

SHORT REPORT

# Regression of ventral striatum hypometabolism after calcium/calcitriol therapy in paroxysmal kinesigenic choreoathetosis due to idiopathic primary hypoparathyroidism

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**Abstract**

**A [<sup>18</sup>F]-FDG PET study was performed in a 44 year old man with proximal kinesigenic choreoathetosis (PKC) secondary to idiopathic primary hypoparathyroidism (IPH) before and 1 year after calcium/calcitriol therapy. The [<sup>18</sup>F]-FDG PET performed before the start of the therapy disclosed a significant bilateral hypometabolism in the ventral striatum. One year later, with the patient still under calcium/calcitriol therapy and free of any occurrence of PKC episodes, the [<sup>18</sup>F]-FDG PET did not show the previously detected hypometabolism. The hypometabolism of the ventral striatum secondary to hypocalcaemia seems to play a crucial part in the pathogenesis of paroxysmal kinesigenic choreoathetosis associated with IPH.**

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Paroxysmal kinesigenic choreoathetosis (PKC) is a rare disorder characterised by brief attacks of any combination of dystonic postures, chorea, athetosis, and ballism, precipitated by sudden movement or a startle. In most cases PKC occurs as sporadic or familiar disease of unknown aetiology.<sup>1</sup> Less commonly PKC occurs in association with multiple sclerosis,<sup>2</sup> head injury,<sup>3</sup> thalamic infarcts,<sup>4</sup> progressive supranuclear palsy,<sup>5</sup> hyperthyroidism,<sup>6</sup> diabetes mellitus,<sup>7</sup> hypoglycaemia,<sup>8</sup> and, rarely, with idiopathic primary hypoparathyroidism (IPH).<sup>9-12</sup>

In IPH, neuropsychiatric and neurological manifestations are common, and include emotional instability, anxiety, depression, confusional states, delusions, hallucinations, dementia, epileptic seizures, paraesthesias, and muscle cramps. Less often, cerebellar ataxia, dysarthria, parkinsonism, torticollis, oculogyric spasms, chorea and athetosis have also been found, whereas only four cases of PKC have been reported so far, all occurring in adolescent patients.<sup>9-12</sup>

In the present report we describe a case of PKC secondary to IPH occurring in adulthood, and provide [<sup>18</sup>F]-FDG positron emission tomography (PET) evidence regarding the possible anatomofunctional correlates underlying such a neurological disorder.

**Case report**

A 44 year old man was admitted to the Department of Neurology of the Istituto San Raffaele because he had had 2 years of repeated spells of involuntary movements characterised by dystonic postures starting from his right foot and then involving the ipsilateral leg, arm, and face, without any alteration of consciousness. Spells were characterised by leg hyperextension, arm flexion, and face grimacing. The episodes were sudden, of brief duration (10 to 20 seconds), and triggered by movements such as standing up, starting to run or walking rapidly, particularly after prolonged sitting. The frequency of these spells was initially low (one attack/week) and then gradually increased to 10 episodes/day. Sometimes the patient reported sensations of paraesthesias, a feeling of stiffness or a tense feeling at the beginning of the paroxysms. Some attacks were aborted by stopping movement or slowly warming up.

On admission, general and neurological examinations were normal. Routine laboratory tests were normal except for decreased serum

Table 1 Stereotactic coordinates related to the regions of reduced metabolism in the basal ganglia

Right ventral basal ganglia			
x	y	z	Z
10	6	-16	3.8
20	10	-16	3.5
26	14	-4	3.1
18	4	4	2.5
Left ventral basal ganglia			
x	y	z	Z
-20	4	-12	3.5
-10	2	-16	3.3
-22	-6	-8	3.1
-10	4	-4	3.0

x, y, z=stereotactic coordinates in the Tailarach and Tournoux atlas and Z scores according to the SPM-96 procedures (see methods).

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Table 2 Quantitative measurement of local cerebral glucose consumption (mg/100 g/min)

	1st PET study	2nd PET study	Normal values (SD)
Right dorsal basal ganglia:			
Caudate nucleus	6.5	6.8	7.6 (1.0)
Putamen	8.3	7.8	8.7 (1.2)
Left dorsal basal ganglia:			
Caudate nucleus	6.3	6.3	7.4 (0.9)
Putamen	7.1	7.6	8.6 (1.1)
Right ventral basal ganglia	5.3*	7.5	7.3 (1.0)
Left ventral basal ganglia	5.0*	7.0	7.6 (0.8)

\*Glucose metabolic values below 2 SD of normal values.

total and ionised calcium concentrations (1.30 mmol/l, normal value 2.10–2.60; 0.69 mmol/l, normal value 1.18–1.30, respectively) and increased serum phosphate concentrations (1.60 mmol/l, normal value 0.8–1.5). Plasma parathyroid hormone (PTH) concentrations were not detectable. Echography of the neck was normal. Brain MRI showed low signal T2 weighted images and hyperintense signal T1

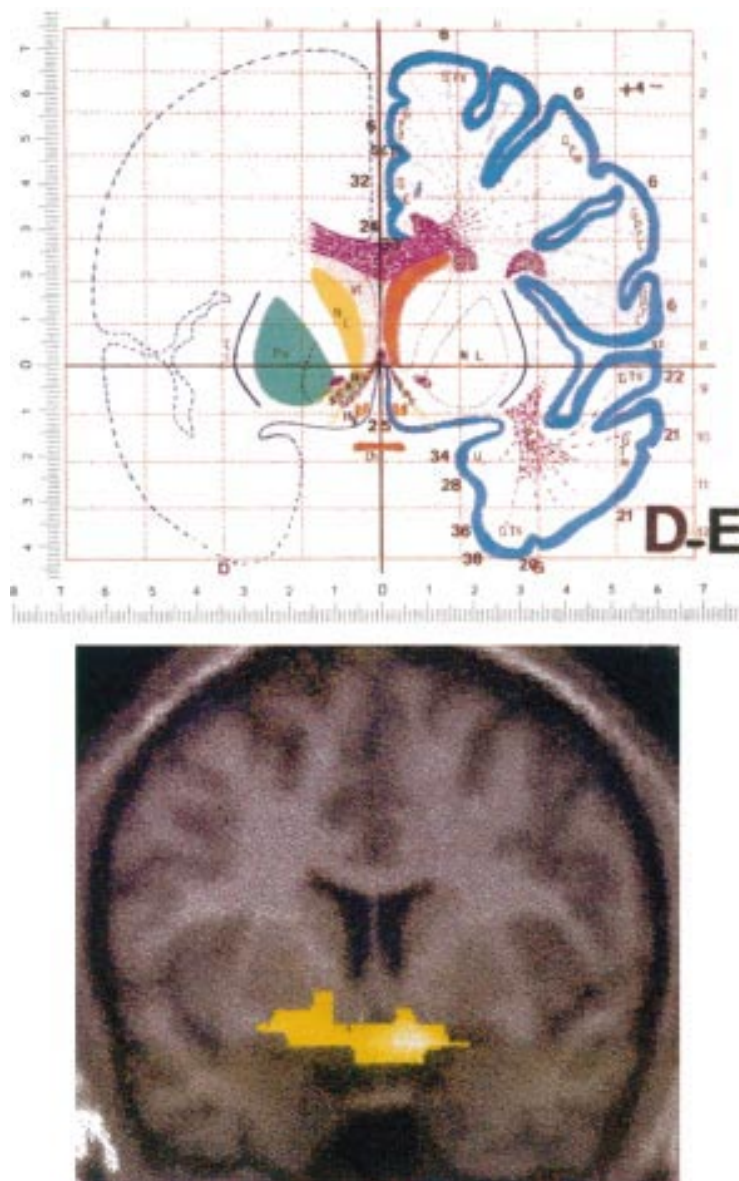


Figure 1 Bottom: three dimensional SPM brain rendering with superimposed regions of significant hypometabolism according to a colour scale ( $p < 0.01$ ,  $Z: 2.33$ ). Top: the corresponding coronal slice of the atlas of Talarach and Tournoux.<sup>14</sup>

weighted images in bilateral basal ganglia, thalamic and dentate nuclei, and cerebral white matter, suggesting calcium deposits. Repeated EEG examinations, including two 24 hour recordings, failed to show electrical abnormalities even during bursts of involuntary movement. A diagnosis of PKC secondary to IPH was made. A quantitative [ $^{18}\text{F}$ ]-FDG PET study was performed and the methods and the results are reported below.

## Methods

### [ $^{18}\text{F}$ ]-FDG PET METHOD AND DATA ANALYSIS

The patient was studied by 2- [ $^{18}\text{F}$ ]-fluoro-2-deoxy-D-glucose ([ $^{18}\text{F}$ ]-FDG) PET in a resting state. The PET studies were performed on a three dimensional GE-Advance (General Electric Medical System, Milwaukee, WI, USA). The system allows 35 transaxial images with a slice thickness of 4.25 mm covering an axial field of view of 15.2 cm. Transmission data were acquired using a pair of rotating pin sources filled with  $^{68}\text{Ge}$  (10 mCi/pin). Image reconstruction was performed with a filtered back projection algorithm on a  $128 \times 128$  matrix with a pixel size of 1.9 mm, using a Hanning filter (cut off 4 mm filter width) in the transaxial plane, and a Ramp filter (cut off 8.5 mm) in the axial direction. The acquisition protocol consisted of blank and transmission scans for attenuation correction, tracer injection followed by rapid arterial blood sampling to obtain the arterial input function, and an emission scan in the steady state condition 45 minutes after the injection. Regional cerebral glucose metabolism (rCMRglc) was measured by recording the distribution of radioactivity after an intravenous bolus injection of 250–300 Mbq 2- [ $^{18}\text{F}$ ]-FDG, through a forearm cannula. Values of rCMRglc were calculated according to Reivich *et al.*<sup>13</sup>

Reconstructed images of quantitative [ $^{18}\text{F}$ ]-FDG values were transferred to a SUN (SPARC) workstation for image processing. The data were analyzed with Statistical Parametric Mapping 1996 (using software from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab version 4.2 (Mathworks Inc, Sherborn MA, USA). PET images were first transformed into a standard stereotactic space.<sup>14 15</sup> To increase the signal to noise ratio and accommodate normal variability in functional gyral anatomy each image was smoothed with a low pass gaussian filter (FMWN=20 $\times$ 20 $\times$ 12 mm). After specifying the appropriate design matrix, group, subject, the condition, and covariate effects were estimated according to the general linear model at each and every voxel.<sup>16</sup> To test hypotheses about regionally specific effects, the estimates were compared using linear contrasts and the resulting set of voxel values for each contrast constitute a statistical parametric map of the  $t$  statistic SPM  $\{t\}$ .

To evaluate functional metabolic changes in the patient, his regional cerebral glucose metabolism was compared with regional cerebral glucose metabolism of an age matched control group (n=18). The SPM  $\{t\}$  were transformed to the unit normal distribution

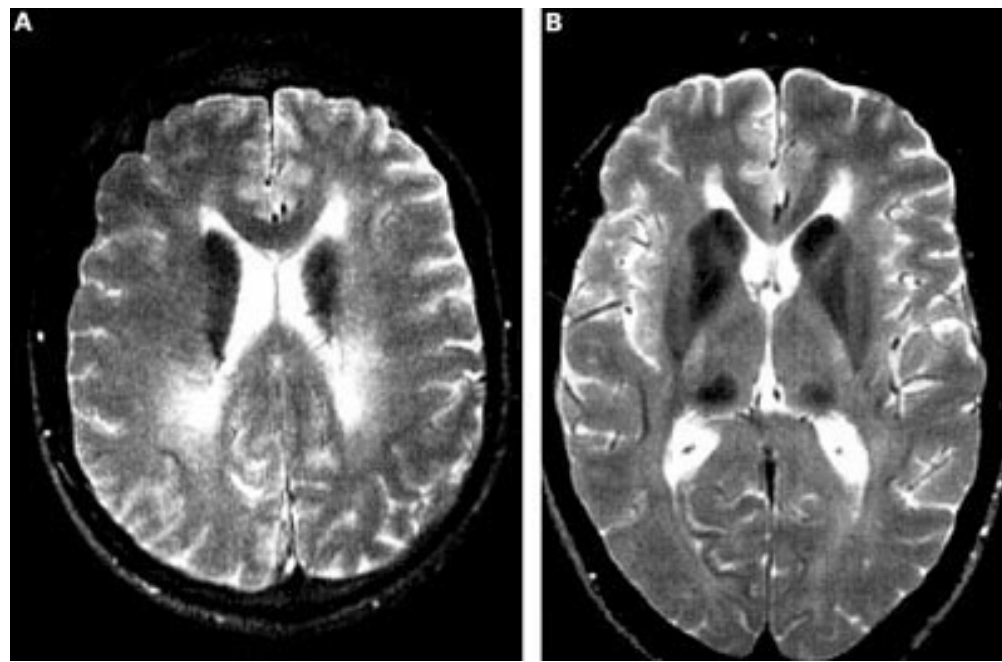


Figure 2 Superimposable MRI images before (1A) and 1 year after (1B) therapy, showing no changes of calcifications in bilateral basal ganglia, thalamic and dentate nuclei, and cerebral white matter.

(SPM (z)) and thresholded at 2.33 (or  $p=0.01$ ). The resulting differences were then characterised in terms of spatial extent and peak height of reduced or increased rCMRglc. The significance of each region was estimated using distributional approximations from the theory of gaussian fields (see Signorini *et al*<sup>17</sup> for details). In addition, quantitative data were obtained using circular regions of interest with a diameter corresponding to 1.5 FWHM (9.6 mm), manually drawn on the basal ganglia both in the patient and normal controls (see table 2).

### Results

At the first [<sup>18</sup>F]-FDG PET examination, under conditions of overt hypoparathyroidism, the patient showed a significant bilateral hypometabolism in the ventral striatum—namely, the inferior component of the caudate nucleus and the putamen. This was shown by the SPM procedures (table 1 and fig 1), as well as in comparison with normative values using ROIs (table 2). Indeed, quantitative measurements of glucose consumption in the ventral striatum showed a reduction below 2 SD of normal values before, and a recovery after treatment. The SPM map showed a hypofunction extended to the left striatum.

Oral calcitriol (0.25 mg three times daily) and calcium supplementation (1 g/day) therapy was then started. Progressive disappearance of the motor attacks was seen concomitantly with normalisation of serum calcium concentrations, and the patient was able to resume his working activity. One year later, the patient was readmitted to the Department of Neurology of the Istituto San Raffaele for clinical and instrumental re-evaluations. Under conditions of normal serum total and ionised calcium concentrations (2.30 and 1.25 mmol/l, respectively) he was free of any occurrence of

episodes of PKC. A brain MRI was superimposable on the previous one (fig 2, A and B). Specifically, calcifications in the dorsal basal ganglia and in the dentate nuclei were still evident, and unmodified in size. On the other hand, ROI measurements of glucose consumption showed values within the normal range in the dorsal basal ganglia and the SPM analysis did not show any difference between patient and controls in this region.

### Discussion

Paroxysmal dyskinesias are a heterogeneous group of disorders characterised by involuntary movements in bursts with return to normality within variable periods. There are two forms of paroxysmal dyskinesias: prolonged attacks lasting for more than 5 minutes (paroxysmal dystonia) and brief attacks precipitated by movement, lasting less than 5 minutes (PKC). Both can be familial or sporadic, and the second may be primary or secondary. Among the secondary forms of PKC, four patients have been described in association with IPH. All the affected patients previously reported on were young, had the typical picture of hypoparathyroidism (hypocalcaemia, basal ganglia calcifications), and showed remission of dyskinesias after calcium/calcitriol supplementation therapy. The patient of the present report, who developed his symptoms at the age of 42, represents, therefore, the fifth case of PKC associated with IPH described so far, and the first showing onset of the disease in adulthood. Furthermore, the instrumental examinations performed on our patient allowed new insight into the mechanisms underlying the development of PKC in IPH. Different hypotheses have been proposed in the past. One emphasised the role of calcium deposits in the basal ganglia and of their consequent dysfunction.

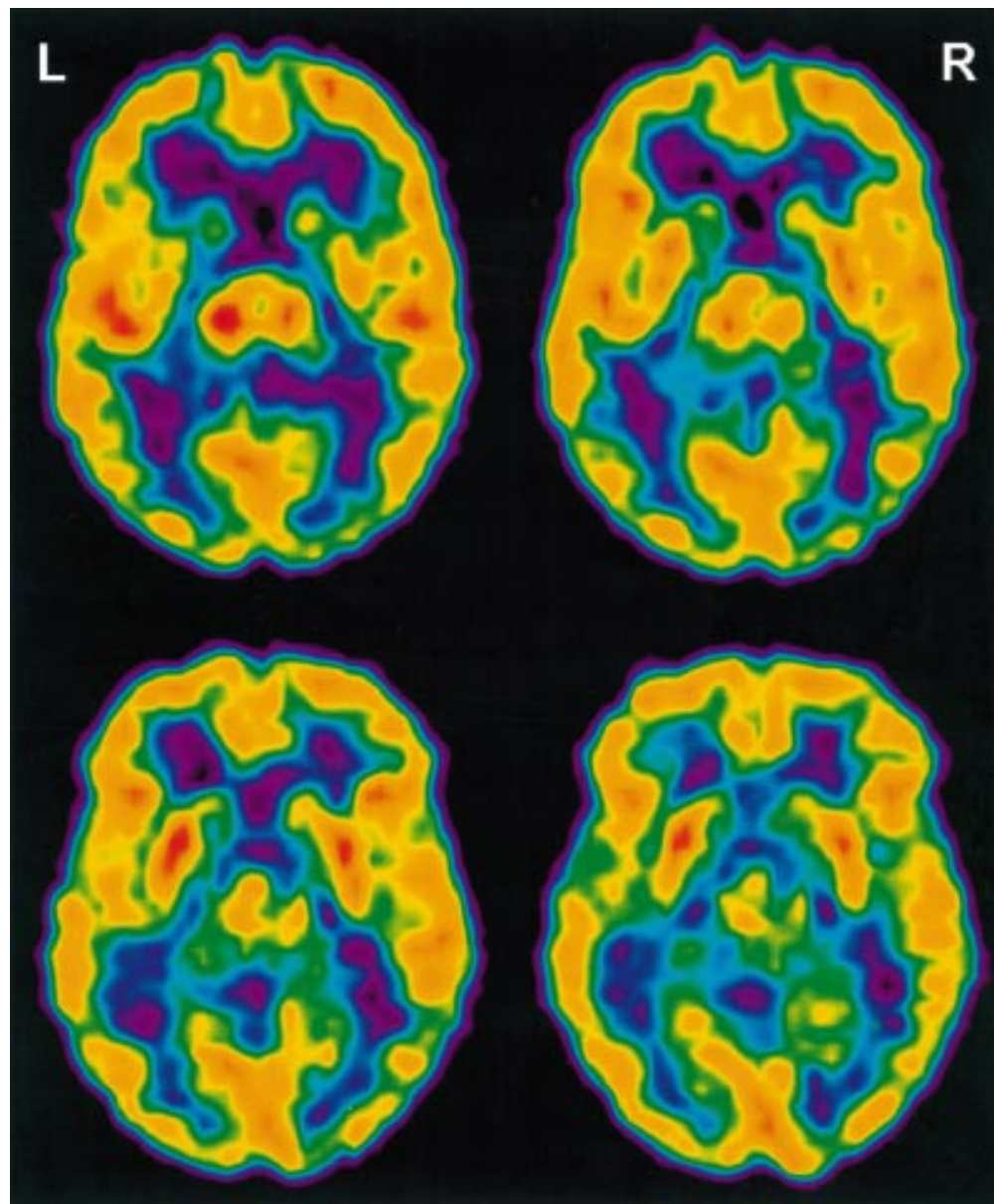


Figure 3 Comparable axial slices of the first and second [ $^{18}$ F]-FDG PET study showing normal glucose metabolism at the level of the dorsal striatum (see text for comments).

Another considered PKC a sort of “reflex epilepsy”, based on the sporadic finding of EEG abnormalities and on the efficacy of anticonvulsant drugs in reducing the frequency of the episodes. The data of the present study seem to rule out the epileptic nature of the PKC, as the repeated EEG recordings performed, also during clinical attacks, failed to show any abnormalities. Our findings rather suggest that an impaired function of the basal ganglia plays a crucial part in the pathogenesis of PKC associated with IPH. A significant hypometabolism of the ventral putamen and inferior caudate was found with [ $^{18}$ F]-FDG PET. Furthermore, normal metabolism of the basal ganglia, together with disappearance of the clinical symptoms were found after calcium/calcitriol therapy, suggesting that hypocalcaemia, and not calcium deposits (that were still present 1 year after the start of the therapy), are responsible for the altered function of the basal

ganglia found with [ $^{18}$ F]-FDG PET. Noteworthy, the calcifications shown by the MRI in the dorsal striatum seem not to affect glucose metabolism as indicated by the ROI quantitative values and SPM analysis (table 2 and fig 3). In addition, the patient never had parkinsonism or related neurological signs. It is possible that calcium deposits are confined to the pericellular space with no effect on neuronal viability.

The [ $^{18}$ F]-FDG PET data also suggest that hypocalcaemia leads to PKC by determining neural hypofunction; this is by contrast with what was previously hypothesised by some authors,<sup>18</sup> who considered PKC the consequence of a neural hyperexcitability due to an increased membrane permeability. Of note is that the reduction of glucose metabolism in the striatum has also been reported in other movement disorders, such as different types of dystonias.<sup>19</sup> Furthermore, previous reports by Janavs *et al*<sup>20</sup> suggest an impairment of the

indirect pathway of the thalamocorticobasal ganglionic circuitry as the cause of the choreic phenomena. Indeed, the hypofunction of the indirect pathway from the striatum to the internal globus pallidus may lead to inappropriate disinhibition of thalamic projections to the premotor and motor cortex.

In conclusion, our data provide experimental evidence for the possible anatomofunctional correlates underlying PKC associated with IPH, and provide a basis for further studies to fully elucidate the neural networks involved in such a neurological disorder.

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