Dopamine Transporter Positron Emission Tomography in Spinocerebellar Ataxias Type 1, 2, 3, and 6

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Background: The spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominant ataxias: some mutations, including SCA1, SCA2, and SCA3, are multisystemic disorders characterized by a variety of noncerebellar symptoms while others, like SCA6, give rise to a pure cerebellar syndrome.

Objective: To identify impairments of the dopaminergic system and regional changes of glucose metabolism in SCA1, SCA2, SCA3, and SCA6.


Results: The binding potential of [11C]d-threo- methylphenidate was reduced in the striatum in SCA2 and SCA3; in contrast to patients with Parkinson disease, no increased susceptibility of the putamen was evident. Decreased regional cerebral glucose metabolism was found in the cerebellum of all patients with SCA, the brainstem of SCA1, SCA2, SCA3, the thalamus and putamen of SCA3, and the parietal cortex of patients with SCA2. A trend toward increased regional cerebral glucose metabolism was found in the temporal cortex of all patients with SCA, pronounced in SCA6.

Conclusions: Specific biochemical patterns point to different mechanisms of neuronal dysfunction in SCA1, SCA2, SCA3, and SCA6; dopamine terminal loss is severe in SCA2 but distinct from Parkinson disease.

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Ataxia Rating Scale. All patients were ambulant with only minor functional disabilities (Table 1). None of the patients with SCA had overt parkinsonian signs, ie, rest tremor or rigidity. The condition of patients with PD were diagnosed according to the Parkinson’s Disease Society (London, England) brain bank criteria and received the last dopaminergic medication the night before the PET scans. The study was approved by the local ethics committee and all subjects gave informed consent.

PATIENTS

We studied 21 patients with SCA1, SCA2, SCA3, and SCA6; 10 patients with PD in Hoehn and Yahr stage II (Unified Park-

inson’s Disease Rating Scale III: mean ±SD, 23 ±10), and 10 healthy volunteers without any overt neurological or psy-

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RADIOCHEMISTRY

To synthesize [11C]dMP, the free acid of N-protected d-threo-
methylphenidate was alkalized using [11C]methyliodide. High

specific activity [11C]methyliodide was prepared in an auto-

mated module (PETtrace M6 Microlab; General Electric Medi-

cal Systems, Uppsala, Sweden). The radio labeling was per-

formed in a PET tracer synthesizer for [11C]methylations (Nu-

clearInterface, Münster, Germany). After purification and

formulation, the product was obtained in 45% to 65% radio-

chemical yield with specific activities of 30 to 50 GBq/µmol at

the end of synthesis (60 minutes). Chemical and radiochemi-

cal purities of the final formulated radiotracer were greater than

95% as determined by high-performance liquid chromatogra-

phy; [18F]FDG was prepared in a PET trace FDG Microlab (Gen-

eral Electric Medical Systems).

PET ACQUISITION AND IMAGE RECONSTRUCTION

The patient’s head was fixed in an elastic mold with 3 markers

for correction of head movements. After automated intrave-
nous bolus injection (12 seconds) of 700 MBq [11C]dMP or 400

MBq [18F]FDG, respectively, dynamic data were acquired from

0 to 60 minutes. Post injection, in 2-dimensional mode with a

full-ring PET scanner (GE Advance; General Electrics Medi-

cal System, Milwaukee, Wis), followed by a transmission scan

with 500,000 kilo counts for attenuation correction. Attenua-

tion corrected images were reconstructed with filtered back pro-

jection (128 × 128 pixels corresponding to 30 × 30 cm, Han-

ning filter with a 4.6-mm cutoff). Statistical parametric mapping

(SPM) software (SPM 99; Wellcome Department of Cognitive

Neurology, London, England) was used for realignment and

spatial normalization by comparing summation images 0 to 5

minutes postinjection with the standard SPM perfusion tem-

plate. For [11C]dMP, normalization parameters were esti-

mated from early summation images 0 to 5 minutes postinjec-

tion. Normalized images were calculated with standard SPM99

settings including 4 × 5 × 4 basis functions and with affine

transformation only for region of interest (ROI) analysis.

QUANTIFICATION OF dMP AND FDG BINDING

Binding of [11C]dMP and FDG were analyzed by a standard-

ized ROI technique. Additionally, group differences of

SCA3, SCA6, and control subjects were assessed on a voxel

basis (SPM99 perfusion template, 12-mm smooth mask: iso-

contour 65% of maximum in SPM template; threshold:
P < .001 uncorrected, t > 3.93). The ROI template consists of

31 three-dimensional regions defined in stereotactic stan-

dard space, including 2 striatal regions with small vol-

umes (eg, dorsal putamen 2 × 0.67 mL). For this study, we

analyzed cerebellum, brainstem, thalamus, putamen, cauda-

ture, nucleus, parietal, and temporal cortex. The position of all

ROIs was compared with the early summation images of each

patient and adjusted manually. Dopamine transporter availability (dMP binding potential, BPdMP) in the 2 striatal

regions of interest was calculated with Logan’s graphical

analysis and the occipital cortex as a reference region. The

washout from the occipital cortex (k, ′) was assumed to be

0.05 per minute and 18 to 60 minutes postinjection was

chosen as the interval for linear regression. Binding potential

for dMP was calculated from (slope−1), aiming at quantifi-

cation of binding potential = k3/k4=(f2

BMax)/KD with k3 and

k4 being transfer rate constants in the 2-tissue compartment

model, k 2

left−right

right/[specific binding]mean left +

right]relative to the more affected side; specific

<table>
<thead>
<tr>
<th>Table 1. Patient Data*</th>
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<tr>
<td><strong>Age, y</strong></td>
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</tr>
<tr>
<td>SCA1 (n = 5)</td>
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<tr>
<td>SCA2 (n = 4)</td>
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<tr>
<td>SCA3 (n = 6)</td>
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<tr>
<td>SCA6 (n = 6)</td>
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<td>PD (n = 10)</td>
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<td>Control (n = 10)</td>
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‡Ataxia score: mean (± SD) of sums of subscores for ataxia of stance and gait, kinetic functions (finger-to-nose and knee-tibia test), speech, and oculomotor disturbances.
†Using the International Cooperative Ataxia Rating Scale.
*Abbreviations: PD, Parkinson disease; SCA, spinocerebellar ataxia.
binding putamen–caudate/[specific binding][mean putamen + caudate] were calculated and assessed with 2-tailed unpaired t tests.

The index of regional cerebral metabolic rates of glucose (rCMRglu) was calculated as the ratio of the average [18F]FDG concentration 42 to 54 minutes postinjection over the average concentration in a modified whole-brain mask created from a standard whole-brain mask by manually excluding the cerebellum, brainstem, diencephalon, and striatum. Voxel-wise group differences were calculated as percentage change of the index of rCMRglu. Areas with average FDG concentrations below threshold, eg, white matter, were excluded and a gaussian smoothing filter (12 mm) was applied.

**STATISTICS**

Statistical analysis of the ROI data was performed using analysis of variance and post hoc Tukey tests for group comparisons and multiple testing, and 2-tailed paired t tests for intraindividual asymmetries (JMP501; SAS Institute Inc, Cary, NC).

### RESULTS

#### [11C]D-THREO-METHYLPHENIDATE

Striatal [11C]dMP binding potential (BPdMP) was markedly reduced in SCA2, SCA3, and patients with PD (P<.01), but no significant changes were found in SCA1 and SCA6 (**Figure 1**).

Putamen and caudate nucleus displayed the same degree of BPdMP decrease in SCA2 (57% and 55%) and SCA3 (29% and 20%), whereas a more severe loss of BPdMP was evident in PD putamen (69% vs 46%; asymmetry index [mean±SD], 44±17 vs 10±7 in SCA2, 15±11 in SCA3, and 14±11 in control, P<.001). Similarly, a pronounced side-to-side asymmetry was found in the more affected vs less affected putamen in PD (asymmetry index, 38±23 vs 5±5 in control, P<.001), but not in either SCA.

No correlation was found between striatal BPdMP and repeat length in SCA2 or SCA3, although it must be noted that the patients studied had repeat lengths in very narrow ranges (42±3 and 72±5, respectively). Also, no significant correlation between striatal BPdMP and age or (apparent) disease duration was observed in SCA2 and SCA3.

#### [18F]FLUORODEOXYGLUCOSE

Reduced rCMRglu was found in the cerebellum of all patients with SCA, the brainstem of SCA1, SCA2, SCA3, and the thalamus of patients with SCA3 (**Table 2**). Patients with SCA2 and PD displayed reduced rCMRglu in the parietal cortex. A trend toward reduced rCMRglu was found in the putamen in SCA3 and SCA6, whereas no changes were present in putamen or caudate nucleus of patients with PD or SCA2. A trend toward increased rCMRglu was noted in the temporal cortical ROI in SCA2 and SCA3, which theoretically may be a normalization artifact because of reduced parietal rCMRglu, especially in patients with SCA2.

The SPM analysis confirmed the results obtained with the ROI analysis and revealed a distinctive pat-
tern of changes for either disease: in SCA3, we found areas of decreased metabolism extending from cerebellar midline structures to adjacent pons and midbrain; in SCA6, we found decreased metabolism confined to the cerebellum (Figure 2 and Figure 3). Both patients with SCA3 and SCA6 display areas of increased metabolism (>control, bottom) in the superior and middle temporal gyri.

We found decreased BP_{str} in the striatum of patients with SCA2 and SCA3 (and PD), but not in those with SCA1 or SCA6. The pattern of dopamine terminal loss in SCA2 and SCA3 differed from PD because no increased susceptibility of the putamen or a significant asymmetry could
be detected. The FDG study in addition to the expected reductions of rCMRglu in the cerebellum and brainstem identified the thalamus as an affected brain region in patients with SCA3.

Our findings comply with recently published data of dopamine transporter single-photon emission computed tomography (DAT-SPECT) in patients with SCA2 and earlier $[^{18}F]$FDG-PET studies in patients with SCA3. For SCA2, the first imaging studies of members of the Alberta family presenting clinically with parkinsonism revealed DAT loss similar to PD with a more severely affected putamen. None of our patients displayed parkinsonian signs, yet similar to patients with PD, all patients with SCA2 in our PET study and in the SPECT study of Varrone et al displayed severe DAT loss throughout the striatum, suggesting that the dopaminergic system is particular sensitive to the SCA2 mutation. In her study of clinical and neuropathological features in SCA2, Dürr et al already emphasize the striking discrepancy between the severe pathological changes observed in the substantia nigra and the lack of overt parkinsonian features. Thus, either additional factors are required for parkinsonian signs to appear or severe cerebellar dysfunction may mask parkinsonian signs. Interestingly, patients with SCA2 with parkinsonian signs reported to date all had relatively short repeat expansions and possibly less severe cerebellar pathology. Alternatively, although less likely, loss of DAT may represent a necessary but not a sufficient condition to elicit the typical parkinsonian motor features in PD.

In contrast to SCA2, loss of DAT was less severe in patients with SCA3. Only 1 patient showed a reduction of BP$_{dmp}$ in the striatum below 2.5 SDs, whereas 4 patients had BP$_{dmp}$ reductions below 1 SD (of the mean normal control value). Almost identical, in the study by Shinotho et al, 2 out of 6 patients with SCA3 showed a significant reduction of putaminal and caudate Ki below 2.5 SDs, while 4 patients had Ki values below 1 SD. Similar to SCA2, no patient with SCA3 in our study had overt parkinsonian signs (despite a BP$_{dmp}$ loss of 69% in 1 case). Thus, in SCA3, the available imaging data indicate a variable degree of damage of the dopaminergic system with little correlation to the clinical presentation.

Our PET data revealed no clear-cut difference of BP$_{dmp}$ between putamen and caudate nucleus in patients with SCA2 and SCA3, even though Taniwaki et al reported a significant reduction of $[^{18}F]$florodopa uptake only in the putamen. In that study however, mean putamen and caudate nucleus values were in the same order of magnitude (70% vs 77% of control) and no individual results were reported. A uniform involvement of striatal dopaminergic terminals in patients with SCA2 and SCA3 as observed with the DAT ligand $[^{11}C]$dMP is in line with diffuse nigral cell loss reported post mortem. In addition to dopaminergic cell loss, global synaptic impairment might contribute to the alterations of DATs in patients with SCA3; recent bioinformatics and experimental data suggested that ataxin-3 functions as a ubiquitin protease involved in the regulation of synaptic activity. Reduced synaptic activity could also ex-
plain the (minor) reductions of rCMRglu in the putamen of patients with SCA3.

Although SCA1, like SCA2 and SCA3, is considered a multisystemic disease, the dopaminergic system appears to be spared, which reflects the specific pattern of neuronal vulnerability encountered in each polyglutamine disorder. On the other hand, both ROI and SPM analyses pointed toward an increased rCMRglu at rest in temporal cortical areas, suggesting either a common compensatory mechanism or cortical hyperactivity as a consequence of the cerebellar and brainstem dysfunction. Similarly, Wessel et al.13 using a sequential finger movement paradigm and [15O]H2O PET found, that specific motor areas were more active in patients with cerebellar degeneration.

The complex pattern of rCMRglu, which increases and decreases in distinct brain regions, might allow the characterization of spatially distributed neural networks and compensatory changes in response to either mutation. Our findings reflect the specific pathology observed in patients with SCA1, SCA2, SCA3, and SCA6 and provide a noninvasive phenotype that might be useful as a quantitative marker in future trials of neuroprotective drugs.

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REFERENCES


