

## 8.1 Introduction

As the title indicates, this chapter comprises a mixed group of six individual organic acidurias. Two are disturbances of the citric acid cycle (2-ketoglutaric aciduria and fumaric aciduria). Two further organic acidurias are characterised by excretion of high levels of 2-hydroxyglutaric acid: D-2-hydroxyglutaric aciduria and L-2-hydroxyglutaric aciduria. The other two organic acidurias described in this chapter are malonic aciduria and N-acetyl-aspartic aciduria (Canavan disease).

The 2-ketoglutarate dehydrogenase (2-KGD) complex is composed of three separate enzymes: 2-ketoglutarate decarboxylase, or E1; lipoate succinyltransferase, or E2; and lipoamide dehydrogenase, or E3. The complex catalyses the oxidation of 2-ketoglutarate to yield succinyl-CoA and NADH. 2-KGD deficiency together with pyruvate dehydrogenase deficiency and branched chain ketoacid decarboxylase deficiency has been ascribed to E3 deficiency because the three enzyme complexes have the E3 component in common. E3 deficiency will not be discussed.

To date, isolated 2-KGD deficiency (E1 or E2) has only been described in five families [1–6]. The clinical presentation of the disease is heterogeneous. Age of onset varies between the neonatal period and 16 months of life. Symptoms include axial hypotonia, developmental delay, variable pyramidal and extrapyramidal dysfunction, spasticity and hepatomegaly. One male patient presented with only mild neurological symptoms, which might have been an unspecific consequence of a complicated neonatal period and which ameliorated with age. Some patients died in infancy, whereas the mildly affected patient is still alive at age 14 years.

In most patients, the urinary organic acid profile showed an elevated excretion of 2-ketoglutaric acid. However, 2-ketoglutaric aciduria is not a consistent finding as it can be absent or intermittently present. Sometimes, other Krebs cycle intermediates are increased in urine. In some patients high glutamine and glutamic acid concentrations in plasma were observed. Elevated concentrations of lactate with high lactate/pyruvate ratios were permanently present in some, but absent in other patients. Activity of 2-KGD was measured in fibroblasts and/or muscle homogenates from all pa-

tients but one and was found to be decreased (5–29% of control value). The E1 and E3 subunits were measured separately and found to be normal in some of the patients, suggesting that at least in some patients the E2 component is responsible for the defect.

Fumarase (fumarate hydratase) catalyses the conversion of fumarate to malate. There are two isoenzymes, a mitochondrial and a cytosolic one. The presence of a single fumarase gene explains the reduced activities of both the mitochondrial and the cytosolic isoenzymes in fumarase-deficient patients. Only the mitochondrial isoenzyme is expressed in brain tissue. Twenty six patients in 16 families with a defect in fumarase have been described [7–10]. Affected children exhibit progressive severe infantile encephalopathy, feeding problems, failure to thrive, hypotonia, lethargy, microcephaly, and absent or severely retarded development. The manifestation of the disease in some patients even began before birth, in the form of polyhydramnios and a suspicion of congenital hydrocephalus [7]. In a number of cases, dysmorphia and relative macrocephaly were reported. However, the intracranial pressure in these patients was normal and the head small, indicative of atrophy rather than hydrocephalus as cause of the ventricular enlargement. Infantile spasms have also been described. In some patients, hepatic dysfunction was present in the neonatal period. The clinical course can be fatal (<5 years). A direct relationship between the severity of the defect, its distribution among tissues, and the fatal course of the disease has not been observed [8].

In addition two mentally retarded adults with fumaric aciduria have been described, but the abnormality was thought to be due to a renal fumaric acid resorption defect. Fumarase activity was not determined in these patients.

Deficiency of fumarase causes marked elevations of fumaric acid and often other Krebs cycle intermediates in the urinary organic acids profile. The diagnosis is confirmed by measurement of fumarase activity in cultured skin fibroblasts, leukocytes or affected organs. For defining the carrier status of family members, fumarase activity measurement in blood mononuclear cells appears to be a good, easy screening tool [7–9]. Mutation analysis can confirm the results of enzyme studies [11].

Malonic aciduria is caused by a reduced activity of mitochondrial malonyl-CoA decarboxylase, the enzyme responsible for conversion of intramitochondrial malonyl-CoA to acetyl-CoA. Hitherto, the disorder has been confined to nine patients. Clinical symptoms, which can develop soon after birth or in early childhood, include delayed neurological development, seizures, episodes of vomiting and anorexia, mild to severe metabolic acidosis and cardiomyopathy [12–15]. One patient died at the age of 8 days [15]; the other patients are still alive, the oldest being 13 years of age.

Biochemically, malonyl-CoA decarboxylase deficiency is characterised by the excretion of excess malonic and methylmalonic acids in urine, mostly

during episodes of vomiting or febrile convulsions. Sometimes also increased excretions (lower) of succinic, ethylmalonic, glutaric, adipic, and suberic acids are observed. Grossly reduced malonyl-CoA decarboxylase activities have been demonstrated in fibroblasts. Recently, the molecular basis of malonic aciduria has been reported [16, 17].

2-Hydroxyglutaric (HG) acid is an optically active organic acid. With respect to 2-HG acid two distinct disorders with very different phenotypes are known; in one D-2-HG acid accumulates and in the other it is the L-form. Therefore it is important to determine the configuration of accumulating 2-HG acid. The separation of D- and L-2-HG acid requires the use of chiral GC- and/or HPLC-columns or the preparation of chiral derivatives using D-2-butanol [18].

D-2-HG aciduria has been reported in about 30 patients [19, 20]. There appear to be two phenotypes: a severe neonatal and a mild infantile phenotype. The most frequent findings, regardless of the phenotype, are epilepsy, hypotonia, and psychomotor retardation. Additional findings, mainly occurring in the severe phenotype, are episodic vomiting, cardiomyopathy, inspiratory stridor, and apneas. The most consistent MRI finding is enlargement of the lateral ventricles, occipital more than frontal. Regardless of the clinical phenotype, early infantile MRI shows subependymal cysts and signs of delayed cerebral maturation. The subependymal cysts disappear within a few months. Minor facial anomalies, including a “coarse” facial appearance, broad nasal bridge and large protruding ears, have been described [21]. D-2-hydroxyglutaric aciduria should be considered in patients with minor facial anomalies and epileptic encephalopathy of unknown origin.

The D-2-HG acid concentration is elevated in urine, sometimes accompanied by increased 2-ketoglutaric acid excretion. Elevated concentrations of D-2-HGA in plasma and CSF, and total GABA in CSF were also reported [18–20].

More than 40 patients with L-2-HG aciduria have been reported and at least 75 patients are known to the authors. The clinical phenotype is one of a progressive neurodegenerative disorder manifested by extrapyramidal and cerebellar signs, seizures and magnetic resonance imaging findings indicative of spongiform changes in the subcortical white matter [22]. Usually, the disease presents in childhood, but an increasing number of cases with adult onset has been reported [23, 24]. L-2-hydroxyglutaric aciduria associated with lactic acidosis with onset of neurological symptoms in the neonatal period and neonatal death has been described in two patients [25, 26].

The L-2-HGA concentration is persistently elevated in urine, plasma and CSF without additional organic aciduria. Lysine is often elevated in CSF.

A few patients with combined D-2- and L-2-hydroxyglutaric aciduria have been reported. Whether these patients represent another clinical and/

or biochemical entity remains to be established [27]. The origins of D- and L-2-HG acids are still unknown. A number of loading and fasting studies have been conducted without conclusive results. Little is known about the roles of D- and L-2-HG acids in mammalian metabolism and so far no definite clue to the metabolic blocks have been found.

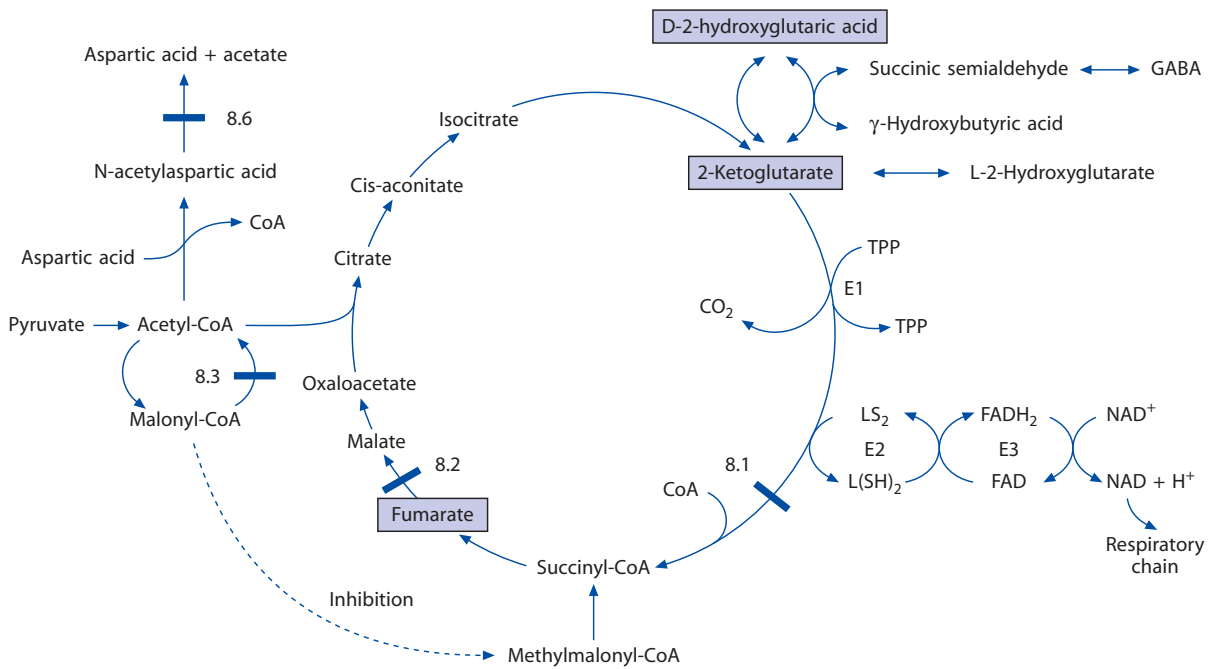
N-acetylaspartic aciduria (Canavan disease, Van Bogaert Bertrand disease) is caused by a deficiency of aspartoacylase (N-acetyl-aspartate amidohydrolase). Three forms have been described: a congenital form presenting at or shortly after birth, an infantile form presenting between 3 and 6 months of age and a rare juvenile form, which presents after age 5 years. Clinically, the disease manifests itself with absence of or regression of development, hypotonia, poor head control, optic atrophy, and accelerated head growth resulting in macrocephaly [28, 29]. MRI of the brain shows a diffuse white matter disease and typically involvement of the thalamus and globus pallidus [30]. Diagnosis can be established by analysis of N-acetylaspartic acid in urine, which is pathognomonic for Canavan disease [31]. Furthermore, aspartoacylase can be assayed in cultured skin fibroblasts and mutation analysis can be performed [32].

## 8.2 Nomenclature

No.	Disorder-affected component	Tissue distribution	Chromosomal localisation	McKusick
8.1	2-Ketoglutarate dehydrogenase complex deficiency: E1 E2	M, F	7p13–p11.2, 14q24.3	203740
8.2	Fumarase deficiency	M, Lym, F	1q42.1	136850
8.3	Malonyl-CoA decarboxylase deficiency	F, Leu	16q24	248360
8.4	L-2-Hydroxyglutaric aciduria (enzyme defect unknown)			236792
8.5	D-2-Hydroxyglutaric aciduria (enzyme defect unknown)			600721
8.6	Aspartoacylase deficiency	F	17p13-ter	217900

M, muscle; H, heart; K, kidney; B, brain; F, fibroblasts; Liv, liver; Lym, lymphocytes; Leu, leukocytes.

### 8.3 Metabolic Pathways



**Fig. 8.1.** Pathways of 2-ketoglutarate, fumarate, malonate and N-acetylaspargate metabolism and proposed pathways of D- and L-2-hydroxyglutarate metabolism. 8.1, 2-Ketoglutarate dehydrogenase complex (E1 or E2); 8.2, fumarase; 8.3, malonyl-CoA decarboxylase; 8.6, aspartoacylase

## 8.4 Signs and Symptoms

### ■ 2-Ketoglutaric Aciduria (5 Families)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Normal initial development	±				
	Motor deterioration > mental deterioration		+	+		
	Mainly pyramidal or extra-pyramidal symptoms		+	+		
Routine laboratory	Episodic course	±	±	±		
	Glucose	↓-N	↓-N	↓-N		
	Acidosis	±	±	±		
	ASAT/ALAT	N-↑	N-↑			
	Lactate (B)	N-↑	N-↑	N-↑		
	Pyruvate (B)	N	N	N		
	Lactate/pyruvate ratio (B)	N-↑	N-↑	N-↑		
	3-Hydroxybutyrate/acetoacetate ratio (B)		N-↓	N-↓		
Special laboratory	CAT: cortical atrophy		±	±		
	Organic acids (U):					
	2-ketoglutarate succinate, fumarate, citrate, malate	N-↑	N-↑	N-↑		
GI	Failure to thrive	±	±	±		
Respiratory	Tachypnea	±	±	±		
Liver	Hepatomegaly	-	±	±		
CNS	Hypotonia, axial >limbs	±	+	+		
	Motor >mental deterioration		+	+		
	Absent head control	±	+	+		
	Extrapyramidal movement disorder	±	±	+		
	Spasticity		±	+		
	Psychotic behavior			±		
	Epileptic seizures		±	±		
	Hypertrophic cardiomyopathy		±	±		
Cardiac						

## ■ Fumaric Aciduria (26 Patients, 16 Families)

System	Symptoms/markers	Prenatal	Neonatal	Infancy	Childhood	Adolescence
Characteristic clinical findings	Polyhydramnion	+				
	Cerebral ventriculomegaly	+	+	++	+++	
	Absent development <sup>a</sup>			+	+	
Routine laboratory	Acidosis		±	±		
	ASAT/ALAT		↑			
	Lactate (B)		N-↑	N-↑		
	Lactate (CSF)		N-↑	N-↑		
	Pyruvate (B)		N-↑	N-↑		
	Pyruvate (CSF)		N-↑	N-↑		
	Lactate/pyruvate ratio (B)		N-↑	N-↑		
	3-hydroxybutyrate/acetoacetate ratio (B)		N-↓	N-↓		
Special laboratory	CAT: progressive atrophy	+	+	+	+	
	EEG abnormalities		+	+	+	
	Organic acids (U):					
	Fumarate,	↑	↑	↑	↑	
	Succinate, citrate, malate, 2-keto-glutarate	N-↑	N-↑	N-↑	N-↑	
G.I.	Vomiting		+	+	+	
	Prolonged icterus		±			
Liver CNS	Hepatomegaly		±			
	Lethargy		+	+	+	
	Irritability		+	+	+	
	Hypotonia		+	+	+	
	Opisthotonus		+	+	+	
	Visual failure		+	+	+	
	Severe MR/DD			+	+	
	Seizures		±	±	±	
	Microcephaly			±	±	
	Relative macrocephaly		±			
	Neutropenia			±		
	Dysmorphia					

<sup>a</sup> Some development reported in one patient.

## ■ Malonic Aciduria

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Dysmorphism		±	±		
	Short stature		±	±		
Routine laboratory	Glucose (B)	↓	↓ <sup>a</sup>			
	Ketones (U)		N-↑			
	Acidosis	+	±	±		
	ASAT/ALAT (P)		N-↑			
	Urea (P)		↑	↑		
Special laboratory	Organic acids (U):					
	Malonate	↑	↑	↑		
	Methylmalonate, ethylmalonate, succinate, adipate, suberate, glutarate	↑	N-↑	N-↑		
	Free carnitine (U)		↓			
	Acylcarnitine (U)		↑			
G.I.	Episodic vomiting	±	+	+		
CNS	Mild mental retardation		+	+		
	Hypotonia	±	±	±		
	Febrile or nonfebrile convulsions		±	±		
Cardiac	Cardiomyopathy	±	±	±		

<sup>a</sup> After high fat/low carbohydrate load.

## ■ L-2-Hydroxyglutaric Aciduria

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Unique clinical findings	Progressive ataxia		±	+	+	+
	Progressive mental def.		±	+	+	+
Routine laboratory	Lactate (B)	N-↑				
	Ammonia (B)	N-↑				
	Protein (CSF)		↑	↑		
Special laboratory	CT/MRI white matter abnormalities	±	+	+	+	+
	EEG abnormalities		+	+	+	+
	NCV	N	N	N	N	N
	Evoked potential abnormalities	±	±	±	±	±
	L-2-hydroxyglutarate (U, P, CSF)	↑	↑	↑	↑	↑
	Lysine (U, P, CSF)	N	N-↑	N-↑	N-↑	N-↑
CNS	Dysarthria		±	+	+	+
	Hypotonia	±	±	±	±	±
	Spasticity			±	±	±
	Choreoathetosis, dystonia			±	±	±
	Tremor				±	±
	Seizures		±	±	±	±
	Macrocephaly		±	±	±	±



### ■ D-2-Hydroxyglutaric Aciduria

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Special laboratory	CT/MRI:					
	Enlarged ventricles	+	±	-		
	Subependymal cysts	+	±	-		
	Delayed myelination/gyration	+	±	-		
	Organic acids (U):					
	D-2-hydroxyglutarate					
	2-Ketoglutarate	↑	↑	↑		
	D-2-hydroxyglutarate (P, CSF)	↑	↑	↑		
GI Face CNS	GABA (CSF)	N-↑	N-↑	N-↑		
	Episodic vomiting	±	±	±		
	Facial dysmorphism	±	±	±	+	
	Epilepsy	+	+	±	+	
	Hypotonia	+	+	±	+	
	Cerebral visual failure	+	+	±	+	
	Developmental delay	+	+	±	+	
	Extrapyramidal movement abnormalities	±	±	±		
	Macrocephaly	±	±	±		
	Cardiomegaly	±	±	±	+	

### ■ N-Acetylaspartic Aciduria (Canavan Disease)

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
Characteristic clinical findings	Regression of development	+	+	+	+	+
	Macrocephaly (disproportionate)	+	+	+	+	+
	Poor head control	+	+	+	+	+
	Inability to fix or track/blindness	+	+	+	+	+
	Optic atrophy	+	+	+	+	+
	Hypotonia	±	±	±	±	±
	Spasticity (diplegia, quadriplegia)	±	±	±	±	±
Special laboratory	MRI/CT: leukodystrophy	±	+	+	+	+
	Organic acid (U):					
CNS	N-Acetylaspartic acid		↑	↑	↑	↑
	N-Acetylaspartic acid (P, CSF)		↑	↑	↑	↑
	Mental + motor retardation	+	+	+	+	+
	Seizures	±	±	±	±	±
	Nystagmus	±	±	±	±	±
	Opisthotonus	±	±	±	±	±
	Ataxia	±	±	±	±	±
	Dysarthria	±	±	±	±	±
	Deafness	±	±	±	±	±
	Choreoathetosis, dystonia, tremors	±	±	±	±	±

System	Symptoms/markers	Neonatal	Infancy	Childhood	Adolescence	Adulthood
GI	Feeding difficulties	±	±	±	±	±
	Failure to thrive	±	±	±	±	±
	Cholelithiasis	±	±	±	±	±
	Vomiting	±	±	±	±	±
Respiratory	Inspiratory stridor	±	±	±	±	±
	Cyanotic spells	±	±	±	±	±
Other	Fevers of unknown origin	±	±	±	±	±

## 8.5 Reference Values

### ■ 2-Ketoglutaric Acid (2-KGA)

Age	2-KGA (U) mmol/mol creat	2-KGA (S/P) μmol/l	2-KGA (CSF) μmol/l
<1 year	20–340	4–14	2–16
>1 year	10–80		

### ■ Fumaric Acid (FA)

Age	FA (U) mmol/mol creat	FA (S/P) μmol/l	FA (CSF) μmol/l
<1 year	<100	0.49–1.4	0.06–0.18
>1 year	<20		

### ■ Malonic Acid (MA)

Age	MA (U) mmol/mol creat	MA (S/P) μmol/l	MA (CSF) μmol/l
	<5		

### ■ L-2-Hydroxyglutaric Acid (L-2-HGA)

Age	L-2-HGA (U) mmol/mol creat	L-2-HGA (S/P) μmol/l	L-2-HGA (CSF) μmol/l
	1.3–19	0.5–1.0	0.3–2.3

### ■ D-2-Hydroxyglutaric Acid (D-2-HGA)

Age	D-2-HGA (U) mmol/mol creat	D-2-HGA (S/P) μmol/l	D-2-HGA (CSF) μmol/l
	2.8–17	0.3–0.9	0.07–0.3

### ■ N-Acetylaspartic Acid (NAA)

Age	NAA (U) mmol/mol creat	NAA (P) μmol/l	NAA (CSF) μmol/l
	6–36	0.17–0.84	0.25–2.8

## 8.6 Pathological Values/Differential Diagnosis

### ■ Disorder 8.1: 2-Ketoglutaric acid (2-KGA)

Age	2-KGA (U) mmol/mol Creat	2-KGA (S/P) μmol/l	2-KGA (CSF) μmol/l
	5–1700 <sup>a</sup>	17–37 <sup>b</sup>	4–13

<sup>a</sup> The organic acid profile might also show elevations of other Krebs cycle intermediates: succinate, fumarate, citrate and malate.

<sup>b</sup> The molar ratio of blood lactate/pyruvate is increased and the 3-hydroxybutyrate/acetate ratio is decreased.

### ■ Disorder 8.2: Fumaric acid (FA)

Age	FA (U) mmol/mol creat	FA (S/P) μmol/l	FA (CSF) μmol/l
	n–3829 <sup>a</sup>	22–28	6.8

<sup>a</sup> The organic acid profile might also show elevations of other Krebs cycle intermediates: succinate, citrate, malate, 2-ketoglutarate.

### ■ Disorder 8.3: Malonic acid (MA)

Age	MA (U) mmol/mol creat	MA (S/P) μmol/l	MA (CSF) μmol/l
	21–5440 <sup>a</sup>		

<sup>a</sup> Next to malonate, elevations of methylmalonate and sometimes ethylmalonate, succinate, glutarate, adipate suberate are found.

**■ Disorder 8.4: L-2-Hydroxyglutaric acid (L-2-HGA)**

Age	L-2-HGA (U) mmol/mol creat	L-2-HGA (S/P) μmol/l	L-2-HGA (CSF) μmol/l
	226–4294	7–84	23–474

**■ Disorder 8.5: D-2-Hydroxyglutaric acid (D-2-HGA)**

Age	D-2-HGA (U) mmol/mol creat	D-2-HGA (S/P) μmol/l	D-2-HGA (CSF) μmol/l
	676–7076	38–283	5–313

Sometimes, the organic acid profile also shows elevations of 2-ketoglutarate.

**■ Disorder 8.6: N-Acetylaspartic acid (NAA)**

Age	NAA (U) mmol/mol creat	NAA (P) μmol/l	NAA (CSF) μmol/l
	61–9647	9.3	

**8.7 Loading Tests****■ Disorders 8.1 and 8.2**

Investigation of the redox status in plasma on the basis of the molar L/P and B/A ratios in vivo can help to discriminate between several causes of congenital lactic acidosis. An intravenous glucose loading test (GTT; 2 g/kg b.w.) might be advantageous to get more information about the redox status. An increased L/P ratio and a normal or decreased B/A ratio would be suggestive for a defect in the citric acid cycle.

**■ Disorder 8.3**

During ketogenic (high fat) diet, urine of patients showed excess malonic acid excretion, whereas organic acid excretions of the parents were normal. Therefore it is considered that ketogenic challenge, although of proven diagnostic value in homozygous subjects, is not a useful tool in the investigation of potential heterozygotes.

When patients are in good condition, a ketogenic diet may be considered in order to promote urinary excretion of excess malonate for diagnostic purposes.

### ■ Disorders 8.4 and 8.5

A number of loading and fasting studies have been conducted without conclusive results.

### ■ Disorder 8.6

No loading tests are available for Canavan disease.

## 8.8 Specimen Collection

Disorder No.	Test	Preconditions	Material	Pitfalls
8.1	Organic acids	none	Urine	May decompose to form succinate
	L/P ratio, ketone body ratio		Plasma	
8.2	Organic acids	none	Urine	
	L/P ratio, ketone body ratio		Plasma	
8.3	Organic acids, acyl-carnitines	none	Urine	Separation from methylmalonate by GC sometimes difficult
8.4	Organic acids, followed by specific D-2-HG and L-2-HG isomers separation	none	Urine	
8.5	Organic acids, followed by specific D-2-HG and L-2-HG isomers separation	none	Urine	Compound may be a prominent abnormality in multiple acyl-CoA dehydrogenase deficiency
8.6	Organic acids (N-acetylaspartic acid)	none	Urine	Compound has bad recovery in organic solvent extraction

## 8.9 Prenatal Diagnosis

Disorder No.	Material	Timing trimester	Pitfalls
8.1	Chorionic villi (potentially) Amniotic fluid, amniocytes (potentially)	I II	
8.2	Chorionic villi (accomplished) Amniotic fluid, amniocytes (accomplished)	I II	
8.3	Chorionic villi (potentially) Amniotic fluid, amniocytes (potentially)	I II	
8.4	Amniotic fluid (accomplished)	II	
8.5	Amniotic fluid (accomplished)	II	Mild and combined DL forms are risky.
8.6	Chorionic villi (accomplished) Amniotic fluid, amniocytes (accomplished)	I II	Assay of aspartoacylase in amniocytes is not reliable. A combination of mutation analysis and metabolite measurement is recommended [33]

### ■ DNA Analysis

Disorder	Tissue/specimen	Methodology
8.1		
8.2	FB LYM	Sequencing
8.3	FB	Sequencing
8.4		
8.5		
8.6	FB	Sequencing

## 8.10 Initial Treatment

### ■ Disorder 8.1

Nasogastric tube feeding during the night with a diet low in carbohydrate (40%) and supplementation with bicarbonate in order to prevent further acidotic episodes have been recommended.

### ■ Disorder 8.2

There is no known treatment. Theoretically, aspartic acid supplementation might offer some benefit.

### ■ Disorder 8.3

It has been demonstrated that a low fat, high carbohydrate diet (18% and 67% of energy intake respectively), given for a period of five months, led to near normalization of the urinary organic acid excretion. Long-term outcome in affected individuals may be improved by implementing this diet as a permanent regimen. In another patient, treatment with 100 mg/kg b.w. of L-carnitine improved patient's muscle strength and tone and development. Supplementation of L-carnitine may therefore be beneficial in this disorder.

### ■ Disorders 8.4, 8.5 and 8.6

To date, there is no rational therapy for these disorders. For Canavan disease, gene transfer therapy is being developed [34].

## 8.11 Summary/Comments

### ■ Disorders 8.1 and 8.2

The mitochondrial encephalomyopathies are a heterogeneous group of disorders characterized by a wide range of clinical signs and symptoms. Onset of these disorders may occur at any time of life, including in utero. They may affect skeletal muscle, cardiac muscle or both, and involve other organs including brain, liver and kidney. Clinical symptoms associated with hyperlactic acidemia or hyperlactatorachia suggest a mitochondrial defect such as a disorder of pyruvate metabolism, respiratory chain defect or an inherited defect of the citric acid cycle. Urinary organic acids analysis and determination of the oxidoreduction (redox) status in plasma can help in differential diagnosis. One should keep in mind that excretion of 2-ketoglutarate and fumarate in these disorders is not always elevated, and that elevations can be intermittently present.

### ■ Disorder 8.3

Patients affected by this disorder were often diagnosed during episodes of vomiting and febrile convulsions associated with developmental delay. This finding again illustrates the importance of collecting urines for organic acids analysis during acute episodes of illness. The excretion of abnormal metabolites in this disorder can drop markedly within a short time.

## ■ Disorders 8.4 and 8.5

These “cerebral” organic acid disorders often appear to remain undiagnosed. Abnormalities such as hypoglycemia, metabolic acidosis or lactic acidemia, the usual concomitants of disorders of organic acid metabolism, are generally absent. Therefore, the correct diagnosis requires an increased awareness of these disorders by the referring physician as well as the clinical biochemist in the metabolic laboratory. Additional important diagnostic clues can be derived from neuro-imaging. Since the first description of these disorders in 1980, only recently an increasing number of reports of cases came to our attention.

## ■ Disorder 8.6

Canavan disease usually presents in early childhood with hypotonia, visual loss and accelerated head growth. MRI of the brain shows a leukodystrophy. In urine, plasma, and CSF N-acetylaspartic acid is elevated. However, sometimes the elevation in urine is marginal. The diagnosis can be confirmed by analysis of aspartoacylase and by mutation studies. Prenatal diagnosis is possible, preferably by the combined analysis of N-acetylaspartic acid in amniotic fluid and mutation studies.

## References

1. Rustin P, Bourgeron T, Parfait B, Chretien D, Munnich A, Rotig A. Inborn errors of the Krebs cycle: a group of unusual mitochondrial diseases in human. *Biochim Biophys Acta* 1997; **1361**(2): 185–197
2. Kohlschütter A, Behbehani A, Langenbeck U et al. A familial progressive neurodegenerative disease with 2-oxoglutaric aciduria. *Eur J Pediatr* 1982; **138**: 32–37
3. Bonnefont JP, Chretien D, Rustin P et al. Alpha-ketoglutarate dehydrogenase deficiency presenting as congenital lactic acidosis. *J Pediatr* 1992; **121**:255–258
4. Guffon N, Lopez-Mediavilla C, Dumoulin R et al. 2-Ketoglutarate dehydrogenase deficiency, a rare cause of primary hyperlactataemia: report of a new case. *J Inher Metab Dis* 1993; **16**: 821–830
5. Al Aqeel A, Rashed M, Ozand PT, Gascon GG, Rahbeeni Z, Al Garawi S, Al Odaib A, Brismar J. A new patient with  $\alpha$ -ketoglutaric aciduria and progressive extrapyramidal tract disease. *Brain Develop* 1994; **16** (suppl): 33–37
6. Dunckelmann RJ, Ebinger F, Schulze A, Wanders RJA, Rating D, Mayatepek A. 2-ketoglutarate dehydrogenase deficiency with intermittent 2-ketoglutaric aciduria. *Neuropediatrics* 2000; **31**: 35–38
7. Remes AM, Rantala H, Hiltunen JK, Leisti J, Ruokonen A. Fumarase deficiency: two siblings with enlarged cerebral ventricles and polyhydramnios in utero. *Pediatr* 1992; **89**: 730–734
8. Elpeleg ON, Amir N, Christensen E. Variability of clinical presentation in fumarate hydratase deficiency. *J Pediatr* 1992; **121**: 752–754



9. Bourgeron T, Chretien D, Poggi-Bach J et al. Mutation of the fumarase gene in two siblings with progressive encephalopathy and fumarase deficiency. *J Clin Invest* 1994; **93**: 2514–2518
10. Coughlin EM, Christen E, Kunze PL et al. Molecular analysis and prenatal diagnosis of human fumarase deficiency. *Mol Genet Metab* 1998; **63**: 254–262
11. Kerrigan JF, Aleck KA, Tarby TJ, Bird CR, Heidenreich RA. Fumaric aciduria: Clinical and Imaging Features. *Ann Neurol* 2000; **47**: 583–588
12. Haan EA, Scholem RD, Croll HB, Brown GK. Malonyl co-enzyme A decarboxylase deficiency. Clinical and biochemical findings in a second child with a more severe defect. *Eur J Pediatr* 1986; **144**: 567–570
13. MacPhee GB, Logan RW, Mitchell JS, Howells DW, Tsotsis E, Thorburn DR. Malonyl co-enzyme A decarboxylase deficiency. *Arch Dis Child* 1993; **69**: 433–436
14. Matalon R, Michaels K, Kaul R et al. Malonic aciduria and cardiomyopathy. *J Inher Metab Dis* 1993; **16**: 571–573
15. Buyukgebiz B, Jakobs C, Scholte HR, Huijman JGM, Kleijer WJ. Fatal neonatal malonic aciduria. *J Inher Metab Dis* 1998; **21**: 76–77
16. Gao J, Waber L, Bennett MJ, Gibson KM, Cohen JC. Cloning and mutational analysis of human malonyl-coenzyme A decarboxylase. *J Lipid Res* 1999; **40**: 178–182
17. FitzPatrick DR, Hill A, Tolmie JL, Thorburn DR, Christodolou J. The molecular basis of malonyl-CoA decarboxylase deficiency. *Am J Hum Genet* 1999; **65**: 318–326
18. Gibson KM, ten Brink HJ, Schor DSM, Kok RM, Bootsma AH, Hoffmann GF, Jakobs C (1993) Stable isotope dilution analysis of D- and L-2-hydroxyglutaric acid: application to the detection and prenatal diagnosis of D- and L-2-hydroxyglutaric acidemias. *Pediatr Res* 34: 277–280
19. van der Knaap MS, Jakobs C, Hoffmann GF et al. D-2-hydroxyglutaric aciduria: biochemical marker or clinical disease entity? *Ann Neurol* 1999; **45**: 111–119
20. van der Knaap MS, Jakobs C, Hoffman GF et al. D-2-hydroxyglutaric aciduria – further clinical delineation. *J Inher Metab Dis* 1999; **22**: 404–413
21. Amiel J, de Longlay P, Francannet C et al. Facial anomalies in D-2-hydroxyglutaric aciduria. *Am J Med Genet* 1999; **86**: 124–129
22. Barth PG, Hoffmann GF, Jaeken J et al. L-2-Hydroxyglutaric acidemia: clinical and biochemical findings in 12 patients and preliminary report on L-2-hydroxyacid dehydrogenase. *J Inher Metab Dis* 1993; **16**: 753–761
23. Fujitake J, Ishikawa Y, Fujii H et al. L-2-hydroxyglutaric aciduria: two Japanese adult cases in one family. *J Neurol* 1999; **246**: 378–382
24. Clerc C, Bataillard M, Richard P, Divry P, Kraehenbuhl, Rumbach L. An adult form of L-2-hydroxyglutaric aciduria revealed by tremor. *Eur Neurol* 2000; **43**: 119–120
25. Chen E, Nyhan WL, Jakobs C, Greco CM, Barkovich AJ, Cox VA, et al. L-2-Hydroxyglutaric aciduria: neuropathological correlations and first report of severe neurodegenerative disease and neonatal death. *J Inher Metab Dis* 1996; **19**: 335–343
26. Barth PG, Wanders RJ, Scholte HR, Abeling N, Jakobs C, Schutgens RB et al. L-2-hydroxyglutaric aciduria and lactic acidosis. *J Inher Metab Dis* 1998; **21**: 251–254
27. Muntau AC, Roschinger W, Merckenschlager A, van der Knaap MS, Jakobs C, Duran M, Hoffmann GF, Rosher AA. Combined D-2- and L-2-hydroxyglutaric aciduria with neonatal onset encephalopathy: A third biochemical variant of 2-hydroxyglutaric aciduria? *Neuropediatrics* 2000; **31**: 137–140
28. Traeger EC, Rapin I. The clinical course of Canavan Disease. *Pediatr Neurol* 1998; **18**: 207–212
29. Zelnik N, Luder AS, Elpeleg ON et al. Protracted clinical course for patients with Canavan disease. *Develop Med Child Neurol* 1993; **35**: 346–358
30. Toft PB, Geib-Holtorff R, Rolland MO et al. Magnetic resonance imaging in juvenile Canavan disease. *Eur J Pediatr* 1993; **152**: 750–753.

31. Jakobs C, ten Brink HJ, Langelaar SA et al. Stable isotope dilution analysis of N-acetylaspatic acid in CSF, blood, urine and amniotic fluid: accurate postnatal diagnosis and the potential for prenatal diagnosis of Canavan disease. *J Inher Metab Dis* 1991; **14**: 653–660
32. Matalon R, Kaul R, Michaels K. Canavan disease: biochemical and molecular studies. *J Inher Metab Dis* 1993; **16**: 744–752
33. Besley GTN, Elpeleg ON, Shaag A, Manning NJ, Jakobs C, Walter JH. Prenatal diagnosis of Canavan Disease: Problems and dilemmas. *J Inher Metab Dis* 1999; **22**: 263–266
34. Leone P, Janson CG, Bilianuk L et al. Aspartoacylase gene transfer to the mammalian central nervous system with therapeutic implications for Canavan disease. *Ann Neurol* 2000; **48**: 27–38