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Motor activation in patients with Pantothenate-Kinase Associated Neurodegeneration: A functional magnetic resonance imaging study

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ABSTRACT

Background: In a variety of dystonias, functional magnetic resonance imaging has shown deviations of cortical and basal ganglia activations within the motor network, which might cause the movement disturbances. Because these investigations have never been performed in secondary dystonia due to Pantothenate-Kinase Associated Neurodegeneration, we report our results in a small group of such patients from the Dominican Republic.
Methods: Functional magnetic resonance imaging was carried out in 7 patients with a genetically confirmed mutation of the PANK2 gene and a non-affected control group (matched pairs) using an event-related motor activation paradigm (hand movements).
Results: Compared to the control group ($p \leq 0.01$), patients showed a larger amount of activated voxels starting in the contralateral cerebellum and contralateral premotor cortex 2 s before the actual hand movement. Whereas these "hyperactivations" gradually diminished over time, activations in the contralateral primary motor cortex and the supplementary motor area peaked during the next second and those of the contralateral putamen at the time of the actual hand movement. In a multiple regression analysis, all these areas correlated positively with the degree of dystonia of the contralateral arm as judged by the Burke–Fahn–Marsden-scale ($p \leq 0.001$).
Conclusion: As in other forms of dystonia, the increased activations of the motor system found in our patients could be related to the origin of the dystonic movements. Because in this condition the primary lesion affects the pallidum, a defect of the feed-back control mechanism between basal ganglia and cortex might be the responsible factor.

1. Introduction

Patients with the complex syndrome of dystonia form a heterogenic group with respect to the etiology which might be primarily genetic or secondarily acquired, and the clinical appearance corresponds to either a more focal or a more generalized type. Mainly based on imaging studies, a functional network model is discussed [1,2] proposing several patho-physiological mechanisms: a hyperactivation of the motor system due to a reduced feed-back inhibition [3,4], a senso-motor dysbalance [5] and a generalized hyper-plasticity with a reduced capability to maintain homeostasis [6]. In primary torsion dystonia (PTD) which resembles the clinical picture of Pantothenate-Kinase Associated Neurodegeneration (PKAN), the results of structural and functional Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) studies are consistent with the view of PTD as a neuro-developmental circuit disorder involving cortico-striatal-pallido-thalamo-cortical and related cerebellar-thalamo-cortical pathways [7]. Some of these changes are thought to be more related to genetic conditions whereas others could represent adaptive responses. Although PKAN is a secondary dystonia due to a known mutation of the PANK2 gene and a known metabolic defect causing the typical lesion in the internal pallidum [8,9], the patho-physiologic background may not be so different from models of impaired cortico-basal ganglia-cortical pathways in PTD [10]. Whereas the hallmark of PKAN, the lesion and iron accumulation in the Globus pallidus, is well-known as the "eye-of-the-tiger-sign", studies of structural abnormalities of gray and white matter in this condition are rare [11] and to our knowledge, functional fMRI results of cerebral activation have not yet been reported in this condition.

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In the region around the town of Cabral in the southwest of the Dominican Republic, lives a group of more than 20 individuals with PKAN which is unique worldwide because all present the same mutation of the PANK2 gene. All patients are characterized genetically and neurologically including scaling of dystonia. MRI showed the typical signal reduction in the pallidum in all cases and some reduction of frontal white matter tracts [12]. Here, we present the results of a motor activation study of a subgroup of 7 patients which could perform the motor task with fMRI.

2. Patients and methods

2.1. Patients

Having given written informed consent, 8 patients and one preclinical case with a homozygous mutation but without clinical manifestation of dystonia, were included into this prospective study, which had been approved by the local ethics committee. All of them show a specific missense PANK2 gene mutation (c.680A > G, p.Y227C). The patients were selected by their ability to tolerate MR examinations without sedation. However, because scan quality was insufficient in 2 of them, final evaluation had to be confined to 6 patients (3 females and 3 males, mean age 17.7 years) and one preclinical case, an 11 year old boy with a homogeneous mutation and an "eye-of-the-tiger-sign" on MRI, but without clinical symptoms of dystonia. Patients were examined neurologically by an experienced specialist (PRS) who graded their dystonia using the Burke–Fahn–Marsden dystonia scale. Clinically, all patients showed signs of pure dystonia (mean dystonia score of the right arm being 2.5), sometimes with a slight increase of tonus, but no further extrapyramidal signs. As controls, we used a group of 7 gender- and age-matched healthy volunteers (4 females and 3 males, mean age 17.9 years), who were examined and scanned in the same way as the patients. Although we did not perform genetic tests in the control group, we are confident that we did not include gene carriers or further "preclinical" cases because apart from a circumscribed area in the southwest of the Dominican Republic with a rather high mutation rate, the general population (where the volunteers came from) is not specially affected by this rare disease, and all volunteers showed normal imaging findings without accumulation of iron in the pallidum.

2.2. MR examination

MR examinations were carried out on a 3T Achieva scanner (Philips) and included the following sequences:

T2W sequence: TR/TE = 2050/80 ms, 25 transversal slices, thickness 5 mm,

T1W (TFE) sequence: TR/TE = 6.73/3.11 ms, 180 sagittal slices, voxel size 1 mm^3

EPI-GE sequence: TR 2000 ms, 34 slices of 3 mm thickness, gap 0.75 mm, FOV 192 mm, voxel size 2.38 × 2.38 × 3 mm.

2.3. Motor activation paradigm and evaluation

Applying our event-related motor activation paradigm, subjects lying in the scanner were requested to shortly press the pneumatic ball of an acoustic alarm system with their right hand in response to a visual cue in approximate intervals of 15 s. One severely affected patient had to use his less impaired left hand and his fMRI data was flipped, targeting the motor cortex. The induced noise was recorded on a PC sound track and converted into a time line of events. Image preprocessing and statistical analysis were performed with Statistical Parametric Mapping (SPM8, www.fil.ion.ucl.ac.uk/spm) running under Matlab (MathWorks). The preprocessing involved slice timing, realignment, spatial normalization to a standard EPI template and smoothing with an 8 mm Gaussian kernel. Because only 3 of the patients were younger than 18 we decided to use the standard EPI template for the whole group. The recorded time line indicated the "onset" of responses in the SPM matrix at the moment of muscle contraction at the time point of 0 s. By subtraction of 1 and 2 s from this time line, we were able to model the time course of preceding cerebral activations. For data analysis the approach of the general linear model was used, modeling the event "motor response" in a first level matrix for each subject. For every time line (0 s, −1 s, −2 s) a new first level matrix was estimated to prevent correlation of the regressors. Coefficients for all regressors were estimated with the approach of least squares, effects were tested with appropriate linear contrasts of the parameter estimates for the hemodynamic response function regressor, resulting in a *t*-value for each voxel. The main effect of "motor response" from the first level analysis was used in a second level matrix to contrast groups in a paired *t*-test model, and a multiple regression model with the Burke–Fahn–Marsden-scale as predictor, setting the threshold for significance to $p < 0.01$ for group comparison and to $p < 0.001$ for correlation analysis, because in this special case of rare disease we have to deal with small effects in the group analysis for we can only investigate a few subjects. Nevertheless, we also applied family-wise error (FWE) correction, which is implemented in SPM, to correct for multiple comparisons. For setting up the multiple regression model, the correlating Burke–Fahn–Marsden-scale was used as a parametric regressor, implementing different weights of values from imaging data, depending on the single persons severity of dystonia.

3. Results

The individual analysis showed activation of the motor system mainly 2 and 1 s before the actual hand movement which appeared to be more pronounced in the patient group. Group comparison (patients vs. volunteers, Table 1, Fig. 1) showed a maximal difference of activation in the premotor cortex, the primary motor area and the SMA before the hand movement started. This maximum appeared early (−2 s) in the premotor cortex, mainly on the contralateral side, and faded away during the next 2 s before hand movement, there was also additional activation in the contralateral cerebellum. In the contralateral Supplementary Motor Area (SMA) and the primary motor area, the difference between patients and volunteers reached its maximum 1 s later (−1 s), and the putamens showed more activation at the time of the actual hand movements.

All these areas showed a significant ($p \leq 0.001$) activation in a multiple regression analysis, revealing a correlation to the degree of dystonia of the contralateral arm as measured by the

Table 1
Difference of number of activated voxels, patients > volunteers, SPM 2nd level paired *t*-test, and number of voxels correlating to degree of dystonia of right arm, patients and volunteers, SPM 2nd level multiple regression analysis.

Localization	Difference of number of activated voxels, patients > volunteers					Voxels correlating to degree of dystonia of right arm, patients and volunteers				
	Time/No. of activated voxels			*P* value of maximum	Coordinates of maximum	Time/No. of activated voxels			*P* value of maximum	Coordinates of maximum
	−2 s	−1 s	0 s	–	–	−2 s	−1 s	0 s	–	–
SMA right	0	0	0	–	–	0	0	0	–	–
SMA left	30	74	22	0.002	−4/4/60	0	53	225	0.000	−6/4/70
Premotor cortex right	23	22	0	0.002	42/22/36	41	0	0	0.000	30/22/52
Premotor cortex left	473	89	5	0.000	−46/20/38	0	17	0	0.000	−36/4/36
Precentral gyrus right	0	0	0	–	–	0	0	0	–	–
Precentral gyrus left	0	19	10	0.004	−30/−22/62	0	77	41	0.000	−32/−20/60
Parietal lobe right	0	0	0	0.004	54/−62/20	0	0	0	–	–
Parietal lobe left	0	0	0	0.001	−38/−56/20	0	0	0	–	–
Post. cingulum/precuneus R.	0	0	0	–	–	132	36	0	0.000	10/−50/32
Post. cingulum/precuneus L.	0	0	0	–	–	0	4	0	0.000	−10/−42/14
Putamen right	0	0	18	0.005	28/−2/14	0	0	0	–	–
Putamen left	0	0	38	0.002	−26/4/8	0	8	24	0.000	−24/4/8
Cerebellum right	0	0	0	–	–	0	0	0	–	–
Cerebellum left	17	0	0	0.000	−16/−40/−50	18	0	0	0.000	−14/−42/−50