Potential Time Course of Human Immunodeficiency Virus Type 1–Associated Minor Motor Deficits

Electrophysiologic and Positron Emission Tomography Findings

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Background: We tested whether metabolic abnormalities in the prefrontal-striatal circuitry as demonstrated by positron emission tomography (PET) were present in patients seropositive for human immunodeficiency virus type 1 (HIV-1) with HIV-1–associated minor motor deficits as demonstrated by quantitative motor testing.

Patients: We examined 19 HIV-1–positive patients, covering the range from normal results of quantitative motor testing to clearly pathologic psychomotor slowing indicative of HIV-1–associated minor motor deficits. None fulfilled the clinical criteria for HIV-1–associated dementia. Results were compared with those of 15 healthy volunteers.

Methods: All subjects underwent clinical examination, routine magnetic resonance (MR) imaging, and electrophysiologic motor testing at the time of PET.

Results: Seven HIV-1–positive patients showed significant hypermetabolism in the basal ganglia. Nine patients showed a significant frontomesial hypometabolism.

Conclusions: The data of our cross-sectional study strongly suggest a characteristic time course in the development of HIV-1–associated minor motor deficits. Hypermetabolism in the basal ganglia is associated initially with normal motor performance. Moderate motor slowing appears at a later stage when basal ganglia hypermetabolism drops toward hypometabolism. More severe functional deficits and highly pathologic motor slowing become manifest when hypometabolism is most widespread in the basal ganglia. This stage leads to dementia.

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PATIENTS AND METHODS

PATIENTS AND CONTROLS

Nineteen HIV-1–positive men (15 homosexual, 3 bisexual, and 1 heterosexual) were recruited from the Department of Neurology, Heinrich-Heine-University, Düsseldorf, Germany. Ages ranged from 25 to 62 years (mean, 42±11 years). Patients covered the entire spectrum of motor function, ranging from normal psychomotor speed to highly pathologic psychomotor slowing. Mean time span since establishment of seropositivity was 4.8±4.3 years. Data on plasma viral load were available for 11 patients (below detection threshold, 5 patients; <1000 copies/mL, 1 patient; 1000-10,000 copies/mL, 1 patient; 10,000-30,000 copies/mL, 4 patients). Nine patients had acquired immunodeficiency syndrome (AIDS).17 Three patients had not yet received any antiretroviral treatment (no ART); 7 used only reverse transcriptase inhibitors (ie, received ART); and 9 used highly active antiretroviral therapy (HAART). None of the patients fulfilled the clinical criteria for HIV-1–CMC,1 ie, the AIDS dementia complex. None had evidence of HIV-1–associated myelopathy. None of the patients had any history of cerebral lymphoma or opportunistic cerebral infection. One patient had signs of HIV-1–associated polyneuropathy. All patients underwent scoring with regard to the 14 motor examination items of the Unified Parkinson’s Disease Rating Scale (UPDRS). Mehrfach-Wortwahl-Test, Version B (MWT-B)18 and Raven’s progressive matrices19 were performed. To assess the psychopathological status, the Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (AMDP) system20 and the Hamilton Depression Rating Scale21 were used. Patient data were compared with those of a group of 15 healthy HIV-1–negative volunteers (10 men, 5 women; mean age, 38±11 years) with no histories of any neurologic, psychiatric, or seizure disorders. Results of general physical and neurologic examinations were unremarkable. Written informed consent was obtained in accordance with guidelines of the Declaration of Human Rights, Helsinki, 1975. The study was approved by the university ethics committee. All individuals were informed that the purpose of this study was to investigate the rCMRGlc pattern during resting wakefulness. None had undergone previous PET scanning.

MAGNETIC RESONANCE IMAGING

Axial, coronal, and sagittal T1- (repetition time [TR], 2000 milliseconds; echo time [TE], 20 milliseconds) and axial and coronal T2-weighted (TR, 2000 milliseconds; TE, 80 milliseconds) images and proton density–weighted magnetic resonance (MR) images were acquired using a 1.0-T scanner (Siemens Magnetom; Siemens, Erlangen, Germany).

RESULTS

CLINICAL FINDINGS

Mean premorbid verbal intelligence (MWT-B) score was 107±16; current nonverbal intelligence (Raven) score, 114±13. These values did not differ among the patients. None of the patients showed more than mild impairment in the following domains: disturbances of attention and memory, formal disorders of thought, disturbance of affect, and disturbances of drive and psychomotority. None showed major depression.

ELECTROPHYSIOLOGIC TESTING

Electrophysiologic test results are summarized in Table 1. Five patients showed completely normal motor results in all 8 variables; 2 patients showed only MRAM slowing of 1 hand. All other patients showed pathologically prolonged CT (bilateral in 10; unilateral in 2), alone or in combination with slowing of MRAM or prolonged RT. Tremor peak frequency was normal in all patients. Electrophysiologic variables were significantly correlated between hemispheres (P values of Fisher’s r-to-z transformation: TPF, P=.03; MRAM, P=.002; RT, P<.001; CT, P=.01). Electrophysiologic variables did not correlate with the current CD4 cell counts.

Electrophysiologic test results were compared with the results of the UPDRS. Five of the 7 patients with normal CTs scored 0; the others, 5 and 6. Of the 12 patients with pathologically longer CTs, only 2 scored 0, and 10 scores were in the pathologic range (1-18; median, 5). The UPDRS scores and CT values of the right hand were weakly but significantly correlated (Spearman rank correlation, r=0.47; P=.05). Individual results of CD4 cell counts, UPDRS, and CT values are provided in Table 2.

MAGNETIC RESONANCE IMAGING

The MR imaging scans were evaluated by a neuroradiologist (F.W.) who was blind to all clinical data. All patients had normal findings on MR imaging scans.

SIGNIFICANT GROUP MEAN METABOLIC ALTERATIONS

Nondemented HIV-1–positive patients demonstrated a characteristic metabolic pattern of mean rCMRGlc alterations...
lights were dimmed. Subjects were asked not to move or to speak but to keep their eyes open during the examination to avoid falling asleep. Serum concentrations of fludeoxyglucose F 18 (FDG) were determined in samples of arterialized venous blood after intravenous bolus injection of 185 MBq. Twenty-minute scanning was centered around 45 minutes after injection, according to steady-state FDG kinetics. The rate of rCMRGlc was quantified according to the method described by Phelps and colleagues. The kinetic constants and the lumped constant 0.52 were taken from Reivich et al. The rate of rCMRGlc was determined in visually placed, anatomically oriented, homologous regions of interest (ROIs) in both hemispheres. The ROIs were drawn on each axial image along the boundary of the gray matter by using anatomical criteria provided by Talairach and Tournoix. Since regional hypometabolism might change the size of a subjectively drawn region, regions on both hemispheres were traced as mirror images so that they would not differ in size by more than 10%. In our control group, the mean metabolic asymmetry between homologous regions in the cerebral hemispheres was 2.2%±1.6%. In addition, co-registered T1-weighted MR images were available for anatomical verification of the ROIs. The ROIs were selected to cover the prefrontal-striatal-thalamic loop (including the frontomesial and cingulate cortex; mean metabolic asymmetry, 2.6%±1.9%), the dorsolateral prefrontal cortex (mean metabolic asymmetry, 2.0%±1.5%), the thalamus (mean metabolic asymmetry, 2.5%±1.97%), and the basal ganglia (mean metabolic asymmetry, 2.1%±1.3%). For comparisons, the primary visual cortex (mean metabolic asymmetry, 1.9%±1.4%) was chosen. Figure 1 illustrates ROI placement.

The ROI data were averaged across 2 axial slices. Each mean ROI value was normalized by dividing it by the value of the individual's whole-brain metabolism to control for global differences in rCMRGlc between subjects and to allow comparisons between groups. Whole-brain metabolism was determined by averaging the values of gray matter ROIs from all slices, taking into account the actual size of single ROI areas relative to whole-brain area (volume). Values were rated as pathologic if they fell outside the range of the mean plus 2 SDs. Only the data of an investigator (C.A.) who was blind to all clinical information were used for this analysis.

**ELECTROPHYSIOLOGIC MOTOR TESTING**

Electrophysiologic motor testing included the analysis of the following: (1) postural tremor of the outstretched hands (tremor peak frequency [TPF]); (2) most rapid alternating movements of index fingers (MRAM); and (3) most rapid voluntary isometric index finger extensions (MRC). The variables measured in the last context were simple reaction time (RT), ie, the time span between a short go signal and the onset of contraction, and contraction time (CT), ie, the time span between the onset and the peak force of a contraction (methodological details are described elsewhere).

Normal values for 98 HIV-1-negative subjects have been published. Individual values were rated pathologic if a frequency (TPF or MRAM) was below the mean−2 SD or if a time span (RT or CT) was longer than the mean+2 SD.

**STATISTICS**

Statistical analysis was performed using a commercially available software package (Statview; Abacus Concepts, Inc, Berkeley, Calif).

Unless otherwise indicated, data are given as mean±SD.

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**COMMENT**

The present study was designed to test the hypothesis that PET scanning can expose metabolic abnormalities constituting the pathophysiologic and functional correlate of HIV-1-associated minor motor deficits. The PET findings in our patients were clearly abnormal in the prefrontal-striatal circuitry. These data corroborate earlier findings of relative hypermetabolism in the basal ganglia, especially in the striatum. Hypermetabolism is one of the most characteristic findings in HIV-1-positive patients with subclinical neurologic dysfunction. Secondarily, late cortical and subcortical hypometabolism or

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**Figure 1. Placement of regions of interest.** A, Region of interest placement in thalamus, basal ganglia, and primary visual cortex. B, Region of interest placement in frontomesial cortex, including cingulate cortex and dorsolateral prefrontal cortex.
globally reduced cortical uptake of glucose have also been described. This combination of hypermetabolism and hypometabolism may well be the reason that in our patients, metabolic alterations in the basal ganglia failed to reach significance at a group statistical level. However, on an individual basis, 7 patients showed significantly pathologic unilateral or bilateral hypermetabolism, and in 1 patient, unilateral basal ganglia metabolism was significantly reduced. In contrast to reports describing hypermetabolism in the thalamus or alterations in the temporal or parietal lobes, we did not find such changes in our patients but did detect a second, significantly hypometabolic region, the frontomesial cortex (including the cingulate cortex). On an individual basis, 9 patients showed significantly pathologic unilateral or bilateral hypometabolism in the frontomesial cortex/cingulate cortex. These areas are known to be closely connected with the basal ganglia.

For an individual analysis of patient data (Table 2), we focused on disturbances in the metabolism of the basal ganglia and compared these findings with levels of motor function. Five patients (patients 1-5) showed normal metabolic rates in the basal ganglia on both sides and in the CTS of both hands. Four of these 5 patients scored

### Table 1. Results of Electrophysiologic Motor Testing*

<table>
<thead>
<tr>
<th>HIV-1–Seronegative Controls (n = 98)</th>
<th>HIV-1–Seronopositive Patients (n = 19)</th>
<th>Bonferroni-Adjusted P</th>
<th>Absolute No. of Pathologic Results Outside the Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td>TPF, Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hand</td>
<td>9.5 ± 2.2</td>
<td>8.5 ± 0.9</td>
<td>4.0 NS</td>
</tr>
<tr>
<td>Left hand</td>
<td>9.4 ± 2.1</td>
<td>9.0 ± 1.9</td>
<td>.42 NS</td>
</tr>
<tr>
<td>MRAM, Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hand</td>
<td>6.5 ± 1.1</td>
<td>5.2 ± 1.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left hand</td>
<td>5.6 ± 0.9</td>
<td>4.6 ± 0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RT, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hand</td>
<td>146.9 ± 25.0</td>
<td>164.3 ± 67.3</td>
<td>.06 NS</td>
</tr>
<tr>
<td>Left hand</td>
<td>147.9 ± 25.9</td>
<td>175.3 ± 92.1</td>
<td>.003</td>
</tr>
<tr>
<td>CT, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hand</td>
<td>115.4 ± 20.0</td>
<td>160.2 ± 45.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left hand</td>
<td>119.6 ± 22.1</td>
<td>177.9 ± 68.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Results are given as mean ± SD. The normal range was defined as mean ± 2 SD. Individual frequencies of less than mean−2SD and times of greater than mean+2SD were rated pathologic. Patients and controls were compared using unpaired t tests; after Bonferroni adjustment, the level of significance was set at P < .006. HIV-1 indicates human immunodeficiency virus type 1; TPF, tremor peak frequency; NS, not significant; MRAM, most rapid alternating movements of index fingers; RT, simple reaction time; and CT, contraction time.

### Table 2. Normalized Metabolic Ratios and Electrophysiologic Test Results*

<table>
<thead>
<tr>
<th>Patient No. (Individual UPDRS Motor Finding)</th>
<th>CD4 Cell Count, per µL (Type of Treatment)</th>
<th>Normalized Metabolic Rates, PET Results in Basal Ganglia</th>
<th>Electrophysiologic Motor Test Findings, CT, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Controls, mean (SD)</td>
<td></td>
<td>1.35</td>
<td>1.35</td>
</tr>
<tr>
<td>1 (0)</td>
<td>488 (HAART)</td>
<td>1.35</td>
<td>1.32</td>
</tr>
<tr>
<td>2 (0)</td>
<td>600 (no ART)</td>
<td>1.39</td>
<td>1.30</td>
</tr>
<tr>
<td>3 (0)</td>
<td>197 (HAART)</td>
<td>1.39</td>
<td>1.41</td>
</tr>
<tr>
<td>4 (6)</td>
<td>159 (ART)</td>
<td>1.39</td>
<td>1.42</td>
</tr>
<tr>
<td>5 (0)</td>
<td>212 (ART)</td>
<td>1.46</td>
<td>1.41</td>
</tr>
<tr>
<td>6 (0)</td>
<td>452 (HAART)</td>
<td>1.49</td>
<td><strong>1.50</strong></td>
</tr>
<tr>
<td>7 (0)</td>
<td>480 (ART)</td>
<td><strong>1.50</strong></td>
<td>1.45</td>
</tr>
<tr>
<td>8 (5)</td>
<td>448 (HAART)</td>
<td><strong>1.64</strong></td>
<td><strong>1.58</strong></td>
</tr>
<tr>
<td>9 (18)</td>
<td>5 (ART)</td>
<td><strong>1.59</strong></td>
<td><strong>1.74</strong></td>
</tr>
<tr>
<td>10 (5)</td>
<td>797 (no ART)</td>
<td><strong>1.51</strong></td>
<td><strong>1.50</strong></td>
</tr>
<tr>
<td>11 (3)</td>
<td>349 (HAART)</td>
<td><strong>1.51</strong></td>
<td><strong>1.50</strong></td>
</tr>
<tr>
<td>12 (0)</td>
<td>662 (no ART)</td>
<td><strong>1.58</strong></td>
<td><strong>1.48</strong></td>
</tr>
<tr>
<td>13 (5)</td>
<td>324 (HAART)</td>
<td>1.48</td>
<td>1.45</td>
</tr>
<tr>
<td>14 (7)</td>
<td>39 (HAART)</td>
<td>1.44</td>
<td>1.49</td>
</tr>
<tr>
<td>15 (7)</td>
<td>800 (HAART)</td>
<td>1.40</td>
<td>1.40</td>
</tr>
<tr>
<td>16 (6)</td>
<td>237 (ART)</td>
<td>1.41</td>
<td>1.37</td>
</tr>
<tr>
<td>17 (11)</td>
<td>679 (ART)</td>
<td>1.30</td>
<td>1.33</td>
</tr>
<tr>
<td>18 (4)</td>
<td>254 (HAART)</td>
<td>1.23</td>
<td>1.27</td>
</tr>
<tr>
<td>19 (5)</td>
<td>613 (ART)</td>
<td><strong>1.21</strong></td>
<td>1.28</td>
</tr>
</tbody>
</table>

* Values lying outside the range of mean ± 2 SD are given in boldface. UPDRS indicates Unified Parkinson’s Disease Rating Scale; PET, positron emission tomography; CT, contraction time; ART, antiretroviral therapy; HAART, highly active ART; upward arrow, above normal range; and downward arrow, below normal range.
A hypothesis of disease kinetics can be set up through 12.

Patients was generally more pathologic than in patients 6 through 12, but not as severely hypometabolic as in patients 9 through 12, with electrophysiologic function normal or compensated; phase 3, secondary hypometabolism (pseudonormalization), with first functional deficits detected; phase 4, late secondary hypometabolism with more severe functional deficits leading toward HIV-1–associated cognitive/motor complex; and CT, contraction time.

Although there was a tendency toward basal ganglia hypermetabolism and frontomesial hypometabolism, only the ratio of basal ganglia to frontomesial cortex remained significant after Bonferroni adjustment for multiple comparisons (P < .05/12, ie, P < .004). Numbers in parentheses indicate the absolute number of pathologic results outside the normal range (mean ± 2 SD). HIV indicates human immunodeficiency virus type 1; ROI, region of interest; and NS, not significant.

<table>
<thead>
<tr>
<th>Normalized Metabolic Rates in ROIs of Patients and Controls*</th>
<th>HIV-1–Positive Patients</th>
<th>HIV-1–Negative Controls</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1.436 (7)</td>
<td>1.350</td>
<td>.02 NS</td>
</tr>
<tr>
<td>Left</td>
<td>1.431 (5)</td>
<td>1.350</td>
<td>.03 NS</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1.423</td>
<td>1.378</td>
<td>.18 NS</td>
</tr>
<tr>
<td>Left</td>
<td>1.438</td>
<td>1.393</td>
<td>.09 NS</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1.307</td>
<td>1.329</td>
<td>.55 NS</td>
</tr>
<tr>
<td>Left</td>
<td>1.331</td>
<td>1.345</td>
<td>.71 NS</td>
</tr>
<tr>
<td>Frontomesial cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right including cingulum</td>
<td>1.189 (6)</td>
<td>1.299</td>
<td>.01</td>
</tr>
<tr>
<td>Left including cingulum</td>
<td>1.216 (9)</td>
<td>1.318</td>
<td>.02</td>
</tr>
<tr>
<td>Primary visual cortex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1.493</td>
<td>1.437</td>
<td>.10 NS</td>
</tr>
<tr>
<td>Left</td>
<td>1.527</td>
<td>1.457</td>
<td>.08 NS</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontomesial right</td>
<td>1.220 (18)</td>
<td>1.042</td>
<td>.001</td>
</tr>
<tr>
<td>Frontomesial left</td>
<td>1.190 (18)</td>
<td>1.025</td>
<td>.002</td>
</tr>
</tbody>
</table>

Although there was a tendency toward basal ganglia hypermetabolism and frontomesial hypometabolism, only the ratio of basal ganglia to frontomesial cortex remained significant after Bonferroni adjustment for multiple comparisons (P < .05/12, ie, P < .004). Numbers in parentheses indicate the absolute number of pathologic results outside the normal range (mean ± 2 SD). HIV indicates human immunodeficiency virus type 1; ROI, region of interest; and NS, not significant.

* Determined using t test.

When the data of all the subgroups are compared, a hypothesis of disease kinetics can be set up (Figure 3).

Initial increasing hypermetabolism turns toward hypometabolism as the disease progresses.

We correlated CT values of both hands with a metabolic index for the basal ganglia on an individual basis. The sum of the differences between the mean rate of basal ganglia metabolism (1.35 each side) and the individual metabolic rates was calculated: eg, for patient 6 (1.49−1.35) + (1.50−1.35) = 0.14 + 0.15 = 0.29, or basal ganglia index = 29. Second- and fourth-order polynomial regression yielded comparable results. A potential time course for the development of minor motor deficits is presented in Figure 2.

Our interpretation of individual data is compatible with the results of an earlier study describing a positive correlation between measures of fine motor control and metabolic abnormalities (which would appear relatively early in the course of the disease, eg, in phase 2 in Figure 2). A later study by the same group found no correlation at all (which would be the case if the disease were not advanced enough). This slowing cannot be attributed to peripheral nerve abnormality.32 The tests are therefore sensitive quantitative variable for recognizing a major feature of all basal ganglia disorders, ie, slowing of movement. This slowing cannot be attributed to peripheral nerve abnormality.32 In normal motor function, the maximal force of a contraction is independent of the ampli-
tude of the contraction curves. Mildly abnormal CT curves in HIV-1 infection resemble those of patients in early phases of Huntington disease.\textsuperscript{13,33} More impaired HIV-1-positive patients show additional findings consistently seen in Parkinson or Wilson disease.\textsuperscript{36} The PET scans of patients with manifest Huntington disease\textsuperscript{37} or Wilson disease\textsuperscript{38} show basal ganglia hypometabolism resembling that in our late-phase HIV-1-positive patients. One may speculate about the possible effects of ART and HAART on our patients. An improvement of psychomotor slowing has been demonstrated during use of ART\textsuperscript{14} and HAART.\textsuperscript{39} This effect cannot account for pathologic slowing which we observed in our patients during use of ART or HAART.\textsuperscript{39} It is therefore unlikely that patients 13 through 19 showed normalized metabolic function of the basal ganglia due to effective therapy, and yet continued to show pathologic motor slowing. Conversely, patients 1 through 5 showed consistent normal motor performance. However, CNS abnormalities may respond to ART or HAART at certain defined points during the course of the disease that are not yet known.

Finally, there is no close correlation between CNS abnormalities (as measured by psychomotor speed and PET findings) and immunological status (CD4 cell count). This could result in part from the fact that the immunological status of a patient may improve differently under therapy than does the CNS. Most patients actually had lower CD4 cell counts before the time of PET scanning (e.g., patient 17 had a documented CD4 cell count of 0.069 × 10\(^{3}\)/L [69 cells/µL] before therapy and 0.679 × 10\(^{3}\)/L [679 cells/µL] at the time of PET scanning). Thus a pathologic process within the CNS conceivably may have begun before the immunological response to ART or HAART.

**CONCLUSIONS**

There is substantial theoretical and clinical evidence that CT in particular is a specific marker of basal ganglia dysfunction and can describe and quantify basal ganglia dysfunction reliably in HIV-1–associated minor motor disorders. Together with neuroimaging procedures, these tests may prove to be an appropriate tool to assess the time course of HIV-1–associated brain disease in larger prospective studies. Individual data could be essential for establishing specific neurologic therapeutic strategies.

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**Figure 3.** Polynomial regression (fourth order) between basal ganglia metabolic index (positive index indicates hypermetabolism; negative index, hypometabolism) and contraction times (CTs) of right (A) and left (B) hands of all patients (patient 13 was excluded because of exceptionally prolonged CTs).
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