Structural and perfusion arterial spin labeling brain MR imaging in Paroxysmal Kinesigenic Dyskinesia (PKD) patients versus controls

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**Purpose**

*Paroxysmal kinesigenic dyskinesia*

Paroxysmal kinesigenic dyskinesia (PKD) is a rare hyperkinetic movement disorder of unknown origin. It was first described by Kertesz in 1967. [1] Patients experience dystonic, choreatic, ballistic, and choreoathetotic movements immediately after the initiation of a movement, hence the name of the disease.[2-4]

*There are three main types of paroxysmal dyskinesias (PDs)* [2, 5-7]:

1. Paroxysmal kinesigenic dyskinesia (PKD)
2. Paroxysmal non-kinesigenic dyskinesia (PNKD)
3. Paroxysmal exertion-induced dyskinesia (PED)

PKD is the most common of the three, with an estimated prevalence of 1:15.000 - 150.000.[6, 8]

*A set of diagnostic criteria have been set up by Bruno* [9]:

- An identified kinesigenic trigger for the attacks
- Short duration of attacks (<1 minute)
- No loss of consciousness or pain during attacks
- Age of onset between 1 and 20 years (if no family history)
- Normal interictal neurological examination
- Exclusion of secondary causes
- Control of attacks with carbamazepine or phenytoin

The age of onset of the disease is usually during childhood or adolescence. However, symptoms generally disappear, usually in early adulthood.

PKD-affected patients often have family members with other paroxysmal disorders or have additional paroxysmal disorders themselves. In our patient group, some patients (and their family members) also suffered from benign febrile infantile convulsions (BFIC), migraine and writer's cramp.

*Pathogenesis*
Most functional imaging studies regarding PKD, show abnormal activation patterns in either thalamus\textsuperscript{[10, 11]} or basal ganglia\textsuperscript{[12-18]}. According to some studies, the disturbances found in the basal ganglia and thalamus may be the result of a faulty feedback loop system that leads to disinhibition of movements. Other authors believe PKD to be a form of reflex epilepsy, originating from deep inside the brain\textsuperscript{[19-21]}

Several loci for PKD have been found on chromosome 16.\textsuperscript{[22]} EKD1 and EKD2 have been found and the existence of EKD3 has been postulated.\textsuperscript{[22-25]} Recently, a gene was isolated by Wang et al.\textsuperscript{[26]}, PRRT2 (proline-rich transmembrane protein 2) and more research is currently being done to find out how a mutation in PRRT2 leads to the PKD symptomatology.

**Study purpose**

To assess structural and perfusion brain changes in patients with PKD compared with healthy age- and gender-matched controls. This is done with T1-weighted and Proton Density (PD)-weighted MRI scans, and Arterial Spin Labeling MR perfusion imaging respectively.

**Methods and Materials**

**Patients**

Nine patients (\textit{Table 1}) diagnosed with PKD were recruited from the Department of Clinical Genetics, Erasmus MC, Rotterdam (NL). Three patients were still symptomatic at the time of scanning. In addition nine age- and gender-matched controls were recruited from the general population.

**Materials**

Scanning was performed on a 3T MR system (MR Discovery 750, GE Healthcare, Milwaukee, WI, US). All patients and controls underwent a full protocol including structural T1- and PD-weighted scans, as well as Arterial Spin Labeling (ASL) MR perfusion imaging.
• The T1-weighted scan was a sagittal 3D inversion recovery (IR) fast spoiled gradient recalled echo (FSPGR) scan with TR 8.14ms, TE 3.192ms, TI 450ms, flip angle 12°, slice thickness 1mm without interslice gap, and matrix size 256x224, FOV 24x24 cm².
• The PD-weighted images were obtained axially in 2D, focused on the basal ganglia and thalami, with TR 6283ms, TE 10.952ms, TI 0, flip angle 90°, slice thickness 1.2mm without interslice gap, and matrix size 256x224, FOV 16x16 cm².
• The ASL images were obtained axially using a spiral 3D pseudocontinuous labeling sequence with TR 4632ms, TE 10.536ms, flip angle 111°, inversion delay 1525ms, slice thickness 4mm, matrix size 128x128, 3.75mm² in-plane resolution.

**Image analysis**

Whole brain voxel-based morphometry (VBM) was performed on both T1- and PD-weighted scans with Statistical Parametric Mapping software (SPM8, Wellcome department, London, UK). Thalami were manually outlined on the PD-weighted scans in MRICron[27] (Figure 1), by a researcher blinded for patient/control information.

Cerebral Blood Flow (CBF) maps from the ASL scans were calculated in Functool (GE Healthcare, US) (Figure 2) and a Region of Interest (ROI) analysis was performed on grey matter only (Figure 3), with SPM8 and MarsBar (Marseilles, FR).

With SPM8 the CBF and T1-weighted images were co-registered and the T1-weighted image was segmented into grey matter, white matter, and cerebrospinal fluid. The grey matter image created with the segmentation was then normalized, as was the CBF image, using the same dimensions (voxel size 1x-1x-1 mm³). With the ImCalc function in SPM8 the normalized grey matter images were thresholded at a probability of threshold of 0.5 and multiplied by the normalized CBF images. The resulting CBF maps of grey matter only were imported in MarsBar to create regions of interest (ROIs). The largest ROI contained all grey matter of the supratentorial brain. This ROI was then combined with the ROI templates from MarsBaR (i.e. basal ganglia, thalamus, temporal, parietal, and frontal cortices). The CBF values from each ROI were then extracted.

**Images for this section:**
Table 1: Study population 1) Patient 2 had migraine attacks in the same time period as the PKD attacks. He also appears to suffer from a form of writer's cramp, which started 5 years ago. 2) Patient 3 also suffers from writer's cramp 3) Patient 4 also suffers from benign febrile infantile convulsions 4) Patient 7 also suffers from unspecified cramps.

Fig. 1: a) PD-weighted image as depicted in grayscale in MRIcron; b) bluegray image with manually outlined thalami.
Fig. 2: Cerebral Blood Flow (CBF) map, extracted from an Arterial Spin Labeling (ASL) scan with Functool, superimposed onto a T2-weighted image of the same subject.
Fig. 3: Whole brain grey matter Region of Interest (ROI) of a T1-weighted scan co-registered with a normalized CBF map (created in MarsBaR), in a) coronal, b) sagittal, and c) horizontal plane. Images are depicted in SPM Display.
Results

Structural analysis

No significant differences between patients and controls were found in grey matter volume with the whole brain VBM analysis of T1-weighted and PD-weighted images.

There was no significant difference (p=0.410) in mean thalamic volume between patients (11.1 mL) and controls (11.8 mL). When only symptomatic patients considered, also no significant difference was found (p=0.876) between the three symptomatic patients (12.3 mL) and their matched controls (12.7 mL).

Perfusion analysis

For analysis of the perfusion maps, CBF data from one pair (symptomatic patients and his age-matched control) was excluded due to poor quality.

When comparing all eight patients and controls a significant decrease in CBF was found (p_{uncorr} = 0.50) in the right superior frontal cortex (Table 2 and Figure 4). Mean CBF in this region was 36.6 mL/100g/min in patients and of 44.0 mL/100g/min in controls.

When only the two symptomatic patients were considered, a significant increase in CBF was found (p_{uncorr} = 0.047) in the right inferior parietal lobule (Table 3 and Figure 5) compared with their matched controls. Mean CBF in this region was 47.8 mL/100g/min in patients and 44.3 mL/100g/min in controls.

No differences in perfusion were found in basal ganglia and other cortical areas.

Images for this section:
Table 2: Mean CBF values of the right superior frontal gyrus of the 8 patients and their matched controls. Patients are depicted in the same order as in Table 1. The mean CBF in patients is significantly lower than that of controls (puncorr = 0.050).

<table>
<thead>
<tr>
<th>Patients</th>
<th>CBF (mL/100g/min)</th>
<th>Controls</th>
<th>CBF (mL/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>25.8228</td>
<td>C1</td>
<td>41.2889</td>
</tr>
<tr>
<td>P2</td>
<td>29.6063</td>
<td>C2</td>
<td>36.3923</td>
</tr>
<tr>
<td>P3</td>
<td>36.1256</td>
<td>C3</td>
<td>36.7953</td>
</tr>
<tr>
<td>P4</td>
<td>35.7392</td>
<td>C4</td>
<td>46.3167</td>
</tr>
<tr>
<td>P5</td>
<td>26.2738</td>
<td>C5</td>
<td>48.7734</td>
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<td>C6</td>
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<tr>
<td>P7</td>
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<td>C7</td>
<td>46.4581</td>
</tr>
<tr>
<td>P8</td>
<td>45.7440</td>
<td>C8</td>
<td>46.8667</td>
</tr>
<tr>
<td>Mean</td>
<td>36.6290</td>
<td>Mean</td>
<td>44.0191</td>
</tr>
</tbody>
</table>

Fig. 4: Right superior frontal gyrus in a) coronal, b) sagittal, and c) horizontal plane. The images are in neurological convention. Images are depicted in SPM Display.

Table 3: Mean CBF values of the right inferior parietal lobule of the 2 symptomatic patients and their matched controls. Patients are depicted in the same order as in Table 1. The mean CBF in patients is significantly higher than that of controls (puncorr = 0.047).

<table>
<thead>
<tr>
<th>Patients</th>
<th>CBF (mL/100g/min)</th>
<th>Controls</th>
<th>CBF (mL/100g/min)</th>
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<td>C6</td>
<td>46.1706</td>
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<tr>
<td>P7</td>
<td>45.6488</td>
<td>C7</td>
<td>42.4019</td>
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<tr>
<td>Mean</td>
<td>47.7939</td>
<td>Mean</td>
<td>44.2863</td>
</tr>
</tbody>
</table>
Fig. 5: Right inferior parietal lobule. in a) coronal, b) sagittal, and c) horizontal plane. The images are in neurological convention. Images are depicted in SPM Display.
Conclusion

- PKD affected patients show no difference in grey matter and thalamic volume compared to healthy age- and gender-matched controls.

- Small differences in CBF found in the right superior frontal gyrus (symptomatic and asymptomatic patients) and the right inferior parietal lobule (symptomatic patients only) seem insufficient to explain the symptomatology of involuntary hyperkinetic movements in PKD patients.

- Brain areas other than those previously reported, namely the thalamus and basal ganglia, are likely to be involved in PKD, and may be explored further with functional MRI and diffusion tensor imaging (DTI).

References


8. Spacey, S., P. Adams, and Editors, GeneReviews [internet]: Familial proxysmal kinesigenic dyskinesia. Copyright (C) 1993-2011, University of Washington, Seattle. All rights reserved.


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