MRI and clinical features of maple syrup urine disease: preliminary results in 10 cases

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PURPOSE
We aimed to evaluate the magnetic resonance imaging (MRI) and clinical features of maple syrup urine disease (MSUD).

METHODS
This retrospective study consisted of 10 MSUD patients confirmed by genetic testing. All patients underwent brain MRI. Phenotype, genotype, and areas of brain injury on MRI were retrospectively reviewed.

RESULTS
Six patients (60%) had the classic form of MSUD with BCKDHB mutation, three patients (30%) had the intermittent form (two with BCKDHA mutations and one with DBT mutation), and one patient (10%) had the thiamine-responsive form with DBT mutation. On diffusion-weighted imaging, nine cases presented restricted diffusion in myelinated areas, and one intermittent case with DBT mutation was normal. The classic form of MSUD involved the basal ganglia in six cases; the cerebellum, mesencephalon, pons, and supratentorial area in five cases; and the thalamus in four cases, respectively. The intermittent form involved the cerebellum, pons, and supratentorial area in two cases. The thiamine-responsive form involved the basal ganglia and supratentorial area.

CONCLUSION
Our preliminary results indicate that patients with MSUD presented more commonly in classic form with BCKDHB mutation and displayed extensive brain injury on MRI.

Maple syrup urine disease (MSUD) is an inherited disease characterized by an impaired metabolism of branched-chain amino acids (BCAA), which is caused by deficiency of the branched-chain α-ketoacid dehydrogenase (BCKD) complex (1). Death within the first year of life is mainly caused by metabolic acidosis. Survivors always have mental retardation, spastic paralysis, cortical blindness, and other neurologic disability. Symptoms are less severe and the cerebral symptoms more delayed in the intermittent and thiamine-responsive forms of MSUD (2). Despite attempts to manage the symptoms of MSUD, most patients suffer from severe and permanent brain damage (3). The mechanisms of brain damage in patients with MSUD are still unclear. Some have suggested that accumulation of BCAA in the brain inhibits the activity of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, disrupting the citric acid cycle and consequently the synthesis of amino acids, causing cerebral edema and abnormal myelination (4).

Diffusion-weighted imaging (DWI) has uncovered alterations in the white and grey matter of newborns with MSUD (5–7). In the present study, we retrospectively analyzed clinical and magnetic resonance imaging (MRI) features of MSUD.

Methods

Patients
Between May 2005 and August 2014, 10 patients (five male and five female patients) were diagnosed with MSUD by tandem mass spectrometry, gas chromatography-mass spec-
were scanned while sedated; sedation was
secured for scanning using a sponge pad (GE Signa). The patient's head was
twice speed superconducting MRI equip-
ment. 

**Image analysis**

MRI scans were performed using a 3.0 T
twinspeed superconducting MRI equip-
ment (GE Signa). The patient's head was
secured for scanning using a sponge pad
and an 8-channel head coil. Eight infants
were scanned while sedated; sedation was
induced by a 0.5 mL/kg dose of 10% chlo-
ral hydrate. The imaging protocol involved
T1-weighted fluid-attenuated inversion
recuperation (T1-FLAIR; repetition time (TR)
2200 ms, echo time (TE) 24 ms, section
thickness 5 mm) and T2-FLAIR (TR 8500
ms, TE 120 ms, section thickness 5 mm).
Sagittal T2-weighted imaging (TR 2200
ms, TE 90 ms) and axial DWI (TR 10000 ms,
TE 70 ms, b=0 s/mm² and b=1000 s/mm²)
were also included in the scan. Among the
patients only three had a follow-up MRI
study.

**Phenotype and genotype**

The severity of the clinical manifestations
of all patients were assessed by a professor
of pediatrics. Genetic testing and mutation
analysis was performed in our Department
of Pediatrics. 

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset</th>
<th>Clinical outcome</th>
<th>Clinical phenotype</th>
<th>Genetic subtype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 days</td>
<td>Severe neurodevelopment delay</td>
<td>Classic</td>
<td>E1β</td>
<td>c[93_103dup11]</td>
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<tr>
<td>2</td>
<td>6 years</td>
<td>Learning difficulties</td>
<td>Intermittent</td>
<td>E1α</td>
<td>c[712G&gt;A]+c[889C&gt;T]</td>
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<td>3</td>
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<tr>
<td>4</td>
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<td>Moderate neurodevelopment delay</td>
<td>Classic</td>
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<td>c[391G&gt;A]+c[1006G&gt;A]</td>
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<tr>
<td>5</td>
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<td>Learning difficulties</td>
<td>Intermittent</td>
<td>E1α</td>
<td>c[1250C&gt;T]+c[475C&gt;T]</td>
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<tr>
<td>6</td>
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<td>Died</td>
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<td>c[660A&gt;T]+c[920C&gt;T]</td>
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<td>Classic</td>
<td>E1β</td>
<td>c[391G&gt;A]+c[920C&gt;T]</td>
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<tr>
<td>8</td>
<td>6 days</td>
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<td>Classic</td>
<td>E1β</td>
<td>c[297T&gt;C]+c[297T&gt;C]</td>
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<tr>
<td>9</td>
<td>3 days</td>
<td>Slight neurodevelopment delay</td>
<td>Thiamine-responsive</td>
<td>E2</td>
<td>[IVS1+5 G&gt;C]+801delA</td>
</tr>
<tr>
<td>10</td>
<td>2 months</td>
<td>Normal neurodevelopment</td>
<td>Intermittent</td>
<td>E2</td>
<td>[IVS4+2 T&gt;G]</td>
</tr>
</tbody>
</table>

**Table 1. Clinical characteristics of the MSUD patients**

MSUD, maple syrup urine disease.

**Main points**

- Extensive alterations in brain tissue and
  specific **BCKDHB** mutations are most
  common in the classic form of maple syrup
  urine disease (MSUD).
- Minor alterations in brain parenchyma
  and specific mutations in the **BCKDHA**
  and **DBT** genes were found in patients with
  the intermittent form and thiamine-responsive
  form of MSUD.
- Diffusion-weighted imaging is the best
  choice for detecting MSUD encephalopathy
  in neonates.

**Results**

Six patients were diagnosed with the clas-
ic form and carried mutations in the **BCK-
DHB** gene. Two patients with the intermit-
tent form of MSUD had a **BCKDHA** mutation
(patient 2 and patient 5) and one patient
had a mutation in the **DBT** gene (patient
10). The patient with thiamine-responsive
MSUD carried a **DBT** mutation (patient 9).

Phenotype, genotype, and brain abnormal-
ities are summarized in Tables 2 and 3.

Eight patients were less than 1-year-old at
the first onset of disease and the other two
patients were older than 1 year (Table 1).
Median age of the patients at the first MRI
scan was 11 months (12 days to 11 years).
Six patients were diagnosed with the classic
form, three with the intermittent form and
one with the thiamine-responsive form. The
severity of the clinical phenotypes (unex-
plained lethargy, developmental delay, im-
paired motor function, mental retardation,
feeding difficulty and maple syrup odor of
the urine) varied considerably between the
patients. More severe clinical phenotypes
were observed in patients with the classic
form of MSUD (Table 1).

The brain parenchyma of all patients was
analyzed by MRI and the findings were sum-
marized in Table 2. Only one patient with a
**DBT** mutation showed a normal MRI scan.
Two children with intermittent MSUD and
one with thiamine-responsive MSUD had
increased signal at T2-FLAIR. Three patients
(patients 2, 5, and 6) had MRI follow-up
after six months. The imaging findings of
patients 2 and 5 showed no progress com-
pared with their initial MRI, but in patient 6,
MRI revealed an expansion of the supraten-
torial area and loss of edema in the thala-
mus and centrum semiovale (Fig. 1).

All patients with the classic form of the
disease (n=6) showed involvement of a
wide range of brain parenchyma, including
the basal ganglia in six cases, the cerebel-
lum, mesencephalon, pons, and supraten-
torial area in five cases, and the thalamus in
four cases (Fig. 2).
Discussion

MSUD is classified into classic, intermediate, thiamine-responsive, and E3-deficient forms on the basis of age of onset of the disease, severity of clinical presentation, and response to thiamine (8). Patients with the classic form are normal at birth, but symptoms suggestive of metabolic crisis already begin to manifest at the end of the first week of life (9). In agreement with previous findings, the thiamine-responsive form had a better prognosis, followed by the intermittent form and finally the classic form, which had the worst prognosis (10).

The BCKD complex is composed of four subunits named E1α, E1β, E2, and E3, around a cubic core of 24 identical dihydrolipoyl transacylase subunits of E2, encoded by the DBT gene (10). Depending on the involved genes, three MSUD genotypes have been identified so far: subtype 1α with mutations affecting the Eα (BCKDHA) gene, subtype 1β with mutations in the Eβ (BCKDHB) gene and subtype II with mutations in the E2 (DBT) gene (11). Mutations that impair BCKD activity can occur in any of the catalytic components of the complex. The gene mutation is an essential factor but not the sole determinant of the severity of the MSUD; alterations in brain parenchyma may also play a role. Previous imaging studies in MSUD patients have shown signs of both diffuse edema and intense local edema during the acute phase of the disease (12, 13). Early diagnosis is essential for the reversal of MSUD encephalopathy and delayed treatment can lead to death (14).

DWI is an MRI technique that can identify cytotoxic or intramyelinic edema. Cytotoxic edema was identified by a high signal on DWI, which reflects the fluid shift into the intracellular compartment resulting from reduced Na+/K+ ATPase activity. Vasogenic or interstitial edemas are identified by a decreased signal on DWI and with increased ADC value (12). Most researchers have found that DWI is the best choice for detecting MSUD encephalopathy in neonates (15, 16). Both diffuse cerebral edema and intense localized edema, called MSUD edemas have been found in neonates with MSUD encephalopathy. MSUD edemas mainly involve the cerebellar white matter, brainstem, globus pallidus, internal capsule, and thalamus (17) and typically occur in areas that are myelinated in normal full-term neonates (18). The brain tissue of juvenile and adult MSUD patients can be most effectively analyzed by DWI in combination with conventional MRI. An increased signal was observed in the white matter on T2-FLAIR images; however, the ADC map does not show any ADC reduction in the corresponding area, which is consistent with demyelination and a disturbed water content of the white matter. Abnormal myelination in MSUD is thought to be secondary to chronic exposure to BCAA (3, 19). In our study, alterations in brain tissue

| Table 2. MSUD phenotypes with alterations in different anatomic brain regions |
|-------------------------------|----------------|--------|------|-----|-----|-----|
| Phenotype          | Total patients | Supratentorial area | Basal ganglia | Thalamus | Pons | Mesencephalon | Cerebellum |
| Classic             | 6              | 5      | 6    | 4   | 5   | 5   | 5   |
| Intermittent        | 3              | 2      | 0    | 0   | 2   | 0   | 2   |
| Thiamine-responsive | 1              | 1      | 1    | 0   | 0   | 0   | 0   |

Involved brain regions show intramyelinic edema or cytotoxic edema; intermittent form and thiamine-responsive form present with increased signal at T2-FLAIR in the affected areas.

| Table 3. MSUD genotypes with alterations in different anatomic brain regions |
|-------------------------------|----------------|--------|------|-----|-----|-----|
| Genetic subtype | Total patients | Supratentorial area a | Basal ganglia b | Thalamus | Pons | Mesencephalon | Cerebellum |
| E1α                | 2              | 1      | 0    | 0   | 2   | 0   | 2   |
| E1β                | 6              | 5      | 6    | 4   | 5   | 5   | 5   |
| E2                 | 2              | 1      | 1    | 0   | 0   | 0   | 0   |

aSupratentorial region comprises the frontal, temporal, parietal, occipital, semiovale centrum, and corona radiate regions of each hemisphere.
bBasal ganglia refers to the internal capsule, the corpus callosum, and the basal ganglia.

Figure 1. a, b. A 20-day-old boy with MSUD (patient 6). Axial DWI image (a) shows abnormally high signal intensity in the bilateral optic tract (long arrow), mesencephalon (short arrow), cerebellar vermis (broad arrow). Axial DWI image (b) shows abnormally high signal intensity in the the basal ganglia (long arrow) and thalamus (short arrow).
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were more evident on DWI images than on T2-FLAIR images. MSUD edema on DWI is consistent with intramyelinic or cytotoxic edema and hypointensity with increased ADC values indicative of vasogenic-interstitial edema in unmyelinated regions. These findings are consistent with a previous report that MSUD edemas are cytotoxic and are not vasogenic-interstitial edemas (20). Extensive DWI hyperintensity was observed in the brain of one of our patients during the initial MRI scan. After 6 months, the areas with low ADC values had expanded. The expansion of hyperintense areas on DWI images can be attributed to a normal increase in myelination with age. We also found that DWI hyperintensity disappeared in the posterior limb of the internal capsule and centrum semiovale, which supports the hypothesis that the brain alterations attributable to MSUD encephalopathy can be reversed by appropriate treatment.

A total of 15 mutations were identified in BCKDHA, BCKDHB, and DBT genes in our MSUD patients. BCKDHB mutations were most common in neonates with the more severe classical form of MSUD in our study, which is in agreement with previous findings (21). However, other studies have reported contradictory findings: one study identified BCKDHB mutations in patients with the intermediate and thiamine-responsive forms of MSUD (22), while another observed BCKDHB mutations in patients with the intermittent or asymptomatic forms of MSUD (11). We believe that these discrepancies between the studies are tightly associated with specific sequence differences between mutations. In our study, patients with the classic form of MSUD harboring BCKDHB mutations had more extensive and severe alterations in brain tissue. Patients with the intermittent form of MSUD harboring heterozygous BCKHDA mutations showed only a mild clinical manifestation. We found one patient with a novel DBT mutation, who presented a milder form of the disease. That patient’s brain tissue was not affected and clinical symptoms were improved by thiamine treatment, which is in line with previous reports (23). Others, however, have identified novel DBT deletions (c.372_377del6 and c.713delC) in patients with the classical form of MSUD, which were associated with serious neuroanatomic symptoms (22). DBT mutations cause either the intermittent/thiamine responsive or the classic form of MSUD, depending on the nature of mutation in the second allele (23). This may explain why our findings are contradictory to other reports. Different genetic mutations lead to different phenotypes and different degrees of brain damage. We believe that BCKDHB, BCKDHA, and DBT mutations play a decisive role in the severity of MSUD. In the present study for example, BCKDHB mutations were primarily responsible for a severe MSUD phenotype.

Our study has some limitations. First, this was a retrospective review, the time elapsed since the initiation of treatment and the stage of the MSUD at which MRI examinations were performed varied among patients. Moreover, only 3 cases had follow-up imaging, thus we could not examine imaging features at the late stages of the disease. In addition, our study population was small.

In conclusion, extensive alterations in brain tissue and specific BCKDHB mutations were most common with the classic form of MSUD. Minor alterations in brain tissue and specific mutations in BCKDHA and DBT genes were found in patients with intermittent and thiamine-responsive forms. Our preliminary results support the hypothesis that alterations in brain tissue identified by MRI and specific genotypes may reliably predict the severity of the MSUD clinical phenotype and may help to diagnose the specific form of MSUD at newborn screening.
Acknowledgements

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References


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