3-Methylglutaconic Acidurias

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Summary

Increased urinary 3-methylglutaconic acid excretion is a relatively common finding in inborn errors of metabolism, especially in mitochondrial disorders. In most cases 3-methylglutaconic acid is only slightly elevated and accompanied by other (disease-specific) metabolites.

There is, however, a group of disorders with significantly and consistently increased 3-methylglutaconic acid excretion, where the 3-methylglutaconic aciduria is a hallmark of the phenotype and the key to diagnosis: inborn errors with 3-methylglutaconic aciduria as a discriminative feature (3-MGA-IEM). One should distinguish between "primary 3-methylglutaconic acidurias" formerly known as type I (3-methylglutaconyl-CoA hydratase deficiency, AUH defect) due to defective leucine catabolism and the—currently known— 11 "secondary 3-methylglutaconic acidurias." The latter should be further classified and named by their defective protein or the historical name as follows: TAZ-defect or Barth syndrome, SERAC1-defect or MEGDEL syndrome, AGK-defect or Sengers syndrome, OPA3-defect or Costeff syndrome, TMEM70, MICOS13, DNAJC19, TIMM50, and HTRA2 defect.

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N. Blau et al. (eds.), *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases*,
https://doi.org/10.1007/978-3-030-67727-5_70

Introduction

The branched-chain organic acid 3-methylglutaconic acid (3-MGA) is an intermediate of the mitochondrial leucine catabolism. In the urine of healthy individuals, 3-MGA is found only in traces (<20 mmol/mol creatinine); in young infants it can be higher (up to 30 mmol/mol creatinine) as the creatinine is relatively lower due to lower muscle mass.

In patients with inborn errors with 3-methylglutaconic aciduria as a discriminative feature **(3-MGA-IEM)**, urinary 3-MGA concentrations can (intermittently) rise above 1000 mmol/mol creatinine (Wortmann et al. 2013a, b).

The leucine pathway shows the metabolic pathway of leucine. 3-MGA, 3-methylglutaric acid (3-MG), and 3-hydroxyisovaleric acid (3-HIVA) accumulate when the conversion of 3-methylglutaconyl-CoA to 3-hydroxy-3-methylglutaryl-CoA by the enzyme 3-methylglutaconyl-CoA hydratase (3-MGH, EC 4.2.1.18 encoded by *AUH*) is disturbed (Fig. 70.1) (Wortmann et al. 2010). This is the primary 3-methylglutaconic aciduria (3-MGA-uria) or AUH-defect, formerly known as 3-MGA-uria type I. **The urinary excretion of 3-MGA is generally higher in primary 3-MGA-IEM, AUH defect, than in all other (secondary) 3-MGA-IEM.** Patients with AUH defect excrete even higher amounts of urinary 3-MGA after a leucine-rich, or in general a protein-rich, meal (Table 70.12) (Wortmann et al. 2014). This is not the case in all other patients with 3-MGA-uria underlining that the excreted 3-MGA does not originate from leucine degradation. Another distinctive feature between primary and secondary 3-MGA-IEM is the elevation of 3-HIVA which is only seen in the AUH defect.

3-MGA-uria can be frequently seen (3% of all urine samples of patients with suspected IEM) in association with several IEM, such as organic acidurias, glycogen storage disorders, fatty acid oxidation disorders, and urea cycle disorders (Fig. 70.1 classification updated from) (Wortmann et al. 2013a, b). Therefore it is important to repeat urinary organic acid analysis in patients with 3-MGA-uria and to carefully interpret the other general clinical chemistry (blood gas analysis, glucose, lactate, ammonia, full blood counts, etc.) and metabolic screening tests (serum amino acids, acylcarnitines in dried blood spot, oligosaccharides in urine). This will allow to confirm that 3-MGA-uria is only an accompanying finding.

In another group of patients, 3-MGA-uria is only slightly and/or intermittently elevated, and 3-MGA-uria is a minor finding. The majority of patients in this group are patients with mitochondrial disorders where it is detected in about 11% of all patients. It is more frequently seen in ATPase-related disorders, with mitochondrial DNA depletion or deletion (e.g., Pearson syndrome), but not in patients with single respiratory chain complex deficiencies with exception of ATPase-related disorders (Wortmann et al. 2013a, b). As 3-MGA-uria is not found in all of these patients with the mentioned specific mitochondrial disorders, these disorders are discussed and not here.

Once 3-MGA-uria has been proven to be an isolated and consistently present finding, 3-MGA-uria as a major finding, the diagnosis of a 3-MGA-IEM can be made. One subgroup is formed by the disorders involving defective phospholipid biosynthesis (*TAZ*, *SERAC1*, *AGK*) (Clarke SL et al. 2013; Thiels C et al. 2016; Mass RR et al. 2017; Roeben B et al. 2018; Wortmann SB et al. 2015; Wortmann SB et al. 2012; Haghighi A et al. 2014; Mayr JA et al. 2012), all other 3-MGA-IEM share mitochondrial (membrane) dysfunction (*OPA3*, *DNAJC19*, *CLPB*, *HTRA2*, *TIMM50*, *TMEM70*, *MIC13*, Fig. 70.2) (Anikster et al. 2006; Ucar SK et al. 2017; Davey KM et al. 2006; Pronicka E et al. 2017; Wortmann SB et al. 2015; Kovacs-Nagy R et al. 2018; Shahrour MA et al. 2017; Magner M et al. 2015; Kishita Y et al. 2020). There are no additional (metabolic) clues that can help to further distinguish between the different types of 3-MGA-IEM with exception of the clinical features (see table on differential diagnosis at the section signs and symptoms). All 3-MGA-IEM show a distinctive pattern of signs and symptoms which allows to distinguish between them; however patients affected by the different 3-MGA-IEM show a spectrum within their subtype (Fig. 70.1).

Nomenclature

No.	Disorder_name	Alternative name	Gene symbol	Chromosomal location	Mode of Inheritance	Affected protein	OMIM No.
70.1	AUH deficiency	3-methylglutaconic aciduria type 1	*AUH*	9q22.31	AR	3-methylglutaconyl-CoA hydratase	600529
70.2	TAZ deficiency	Barth syndrome; Taffazin deficiency	*TAZ*	Xq28	XLR	Taffazin	300394
70.3	SERAC1 deficiency	3-methylglutaconic aciduria with dystonia, deafness, hepatopathy, encephalopathy, and Leigh-like syndrome (MEGDHEL)	*SERAC1*	6q25.3	AR	Serine active site-containing protein 1	614725
70.4	AGK deficiency	Sengers syndrome	*AGK*	7q34	AR	Acylglycerokinase	212350
70.5	OPA3 deficiency	Optic atrophy type 3 (dominant); 3-methylglutaconic aciduria type 3, Costeff syndrome (recessive)	*OPA3*	19q13.2–13.3	AD, AR		606580
70.6	DNAJC19 deficiency	Dilated cardiomyopathy with ataxia (DCMA syndrome); 3-methylglutaconic aciduria type 5	*DNAJC19*	3q26.33	AR	- DNAJ/HSP40 homolog, subfamily C, member 19	608977
70.7	CLPB deficiency	3-methylglutaconic aciduria type 7, with cataracts, neurologic involvement and neutropenia	*CLPB*	11q13.4	AR	- Caseinolytic peptidase B	616254
70.8	HTRA2 deficiency	3-methylglutaconic aciduria type 8	*HTRA2*	2p13.1	AR	- HTRA serine peptidase 2	606441
70.9	TIMM50 deficiency	3-methylglutaconic aciduria type 9	*TIMM50*	19q13.2	AR	Translocase of inner mitochondrial membrane 50	607381
70.10	TMEM70 deficiency	Transmembrane protein 70 deficiency	*TMEM70*	8q21.11	AR	Complex V assembly protein	612418
70.11	MICOS13 deficiency	MICOS complex subunit MIC13 deficiency	*MICOS13*	19p13.3	AR	MICOS complex, 13-KD subunit	618329

Metabolic Pathways

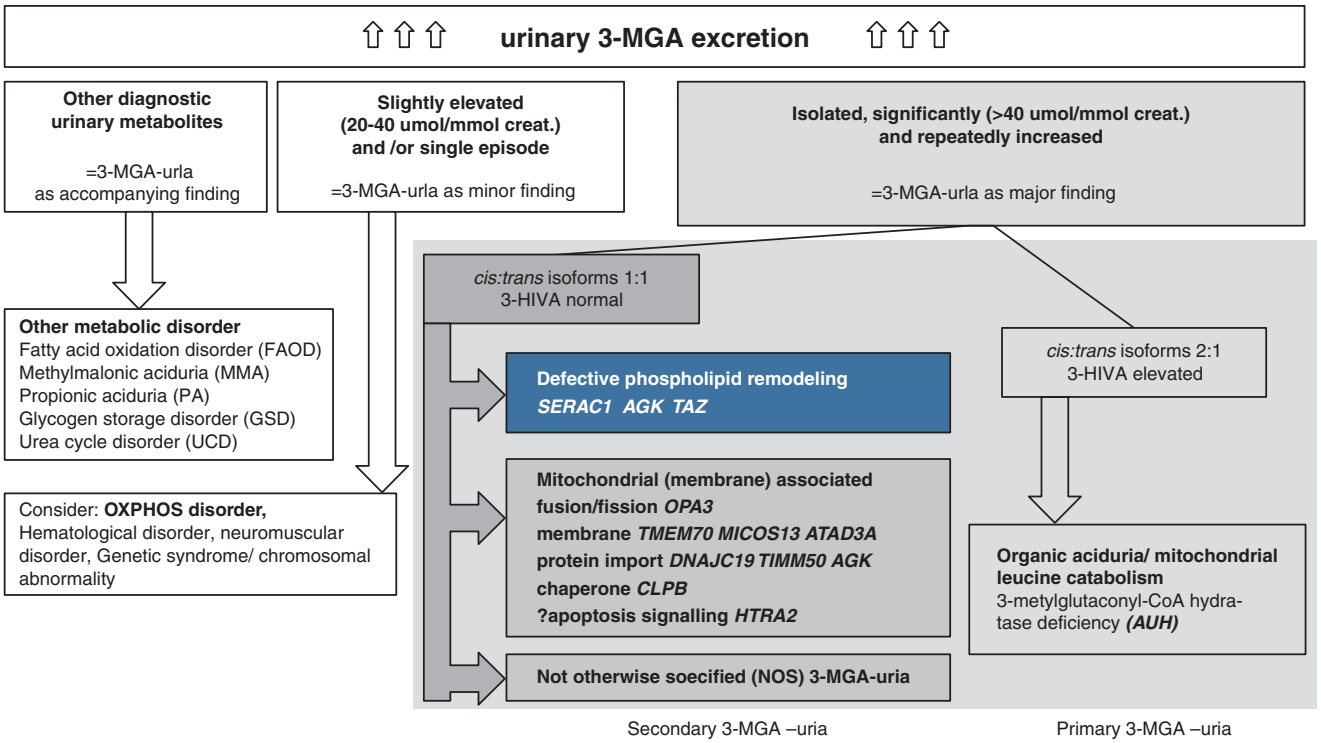

Fig. 70.1 Inborn errors with 3-methylglutaconic aciduria as discriminative feature (3-MGA-IEM). (Updated from Wortmann et al. 2013a, b)

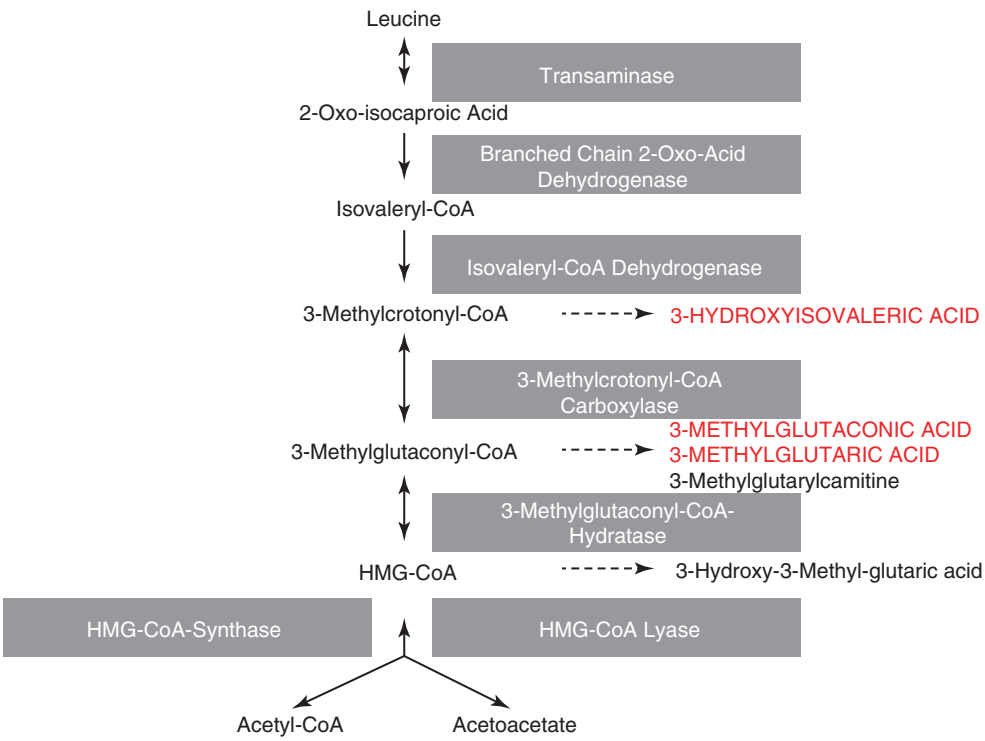

Fig. 70.2 Leucine metabolism (Updated from Wortmann et al. 2013a, b)

Signs and Symptoms

	AUH-def.	TAZ-def.	SERAC1-def.	AGK-def.	OPA3-def.	DNAJC19-def	CLPB-def.	HTRA2-def.	TIMM50-def.	TMEM70-def.	MIC13-defect
MIM #	250950	302060	614739	212350	258501	610198	616271	617248	617698	614052	618329
Gene	*AUH*	*TAZ*	*SERAC1*	*AGK*	*OPA3*	*DNAJC19*	*CLPB*	*HTRA2*	*TIMM50*	*TMEM70*	*MIC13*
3-MGA-uria	x	x	x	x	x	x	x	x	x	x	x
Mode of inheritence	AR	XLR	AR	AR	AR	AR	AR	AR	AR	AR	AR
Typical age at onset	4-5th decade	Neonatal	Neonatal-first year	Childhood	Childhood	Childhood	Neonatal	Neonatal	Neonatal	Neonatal	Neonatal
Developmental delay		(x)	x	(x)	x	x	x	x	x	x	x
Intellectual disability			x			x	x	x	x	x	x
Movement disorder	x		x		x	x	x	x			x
Central hypopnea							x	x			
Optic atrophy			(x)		x						
Deafness			x								
Epilepsy			(x)				(x)		x		x
Cataracts				x			x	x			
Cardiomyopathy		x		x		x				x	
Neutropenia		x					x	x			
Growth failure		x	x	x	x	x	x	x	x	x	x
Liver involvement			x								x

Table 70.1 AUH deficiency

System	Symptoms and Bbomarkers	Neonatal (birth-1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	**Ataxia**	±	±	±	+	+
	Athetosis	±	±	±	±	±
	Basal ganglia lesions (MRI)	±	±	±	±	±
	Cerebellar abnormalities	±	±	±	±	±
	Cerebellar abnormalities	±	±	±	±	±
	Cerebral atrophy (MRI)	±	±	±	±	±
	Dementia	±	±	±	±	±
	Fits	±	±	±		
	Leukoencephalopathy	±	±	+	+	+
	Regression	+	+	+	+	+
	Retardation	+	+	+	+	+
	Retardation, psychomotor	±	+	+	±	±
	Seizures, febrile	±	±	±		
	Spasticity, limbs	±	±	±	±	+
	White matter changes (MRI)	±	±	±	±	±
Digestive	Hepatomegaly	±	±	±	±	±
	Liver dysfunction	±	±	±	±	±
Eye	Nystagmus	±	±	±	±	±
	Optic atrophy	±	±	±	±	±

(continued)

Table 70.1 (continued)

System	Symptoms and Bbomarkers	Neonatal (birth-1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Hematological	Thrombocytopenia	±	±	±		
Metabolic	Metabolic acidosis	±	±	±		
	Hypoglycemia	±	±	±		
Laboratory findings	3-Hydroxyisovaleric acid (MRS)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Hydroxyisovaleric acid (urine)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylglutaconic acid (urine)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	3-Methylglutaconyl-CoA hydratase (fibroblasts)	↓	↓	↓	↓	↓
	3-Methylglutaric acid (urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Ammonia (blood)	n-↑	n-↑	n-↑	n-↑	n-↑
	ASAT/ALAT (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	C5-OH Acylcarnitine (dried blood spot)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C5-OH Acylcarnitine (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	C6-unsaturated acylcarnitine (blood)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	C6-unsaturated acylcarnitine (plasma)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Carnitine, esterified (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Carnitine, free (dried blood spot)	↓-n	↓-n	↓-n	↓-n	↓-n
	Carnitine, free (plasma)	↓-n	↓-n	↓-n	↓-n	↓-n
	Creatine kinase (plasma)	n-↑	n-↑	n-↑		
	Glucose (plasma)	↓-n	↓-n	↓-n		
	N-acetylaspartate (MRS)	↓-n	↓-n	↓-n	↓-n	↓-n

Table 70.2 TAZ deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	Cardiac arrhythmia	±	±	±	±	±
	Cardiomyopathy	+	+	+	+	+
	Cardiomyopathy, dilated	±	±	±	±	±
	Heart failure	±	±	±	±	±
	Left ventricular non-compaction	±	±	±	±	±
Dermatological	Chronic aphthous ulceration	±	±	±	±	±
Digestive	Feeding difficulties	±	±	±	±	±
Hematological	**Neutropenia**	+	+	+	+	+
	Sepsis	±	±	±	±	±
Musculoskeletal	Exercise intolerance	±	±	±	±	±
	Growth retardation	+	+	+	+	+
	Hypotonia, muscular-axial	±	±	±	±	±
	Myopathy	±	±	±	±	±
Respiratory	Respiratory distress	±	±	±	±	±
Other	Mild dysmorphic features	±	±	±	±	±
Laboratory findings	2-Ethylhydracrylic acid (urine)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n
	3-Methylglutaconic acid (urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	Abnormal cardiolipin profile (DBS)	+	+	+	+	+
	Cholesterol (serum)	↓-n	↓-n	↓-n	↓-n	↓-n

Table 70.3 SERAC1 deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1-18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	**Bilateral sensory hearing loss**	+	+	+	+	+
	Cerebellar atrophy (MRI)	+	+	+	+	+
	Cerebral atrophy (MRI)	+	+	+	+	+
	Dystonia	+	+	+	+	+
	Encephalopathy	+	+	+	+	+
	Epilepsy	±	±	±	±	±
	Extrapyramidal signs	±	±	±	±	±
	Hypotonia	±	±	+	+	+
	Leigh-like lesions (MRI)	+	+	+	+	+
	Regression	+	+	+	+	+
	Retardation	+	+	+	+	+
	Spasticity	±	+	+	+	+
Digestive	Feeding difficulties	±	±	±	±	±
	Jaundice	±	±			
	Liver dysfunction	±				
Laboratory findings	ASAT/ALAT (plasma)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
Metabolic	Hypoglycemia	±	±	±	±	±
Other	Failure to thrive	±	±	±	±	±
Laboratory findings	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n
	3-Methylglutaconic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	Cholestasis	n-↑↑↑	n-↑↑↑	n	n	n
	Filipin test	n-↑	n-↑	n-↑	n-↑	n-↑
	Glucose (plasma)	↓-n	n	n	n	n
	Lactate (cerebrospinal fluid)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (plasma)	n-↑↑↑	n-↑↑↑	n-↑↑↑	n-↑↑↑	n-↑↑↑

Table 70.4 AGK deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	**Cardiomyopathy, hypertrophic**	+	+	+	+	+
Eye	**Cataract**	±	±	±	±	±
Metabolic	Lactic acidosis	+	+	±	±	±
	Metabolic acidosis	+	+	+	+	±
Musculoskeletal	**Hypotonia, muscular-axial**	+	+	+	+	+
Laboratory findings	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n
	3-Methylglutaconic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	Lactate (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑

Table 70.5 OPA3 deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	**Ataxia**		±	+	+	+
	Cerebral atrophy (MRI)	±	±	±	±	±
	Extrapyramidal movement disorder		±	+	+	+
	No intellectual disability	+	+	+	+	+
	Spastic paraplegia		±	+	+	+
	Spasticity		±	+	+	+
Eye	Nystagmus	±	+	+	+	+
	Optic atrophy	±	+	+	+	+
Laboratory findings	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n
	3-Methylglutaconic acid (urine)	↑	↑	↑	↑	↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑

Table 70.6 DNAJC19 deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	**Cardiomyopathy, dilated**	+	+	+	+	+
	Cardiac conduction defect/ long QT	+	+	+	+	+
CNS	**Ataxia**	±	+	+	+	+
	Intellectual disability	±	±	±	±	±
	Seizures	±	±	±	±	±
Digestive	Liver steatosis	±	±	±	±	±
Ear	Hearing loss	±	±	±	±	±
Eye	Optic atrophy	±	±	±	±	±
Genitourinary	**Genitourital anomalies**	±	±	±	±	±
	Testicular dysgenesis	±	±	±	±	±
Hematological	**Anemia, microcytic**	+	+	+	+	+
Musculoskeletal	**Growth retardation**	+	+	+	+	+
Laboratory findings	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n
	3-Methylglutaconic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	Lactate (cerebrospinal fluid)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑

Table 70.7 CLPB deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Ataxia	±	±	±	±	±
	Cerebellar atrophy (MRI)	+	+	+	+	+
	Cerebral atrophy (MRI)	+	+	+	+	+
	Dystonia	±	±	±	±	±
	Hyperekplexia	±				
	Hypertonia, extremities	±	±	+	+	+
	Hypotonia, muscular	+	+	±	±	±
	Intellectual disability	+	+	+	+	+
	Retardation	+	+	+	+	+
	Seizures	±	±	±	±	±
	Seizures, intrauterine	±				
	Spasticity					
	Stiffness	±				
Endocrine	Endocrine abnormalities	±	±	±	±	±
Eye	**Cataract**	+	+	+	+	+
Hematological	**Neutropenia**	+	+	+	+	+
Other	Death	±				
	Intrauterine growth retardation	±				
	Ulcerations, oral, genital	±	±	±	±	±
Laboratory findings	3-Methylglutaconic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n

Table 70.8 HTRA2 deficiency

System	Symptoms and Biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	**Apnea**	+	+			
	Brain atrophy (MRI)	+	+			
	Central hypopnea	+	+			
	Developmental delay	+	+			
	Hypertonia, extremities	+	+			
	Hypotonia, muscular	+	+			
	Intellectual disability	+	+			
	Jitteriness	+	+			
	Neurodegeneration	+	+			
	Seizures	+	+			
	Tremor	+	+			
Digestive	**Dysphagia**	+	+			
Hematological	**Neutropenia**	+	+			
Other	**Death**	+	+			
	Loss of skills	+	+			
	Intrauterine growth retardation	+	+			
Laboratory findings	Lactate (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Lactate (cerebrospinal fluid)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	3-Methylglutaconic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n

Table 70.9 TMEM70 deficiency

System	Symptoms and Biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	**Cardiomyopathy, hypertrophic**	+	+	+	+	+
	Wolf-Parkinson-white syndrome	±	±	±	±	±
CNS	Apnea	±	±	±	±	±
	Basal ganglia lesions (MRI)	±	±	±	±	±
	Cerebellar hypoplasia, mild	±	±	±	±	±
	Cortical atrophy (MRI)	±	±	±	±	±
	Encephalopathy	+	+	+	+	+
	Hypotonia, muscular-axial	+	+	+	+	+
	Microcephaly	±	±	±	±	±
	Retardation, psychomotor	±	+	+	+	+
	Subcortical atrophy (MRI)	±	±	±	±	±
Digestive	Gastrointestinal dysmotility	±	±	±	±	±
	Hepatomegaly	+	+	±	±	±
	Liver dysfunction	±	±	±	±	±
Eye	Cataract	±	±	±	±	±
Genitourinary	Cryptorchidism	±	±	±	±	±
	Hypospadias	±	±	±	±	±
Metabolic	**Hyperammonemia, during crisis**	+	+	+	+	±
	Hyperuricemia, during crisis	+	+	+	+	±
	Ketonuria, pronounced during crisis	+	+	+	+	+
	Lactic acidosis	+	+	±	±	±
	Metabolic acidosis	+	+	+	+	±
Musculoskeletal	Contractures	±	±	±	±	±
	Facial dysmorphism	±	±	±	±	±
Renal	Renal tubulopathy	±	±	±	±	±
Respiratory	**Persistent pulmonary hypertension of the newborn**	±				
	Respiratory insufficiency	±	±	±	±	±
Other	Failure to thrive	+	+	+	+	+
	Growth retardation, postnatal	±	±	±	±	±
	Low birth weight	±				
Laboratory findings	Alanine (plasma)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Ammonia (blood and plasma)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Anion gap	↑	↑	↑	↑	↑
	Uric acid	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Citrulline (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Complex V activity (skeletal muscle)	↓	↓	↓	↓	↓
	Creatine kinase (plasma)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Glutamine (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Lactate (cerebrospinal fluid)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Orotate (urine)	n-↑	n-↑	n-↑	n-↑	n-↑
	3-Methylglutaconic acid (urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑

Table 70.10 TIMM50 deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Behavior, aggressive	±	±	±	±	±
	Bilateral symmetric lesions globus pallidus and brain stem (MRI)	±	±	±	±	±
	Brain atrophy (MRI)	±	±	±	±	±
	Developmental delay	+	+	+	+	+
	Epilepsy	+	+	+	+	+
	Hypotonia	+	+	+	+	+
	Hypsarrhythmia (EEG)	+	+	+	+	+
Eye	**Optic atrophy**	+	+	+	+	+
Other	Failure to thrive	+	+	+	+	+
Laboratory findings	3-Hydroxyisovaleric acid (urine)	n	n	n	n	n
	3-Methylglutaconic acid (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	3-Methylglutaric acid (urine)	↑	↑	↑	↑	↑
	Lactate (cerebrospinal fluid)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Lactate (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑

Table 70.11 MICOS13 deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Cortical atrophy (MRI)	±	±			
	Epilepsy	±	±			
	Hypotonia, muscular	±	±			
	Microcephaly	±	±			
	Regression	±	±			
	Retardation, psychomotor	±	±			
	Subcortical atrophy (MRI)	±	±			
	White matter abnormalities (MRI)	±	±			
Digestive	**Liver failure, acute**	+	+			
	Liver dysfunction	+	+			
Metabolic	Hypoglycemia	±	±			
Other	**Death**	+	+			
	Failure to thrive	±	±			
Laboratory findings	3-Hydroxyisovaleric acid (urine)	n	n			
	3-Methylglutaconic acid (urine)	↑↑	↑↑			
	3-Methylglutaric acid (urine)	↑	↑			
	Ammonia (blood)	n	n			
	ASAT/ALAT (plasma)	↑	↑			
	Bilirubin, conjugated (plasma)	↑	↑			
	Disturbed clotting	↑	↑			
	Glucose (plasma)	↓-n	↓-n			
	Lactate (plasma)	↑	↑			

[a]All patients died (maximum age 13 months)

Reference Values

Metabolite	Reference value
3-Hydroxyisovaleric acid (U)	0–25 mmol/mol creatinine (0–2 month) 0–50 mmol/mol creatinine (2 months–2 years) 0–45 mmol/mol creatinine (2–10 years) 0–15 mmol/mol creatinine (10–18 years) 0–20 mmol/mol creatinine (> 18 years) (GCMS, TML laboratory, Radboud university, Nijmegen, NL)
3-Methylglutaconic acid (U)	0–20 mmol/mol creatinine (0–2 month) 0–15 mmol/mol creatinine (2 months–2 years) 0–10 mmol/mol creatinine (>2 years) (GCMS, TML laboratory, Radboud university, Nijmegen, NL)
3-Methylglutaric acid (U)	Absent, if present not quantified (GCMS, TML lab, Radboud University, Nijmegen, NL)

Pathological Values

Metabolite	Pathological value
3-Methylglutaconic acid (U)	20–40 mmol/mol creatinine: Suggestive for mitochondrial dysfunction as it can be seen in numerous inborn errors of metabolism > 40 mmol/mol creatinine: Suggestive for inborn error of metabolism with 3-methylglutaconic aciduria as discriminative feature

Leucine Loading Test

Indication: To distinguish between primary and secondary 3-methylglutaconic aciduria.

Procedure: Collect a urine portion for urinary organic acid analysis and a venous blood sample for serum amino acids. Give 100 mg/kg (max. 6 g) leucine powder orally, and repeat listed investigations 1 h after the leucine gift. Collect a 24-h urine sample for another urinary organic acid analysis.

Interpretation: Table below lists the typical findings before and after leucine loading in several 3-methylglutaconic acidurias. Only in primary 3-MGA_uria due to AU deficiency a clear increase in urinary 3-MGA occurs.

Results of the leucine loading tests in different 3-methylglutaconic acidurias

Defect	Elevated urinary 3-HIVA	Lowest urinary 3-MGA before loading (Ref < 20 mmol/mol creatinine)	Peak urinary 3-MGA after loading (Ref < 20 mmol/mol creatinine)	Ratio *cis:trans* isoforms of 3-MGA	Mean ratio (range, N patients)
AUH	+	400	2982	2:1	4.1 (3.9–4.5; *N* = 3)
TAZ	–	32	192	1:1	1.8 (1.1–5.3; *N* = 9)
OPA3	–	29	26	1:1	0.9 (*N* = 1)
SERAC1	–	60	234	1:1	1.3 (1.3–1.3; *N* = 2)
CLPB	–	52	53	1:1	1.0 (*N* = 1)
NOS	–	21	410	1:1	1 (0.5–1.1; *N* = 5)

3-HIVA 3-hydroxyisovaeleric acid, *3-MGA* 3-methylglutaconic acid

Specimen Collection

Urine for organic acid analysis should be analyzed immediately or frozen at –20 °C.

DNA Testing

All 3-MGA-IEM show a distinctive pattern of signs and symptoms which justifies single gene testing. In less clear presentations, the whole exome or genome sequencing (WES/WGS) is the method of choice. As both point mutations and deletion(s) in the mitochondrial DNA can cause disorders with unspecific 3-methylglutaconic aciduria, one should inquire at the genetic lab and make sure that the genetic test chosen covers these. Leucocyte-derived DNA from 3–5 ml EDTA blood (children, adults) will be enough for all mentioned genetic tests, and WGS can be performed in much less blood even from a dried blood spot.

Treatment Summary

AUH defect is a disorder of leucine catabolism. Acute deteriorations in relation to catabolism as in other intoxication-type IEM has not been described. The clinical manifestation is an adult-onset (fourth decade onwards) slowly progressive leukoencephalopathy with ataxia and spasticity (Wortmann et al. 2010). A leucine-restricted diet or a protein-defined (vegetarian) diet could be considered; data on this are lacking and will be difficult to obtain. In general, only a supportive treatment is available for all 3-MGA-IEM.

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