients became consciously aware, for the first time, of the real importance of visual control: immobilised to minimise involuntary motion artefacts, they could not control their movement. They did perform the required task, but the examiners had to offer continuous support and encouragement. Nevertheless, different movement artefacts caused evident impairment of the f-MRI, and various sequences had to be reproduced a number of times, in order to guarantee the most realistic and reliable results.

As said before, during a simple motor task involving the right hand (Fig. 1A), good activation of the leftRolandic cortex can be observed, associated with discrete activation of the SMA, of the parietal regions, and of the right prefrontal region. On the contrary, during a simple finger opposition task executed with the left (affected) hand (Fig. 1B), we observed clear hypo-activation of the right and left perirolandic cortex (as always seen during non dominant hand movements), associated with clear hypo-activation of the contralateral SMA and, obviously, of the affected parietal region.

During complex sequence execution by the right hand (Fig. 1C), it was possible to observe clear bilateral activation of rolandic areas, of the parietal areas, of the SMA, and of the left frontal region, whereas when the sequence was executed by the left hand (Fig. 1D), the observed activation was limited to the bilateral rolandic region, to the SMA, and to a very limited activation of the parietal regions. Movement, or at least learned movement could be performed, but the cortical organisation of that movement seemed someway altered.

From the perspective of these findings, we have examined literature on this topic. It appears that CBGD is an extensive, rather than circumscribed, brain pathology whose hallmark is the destruction of the parietal lobe, one of the most intriguing encephalic areas.

Gestural disorders due to parietal alteration result in a lack of manual dexterity, reminiscent of kinaesthetic limb apraxia (29). Constructive apraxia can be observed in patients with predominant right parietal lesions (30). In particular cases, such as CBGD patients, parietal disruption led to preservation of gesture recognition, but impairment of all aspects of gesture execution, suggesting that the mental representation or conceptual aspects of gestures are not involved. In agreement with this interpretation, conceptual apraxia is not reported in the absence of a severe cognitive impairment. The most frequent gestural disorder in CBGD therefore seems to be ideomotor apraxia (31).

It is widely accepted that parietal lobe damage is directly involved in fine movement alteration, as well as in directional hypokinesia, optic and mirror ataxia (32). The posterior parietal cortex is intimately involved in attention processes, too (33).

If one investigates which cortical areas are invariably activated during voluntary motor activity, the primary motor area emerges as the only cortical area whose activity is linked to voluntary behaviour. If, on the other hand, one asks which structures are active during voluntary motor action, the list is much longer. During movements of the right hand, large activation increases in the left motor and sensory hand area can be seen, as can bilateral activation increases in the premotor cortex and supplementary sensory areas. The contralateral SMA has been shown to be more activated than the ipsilateral SMA, but the difference was not significant. Neither was the activation increase in the ipsilateral primary motor area (34).

A movement is practically never isolated, but integrated in a complex structure or even in a goal. Representation of the goal might arise in areas that have no direct connection with the motor sectors, and in fact, intention for motor action has been defined as recruitment of those cortical areas whose participation is necessary for the information processing between the idea of a goal and motor execution.

It appeared that, when the sequence of an action had been learned, a fast program for the succession of movements was established in the brain: during the internal rehearsal of the program the SMA was active, and might be a part of the storage site for the sequence program; during learning, sensory feedback is needed. The motor sequence is an example of movements in intrapersonal space; the fingers of the hand are moved in relation to the thumb. The body reference coordinate system is a self-updating system. The afferents from skin, muscles, tendons, and joints continuously provide the somatosensory areas with information about the relative positions of, and changes in the relative positions of, the moving parts. The movements conducted in intrapersonal space also activate the parietal lobe (primary somatosensory and supplementary sensory areas); the regional cerebral blood flow (r-CBF) increases in the parietal lobe and signifies afferent synaptic activity and intrinsic neuronal activity in these regions (34). Moreover, available evidence shows that there are important circuits between the inferior parietal lobe and the inferior premotor area, which are not simply part of a motor system, but activated by sensory stimuli. The functions of
these circuits are much more complex, consisting of the storing of elementary motor acts (motor schemas) and the retrieving of these acts for interaction with the environment (35). Moreover, what has been shown in our study is an asymmetric organisation of engrams of movement sequences, located in the left parietal areas; it is widely known, in fact, that right parietal lesion led to apraxia only in the contralateral hand (and not bilaterally) in most right-handers (36). Heilman has also proposed that the dominant parietal lobe stores representations of learned skilled movements (known as praxicons) that may be converted into motor programs by anterior premotor regions (especially the SMA) upon verbal command or other external or internal signal (37).

Moreover, the parietal lobe participates in motor control, especially as far as spatial control and the coordinate-transformation system for sensory driven strategies of the eyes, arm and hand are concerned (38,39). As part of the sensory-motor transformation process, signals from many different modalities need to be combined in order to create an abstract representation of space that can be used to guide movements. The posterior parietal cortex combines visual, auditory, eye position, head position, velocity, vestibular and proprioreceptive signals, prior to the performance of spatial motor operations. This way, space can be defined by multiple sensory systems, and movement can be performed within well-defined coordinate frames. Our holistic impression of space may be coded in this abstract representation of space in the posterior parietal cortex, along with the awareness of interior program for the motor act (40). The clinical impression we gained from all the patients examined is that plan execution, which normally derives from internal planning and from the storage of knowledge, is disrupted. They could understand perfectly well what to do and, with the right (non affected) hand, were able to do what was required of them. On the contrary, when performing the task with the left hand, they had to pay much more attention, and even then control through visual input the motor execution. The “vision for perception” solution, in order to achieve a “vision for action” execution (previously suggested by us), was a common, unconscious strategy used by all of them (28).

Ungerleider and Mishkin (41) drew attention to the fact that information on the characteristics of objects are processed by the ventral stream, which conducts visual inputs through a succession of cortical areas (from the occipital lobe and progressing along the temporal lobes) carrying information on “what” things are. More important and definite is the information on the location of objects in space, extracted from visual inputs by cortical areas starting in the occipital lobe and progressing into the parietal zone, supporting information about “where” things are.

In our first study (28), we hypothesised that a single OBGD patient, who demonstrated a disrupted motor sequence, performed badly in a fine movement sequence task mainly as a result of interruption of the neural pathway between parietal and other cortical (SMA) and subcortical regions (mainly the globus pallidus). Now, functional data on five more patients allow us to extend the role of parietal cortex, per se; to a region called the anterior intraparietal area, which lies in the posterior bank of the intraparietal sulcus – in the monkey, neurons have been found to discharge in association with specific types of grasp for the manipulation of objects of different shapes (42) – this area is interconnected with a premotor cortex region, called F5, where neurons have been found to discharge for particular types of fine grasping. F5 is interconnected to the primary motor cortex, therefore providing a potential vision to selected movement pathway (43,44).

Our evidence, obtained during simple and complex learned motor sequences in subjects with right parietal disruption, led to the conclusion that parietal alteration, reducing the interconnections between the SMA, the premotor and the motor areas, disrupts the complex storage, retrieving and effective execution of complex learned movements, while leaving the interior program of movement almost correct. Parietal damage leads not only to motor sequence impairment, but also to a lack of sensory feedback and of spatial perception in the intrapersonal dimension of the motor act; the most evident result being a complex interdiction of movement execution in a so-called cognitive space, such as peripersonal space. Movement can still be obtained in these patients, but only by allowing them to look hard and to focus their attention in order to correct continuously, very slowly, their awkward motor actions. Eliminating these feedback circuits, movements with the affected hand become awkward and clumsy.

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