Positron Emission Tomography and Magnetic Resonance Spectroscopy of Cerebral Glycolysis in Children with Congenital Lactic Acidosis

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Congenital lactic acidosis with neurological symptoms may be due to a variety of disorders of energy metabolism. We investigated whether positron emission tomography (PET) and proton magnetic resonance spectroscopy (1H MRS) are capable of demonstrating specific changes to facilitate diagnosis. A corresponding increase of cerebral lactate (with MRS) and rate of glycolysis (with PET) was observed in 2 children with biochemical evidence of defective mitochondrial respiration. No such increase was noted in a child with lactic acidosis due to stress and exercise but normal respiratory chain activity, and in a control case with an epilepsy syndrome without evidence of primary changes of energy metabolism. The results suggest that defects of oxidative phosphorylation may cause a massive increase of glycolysis to cover energy requirements, with corresponding accumulation of lactate in brain tissue. This mechanism can now be demonstrated in vivo and, with further experience, may potentially be used as a diagnostic marker of respiratory chain disorders in brain tissue.


Congenital lactic acidosis (CLA) is a symptom that can occur as a result of an inborn error in the pathway responsible for the metabolism of pyruvate. Common etiologies include defects of the pyruvate dehydrogenase complex, pyruvate carboxylase, mitochondrial respiratory chain enzymes, or the Krebs cycle [1, 2]. The accompanying clinical signs and symptoms may vary considerably depending on the type and the severity of defect. Diagnosis is usually based on biochemical, radiological, and pathological studies. However, evaluation is often invasive, time consuming, and is not always conclusive.

Positron emission tomography (PET) has been used in the evaluation of mitochondrial diseases because it provides a quantitative tracer method for regional measurements of glucose and oxygen metabolism in brain tissue as well as blood flow. A study using 2-[18F]-fluoro-2-deoxyglucose (FDG), [15O] oxygen, and [17O] carbon dioxide in a series of adult patients with mitochondrial encephalomyopathy showed an altered stoichiometry in glucose and oxygen utilization resulting from aerobic glycolysis to lactate [3]. A similar study examining patients with a clinical phenotype of CLA known by the acronym MERRF for myoclonus epilepsy and ragged-red fibers [4], however, revealed no signs of increased aerobic glycolysis. These authors found a chronically low rate of oxidative metabolism [5]. An adult patient with a mitochondrial encephalomyopathy (probable MERRF) also showed a severe decrease in the cerebral metabolic rate of glucose (CMRglc) [6].

Another imaging tool that may be helpful in the noninvasive examination of normal and abnormal brain development is image-guided localized proton magnetic resonance spectroscopy (1H MRS). The information obtained from localized proton MR spectroscopy can be supplemented by information on the spatial distribution of metabolites using 1H MR spectroscopic imaging (SI). In several studies [7-10] increased peaks for lactate have been described in children with Leigh disease [11], a form of CLA that can be caused by a defect in oxidative phosphorylation or pyruvate metabolism.

FDG PET and 1H MRS are complementary with...
regard to investigating the rate of glycolysis. The former basically measures the rate of FDG phosphorylation by hexokinase, which is nearly irreversible and therefore reflects total, oxidative and nonoxidative, glycolytic activity; the latter assesses lactate, which is the principal product of nonoxidative glycolysis. We therefore performed both, FDG PET and $^1$H MRS, for direct comparison of glycolytic rates and lactate levels in 4 children, 2 of whom had biochemical evidence of impaired mitochondrial respiration.

Materials and Methods
This study was performed in accordance with the policies of the Ethics Committee of the Medical Faculty of Cologne University. With the informed consent of parents, all patients were initially examined with PET and MRS under the tentative diagnosis of a congenital metabolic disturbance. $CMR_{gk}$ values were compared with literature data for normal children of birth age to 1 year and 1 to 2 year [12], as listed in Table 1. MRS data of patients were compared with MRS data obtained in children without neurological disorders [13]. Amino acid screening in urine was performed using thin-layer chromatography, or quantitatively in urine and serum using a reverse-phase high-performance liquid chromatographic (HPLC) method. Urinary organic acids were determined quantitatively using gas chromatography—mass spectroscopy. Lactate, pyruvate, β-hydroxybutyrate, acetacetaate, and carnitine concentrations were measured enzymatically. Final diagnosis was based on clinical history, physical examination, imaging studies, laboratory tests, and pathology.

Mitochondrial Studies
Enzyme activities of cytochrome $c$ oxidase, NADH:Q oxidoreductase, succinate:cytochrome $c$ oxidoreductase, pyruvate dehydrogenase complex, and citrate synthetase were measured in skeletal muscle specimens (taken from musculus quadriceps femoris) at the Department of Pediatrics, University Hospital Nijmegen, The Netherlands, using the procedures described by Fischer and colleagues [14] and Korenke and associates [15].

Positron Emission Tomography
$CMR_{gk}$ was studied using FDG PET [16] on a 7-slice positron camera (Scanditronix PC384) with an in-plane resolution of 7.8 mm at a slice thickness of 11 mm or, in one case (Patient 3), on a 47-slice camera (Siemens-CTI ECAT EXACT 921) with 6-mm transaxial and 5-mm axial resolution. After a rapid intravenous bolus injection of FDG (3.7—7.4 MBq/kg of body weight), patients were scanned for a total period of 50 to 60 minutes in a dimly lit room with low ambient noise. Images were recorded with the 7-slice scanner in two table positions from 30 to 40 and 40 to 50 minutes after injection, respectively, yielding a total of 14 slices comprising nearly the entire brain; whereas with the 47-ring scanner, the whole brain was assessed without changing the table position from 20 to 60 min. Plasma activity was measured in multiple arterial blood samples. $CMR_{gk}$ was calculated pixel by pixel with rate constants $K_i$ and $k_3$ adjusted to measured tissue activity [17], and a fixed lumped constant value of 0.42.

All images were initially analyzed visually. Each image was then coregistered three-dimensionally to a reference PET image in standard position (transaxial plane parallel to the intercommissural line) using a multipurpose match program [18] with striatum and thalamus as major landmarks. Regions of interest (ROIs) were placed on multiple transaxial slices using a PC adaptation of an interactive mapping program [19], guided by the atlas of Matsui and Hirano [20], and $CMR_{gk}$ was calculated for major brain structures including cerebral lobes, caudate nucleus, lentiform nucleus, thalamus, cerebellar cortex, and brainstem.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case 1 (Cerebral Palsy)</th>
<th>Case 2 (Possible Complex IV Defect)</th>
<th>Reference Values$^a$</th>
<th>Case 3 (Complex I Defect)</th>
<th>Case 4 (Congenital Epilepsy Syndrome)</th>
<th>Reference Values$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20 mo</td>
<td>14 mo</td>
<td>1—2 yr</td>
<td>2 wk</td>
<td>1 mo</td>
<td>Birth to 1 yr</td>
</tr>
<tr>
<td>Cerebral hemisphere</td>
<td>15.53</td>
<td>53.13</td>
<td>27.36 ± 6.46</td>
<td>96.43</td>
<td>18.20</td>
<td>19.30 ± 4.79</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>15.76</td>
<td>48.13</td>
<td>29.65 ± 7.30</td>
<td>84.57</td>
<td>18.20</td>
<td>19.68 ± 4.84</td>
</tr>
<tr>
<td>Parietal cortex</td>
<td>16.88</td>
<td>54.86</td>
<td>28.76 ± 7.08</td>
<td>87.79</td>
<td>19.22</td>
<td>20.23 ± 5.03</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>15.85</td>
<td>55.63</td>
<td>28.67 ± 8.54</td>
<td>82.29</td>
<td>20.29</td>
<td>20.00 ± 4.23</td>
</tr>
<tr>
<td>Occipital cortex</td>
<td>15.86</td>
<td>59.65</td>
<td>30.39 ± 7.00</td>
<td>78.58</td>
<td>17.55</td>
<td>20.54 ± 5.08</td>
</tr>
<tr>
<td>Sensorimotor cortex</td>
<td>17.13</td>
<td>50.26</td>
<td>29.73 ± 7.44</td>
<td>103.02</td>
<td>21.51</td>
<td>22.17 ± 5.11</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>15.73</td>
<td>54.86</td>
<td>29.61 ± 6.40</td>
<td>108.62</td>
<td>21.60</td>
<td>20.53 ± 4.89</td>
</tr>
<tr>
<td>Caudate nuclei</td>
<td>8.67</td>
<td>69.81</td>
<td>28.77 ± 7.34</td>
<td>189.70</td>
<td>20.08</td>
<td>22.95 ± 7.06</td>
</tr>
<tr>
<td>Lenticular nuclei</td>
<td>14.04</td>
<td>81.51</td>
<td>32.36 ± 8.04</td>
<td>199.24</td>
<td>26.16</td>
<td>26.42 ± 7.14</td>
</tr>
<tr>
<td>Thalamus</td>
<td>14.00</td>
<td>39.40</td>
<td>29.48 ± 5.90</td>
<td>216.96</td>
<td>19.03</td>
<td>27.15 ± 7.86</td>
</tr>
<tr>
<td>Cerebellar cortex</td>
<td>15.61</td>
<td>26.66</td>
<td>19.50 ± 5.00</td>
<td>77.24</td>
<td>17.60</td>
<td>17.59 ± 2.70</td>
</tr>
<tr>
<td>Brainstem</td>
<td>12.53</td>
<td>37.11</td>
<td>21.17 ± 3.60</td>
<td>145.10</td>
<td>23.09</td>
<td>18.63 ± 3.81</td>
</tr>
</tbody>
</table>

$^a$Mean ± SD, from Chugani and colleagues (1987).
Table 2. Metabolic Laboratory Values (Ranges of Values Obtained During Course of Patient Hospitalization)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum lactate (mmol/L)</td>
<td>0.6-2.4</td>
<td>2.0-5.0</td>
<td>2.5-4.4</td>
<td>3.5-11.2</td>
<td>0.9-2.3</td>
</tr>
<tr>
<td>CSF lactate (mmol/L)</td>
<td>&lt;1.5</td>
<td>2.6</td>
<td>4.1-8.0</td>
<td>7.7</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td>Urine lactate (µmol/mmol creatinine)</td>
<td>&lt;100</td>
<td>84-112</td>
<td>130-160</td>
<td>2,187</td>
<td>a</td>
</tr>
<tr>
<td>Serum pyruvate (mmol/L)</td>
<td>0.04-0.06</td>
<td>0.12-0.19</td>
<td>0.06-0.13</td>
<td>0.08-0.18</td>
<td>0.09</td>
</tr>
<tr>
<td>CSF pyruvate (mmol/L)</td>
<td>0.04-0.06</td>
<td>a</td>
<td>0.13</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Serum lactate/pyruvate ratio</td>
<td>&lt;20</td>
<td>16-27</td>
<td>34</td>
<td>68</td>
<td>a</td>
</tr>
<tr>
<td>CSF lactate/pyruvate ratio</td>
<td>&lt;15</td>
<td>a</td>
<td>30</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Serum alanine (µmol/L)</td>
<td>120-480</td>
<td>80</td>
<td>1,595</td>
<td>508-755</td>
<td>162</td>
</tr>
</tbody>
</table>

*Not available.

CSF = cerebrospinal fluid.

**Magnetic Resonance Spectroscopy**

MR investigations were performed using a 1.5-T MR system (Gyroscan S15, Philips). Localized spectra were obtained following conventional MR imaging using a 90°–180°–180° spin-echo sequence with an echo time (TE) of 136 msec. Where applicable, additional measurements using echo times of 272 msec were performed to confirm peak assignment of lactate. Repetition times were 2 seconds. The ROIs were determined from the MR images and comprised the basal ganglia. The obtained spectra were compared with the results of measurements in 11 infants, with postconceptual age of 35 to 132 weeks, who were classified as neurologically normal and did not suffer from known metabolic disorders or other disease [21]. Resonances of choline-containing compounds (Cho) at 3.2 ppm, creatine and phosphocreatine (Cr) at 3.0 ppm, N-acetylaspartate (NAA) and related compounds at 2.0 ppm, and lactate, if present, at 1.3 ppm (inverted with TE 136 msec, positive with TE 272 msec) were evaluated. Signal–intensity ratios were calculated in the frequency domain from the area under the respective signals in the phase-corrected real part of the complex MR spectrum. Lactate concentrations were calculated using brain water (Case 3) and the Cho signal (Case 2) as an internal concentration standard. A brain water content of 80% and a concentration of spectroscopically visible choline-containing compounds of 2 mmol/L was assumed [22]. The metabolite resonances were corrected for relaxation and saturation effects.

In Case 2, additional spectroscopic images were produced from a representative slice of 2.8-cm thickness using a combination of localized excitation and phase-encoded acquisition, applying 32 × 32 phase-encoding steps over a field of view of 225 × 225 mm. The data can be presented as maps representing the distribution of specific biochemical compounds with a nominal in-plane resolution of 7.0 mm, or as sets of spatially resolved spectra, to allow a more precise evaluation of specific foci of interest. Technical details have been described elsewhere [23].

For PET and MRS studies, patients were sedated using pentobarbital with an initial dose of 3 mg/kg of body weight followed by 1 to 2 mg/kg of body weight per hour intravenously.

**Patients and Results**

**Case 1**

The patient was a normal boy until the age of 3 months when he developed progressive hypotonicity and atonic movements. Parents were consanguineous (Grade I). At the age of 1.5 years, he had severe psychomotor delay and a spastic paraplegia. Laboratory evaluation demonstrated an elevated lactate level (Table 2); however, a pyruvate loading test demonstrated a normal pyruvate clearance from blood, which indicates normal pyruvate metabolism [24]. MRI at 20 months showed increased signal on the T2-weighted image and decreased signal on the T1-weighted image in the lateral putamen. MRS was normal. PET at 20 months revealed a global decrease in glucose metabolism with markedly decreased values in the caudate nuclei, lentiform nuclei, thalamus, and frontal cortex (see Table 1, Fig 1). Electrophysiological studies were without abnormality. A muscle biopsy was unremarkable and no mitochondrial abnormalities were found (Table 3). An analysis for chromosomal defects was negative. The patient's condition progressively worsened and he died at the age of 2 years due to sepsis. The final clinical diagnosis was cerebral palsy due to an unidentified metabolic disorder. The lactic acidosis was probably caused by severe physical stress and exercise. Brain autopsy revealed a symmetrical glial poliodystrophy of cortex.

**Case 2**

The patient was the daughter of consanguineous parents (Grade I), born at term after normal pregnancy and delivery. At the age of 3 months she suffered a generalized seizure. At 5 months, she began having recurrent episodes of lactic acidosis (see Table 2). She had severe psychomotor retardation, microcephaly, rolling eye movements, optic atrophy, and severe muscular hypotonia. MRI at 4 months showed cortical atrophy and widening of the cerebrospinal fluid (CSF) spaces. MRS of the right basal ganglia displayed decreased signal intensity ratios of NAA to choline-containing compounds (NAA/Cho), normal ratio of creatine and phosphocreatine to choline-containing compounds (Cr/Cho), and large signals from lactate (3 ± 1 mmol/L). Metabolite maps of a 28-mm-thick slice comprising...
Fig 1. Transaxial metabolic maps at the basal ganglia level of all 4 patients obtained with 2-{\textsuperscript{18}F}fluoro-2-deoxyglucose positron emission tomography. The individual range of values (in \(\mu\text{mol/100 gm/min}\)) displayed with a rainbow scale is shown below each image. (Top row) Cases 2 and 3 with mitochondrial enzyme disorder and increased CMR\(_{\text{g}}\), most pronounced in the basal ganglia. (Bottom row) Cases 1 and 4 without evidence of mitochondrial impairment and low metabolism.

Mitochondrial encephalopathy:

cerebral palsy
0 - 24

complex 1 defect
0 - 200

control
0 - 120

congenital epilepsy
0 - 40

the basal ganglia demonstrated increased lactate in the entire volume (Fig 2). Evaluation with PET (see Fig 1) at 14 months showed remarkably increased metabolic rates of glucose in all regions, with the largest increases in the caudate nuclei, lentiform nuclei, and parietooccipital cortex (see Table 1). Evoked potential (EP) studies were abnormal. Electroencephalogram (EEG) was slow without focal abnormalities. Electromyography (EMG) and nerve conduction velocity (NCV) examinations were normal. A muscle biopsy revealed a mild nonspecific myopathy. Analysis of mitochondrial respiratory chain enzymes revealed a defect in complex IV (cytochrome \(c\) oxidase). The pa-
### Table 3. Activities of Respiratory Chain Enzymes and Pyruvate Dehydrogenase Complex

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Tissue</th>
<th>Cytochrome c Oxidase</th>
<th>NADH:Q&lt;sub&gt;1&lt;/sub&gt; Oxidoreductase</th>
<th>Succinate: Cytochrome c Oxidoreductase</th>
<th>Pyruvate Dehydrogenase Complex</th>
<th>Citrate Synthetase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cerebral palsy (lactic acidosis due to physical stress)</td>
<td>Muscle, frozen</td>
<td>81</td>
<td>27</td>
<td>7.5</td>
<td>3.0</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>Possible complex IV defect</td>
<td>Muscle, frozen</td>
<td>67</td>
<td>16</td>
<td>9.7</td>
<td>4.6</td>
<td>113</td>
</tr>
<tr>
<td>3</td>
<td>Complex I defect</td>
<td>Muscle, fresh</td>
<td>78</td>
<td>1.1</td>
<td>22</td>
<td>1.6</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Liver&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>59</td>
<td>1.7</td>
<td>n.d.</td>
<td>n.d.</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Brain&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>117</td>
<td>0</td>
<td>n.d.</td>
<td>n.d.</td>
<td>223</td>
</tr>
<tr>
<td>4</td>
<td>Congenital epilepsy syndrome</td>
<td>No biopsy taken</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enzyme activities given in milliunits per mg protein (600 g of supernatant was used in case of fresh muscle; total homogenate was used in case of frozen muscle). Citrate synthetase was used as mitochondrial reference enzyme.

<sup>a</sup>Denotes post-mortem tissue.


Tient's condition deteriorated rapidly at the age of 18 months, and she died shortly thereafter due to sepsis and cardiovascular collapse. An autopsy was not performed.

**Case 3**
The patient was a term male newborn delivered spontaneously to consanguineous parents (Grade I) after an uncomplicated pregnancy. On the fifth day postpartum he developed hypotonia as well as increasing hyperglycemia and metabolic acidosis. He eventually required mechanical ventilation secondary to increasing respiratory insufficiency. At 7 days, he developed a severe lactic acidosis (see Table 2) and suffered generalized seizures. Magnetic resonance imaging (MRI) at 2 weeks revealed increased signal intensity predominantly on T2-weighted images in the frontal lobes. MRS of the basal ganglia (Fig 3) revealed markedly decreased NAA/Cho and Cr/Cho ratios with a large lactate signal (8 ± 1 mmol/L). PET at 2 weeks demonstrated globally elevated CMR<sub>glc</sub> in all regions with the largest increases in the thalamus, caudate and lenticular nuclei, and brainstem (see Table 1). EP studies suggested a generalized central nervous system (CNS) disturbance. EEG showed highly irregular background activity with superimposed multifocal epileptic foci. Muscle biopsy was normal. Analysis of mitochondrial respiratory chain enzymes in skeletal muscle, and post-mortem studies of liver and brain tissue, revealed a defect in complex I (NADH—coenzyme Q<sub>1</sub> oxidoreductase) (see Table 3). A chromosome analysis was unremarkable. The child experienced a rapid decline during the third week and died on his 24th day due to cardiovascular collapse. Neuropathological examination revealed symmetrical spongy necrotizing lesions in both hemispheres, the basal ganglia, the thalamus, and the lower brainstem.

**Case 4**
The patient was the daughter of nonconsanguineous parents, born at term after an uneventful pregnancy and delivery. On the second day postpartum, she began experiencing cyanotic episodes that progressively increased in frequency and later became associated with tonic–clonic movements of the arms and legs. Seizure-like episodes decreased after the patient was treated with corticotropin (ACTH). She had hypotonia, tachypnea, and increased respiratory tract sections. Laboratory tests were essentially normal. MRI was unremarkable. MRS showed no abnormal metabolism products, but compared with other signals, NAA signal intensity was below normal level. PET at 1 month revealed a normal metabolic rate of glucose in all regions except for mildly decreased rates in the thalamus (see Table 1). Upon visual evaluation there was an area of increased metabolism in the right mesiotemporal region that could have represented an epileptic focus. EEG showed multifocal spikes with alternating areas of focal
Fig 2. 1H Magnetic resonance spectroscopic study of Patient 2. (A) Axial proton density-weighted image with volume of interest (VOI) indicated. (B) Lactate map within VOI. The numbers indicate the origin of spatially resolved spectra displayed in C. The bright areas near the frontal border of the VOI originate from contaminations by signal of retroorbital and skull fat. (C) Selected spectra demonstrating lactate as a doublet peak with a relative maximum in locations 8 and 9; whereas the broader signal at the same position in locations 1 and 16 indicates contaminations from fat.

Discussion
Results obtained from PET measurements on cerebral glucose metabolism and MRS provide evidence that patients with congenital lactic acidosis due to mito-
Lac
to the massive increase of metabolism observed in Pa­
tient 3 with its maximum in the basal ganglia.

The extent of increase in the metabolic rates may
depend on the type and severity of defect [26]. The
substantially higher rates of glucose metabolism and,
correspondingly, the higher cerebral lactate concentra­
tion in Case 3 compared with Case 2 agree with the
much more decreased activity of the respiratory chain
capacity in Case 3. The cytochrome \( c \) oxidase activity
in Patient 2's muscle was reduced only when expressed
per citrate synthetase activity. In fibroblasts this en­
zyme showed a normal activity.

Glucose uptake and lactate accumulation are two as­
pects of glycolysis. The large resonance peaks for lac­
tate in Cases 2 and 3 show that high amounts of lactate
were present in brain tissue but not in Cases 1 and 4.

Chondriuual defects may have a globally accelerated state
of cerebral glucose metabolism with relatively higher
rates of metabolism in the thalamus and basal ganglia.
Such high rates of metabolism are probably due to a
change in the utilization of glucose: the cell's demand
for energy cannot be covered by defective oxidative
phosphorylation but initiates the glycolytic pathway in
which glucose is catabolized to lactate for the produc­
tion of ATP. To compensate for the smaller yield of
ATP per molecule of glucose from this process, the
rate of glucose breakdown has to be much higher.
The massive increase of glycolysis was observed in spite of
a possible reduction of physiological \( CMR_{glc} \) due to
sedation.

The relatively higher rates found in the basal ganglia
and thalamus probably reflect the maturational changes
in metabolism that are seen during early brain develop­
ment. Chugani and co-workers [12] described that the
developmental increases in \( CMR_{glc} \) occur initially in
the thalamus, the basal ganglia, and the sensorimotor
cortex. Thus, the higher rates seen in these areas prob­
ably result because these structures begin developing
first and express their defect earlier than other sur­
rounding structures. In principle, cortical epileptic dis­
charges, as recorded by EEG in Patients 3 and 4, could
also contribute to the increase of \( CMR_{glc} \). In absence
of an epileptic seizure such epileptic discharges may
lead to small cortical hypermetabolic foci [25], but not

Previous PET studies in adults with mitochondrial
disorders showed globally decreased rates in metabo­
lism [3, 5, 6]. Two of these studies also demonstrated
relatively larger decreases in the thalamus [5, 6] and
basal ganglia [5]. Most likely that type of hypometabo­
lism is the result of chronic brain damage. A similar
pattern was seen in our Patient 1. Chronic energy failure
has been reported in a recent \( ^{13} \)P MRS study [27].
In one study [5] oxidative metabolism was compared
with glucose metabolism and oxidation turned out to
be relatively more impaired than glycolysis, probably
still indicating increased nonoxidative glycolysis in that
chronic stage. Possibly, our Patients 2 and 3 had a more
severe form of the disease with a massive increase of
glycolysis that could not be maintained for a long time.
Theoretically, massive lactate accumulation could exert
toxic effects [28] and thus contribute to the unfortu­
nate outcome; but increased cerebral lactate signals
have also been described in chronic cases of mitochon­
drial encephalomyopathies [29].

PET and MRS now are able to demonstrate the met­
abolish consequences of impaired mitochondrial respiration noninvasively in brain tissue. Although mitochondrial diseases usually can be diagnosed by biochemical analysis of muscle biopsies, the severity of impairment may be different in muscle and brain, as indicated by our Case 2. Furthermore, the severity of the clinical symptoms is often not well correlated with the residual activity of the affected enzyme. Therefore, with further experience, the imaging techniques may possibly provide an estimate of the severity of brain involvement and may permit diagnosis also in cases with little or no muscle involvement. In addition, effectiveness of therapy could be investigated by these techniques.

References