GBA-associated PD: Neurodegeneration, altered membrane metabolism, and lack of energy failure
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GBA-associated PD

Neurodegeneration, altered membrane metabolism, and lack of energy failure

ABSTRACT

Objective: To elucidate possible mechanisms leading to neurodegeneration in patients with glucocerebrosidase (GBA)-associated Parkinson disease (PD) using combined proton (1H) and phosphorus (31P) magnetic resonance spectroscopic imaging (MRSI) in vivo.

Methods: 1H and 1H-decoupled 31P MRSI was performed in 13 patients with PD with heterozygous GBA mutations (GBA-PD) and 19 age- and sex-matched healthy controls to investigate metabolite concentrations in the mesostriatal target regions of PD pathology. NAA as marker of neuronal integrity, choline and ethanolamine containing compounds as markers of membrane phospholipid metabolism, and energy metabolites (notably high-energy phosphates) were quantified.

Results: Compared to controls, NAA was significantly reduced in the putamen (p = 0.012) and in the midbrain of GBA-PD (p = 0.05). The choline concentration obtained from 31H MRSI was significantly decreased in the midbrain of GBA-PD (p = 0.010). The phospholipid degradation product glycerophosphoethanolamine was increased in the putamen of GBA-PD (p = 0.05). Changes of energy metabolism were not detected in any region of interest.

Conclusion: The pattern of neurodegeneration in GBA-associated PD is more pronounced in the putamen than in the midbrain. Our MRSI findings suggest that the neurodegenerative process in GBA-PD is associated with alterations of membrane phospholipid metabolism which might be also involved in abnormal α-synuclein aggregation. Neurology® 2012;79:213–220

GLOSSARY

ADP = adenosine diphosphate; ATP = adenosine triphosphate; CCT = phosphocholine cytidylyltransferase; Cr = creatine; ETS = electron transport system; GBA = glucocerebrosidase; GBA-PD = patients with Parkinson disease with heterozygous GBA mutations; GD = Gaucher disease; GM = gray matter; GPC = glycerophosphocholine; GPE = glycerophosphoethanolamine; 1H = proton; HEP = high-energy phosphate; LB = Lewy body; LEP = low-energy metabolite; MPRAGE = magnetization-prepared rapid gradient echo; MRSI = magnetic resonance spectroscopic imaging; MSA = multiple system atrophy; NAA = N-acetyl aspartate; 31P = phosphorous; PCho = phosphocholine; PCr = phosphocreatine; PDE = Parkinson disease; PEth = phosphoethanolamine; Pi = inorganic phosphate; PtdCho = phosphatidylcholine; PtdSer = phosphatidylserine; SPM = Statistical Parametric Mapping; tCho = total choline; tCr = total creatine; TE = echo time; TR = repetition time; UPDRS-III = motor part of the Unified Parkinson’s Disease Rating Scale; WM = white matter.

Homozgyous mutations in the gene glucocerebrosidase (GBA) cause Gaucher disease (GD), a lysosomal storage disorder with tissue accumulation of glucocerebrosides. Heterozygous mutations in the GBA gene are associated with sporadic Parkinson disease (PD).1 Patients with PD with heterozygous GBA mutations (GBA-PD) more frequently show nonmotor symptoms, such as dementia, neuropsychiatric disturbances, and autonomic impairment, compared with patients with PD without GBA mutations.2 The pathogenesis of GBA-PD is currently not known. In GD, enhanced phosphocholine cytidylyltransferase (CCT) activation with increased synthesis of phosphatidylcholine (PtdCho) as major component of phospholipid cell membranes was reported.3 Alterations in the lipid bilayer composition of membranes cause impaired α-synuclein membrane binding and...
enhanced neurotoxic fibril formation in the cytoplasm. Moreover, a dysfunction of mitochondrial oxidative metabolism with diminished activity in complex I of the electron transport system (ETS) or with uncoupled oxidation from adenosine triphosphate (ATP) production was supposed to be involved in the pathophysiology of sporadic PD.5,6

In vivo phosphorous (31P) magnetic resonance spectroscopic imaging (31P-MRSI) investigations of cerebral ATP concentrations supported the hypothesis of dysfunctional mitochondrial energy metabolism in sporadic PD.7,8 Beyond the investigation of neuronal energy status, 1H combined with 31P MRSI is a valuable tool to monitor choline and ethanolamine-containing compounds involved in the metabolism of membrane phospholipids.9,10 Therefore, we aimed to evaluate whether mitochondrial dysfunction and/or impaired membrane metabolism may play a pathogenic role in GBA-PD with the use of combined 1H and 31P MRSI.

**METHODS** Mutational screening. In preparation of this study, we investigated DNA from 1,000 patients initially diagnosed with sporadic PD. Mutational screening for 2 of the most common mutations of the GBA gene (N370S, L444P) was performed by genotyping with restriction enzyme digest. Primers and conditions are available upon request.

**Study subjects.** A total of 33 GBA-PD from all over Germany were included in this study. The others could not be investigated with MRSI due to the existence of endoprostheses, electrodes for deep brain stimulation, or a degree of clinical impairment that prevented participation. PD diagnosis was defined according to the UK Brain Bank Criteria.11 Severity of motor symptoms was assessed in the “on”-state using the motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS-III).12 Disease stage was categorized according to the modified Hoehn & Yahr Scale.13 Nineteen age- and gender-matched healthy controls without neurologic, psychiatric, or systemic diseases (e.g., severe arterial hypertension, diabetes mellitus) were included for comparison.

**MRSI.** Brain MRSI was performed on a 3-T whole body scanner (Magnetom Trio, Siemens Medical AG, Erlangen, Germany) with a double tuned 1H/31P volume head coil (Rapid Biomedical, Würzburg, Germany). The protocol was previously described by Hattingen et al.; sequence parameters are summarized in table 1. In brief, 2 MRSI slices were recorded with 1H-MRSI: a coronal slice aligned on the dorsal line of the pontine and midbrain tegmentum and an axial slice including the putamen. For 31P MRSI, an axial slab of 100 mm was recorded using a 3D acquisition scheme. Weighted elliptical phase encoding was employed for both modalities with 2 acquisitions for 1H MRSI and 10 acquisitions for 31P MRSI. A combination of the point resolved selective spectroscopy (echo time [TE]/repetition time [TR] 30/1,500) and outer volume suppression was used to select a volume of interest in 1H MRSI which excluded lipsids from the skull. A simple pulse-acquired CSI sequence (flip angle 60°, TR 2,000 msec, TE 2.3 msec) was applied for 31P MRSI.

**Quantitative data processing.** For quantitative data analysis, partial volume effects originating from the CSF were taken into account. The respective information was taken from isotropic T1-weighted 3D image sequences (table 1). Data were processed offline on a Linux workstation. High-resolution anatomic data were segmented into gray matter (GM) and white matter (WM) with the vbm5 extension (http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/) in Statistical Parametric Mapping (SPM) 5 to determine the fraction of GM and WM contributing signal to each voxel (http://www.fil.ion.ucl.ac.uk/spm/). The MRSI-aligned T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) (2-mm resolution) was registered to the high-resolution MPRAGE, using the rotational and translational transformations (6 degrees of freedom) implemented in the flirt function of FSL (http://www.fmrib.ox.ac.uk/fsl/). The inverse registration matrix was then used to transform the segmented data onto the MRSI coordinate system. To ac-

### Table 1 Detailed information on sequence parameters of 1H/31P to MRSI

<table>
<thead>
<tr>
<th>Sequence</th>
<th>TR/TE/TI, ms</th>
<th>Acquisition time, min</th>
<th>FOV</th>
<th>Matrix (extrapolated)</th>
<th>Voxel size, mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D 31P MRSI</td>
<td>WALTZ4 proton decoupling</td>
<td>2,000/NA</td>
<td>18:04</td>
<td>300 x 300 x 200 mm³</td>
<td>30 x 30 x 25</td>
</tr>
<tr>
<td>2D 1H MRSI</td>
<td>PRESS</td>
<td>1,500/30</td>
<td>4:45</td>
<td>240 x 240 mm²</td>
<td>28 x 28 (48 x 48)</td>
</tr>
<tr>
<td>2D 1H MRSI midbrain</td>
<td>PRESS</td>
<td>1,500/30</td>
<td>16:45</td>
<td>240 x 240 mm²</td>
<td>16 x 16 (32 x 32)</td>
</tr>
<tr>
<td>3D MRSI</td>
<td>MPRAGE</td>
<td>1,320/2.1/900</td>
<td>1:39</td>
<td>256 x 176 mm²</td>
<td>128 x 128</td>
</tr>
<tr>
<td>3D MRSI</td>
<td>MPRAGE</td>
<td>1,600/2.63/900</td>
<td>4:08</td>
<td>256 x 256 mm²</td>
<td>256 x 256</td>
</tr>
</tbody>
</table>

Abbreviations: FOV = field of view; 1H = proton; MPRAGE = magnetization to prepared rapid gradient echo sequence; MRSI = magnetic resonance spectroscopic imaging; NA = not available; 31P = phosphorous; PRESS = point resolved selective spectroscopy with outer volume suppression; TE = echo time; TI = inversion time; TR = repetition time; WALTZ4 proton decoupling = wideband alternating phase low power technique for zero residual splitting.

*Phase oversampling 38%.
count for the reduced grid resolution and for blurring caused by the poor point spread function, anatomic information for each MRSI voxel was transformed by down sampling and filtering.14 During filtering, the 31P slab and the 1H slice were adjusted for different offsets using the grid shift theorem.

The 1H MRSI spectra were analyzed with the software tool LC Model (Provencher, http://second-provencher.com). Baseline correction was performed including macromolecules. The 31P data were analyzed with the tool jMRUI as described earlier in detail.7 Phosphocreatine (PCr) was adjusted to 0 ppm and constraints for the chemical shifts of the other signals except for inorganic phosphate (Pi) were applied as a fixed difference with regard to the position of PCr. ATP was represented by 7 exponentially damped sinusoids, defining each multiplet by the respective number of peaks with identical damping and adequate amplitude ratios. The coupling constant was fixed at 18 Hz. One signal with a fixed chemical shift of 2.24 ppm and maximum line width of 50 Hz was used to account for potential macromolecule signals in the phosphodiester region. All spectra from the selected voxels were assessed visually for artifacts according to the criteria described by Kreis.15 Further, the values of the Cramer-Rao lower bounds indicated by the program as SD value were used to measure the quality and reliability of the spectra, i.e., spectra where all metabolites yielded values of more than 20% were discarded. Absolute metabolite concentrations were calculated by referring to an independent measurement in a spherical phantom (containing 100 mmol/L acetate as calibration standard for 1H data, TR = 10 s; and 20 mmol/L phosphate for 31P data, TR = 60 s). For both phantoms, coil loading was within ±20% of the average coil loading of the patients. Corrections for T1 and T2 relaxations were performed as described previously.24 No T2 correction was performed for 31P data. Volume concentrations were converted into tissue concentrations by division with the tissue fraction (sum of GM and WM), i.e., assuming no metabolites in the CSF fraction.

The pathologic increase of anaerobic glycolysis can lead to detectable lactate levels in brain tissue.15 The LC Model software provides a value for the lactate concentration and an estimation of its accuracy is given (% SD). Each complete MRSI dataset was screened for lactate SD values <20%. The presence of a clear positive doublet signal at 1.3 ppm in the spectra was then verified. Voxels fulfilling these criteria were considered to have elevated lactate levels.

### Calculated parameters

The concentrations of adenosine diphosphate (ADP) and unphosphorylated creatine (Cr) were calculated from the local tissue concentrations as reported previously.18 The residual signal resonating at 3.2 ppm in the 1H spectra was calculated as follows:

\[
\text{Residual 3.2 signal} = \text{total choline (tCho)} - \text{(phosphocholine [PCho] + glycerophosphocholine [GPC])}
\]

Further calculations were made for:

- **High-energy phosphates (HEP):** ATP + PCr
- **Low-energy metabolites (LEP):** ADP + (tCr - PCr) + Pi

Differences of metabolite concentrations were calculated for each volume of interest in individual datasets.

### Statistical methods

Statistical analysis was performed with STATISTICA (version 7.1, StatSoft, Tulsa, OK) and SPSS 19.0 for Windows (Chicago, IL; www.spss.com). For each metabolite, values averaged for both cerebral hemispheres were calculated for every volume of interest. In addition, a mean value for the tissue fraction of the respective area was calculated as the sum of GM and WM fractions. Due to small sample sizes, nonparametric testing using the Mann-Whitney U test was performed.

Further, correlations between NAA and membrane metabolite concentrations were determined by linear regression analysis. p Values ≤0.05 were considered significant.

### Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics committee of the Faculty of Medicine at the University of Tübingen (497/2009BO1) and by the Ethics Committee of the Faculty of Medicine at the University of Frankfurt. All participants gave written informed consent.

**RESULTS** For detailed demographic and clinical information of GBA-PD and control subjects, see table 2. Concentrations of all metabolites under investigation are given in table 3.

**Marker of neuronal integrity.** Compared with controls, the neuronal marker NAA was reduced in the putamen (8.69 vs 9.72, p = 0.012) and in the midbrain of GBA-PD (8.94 vs 10.03, p = 0.05).

**Energy metabolism.** Concentrations of high-energy phosphates (ATP and PCr) as well as low-energy metabolites (ADP and Pi) showed no statistically significant between-group differences, either in the putamen or in the midbrain. Patients with GBA-PD presented decreased amounts of tCr and Cr in the putamen compared to controls (5.76 vs 6.58, p = 0.025 and 2.95 vs 3.64, p = 0.009).

**Membrane phospholipid metabolism.** Patients with GBA-PD had lower concentrations of tCho in the midbrain than control subjects (1.70 vs 2.01, p = 0.010). Moreover, the residual 3.2 signal was reduced in the putamen of GBA-PD subjects (0.21 vs 0.48, p = 0.011). In contrast, the membrane-related phospholipid degradation product glycerophosphoethanolamine (GPE) was increased in the putamen of GBA-PD compared to controls (1.40 vs 1.31, p = 0.05). Phosphocholine and phosphoethanolamine (Peth) showed no significant between-group differences in either of the investigated brain regions. NAA
levels did not correlate with GPE and tCho values, either in the putamen ($p = 0.74$ and $p = 0.23$) or in the midbrain ($p = 0.70$ and $p = 0.23$).

**DISCUSSION** We present combined $^1$H and $^31$P MRSI data in patients with PD with heterozygous $GBA$ mutations indicating 1) neuronal loss in the putamen and to a lower extent in the rostral midbrain, 2) preserved levels of high-energy phosphates ATP and PCr, and 3) a disturbed membrane phospholipid metabolism in the putamen.

$GBA$-PD revealed a reduced NAA concentration more pronounced in the putamen than in the midbrain. Previous PET studies in single cases of heterozygous and compound heterozygous $GBA$ mutation carriers with PD suggested a presynaptic dopaminergic cell loss whereas the postsynaptic compartment seems unaffected or even upregulated. With regard to the more severe phenotype compared to idiopathic PD, one might argue that $GBA$-PD exhibits a more pronounced loss of presynaptic integrity. In contrast, MRSI studies of the basal ganglia investigating either absolute NAA levels or ratios like NAA/Cr and NAA/Cho failed to show significant changes in patients with idiopathic PD, but were positive in patients with multiple system atrophy (MSA). The apparent congruence of reduced striatal NAA in $GBA$-PD and MSA might be related to the partial overlap of clinical characteristics in both entities. From a histopathologic point of view, brain specimens from patients with PD with $GBA$ mutations revealed more diffuse Lewy body (LB)-type pathology compared to those from patients with idiopathic PD matched for age, sex, and disease duration.

Although evidence for impaired energy metabolism due to mitochondrial dysfunction in parkinsonian disorders results from recessive hereditary forms of PD, animal and cell models, as well as from post-mortem studies, we did not detect any significant changes of the energy metabolism in patients with $GBA$-PD. This finding is in contrast to our recent MRSI data in idiopathic PD, which were obtained

| Table 3 Concentration of the different metabolites of the respective brain region in GBA to PD vs controls* |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Membrane-related compounds                      | Putamen                                         | Midbrain                                        | Putamen                                         | Midbrain                                        |
| tCho                                            | 2.02 ($1.21$ to $2.44$)                         | 2.14 ($1.48$ to $2.48$)                         | 1.70 ($1.36$ to $2.10$)                         | 2.01 ($1.57$ to $2.55$)                         |
| PCho                                            | 0.18 ($0.14$ to $0.28$)                         | 0.15 ($0.13$ to $0.26$)                         | 0.23 ($0.01$ to $0.28$)                         | 0.22 ($0.03$ to $0.40$)                         |
| Residual 3.2 signal                             | 0.21 ($-0.32$ to $0.45$)                        | 0.48 ($-0.01$ to $0.78$)                        | 0.05 ($-0.61$ to $0.59$)                        | 0.23 ($-0.37$ to $0.73$)                        |
| PEth                                            | 0.92 ($0.73$ to $1.23$)                         | 0.96 ($0.74$ to $1.10$)                         | 1.04 ($0.69$ to $1.21$)                         | 1.13 ($0.82$ to $1.49$)                         |
| GPC                                             | 1.53 ($1.32$ to $1.85$)                         | 1.47 ($1.26$ to $1.67$)                         | 1.42 ($1.20$ to $2.03$)                         | 1.49 ($1.09$ to $1.78$)                         |
| GPE                                             | 1.40 ($1.03$ to $1.84$)                         | 1.31 ($0.99$ to $1.58$)                         | 1.49 ($1.01$ to $2.07$)                         | 1.45 ($0.73$ to $1.88$)                         |

| Neuronal marker                                  | Putamen                                         | Midbrain                                        | Putamen                                         | Midbrain                                        |
| NAA                                             | 8.69 ($7.83$ to $10.42$)                        | 9.72 ($8.37$ to $10.96$)                        | 8.94 ($7.41$ to $12.02$)                        | 10.03 ($7.77$ to $12.00$)                       |

| Energy-related compounds                         | Putamen                                         | Midbrain                                        | Putamen                                         | Midbrain                                        |
| ATP-a                                           | 1.93 ($1.54$ to $2.50$)                         | 1.93 ($1.57$ to $2.20$)                         | 1.75 ($1.21$ to $2.26$)                         | 1.86 ($1.46$ to $2.28$)                         |
| ATP-b                                           | 1.67 ($1.38$ to $2.19$)                         | 1.76 ($1.40$ to $2.09$)                         | 1.12 ($0.79$ to $1.79$)                         | 1.13 ($0.81$ to $1.54$)                         |
| tCr                                             | 5.76 ($5.20$ to $7.43$)                         | 6.58 ($5.29$ to $7.34$)                         | 4.53 ($3.75$ to $5.65$)                         | 5.03 ($4.04$ to $7.15$)                         |
| PCr                                             | 2.82 ($2.33$ to $3.61$)                         | 2.95 ($2.55$ to $3.43$)                         | 3.22 ($2.79$ to $3.47$)                         | 3.30 ($2.60$ to $3.94$)                         |
| Cr                                              | 2.95 ($2.49$ to $4.08$)                         | 3.64 ($2.73$ to $4.36$)                         | 1.31 ($0.33$ to $2.25$)                         | 1.65 ($0.67$ to $4.56$)                         |
| Pi                                               | 1.05 ($0.77$ to $1.23$)                         | 1.08 ($0.75$ to $1.25$)                         | 1.12 ($0.82$ to $1.68$)                         | 1.05 ($0.75$ to $2.11$)                         |

| Other metabolites                                | Putamen                                         | Midbrain                                        | Putamen                                         | Midbrain                                        |
| MI                                               | 5.12 ($4.32$ to $5.91$)                         | 5.21 ($4.10$ to $6.59$)                         | 4.10 ($3.51$ to $5.97$)                         | 5.30 ($4.05$ to $7.23$)                         |
| Glx                                              | 7.22 ($6.07$ to $8.11$)                         | 7.87 ($5.36$ to $9.81$)                         | 7.04 ($4.43$ to $10.74$)                        | 7.15 ($4.04$ to $10.76$)                        |

Abbreviations: ATP = adenosine triphosphate; Cr = unphosphorylated creatine; GBA-PD = patients with Parkinson disease with heterozygous glucocerebrosidase mutations; Glx = glutamate/glutamine; GPC = glycerophosphocholine; GPE = glycerophosphoethanolamine; MI = myo-inositol; PCho = phosphocholine; PCr = phosphocreatine; PEth = phosphoethanolamine; Pi = inorganic phosphate; tCho = total choline; tCr = total creatine.

*Data are given as median (range).

$^a$ p = 0.01.

$^b$ p = 0.05.
with the identical MRSI protocol and proved decreased levels of the HEPs ATP and PCr in the midbrain and in the putamen of patients in early and advanced disease stages. Other groups found evidence for an altered energy metabolism in extrastriatal brain regions in idiopathic PD. Decreased concentrations of HEPs were either attributed to diminished activity of the mitochondrial electron transport system or to uncoupled oxidation from ATP production as suggested in a recent PET study.

In contrast, our patients with GBA-PD demonstrated an increased concentration of the membrane catabolite GPE in the putamen, which was apparently lacking in idiopathic PD. The distinct investigation of mobile phospholipid membrane compounds, such as PCho and PEth being PtdCho and PtdEth precursors and the membrane breakdown metabolites GPC and GPE, became possible due to recent technical advances of the MRSI method. The pathophysiologic role of membrane dysregulation in GBA-associated PD is currently unclear. An increased synthesis of the membrane phospholipid PtdCho due to activation of the enzyme CCT was found in rat neurons treated with a gluco-

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**Figure** Schematic model of altered neuronal membrane metabolism in patients with Parkinson disease (PD) with heterozygous glucocerebrosidase (GBA) mutations (GBA-PD)

Increased turnover of membrane-related ethanolamine-containing compounds in terms of an altered neural membrane metabolism due to increased synthesis of choline-containing compounds in the putamen of patients with PD with heterozygous GBA mutations according to the following findings: 1. increased synthesis of the membrane phospholipid phosphatidylcholine due to activation of the enzyme cytidylyltransferase in Gaucher disease. 2. Increased concentration of the membrane degradation product glycerophosphoethanolamine, primarily recognized in the putamen, but not in the midbrain of GBA-PD. ADP = adenosine diphosphate; ATP = adenosine triphosphate.
The local coincidence of increased membrane degradation products in brain areas with clearly reduced NAA levels raises the question whether membrane dysfunction is primarily responsible for the neurodegenerative process or rather involved in terms of an epiphenomenon. Because the reductions of NAA levels did not correlate with GPE increases, the latter is unlikely, but a clear causal relationship between both parameters cannot be proven by our data. Recently, very interesting experimental data became available that shed light on a possible pathophysiologic relationship between altered membrane characteristics and abnormal α-synuclein deposition in the brain. For example, a higher proportion of PtdCho in membrane lipid bilayers compared to PtdEth seems to decrease the membrane-binding of α-synuclein. Moreover, glycosphingolipids including glucocerebrosides may interfere with the binding of α-synuclein. The membrane-binding of helical α-synuclein prevents the toxic fibrillization and aggregation of α-synuclein in LBs. Other studies suggest that α-synuclein accumulation is promoted by impaired degradation of glucocerebrosides due to enzymatic, lysosomal, or ubiquitin-proteasome dysfunction. Overexpression of human mutant GBA proteins led to α-synuclein accumulation in a cell culture model of PD. Very recent findings suggested a bidirectional pathogenic relation between the loss of glucocerebrosidase activity in GD and α-synuclein aggregation. Finally, the widespread LB-type pathology as important neuropathologic hallmark of GBA-related PD strengthens the hypothesis that GBA-PD is a synucleinopathy.

Mesostriatal membrane metabolites but not energy status were altered in our patients with PD with GBA mutations, whereas the contrary situation was found in idiopathic PD. Different metabolic profiles in MRSI implicate a diverging pathogenesis in both disease entities. This hypothesis is supported by a recent study showing that patients with GBA-PD but not idiopathic PD had lower CSF levels of fatty acids. However, it has to be kept in mind that we included the GBA and idiopathic PD cohorts in 2 separate MRSI studies and did not directly compare them to each other. This explains the fact that both subgroups were not exactly matched for age, sex, and disease duration. For example, GBA-PD had slightly higher UPDRS-III values despite slightly shorter disease duration and a tendency to younger ages at study inclusion and at disease onset. These clinical characteristics are in line with previous observations that GBA-PD present with a more severe clinical phenotype than patients with idiopathic PD. In addition, patients with idiopathic PD from our previous study were not tested for GBA mutations. Therefore, further studies comparing patients with PD with and without GBA mutations as well patients with other forms of hereditary parkinsonism are required to evaluate whether the disturbances of membrane metabolism along with a preserved energy status are specific for GBA mutation carriers. If the MRSI results presented in this article can be validated in larger future studies, subjects with parkinsonism due to GBA mutations should be excluded.
from clinical trials addressing the question of disease-modifying therapies in idiopathic PD.

AUTHOR CONTRIBUTIONS
K. Brockmann, K. Srujies, R. Hilker, D. Berg, and E. Hattingen designed the study. K. Brockmann, K. Srujies, R. Hilker, S. Baudrexel, J. Magerkurth, C.D. Merten, and E. Hattingen obtained the data. K. Brockmann and U. Pilatus performed the statistical analysis. K. Brockmann wrote the first manuscript. All authors were involved in interpretation of the data and critical revision of the manuscript and gave their final approval. R. Hilker, D. Berg, and E. Hattingen supervised the study.

DISCLOSURE
K. Brockmann has received honoraria for lectures from GlaxoSmithKline and Orion Pharma as well as travel grants from GlaxoSmithKline, UCB, and the Movement Disorders Society. R. Hilker has received honoraria from Medtronic, Orion Pharma, GlaxoSmithKline, Teva, Cephalon, Desitin, Boehringer Ingelheim, Archimede Pharm GmbH (speaker honoraria), and for serving on advisory boards for Cephalon GmbH as well as grants from Medtronic, Cephalon (travel grants), Bundesministerium für Bildung und Forschung, Deutsche Parkinson Vereinigung, and Medical Faculty Goethe University Frankfurt am Main (research funding). U. Pilatus and S. Baudrexel report no disclosures. K. Srujies has received honoraria for lectures from TEVA, J. Magerkurth and A.-K. Hauser report no disclosures. C. Schulte has received travel grants from GlaxoSmithKline, UCB, and the Movement Disorders Society. I. Co eti received financial contributions from Novartis Pharma AG for CME workshops and honoraria for taking part in expert meetings and advisory boards. She has received honoraria for presentations from Boehringer Ingelheim, TEVA Pharma GmbH, Lundbeck, Desitin, Orion Pharma, and UCB. C.D. Merten reports no disclosures. T. Gasser serves as an editorial board member of Parkinsonism and Related Disorders and is associate editor of Journal of Parkinson’s Disease. His research is funded by Novartis Pharma, the Federal Ministry of Education and Research (BMBF) (NGFN-Plus and ERA-Net NEURON), the Helmholtz Association (HeiMA, Helmholtz Alliance for Health in an Ageing Society), and the European Community (MeFoPa, Mendelian Forms of Parkinsonism). He received speaker’s honoraria from Novartis, Merck-Serono, Schwarz Pharma, Boehringer Ingelheim, and Valeant Pharma and royalties for his consulting activities from Cephalon Pharma and Merck-Serono. He holds a patent concerning the LRRK2 gene and neurodegenerative disorders. D. Berg has received research grants from the Michael J. Fox Foundation, BnBF, Janssen Pharmaceutica, TEVA Pharma GmbH, dPV (German Parkinson’s Disease Association), Solvay, University of Tübingen, honoraria for talks from Novartis, UCBSchwarzPharma, GSK, TEVA, Lundbeck, Merck, Boehringer, and for advisory boards from Novartis, UCBSchwarzPharma, GSK, and TEVA. E. Hattingen reports no disclosures. Go to Neurology.org for full disclosures.

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