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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-

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Table 1. Clinical characteristics of the MSUD patients

Patient	Onset	Clinical outcome	Clinical phenotype	Genetic subtype	Genotype
1	11 days	Severe neurodevelopment delay	Classic	E1β	c.[93_103dup11]
2	6 years	Learning difficulties	Intermittent	E1α	c.[712G>A]+c.[889C>T]
3	15 days	Severe neurodevelopment delay	Classic	E1β	c.[920C>T]+[IVS8+1G>T]
4	10 days	Moderate neurodevelopment delay	Classic	E1β	c.[391G>A]+c.[1006G>A]
5	11 years	Learning difficulties	Intermittent	E1α	c.[1250C>T]+c.[475C>T]
6	10 days	Died	Classic	E1β	c.[660A>T]+c.[1113G>A]
7	3 days	Died	Classic	E1β	c.[920C>T]+c.[920C>T]
8	6 days	Severe neurodevelopment delay	Classic	E1β	c.[297T>C]+c.[297T>C]
9	3 days	Slight neurodevelopment delay	Thiamine-responsive	E2	[IVS1+5 G>C]+ 801delA
10	2 months	Normal neurodevelopment	Intermittent	E2	[IVS4+2 T>G]

MSUD, maple syrup urine disease.

trometry (Applied Biosystems) and gene test (TIANGEN Biotech) at our Department of Pediatric Endocrinology and Genetic Metabolism. Their intelligence, movement, language ability were evaluated by a pediatrician. The study was approved by the Institutional Review Board of our hospital and written informed consent was obtained from the parents of all patients.

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 Pediatric Research.

Image analysis

MRI scans were performed using a 3.0 T twinspeed superconducting MRI equipment (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% chloral hydrate. The imaging protocol involved T1-weighted fluid-attenuated inversion recovery (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/mm^2 and b=1000 s/mm^2) were also included in the scan. Among the patients only three had a follow-up MRI study.

MRI scans were analyzed by two experienced pediatric neuroradiologists with particular attention to the supratentorial area (including frontal, temporal, parietal and occipital hemisphere regions and the centrum semiovale and corona radiata), the internal capsule, corpus callosum, basal ganglia, thalamus, mesencephalon, pons, and cerebellum. Brain tissue manifesting with high signal on DWI can be identified as cytotoxic or intramyelinic edema. Affected areas with increased signal in T2-FLAIR were recognized as dysmyelination or disturbed water content of the white matter (3).

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 classic form and carried mutations in the *BCKDHB* gene. Two patients with the intermittent 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). The genotypes and clinical phenotypes of the ten patients are summarized in Table 1. Phenotype, genotype, and brain abnormalities 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 (unexplained lethargy, developmental delay, impaired 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 summarized 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 compared with their initial MRI, but in patient 6, MRI revealed an expansion of the supratentorial area and loss of edema in the thalamus 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 cerebellum, mesencephalon, pons, and supratentorial area in five cases, and the thalamus in four cases (Fig. 2).

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

[a]Supratentorial region comprises the frontal, temporal, parietal, occipital, semiovale centrum, and corona radiate regions of each hemisphere.
[b]Basal ganglia refers to the internal capsule, the corpus callosum, and the basal ganglia.

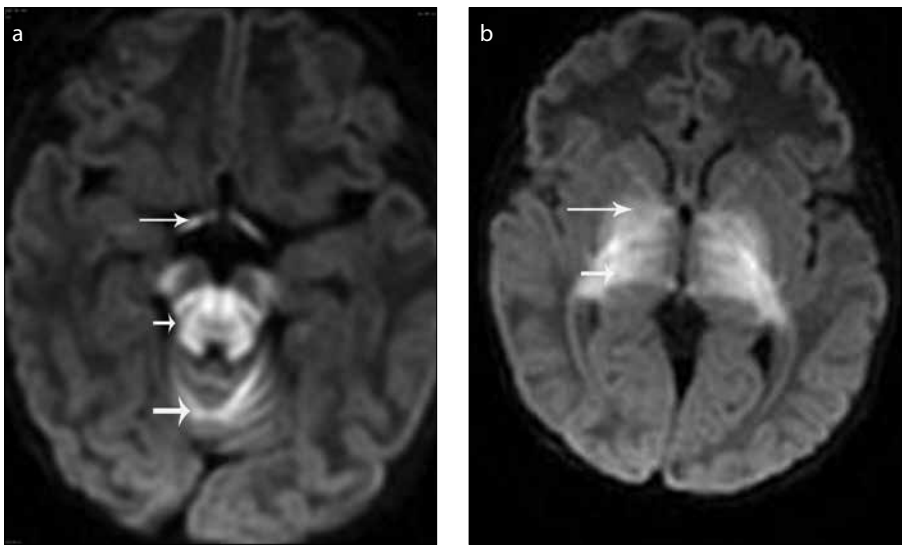

Figure 1. a, b. A 20-day-old boy with MSUD (patient 6). Axial DWI image **(a)** shows abnormally high signal intensity in the bilateral optic tract *(long arrow)*, mesencephalon *(short arrow)*, cerebellar vermis *(broad arrow)*. Axial DWI image **(b)** shows abnormally high signal intensity in the the basal ganglia *(long arrow)* and thalamus *(short arrow)*.

Discussion

MSUD is classified into classic, intermediate, intermittent, 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

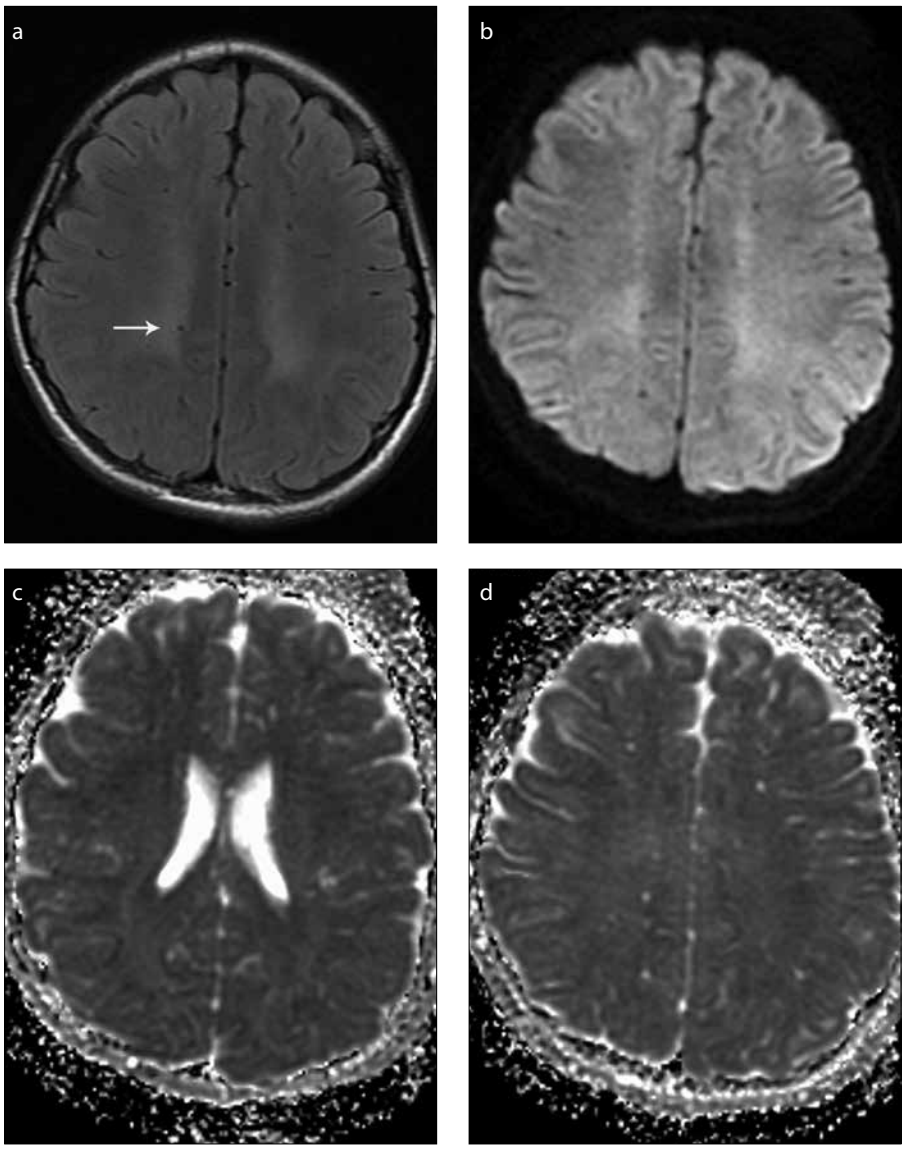

Figure 2. a–d. An 11-year-old female with MSUD (patient 5). Axial T2-FLAIR image **(a)** shows hyperintensity in the centrum semiovale *(arrow)*. Axial sections of the DWI **(b)** show bilaterally symmetrical hyperintensity in the centrum semiovale. Axial ADC map **(c)** does not show any ADC reduction corresponding to FLAIR hyperintenstity signal in periventricular areas and axial ADC map **(d)** does not show any ADC reduction corresponding to the centrum semiovale.

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 neuropathologic 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.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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