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Clinical study

Effect of GPi DBS on functional imaging of the brain in dystonia

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Summary Five patients with idiopathic dystonic conditions, treated successfully with deep brain stimulation (DBS) of the globus pallidus internus (GPi), were studied using single-photon emission tomography (SPET) in order to evaluate brain perfusion in the presence and absence of DBS. Comparison was made between the "on" and "off" DBS scans on an individual basis and also as part of a group analysis. Whilst the individual data suggested great regional variation in cerebral perfusion between individuals, the results of the group analysis revealed several topographically similar areas of the brain where relative hyperperfusion in the absence of DBS was common to all patients. Based on these results we postulate on possible mechanisms for this phenomenon.

Keywords: dystonia, deep brain stimulation, SPET, functional imaging

INTRODUCTION

Dystonia is a syndrome in which sustained muscle contractions cause abnormal movements or postures. This is a purely descriptive definition because we have such a limited understanding of the pathophysiology of the condition. Because many of the secondary dystonias have been associated with pathologic abnormalities that include the basal ganglia, it has become accepted that disruption of circuits connecting the basal ganglia, thalamus, and frontal cortex is responsible for idiopathic as well as secondary dystonic conditions. Basic imaging techniques and post-mortem examination, however, have failed to demonstrate consistent anatomical abnormalities in the basal ganglia in idiopathic dystonia.

One of the great difficulties in developing strategies for treatment for these conditions is the lack of sufficient knowledge about the basic neurophysiological mechanisms underlying the pathogenesis of dystonia. This is also hampered by the inadequacy of animal models. However, functional imaging by means of positron emission tomography (PET),[1] functional magnetic resonance imaging (fMRI)[2] and single photon emission computed tomography (SPET)[3] has recently begun to help to elucidate the pathophysiology of dystonic conditions.

Functional imaging provides a means of studying regional cerebral function in humans in vivo, and it has suggested that the clinical manifestations of dystonia relate to abnormalities in cortico-striato-pallido-thalamo-cortical motor networks. Eidelberg et al. demonstrated that idiopathic torsion dystonia (ITD) patients had increased activity in the lentiform nuclei and in primary motor and premotor cortical regions. Studies on resting blood flow and metabolism in dystonia have produced conflicting results,[1] although a pattern of increased activity in specific cerebral regions has been the general finding amongst most dystonic patients investigated with functional imaging techniques.

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For several years, deep brain stimulation (DBS) of the globus pallidus internus (GPi) has been emerging as the favoured intervention for patients with dystonia resistant to medical therapy. However, there have been few studies that have looked at the effect of accepted treatment strategies for dystonia with concurrent functional imaging of the brain.[4,5]

In this article, we present five cases of idiopathic dystonia that have been satisfactorily treated with GPi DBS and subsequently studied by SPET using technetium 99m-hexamethylpropyleneamineoxime (99mTc-HmPAO). We chose to perform SPET studies because unlike for PET and fMRI, the radioactive tracer can be administered during normal activity, so that restraint or sedation during injection is unnecessary. It binds to active areas of the brain which can then be identified by SPET under sedation if necessary. We aimed to assess the ability of SPET to monitor the effect of DBS in dystonic conditions to further elucidate the underlying pathophysiology of dystonia.

METHODOLOGY

Patient selection

Five right-handed patients were recruited for this study. All had undergone successful treatment with bilateral GPi DBS for varying idiopathic dystonic conditions that could not be satisfactorily treated with medical therapy. All were negative for the DYT1 gene. The age of the patients ranged from 39 to 79 years. Table 1 summarises patient demographics and clinical presentation. The patients were assessed clinically by interview and video recording. The Burke, Fahn and Marsden dystonia rating score (BFMDRS) was employed for patients with generalised dystonia, the Toronto spasmodic torticollis rating scale (TWSTRS) for the patient with cervical dystonia and the abnormal involuntary movement scale (AIMS) for the individual with myoclonic dystonia. Assessments were carried out pre-operatively and at most recent follow-up.

Surgical methods

After detailed explanations of the risks and potential benefits of the procedure, written informed consent was obtained from each

Table 1 Clinical and demographic data of patients included in the study

Patient	Gender	Clinical details	Age at onset (years)	Age at operation (years)	Length of follow-up (months)	Pre-operative total rating score	Post-operative total ratings score
#1	F	Generalised dystonia Predominantly right-sided	13	58	15	BFMDRS = 52/150	17.5/150
#2	M	Cevical dystonia	65	79	15	TWSTRS = 56.5/87	31.5/87
#3	M	Generalised dystonia Predominantly right-sided	33	45	18	BFMDRS = 32.5/150	25.5/150
#4	F	Myoclonic dystonia	3	39	15	AIMS = 25/42	10/42
#5	M	Generalised dystonia	38	49	3	BFMDRS = 79/150	49/150

Total values for respective rating scores are displayed. Pre-operative and most recent follow-up scores are included.

patient. Under general anaesthesia, the patients underwent bilateral implantation of Medtronic quadripolar 3387 DBS electrodes into the postero-ventral GPi using Image Fusion™ and Stereoplan™ [6] to localise the targets by fusing the MRI to the stereotactic CT scan.[7] A more detailed explanation of surgical technique employed by our group has been described previously.[8] Having identified the targets, the TM electrode was removed and replaced by a Medtronics 3387 electrode that was then plated to the skull. These were then connected to a subcutaneous programmable pulse generator (Kinetra or Synergy, Dual Channel Itrel, Medtronic Inc., Minneapolis, MN) implanted in the subclavicular tissue. No significant peri-operative complications occurred. Post-operative MRI scan confirmed the electrode positions. All peri-operative CT and MRI scans were noted to be normal.

SPET acquisition and processing

SPET studies were carried out using a triple-head Trionix TRIAD dedicated cerebral gamma camera with ultra-high resolution collimators. The subject was relaxed in a dimly lit room with their eyes closed at the time of intravenous injection of 99mTc-HMPAO (500 MBq; Amersham International, UK) and for several minutes thereafter. Following this each patient was sedated using intravenous midazolam in order to abolish any hyperkinetic movements prior to image acquisition.

Filtered back projection with a Butterworth filter and Parzen attenuation correction were employed, providing 128×128 matrix images. Using a Nuclear Diagnostic (Sweden) Hermes workstation and software, the reconstructed scans were fitted individually onto a standard database template in Talairach coordinates. This was performed by a fully automated, linear nine-parameter (scale, translation and rotation for each x, y and z) fit, initially by a principal axis transformation and then refined by a count difference minimisation algorithm (BRASS, Huddinge template, Nuclear Diagnostic, Sweden).[9] The registration process permits quantification, of both severity and size, of any perfusion differences as well as 'manual' inspection of the original and registered images. All the processing was performed blinded as to whether the DBS was "on" or "off".

Once the studies were in common, standardised brain space, comparison was made between SPET images taken whilst "on" or "off", for each individual patient. In each patient comparison, only regions revealing $\geq$10% change in counts, relative to the corresponding scan were included. Each of these regions was identified in accordance with the named regions within the Huddinge atlas.

All studies were also grouped together according to whether they were "on" or "off". A template was formed for each group using Modelgen software (Nuclear Diagnostics, Sweden). In effect, each template represents the mean SPET scan appearance for that group of subjects (either "on" stimulation or "off") and exploits the power of averaging out "noise". Since these templates are registered to the same coordinates in Talairach space, direct comparisons can be made between "on" and "off" states in all the patients. Any perfusion differences demonstrated do not rely on prior assumptions, since entire brain templates are compared and not just regions of interest.

RESULTS

All patients were investigated by SPET scanning both before and during stimulation of the GPi. It was therefore possible to construct two groups of SPET images, the "on-DBS" group representing the patients in their best clinical state during treatment with DBS, whilst the "off-DBS" group corresponded to the patients in their worst clinical state.

A total of 10 sets of SPET images were acquired (5 "on-DBS" and 5 "off-DBS"). By employing BRASS analysis, the "on-DBS" were compared with the "off-DBS" images for each individual patient by subtracting one image from the other and vice versa. This allowed comparison to be made in both directions in order to look for perfusion defects in the presence or absence of DBS. Thus, areas that decreased their perfusion with stimulation switched on could be identified and, conversely, areas that increased their perfusion during DBS exhibited relative perfusion deficits in the "off-DBS" images.

In the comparisons that follow, only regions revealing $\geqslant$10% change in counts, relative to a common, absolute scale of counts, were included. This value was chosen so as to be clinically useful as well as significant, since a region with a 10% reduction in perfusion can usually be reported confidently on an individual's scan.[10] Only regions of perfusion deficit in excess of 1 ml volume were included in the analysis.

Several regions of decreased cerebral perfusion were revealed in both sets of results for all patients, denoting areas of relative hyper- and hypo-perfusion in the absence of DBS compared with chronic DBS. The percentage of total brain volume demonstrating 10% decreased perfusion was also substantial for each respective patient. Percentage total brain volumes exhibiting perfusion change ranged from 10.1% to 22.9% amongst individuals in the "on-DBS" group and from 11.1% to 26.9% in the "off-DBS" analysis. Employing the Huddinge atlas to co-register regions of interest, the major areas of perfusion change could be identified. The individual patient results indicating regions, together with the total percentage volumes, of brain involved are displayed in Table 2. Because of the great topographic variation in cerebral perfusion changes revealed by the analysis, it was not possible to identify by visual inspection any common areas of interest relating to either the presence or absence of chronic DBS. Neither was it possible to discern with confidence any gross differences between different types of dystonic conditions in the patients studied.

