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Review Article

Inborn errors of ketone body utilization

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Abstract Succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency and mitochondrial acetoacetyl-CoA thiolase (beta-ketothiolase or T2) deficiency are classified as autosomal recessive disorders of ketone body utilization characterized by intermittent ketoacidosis. Patients with mutations retaining no residual activity on analysis of expression of mutant cDNA are designated as severe genotype, and patients with at least one mutation retaining significant residual activity, as mild genotype. Permanent ketosis is a pathognomonic characteristic of SCOT-deficient patients with severe genotype. Patients with mild genotype, however, may not have permanent ketosis, although they may develop severe ketoacidotic episodes similar to patients with severe genotype. Permanent ketosis has not been reported in T2 deficiency. In T2-deficient patients with severe genotype, biochemical diagnosis is done on urinary organic acid analysis and blood acylcarnitine analysis to observe characteristic findings during both ketoacidosis and non-episodic conditions. In Japan, however, it was found that T2-deficient patients with mild genotype are common, and typical profiles were not identified on these analyses. Based on a clinical study of ketone body utilization disorders both in Japan and worldwide, we have developed guidelines for disease diagnosis and treatment. These diseases are treatable by avoiding fasting and by providing early infusion of glucose, which enable the patients to grow without sequelae.

Key words inborn errors of ketone body utilization, ketone body, ketone body metabolism, mitochondrial acetoacetyl-CoA thiolase (beta-ketothiolase/T2) deficiency, succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency.

Ketone bodies are important alternative energy sources for maintaining blood glucose level. Ketone bodies, however, are acids and cause ketoacidosis when accumulated, which is hazardous to life.[1] Among patients with severe ketoacidosis, some are affected with inborn errors of ketone body metabolism. Succinyl-CoA:3-ketoacid CoA transferase (SCOT, gene symbol *OXCT1*) deficiency and mitochondrial acetoacetyl-CoA thiolase (beta-ketothiolase or T2, gene symbol *ACAT1*) deficiency are rare inherited metabolic disorders. Approximately 130 cases worldwide and 10 families in Japan have been reported to present with these two disorders.[2–44] Both SCOT and T2 deficiencies are autosomal recessive disorders, characterized by intermittent ketoacidosis. Some patients who experience severe ketoacidosis develop psychomotor retardation or even die. If, however, patients are properly diagnosed, inexpensive preventive measures can be effective, and normal development is expected.

We have been studying the pathophysiology of these disorders and have diagnosed both Japanese patients and those of other nationalities with these disorders. We found that patients with mutations that retain some residual activity are biochemically different from typical patients with these disorders, based on analysis of Japanese patients.[5,6,16,22,26,27,32,38,43]

In this review, we provide an overview of ketone body metabolism and summarize cases of SCOT deficiency and T2 deficiency in Japan. Furthermore, we provide an English-language version of recent guidelines for the diagnosis and treatment of these diseases, originally developed in Japanese in 2012 with support from Health and Labour Science Research Grants for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan.

Ketone body metabolism

Acetoacetate (AcAc) and 3-hydroxybutyrate (3HB) are the two main ketone bodies. They are 4-carbon carboxylic acids, hence accumulation in excess results in ketoacidosis. Ketone bodies, however, play an important role as vectors of energy transport from the liver to extrahepatic tissues, especially during shortages of glucose. It should be noted that the brain uses ketone bodies as an energy source.[1]

An overview of ketone body metabolism is given in Figure 1. Free fatty acids (FFA) are supplied from adipose tissues. In hepatocytes, beta-oxidation produces large amounts of

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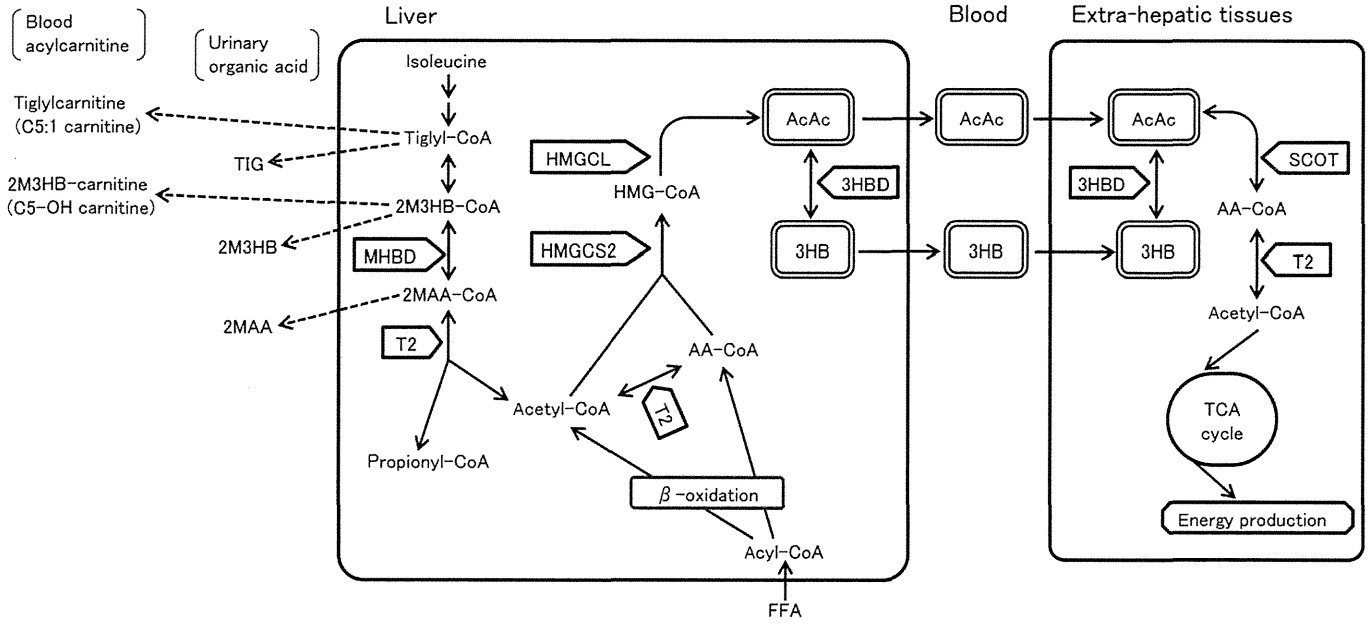

Fig. 1 Overview of ketone body metabolism. 2M3HB, 2-methyl-3-hydroxybutyrate; 2M3HB-, 2-methyl-3-hydroxybutyryl-; 2MAA, 2-methylacetacetate; 2MAA-, 2-methylacetoacetyl-; 3HB, 3-hydroxybutyrate; 3HBD, 3-hydroxybutyrate dehydrogenase; AA-, acetoacetyl-; AcAc, acetoacetate; FFA, free fatty acids; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCL, HMG-CoA lyase; HMGCS2, mitochondrial HMG-CoA synthase; MHBD, 2-methyl-3-hydroxybutyryl-CoA dehydrogenase; SCOT, succinyl-CoA:3-ketoacid CoA transferase; T2, mitochondrial acetoacetyl-CoA thiolase; TIG, tiglylglycine.

acetyl-CoA and acetoacetyl-CoA. They are condensed to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by mitochondrial HMG-CoA synthase (HMGCS2). AcAc is produced from HMG-CoA by HMG-CoA lyase (HMGCL). AcAc is in part converted into 3HB and then both are transferred to extrahepatic tissues via the bloodstream. There, 3HB is again converted into AcAc and activated into acetoacetyl-CoA by SCOT. Acetoacetyl-CoA is cleaved to acetyl-CoA by T2. These steps are essential for energy production from ketone bodies in extrahepatic tissues.[1]

Ketone body utilization disorders

Clinical symptoms and laboratory findings

SCOT deficiency and T2 deficiency are classified as disorders of ketone body utilization. SCOT deficiency was first described in 1972,[2] since when more than 30 patients have been reported.[2–24] T2 deficiency was first described in 1971,[25] and more than 100 patients have been reported.[25–44] Patients develop ketoacidosis during ketogenic stress such as starvation, febrile conditions and physical stresses because ketone bodies produced in the liver accumulate due to defective utilization in extrahepatic tissues. In physiological ketosis in normal children, both FFA and total ketone bodies (TKB) are elevated proportionally in the blood. TKB, however, are much higher compared with FFA, and the FFA/TKB ratio falls below 0.3 early in fasting patients with these disorders. Generally, ketoacidosis presents prior to hypoglycemia and there are reports of a few cases of hypoglycemia during ketoacidosis. Patients with these disorders have no clinical signs and symptoms during non-ketoacidotic periods if they do not have neurological sequelae of severe ketoacidotic events.

Because deficient use of ketone bodies in extrahepatic tissues is the main pathogenic trait of both diseases, they cannot be distinguished by clinical signs, symptoms or routine laboratory findings, but there are some differences (Table 1).

The first ketoacidotic crisis occurs during the neonatal period in approximately half of SCOT-deficient patients and between 5 months and 2 years of age in the other half. Neonatal onset, however, is very rare in T2 deficiency. Only one case has been diagnosed due to mild ketoacidosis in the neonatal period.[28] The first ketoacidotic event in T2 deficiency is triggered by infection or starvation between approximately 5 months and 2 years of age in almost all cases.

In this review, the term "severe genotype" is used to describe patients whose mutations retain no residual activity on analysis of mutant cDNA expression, and patients with at least one mutation that retains significant residual activity are designated as having the mild genotype. Permanent ketosis has been reported to be a pathognomonic feature of SCOT deficiency. Thus, a patient's urine is almost always ketone positive even when they are well. We did not observe permanent ketosis, however, in Japanese SCOT-deficient patients with mild genotype. Permanent ketosis has not been reported in patients with T2 deficiency, even with severe genotype.

In ketone body utilization, SCOT is the only enzyme to catalyze acetoacetyl-CoA formation in mitochondria, but the T2 catalytic step of acetoacetyl-CoA cleavage can be catalyzed by another thiolase, mitochondrial medium-chain 3-ketoacyl-CoA

Table 1 Clinical profile of ketone body utilization disorders

	SCOT deficiency		T2 deficiency	
	Genotype		Genotype	
	Severe	Mild	Severe	Mild
Onset	Between neonatal period and 2 years old		Between approx. 5 months and 2 years (rarely during neonatal period)	
Permanent ketosis	Observed	Not observed	Not observed	Not observed
Urinary organic acid analysis	No characteristic finding	No characteristic finding	Elevated TIG, 2M3HB and 2MAA	During ketoacidosis, no or slightly elevated TIG, elevated 2M3HB and 2MAA. During non-episodic conditions, slightly elevated 2M3HB or no characteristic finding.
Blood acylcarnitine analysis	No characteristic finding	No characteristic finding	Elevated tiglylcarnitine and 2M3HB carnitine	During ketoacidosis, slightly elevated tiglylcarnitine and 2M3HB carnitine or no characteristic finding.
No. patients worldwide	>30 patients		>100 patients	
No. patients in Japan	2 cases in 1 family	4 cases in 3 families	1 case	7 cases in 6 families

2MAA, 2-methylacetoacetyl; 2M3HB, 2-methyl-3-hydroxybutyryl; SCOT, succinyl-CoA:3-ketoacid CoA transferase; T2, mitochondrial acetoacetyl-CoA thiolase; TIG, tiglylglycine.

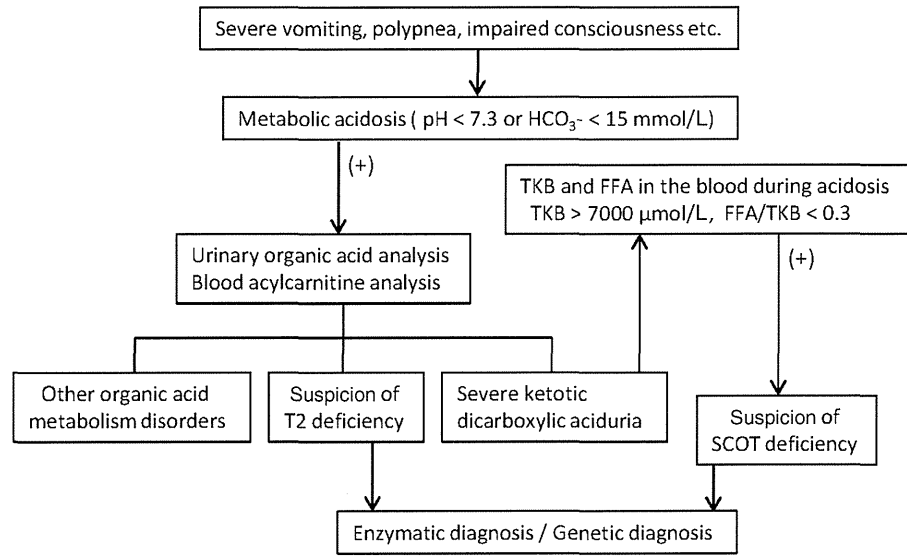

Fig. 2 Diagnostic flow chart of ketone body utilization disorders. FFA, free fatty acids; SCOT, succinyl-CoA:3-ketoacid CoA transferase; TKB, total ketone bodies; T2, mitochondrial acetoacetyl-CoA thiolase.

thiolase.[1] Therefore, complete SCOT deficiency may encompass a complete defect of ketone body utilization in extrahepatic tissues; even in complete T2 deficiency, however, ketone bodies can be used to some extent in extrahepatic tissues. This may explain why permanent ketosis is present in complete SCOT deficiency but not in complete T2 deficiency.

The SCOT step is used only for ketone body utilization, and there are no characteristic metabolites except for large amounts of ketone bodies. In contrast, T2 catalyzes acetoacetyl-CoA cleavage in ketone body utilization and 2-methylacetoacetyl-CoA (2MAA-CoA) cleavage in the isoleucine catabolic pathway (Fig. 1). Hence, T2 deficiency is characterized by accumulated metabolites in isoleucine catabolism. In urinary organic acid analysis, excretion of tiglylglycine (TIG), 2-methyl-3-hydroxybutyrate (2M3HB) and 2-methylacetacetate (2MAA) are characteristic of T2 deficiency. In blood acylcarnitine analysis, elevated blood tiglylcarnitine (C5:1 carnitine) and 2-methyl-3-hydroxybutyrylcarnitine (2M3HB-carnitine/C5-OH carnitine) are observed. T2-deficient patients with mild genotype, however, do not show typical profiles in these analyses.

Enzyme assay and/or molecular diagnosis are essential for confirming diagnosis because (i) SCOT deficiency cannot be diagnosed on metabolite analysis such as urinary organic acid analysis or acylcarnitine analysis; and (ii) some T2-deficient patients do not have typical metabolic profiles.

SCOT deficiency in Japan

Five cases of SCOT deficiency from three families in Japan are summarized in Table 2. Patient GS02 and the younger sister (GS02s) were typical SCOT-deficient patients presenting

Table 2 Japanese SCOT-deficient patients

Case	Onset	No. ketoacidotic crises	Typical crisis			Well condition		Prognosis		*OXCT1* mutation	References
			Blood gas		TKB (μmol/L)	Urinary ketone	TKB (μmol/L)	Age in 2014 (years)	MR		
			pH	HCO_3^- (mmol/L)							
GS02	6 months	3	7.08	5.1	12 200	Always positive	858	10	(–)	[c.398T>A (p.V133E)]+[c.1367G>T (p.C456F)]	5,6
GS02s	Prenatal diagnosis	1	7.29	ND	11 400		893	8	(–)		
GS08	1 year 5 months	3	7.12	3.7	18 500	Usually negative	164	16	(–)	[c.1304C>A (p.T435N)]+[=]	16
GS09	10 months	Several	7.00	5.8	ND		341	14	(–)		
GS09b	10 months	4	7.09	5.4	ND		285	18	(–)		
GS21	2 d	1	7.07	5.8	ND		240	8	(–)	[c.1304C>A (p.T435N)]+[c.658_666dup9bp]	22

GS02s, affected sister of GS02; GS09b, affected brother of GS09; MR, mental retardation; ND, not determined; *OXCT1*, SCOT gene symbol; SCOT, succinyl-CoA:3-ketoacid CoA transferase; TKB, total ketone bodies.

Table 3 Japanese T2-deficient patients

Case	Onset	No. ketoacidotic crises	Typical crisis		Prognosis		Urinary organic acids				Acylcarnitines				*ACAT1* mutation	Refs.
			Blood gas		Age in 2014 (years)	MR	Acute phase		Stable phase		Acute phase		Stable phase			
			pH	HCO_3^- (mmol/L)			TIG	2M3HB	TIG	2M3HB	C5:1	C5OH	C5:1	C5OH		
GK01	20 months	1	7.15	4.2	33	(+)	D	D	D	D	–	–	D	D	[c.997G>C(p.A333P)]+[c.149delC]	26,27,32
GK19	23 months	1	7.17	3.8	22	(–)	ND	D	ND	FD	–	–	ND	FD	[c.935C>T (p.I312T)]+[c.278A>G (p.N93S)]	27,32
GK30	9 months	3	7.01	3.3	18	(–)	D	D	ND	FD	–	–	ND	FD	[c.2T>C] + [c.149delC]	32
GK31	18 months	1	7.07	2.9	18	(–)	D	D	ND	FD	–	–	ND	FD	[c.935C>T (p.I312T)]+[c.149delC]	32
GK64	7 months	1	7.00	8.0	9	(–)	ND	D	ND	FD	–	–	ND	ND	[c.556G>T (p.D186Y)]+[c.951C>T]	38
GK69	9 months	2	7.075	4.6	31	(–)	–	–	ND	FD	–	–	ND	ND	[c.431A>C (p.H144P)]+[c.1168T>C (p.S390P)]	43
GK77	3 years	1	7.135	6.3	9	(–)	ND	D	ND	FD	ND	ND	FD	ND	[c.431A>C (p.H144P)]+[=]	43
GK77b	3 years	1	6.88	1.1	3	Died	ND	D	–	–	ND	ND	ND	ND		

Underline, retaining some residual enzyme activity. p.A333P, c.149delC, p.D186Y, p.S390P retained no residual activity. GK77 and GK77b, identical twin siblings who developed ketoacidotic crises at 3 years of age. GK01, typical T2-deficient patient and others are patients with mild mutations on at least one of two mutant alleles. –, not tested; 2M3HB, 2-methyl3-hydroxybutyrate; *ACAT1*, beta-ketothiolase or T2 gene symbol; D, detected; FD, faintly detected; MR, mental retardation; ND, not detected; T2, mitochondrial acetoacetyl-CoA thiolase; TIG, tiglylglycine.

Table 4 Guidelines for diagnosis of ketone body utilization disorders

Characteristics of clinical symptoms
Ketone body utilization disorders should be suspected in the following patients:
(1) Neonates with symptoms including poor sucking, vomiting, hypotonia of muscles and so-called "not doing well" with severe metabolic acidosis
(2) Patients with symptoms including severe vomiting, polypnea and impaired consciousness with severe metabolic acidosis during acute respiratory infection or acute gastroenteritis during infancy (especially after 5 months of age) or early childhood
(3) Patients with more severe ketosis than expected with a clinical history of fasting and/or febrile condition
(4) Patients with urinary ketone positive repeatedly despite being well or symptomless
Ketone bodies accumulate owing to ketogenic stresses such as fasting, febrile conditions or infection at higher levels in patients with ketone body utilization disorders compared with healthy controls, and ketoacidosis occurs. Patients are symptomless during non-ketoacidotic conditions.
Tests for diagnosis
(1) First-line screening tests: blood gas, blood glucose, ammonia etc.
Patients usually show severe ketoacidosis (pH <7.3 or HCO_3^- < 15 mmol/L) during crises. Severe ketoacidosis is observed in patients with other organic acidurias; therefore, urinary organic acid analysis should be performed for differential diagnosis. It is necessary to judge whether the severity of acidosis is beyond physiological metabolic acidosis caused by fasting ketosis etc. In the case of ketone body utilization defects, blood pH is usually very low (6.8–7.2) during crises. Blood ammonia during ketoacidosis is normal or slightly elevated (up to approx. 200–400 μg/dL) and hemodialysis is usually unnecessary. Blood glucose is usually normal, but mild hyperglycemia is also observed. Hypoglycemia may be observed during ketoacidotic episodes during neonatal periods or infancy.
(2) TKB and FFA in the blood
It is critical for the evaluation of ketone body metabolism to measure both TKB and FFA simultaneously during ketoacidosis. TKB is ≥7000 μmol/L or over (often >10 000 μmol/L) during acidosis. Both fasting and postprandial high TKB may suggest defects in ketone body utilization. In cases of physiological ketosis, FFA are also proportionally high, but for ketone body utilization defects, TKB are disproportionally higher than FFA, with an FFA/TKB ratio ≤0.3 in early stages of fasting. Fasting tests are not recommended for all patients and should be conducted at a specialized medical facility under careful control. Some patients may develop ketoacidosis after only 15 h of fasting.
(3) Urinary organic acid analysis
In patients with SCOT deficiency, the characteristic profile of urinary organic acid analysis is not present except for large amounts of 3-hyroxybutyrate and acetoacetate (ketotic dicarboxylic aciduria) even during ketoacidosis.
In typical patients with T2 deficiency, elevated TIG, 2M3HB and 2MAA are found on urinary organic acid analysis during ketoacidosis as well as during non-episodic conditions, which makes biochemical diagnosis possible. In T2-deficient patients with mutations that retain some residual activity, however, the characteristic profile of urinary organic acid analysis may not be observed even during ketoacidosis, and only subtle elevation of 2M3HB may be observed during non-episodic normal conditions. Thus, it is sometimes difficult to suspect T2 deficiency on urinary organic acid analysis during non-episodic conditions. Elevated TIG and 2M3HB in the absence of 2MAA might indicate HSD10 disease rather than T2 deficiency, although 2MAA is unstable and is difficult to detect in some laboratories.
Urinary organic acid analysis during ketoacidosis is necessary to exclude other organic acidemia.
(4) Acylcarnitine analysis
In typical patients with T2 deficiency, elevated C5:1 and C5-OH are found on blood acylcarnitine analysis using tandem mass spectrometry during ketoacidosis as well as during non-episodic conditions. Serum is more informative than blood spots. Additional to urinary organic acid analysis, however, T2-deficient patients with mutations that retain some residual activity cannot be detected on acylcarnitine analysis. SCOT deficiency cannot be identified using this method.
(5) Enzymatic and genetic diagnosis
Enzyme assay and mutation analysis are tests for definitive diagnosis.
Enzyme assay using blood mononuclear cells is sometimes difficult for the correct evaluation of T2 activity. Enzyme assay using fibroblasts is recommended to confirm T2 deficiency.

2M3HB, 2-methyl-3-hydroxybutyrate; 2MAA, 2-methylacetacetate; FFA, free fatty acids; HSD10, 17β-hydroxysteroid dehydrogenase type 10; SCOT, succinyl-CoA:3-ketoacid CoA transferase; T2, mitochondrial acetoacetyl-CoA thiolase; TIG, tiglylglycine; TKB, total ketone bodies.

permanent ketosis. They were compound heterozygotes of two mutations that retained no residual activity, judged to be SCOT-deficient patients with severe genotype.[5,6] In contrast, three patients from two other families (GS08, GS09 and GS09s) had no permanent ketosis and were homozygotes of the T435N mutation that retained significant residual SCOT activity.[16,22] They all developed severe ketoacidotic episodes.

The siblings with severe genotype were reexamined at the age of 9 years (elder brother) and 7 years (younger sister). Urinary ketone was examined for 5 days and all urine samples tested were ketone positive. After 14–15 h of fasting, blood TKB levels exceeded 2 mmol/L and even 2 h after eating, TKB remained at 2 mmol/L, although blood FFA decreased to <0.25 mmol/L after eating. The siblings have not developed severe metabolic acidosis after confirmation of diagnosis.[16]

The siblings with mild genotype have not developed severe metabolic acidosis after confirmation of diagnosis. They were reexamined at the age of 8 years (older brother) and 4 years (younger brother). Urinary ketone was only positive after a 15 h fast, when blood TKB was <0.5 mmol/L in the older brother and <1 mmol/L in the younger brother. TKB 2 h after eating in both patients decreased to half of the fasting levels.[16]

A guarded fasting test in patient GS08 with mild genotype was performed at 2 years of age. TKB exceeded 2, 6, and 9 mmol/L at 12, 14, and 16 h of fasting, respectively. Because TKB exceeded 10 mmol/L at 17 h of fasting, sodium bicarbonate and

Table 5 Guidelines for treatment of ketone body utilization disorders

Treatment in acute episodes
(1) Treatment of hypoglycemia and suppression of ketone body synthesis
It is important to avoid fasting in ketone body utilization disorders. Hypoglycemia should be treated by i.v. injection of 2 mL/kg (1.1 mmol/kg) 10% glucose, followed by continuous infusion of 10% glucose and an appropriate concentration of electrolyte. Target blood glucose level is the upper limit of normal. Even if hypoglycemia is not observed during ketoacidosis, ketoacidosis will not be improved without sufficient glucose supply.
(2) Treatment of acidosis
To treat ketoacidosis, a sufficient glucose supply to suppress ketone body synthesis is important. Sufficient glucose infusion often improves acidosis in several hours.
Although there are various opinions regarding treatment for severe acidosis, the minimum consensus is as follows: when blood pH is <7.1, the patient has no circulatory failure or respiratory failure and is conscious, 1 mmol/kg sodium bicarbonate is injected i.v. over 10 min, followed by continuous infusion of sodium bicarbonate. pH >7.1, PCO_2 >20 mmHg and HCO_3^- > 10 mmol/L are targeted. When blood test data are improved, infusion of sodium bicarbonate is tapered promptly and stopped. There is a report that overdose of sodium bicarbonate may cause hypernatremia and cerebral hemorrhage; thus, attention to dosing is required. Although dialysis is useful to control acidosis, it is not often required.
Treatment in non-episodic conditions
(1) Prevention of severe ketoacidotic episodes
Patients diagnosed with ketone body utilization disorders should avoid long fasting as much as possible. They should have meals rich in carbohydrates frequently during physical stress such as mild infection. In cases of poor feeding due to gastroenteritis or catabolic conditions, glucose infusion should be performed without hesitation. It is useful for patients to monitor urinary ketones using test strips at home.
(2) Restriction of fat intake
Patients diagnosed with ketone body utilization disorders should restrict excess fat intake. A ketogenic diet is contraindicated for them. Fat restriction is usually unnecessary for normal Japanese-style meals, while fat restriction is advisable for Western-style meals.
(3) Restriction of protein intake
Mild restriction of protein intake is a reasonable measure for patients with SCOT deficiency to avoid ketogenic amino acid load, but the long-term effects are unclear. In patients with T2 deficiency, 1.5–2.0 g/kg/day protein intake may be applicable.
(4) Carnitine supplementation
For patients with ketone body utilization disorders who have low blood carnitine, carnitine supplementation is considered.

SCOT, succinyl-CoA:3-ketoacid CoA transferase; T2, mitochondrial acetoacetyl-CoA thiolase.

glucose were injected i.v. to terminate the test. The FFA/TKB ratio fell below 0.3 at 14 h of fasting.[16]

Based on these results, the following are suggested. Patients with severe genotype have typical SCOT deficiency and may have permanent ketosis. Therefore, SCOT deficiency is likely suspected. Patients with mild genotype may develop severe ketoacidotic episodes similar to patients with severe genotype but may not develop permanent ketosis. In general, the long fasting test is not recommended for diagnosis, but the fasting test at 15–20 h is useful for evaluation of fasting tolerance, and should be conducted under careful control because of a risk of acute ketoacidosis.

T2 deficiency in Japan

The cases of eight patients from seven families of T2 deficiency in Japan are summarized in Table 3. Patient GK01 is the only one with severe genotype in Japan. In GK01, elevated TIG and 2M3HB were persistently observed in urine samples during non-episodic normal conditions as well as at the time of ketoacidosis.[26,27,32] In contrast, the other seven patients have mild genotype. TIG was not detected in four of six patients at the time of ketoacidosis, and was not detected in any patients during non-episodic normal conditions. 2M3HB was definitely detected in all patients during ketoacidosis, but was only faintly detected in all cases during non-episodic normal conditions. On blood acylcarnitine analysis, C5:1 carnitine and C5-OH carnitine were elevated in GK01 even during non-episodic normal conditions, but were not detected or were faintly detected in the other six patients with mild genotype.[27,32,38,43] It should be emphasized that in the siblings with mild genotype (GK77 and 77b), these characteristic acylcarnitine levels were not elevated, even during acute episodes.

T2 deficiency is a target disease for newborn mass screening tests using tandem mass spectrometry. There are some reports that asymptomatic T2 deficiency has been diagnosed on newborn mass screening tests.[41,42] In the USA, siblings not positively detected on newborn screening testing were later diagnosed with T2 deficiency.[42] As stated here, patients with mild genotype may be common in Japan, therefore some T2-deficient patients cannot be identified on newborn screening testing.

In the differential diagnosis for T2 deficiency, we should consider 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency, also known as 17β-hydroxysteroid dehydrogenase type 10 (HSD10) disease, which is an X-linked recessive disorder with clinical symptoms including rapidly progressive retardation of psychomotor performance, convulsion, ablepsia and progressive cardiomyopathy.[45–60] MHBD catalysis is one step upstream from the T2 step in isoleucine catabolism. The results of urinary organic acid analysis and blood acylcarnitine analysis in HSD10 disease are the same as those in T2 deficiency except that 2MAA is not detected in HSD10 disease (Fig. 1).[1] Approximately 20 cases of HSD10 disease have been reported, but clinical heterogeneity is noted. We recently identified the first case of HSD10 disease in Japan. The patient was initially suspected to have T2 deficiency on urinary organic acid analysis, and was then confirmed to have

HSD10 disease on enzyme assay and mutation analysis. He had no neurological regression until 6 years of age, thus a much milder phenotype compared with the previously reported cases.[61]

Guidelines for diagnosis and treatment

Based on clinical information of patients with ketone body utilization disorders in Japan and worldwide, we developed guidelines for its diagnosis (Table 4; Fig. 2) and treatment (Table 5). These diseases are treatable by avoiding fasting and by providing early infusion of glucose, which enable patients to grow without sequelae.

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