

5.1 Introduction

The primary disorders of histidine metabolism are histidinemia and urocanase deficiency (urocanic aciduria).

Histidinemia is an autosomal recessive disorder that is benign in most affected individuals. The incidence from newborn screening is 1:10 000, making histidinemia one of the most frequent of the inborn errors of metabolism. The enzyme defect is histidase, an enzyme normally expressed only in skin and liver. The block in conversion of histidine to urocanic acid results in an increased concentration of histidine in blood and urine and the abnormal presence of histidine metabolites in urine.

There is biochemical heterogeneity in histidinemia, as there is in other inborn errors of metabolism. There are two groups with respect to residual skin histidase activity. One group, the larger, is characterized by the lower residual enzyme activity and the other group by the higher activity. Lower fasting blood histidine levels and higher tolerances to dietary histidine correspond to the higher residual histidase activity in the second group. However, there were no differences between the two groups in clinical phenotypes.

The diagnosis of histidinemia is based on finding an elevation of histidine in the blood and increased excretion of histidine and imidazolepyruvic acid in the urine. The urinary metabolite, imidazolepyruvic acid, can usually be detected by the ferric chloride test or by dipping the Phenistix reagent strip into the urine. The diagnosis is confirmed by demonstrating the absence or marked reduction of histidase activity in skin or the absence of urocanic acid in skin.

Treatment with a histidine-restricted diet normalizes the biochemical phenotype but is not indicated for this probably harmless disorder although the treatment might be considered in any histidinemic infant who also has clinical abnormalities.

Urocanase deficiency is a very rare autosomal recessive disorder that may be benign in most affected individuals. The reported cases with the disorder are less than ten. The enzyme defect is urocanase, an enzyme normally expressed in liver. The block in conversion of urocanic acid to imida-

zolonepropionic acid results in a greatly increased concentration of urocanic acid in urine, while histidine and histidine metabolites are normal or only mildly increased.

The diagnosis of urocanase deficiency is based on finding increased excretion of urocanic acid in the urine. A histidine loading test exaggerated the urocanic acid excretion and also lead to the production of imidazolepropionic acid, a byproduct of urocanic acid. Metabolites such as imidazolonepropionic acid and formiminoglutamic acid, which are distal to the metabolic step catalyzed by urocanase, were not present in urine after loading with histidine. The diagnosis of a urocanase deficiency is confirmed by demonstrating the absence or marked reduction of urocanase activity in liver.

Two patients identified by routine newborn urine screening have maintained normal development without dietary or other therapy. Dietary treatment is not indicated for this disorder although the treatment might be considered in the patients with urocanase deficiency who have clinical abnormalities.

Increased urinary formiminoglutamic acid in the absence of folic acid deficiency or cobalamine C disease is indicative of formiminotransferase deficiency. Accumulation of imidazolonepropionic acid is not observed, but there is an abnormal excretion of its oxidation product, hydantoin-5-propionic acid. Loading tests with histidine will enhance the excretion. Confirmation of the defect is made by enzyme analysis; probably the liver is the only suitable tissue. Affected patients were mentally retarded and/or had convulsions; however, a number of healthy siblings with the biochemical abnormality have been described.

5.2 Nomenclature

No.	Disorder	Affected component	Tissue distribution	Chromosomal localization	MIM
5.1	Histidinemia	Histidase (Histidine ammonia-lyase)	Skin, liver	12q22–q24.1	235800
5.2	Urocanase deficiency	Urocanase	Liver		276880
5.3	Formimino-transferase deficiency	Formiminotransferase	Liver	21q22.3	229100

5.3 Metabolic Pathway

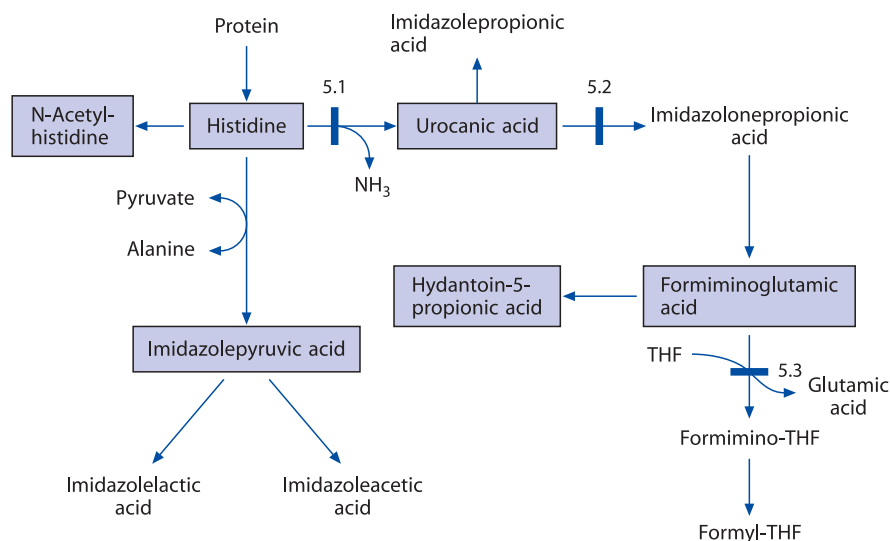


Fig. 5.1. Pathways of histidine catabolism, including possible metabolic defects. 5.1, Histidase (histidine ammonia-lyase); 5.2, urocanase; 5.3, formiminotransferase. THF, tetrahydrofolic acid. Pathological metabolites used as specific markers in the differential diagnosis are marked in squares

5.4 Signs and Symptoms

Table 5.1. Histidinemia

System	Symptoms/ markers	Neonatal	Infancy	Childhood	Adoles- cence	Adulthood
Unique clinical findings	Retardation	–	±	±	±	±
Routine laboratory	Ketones (FeCl ₃ test)	–	+	+	+	+
Special laboratory	EEG			±		
	His (P)	↑	↑	↑	↑	↑
	His (U)	↑	↑	↑	↑	↑
	His (CSF)	↑	↑	↑	↑	↑
CNS	Seizures		±	±		
	MR/DD	–	±	±	±	±
	Speech Difficulty	–	±	±	±	
	Abnormal behaviour	–	±	±		

It is unlikely that the clinical signs and symptoms are associated with the disorders of histidine metabolism; His, histidine.

Table 5.2. Urocanase deficiency

System	Symptoms/ markers	Neonatal	Infancy	Childhood	Adoles- cence	Adulthood
Unique clinical findings	Retardation	–	±	±		
Routine laboratory	Ketones (FeCl ₃ test)	–	±	±		
Special laboratory	Uro A (U)	↑	↑	↑	↑	↑
CNS	MR/DD	–	±	±		

The clinical signs and symptoms may not be related to the metabolic disorder.
Uro A, urocanic acid.

Table 5.3. Formiminotransferase deficiency

System	Symptoms/ markers	Neonatal	Infancy	Childhood	Adoles- cence	Adulthood
Unique clinical findings	Retardation		±	±	±	±
	Seizures	±	±			
	Megaloblastic anemia	±	±	±	±	
	Hypotonia	±	±	±	±	±
Special laboratory	Figlu (U)	↑	↑	↑	↑	↑
	Hydantoin-5- propionic acid (U)	↑	↑	↑	↑	↑
	Folate (B)	n	n	n	n	n

Figlu, formiminoglutamic acid.

5.5 Reference Values

	Neonatal	Infancy	Childhood	Adolescence	Adulthood
His (B) ^a (μmol/l)	77±16	78±14	80±13	80±13	88±16
His (U) ^a (mmol/mol creat)		164–276	114–198	76–228	42–172
His (CSF) ^a (μM)			13±4.4		
IPyA (U)			n.d.		
UroA (U) (mmol/day)			<0.1		
UroA (skin) (μmol/g skin)			26–72		
Histidase (skin) (μmol/h/g skin)		9.49±4.14	12.35±2.81	10.98±1.93	9.36±2.04
Urocanase (l) (nmol/ 100 mg prot/min)			60±12		
Figlu (U)			0–11 (μmol/l) 0–31 (μmol/ day)		

^a see also Chap. B

His, histidine; IPyA, imidazolepyruvic acid; UroA, urocanic acid; Figlu, formiminoglutamic acid; n.d., not detectable.

5.6 Pathological Values/Differential Diagnosis

	His (B) (μM)	His (U) (μmol/g creat)	IPyA (U) (mmol/g creat)	UroA (U) (μmol/day)	UroA (skin) (μmol/g)	Figlu (U) (μmol/day)	Histidase (skin) (μmol/h/g)	Urocanase (liver) (nmol/min/ 100 mg protein)
5.1 Histidinemia, classical	548–1097	3–27	<2	n.d.	↓↓		<0.5	
5.1 Histidinemia, atypical	290–742				↓		1.8–2.7	
5.2 Urocanase deficiency	n–↑	n–↑	↑	n–↑	97, 105		n	0, 19.7
5.3 Formimino- transferase deficiency	n	n	n	n	n	<3500		

n.d., not detectable.

5.7 Loading Test

	His (B)		His (U)		IPyA (U)		UroA (U)		Figlu (U)	
Histidine load (100 mg/kg bw)										
5.1 Histidinemia	0 h	↑			Before	↑			Before	↓
	1 h	↑↑↑			0–24 h	↑↑			0–4 h	↓
	2 h	↑↑↑								
	3 h	↑↑								
	4 h	↑↑								
5.2 Urocanase deficiency	0 h	n–↑	Before	n	Before	↑	Before	n–↑	Before	↓
	1 h	↑↑	0–12 h	↑	0–12 h	↑↑	0–24 h	↑↑	0–12 h	↓
	2 h	↑								
	3 h	↑								
	4 h	n								
Urocanic acid load (350 mg, IV)										
5.2 Urocanase deficiency	0 h	n	Before	n	Before	↑	Before	n–↑	Before	↓
	1 h	n	0–12 h	↑	0–12 h	↑	0–12 h	↑↑	0–12 h	↓
	2 h	n								
Histidine load (190 mg/kg bw)										
5.3 Formiminotrans-ferase deficiency									Before 1470–3320 μmol/day After 8229–10700 μmol/day	

The responses of histidine and its metabolites in blood and urine to histidine and urocanic acid loads in patients with histidinemia, urocanase deficiency and formiminotransferase deficiency.

Figlu, formiminoglutamic acid; IPyA, imidazolepyruvic acid; UroA, urocanic acid. L-histidine monohydrochloride is dissolved in water and given orally after an overnight fast. 350 mg of urocanic acid in a 1 mM solution of NaOH at pH 7.0 was injected slowly i.v. after an overnight fast. The plasma and urine samples should be frozen immediately after collection in order to prevent the decomposition of histidine metabolites.

5.8 Diagnostic Flow Chart

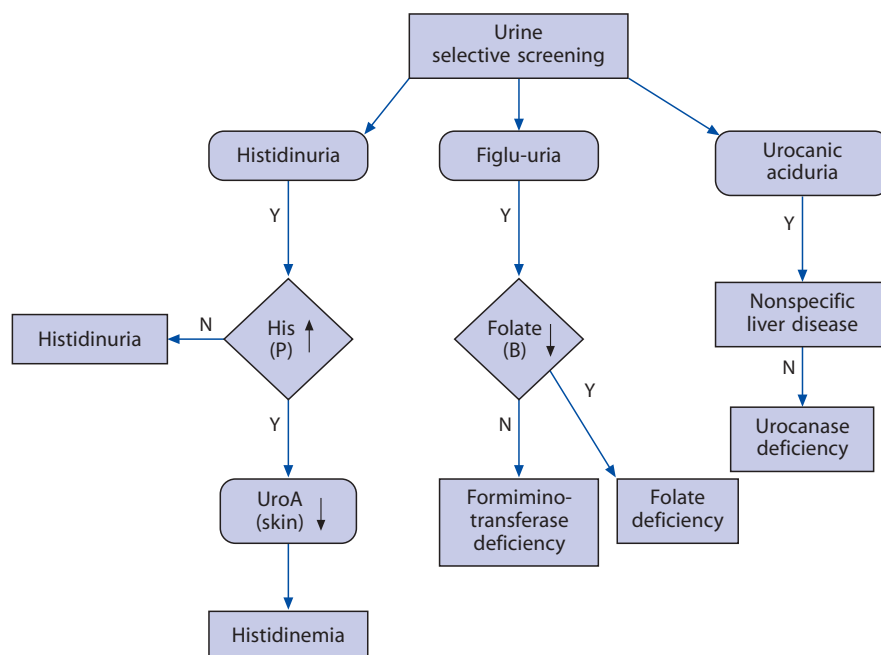


Fig. 5.2. Diagnostic flow chart for disorders of histidine metabolism

The histidinemic urine is sometimes only weakly positive or negative on ferric chloride testing, which reflects either the instability of imidazolepyruvic acid, the relation of its excretion to protein intake, immaturity of histidine transaminase, or a combination of these factors. Even after histidine loading, histidinemic neonates excrete much smaller quantities of imidazolepyruvic acid than do older children. In patients with urocanase deficiency, the levels of blood histidine and urine imidazolepyruvic acid are normal or slightly elevated. Therefore, it is necessary to do a quantitative analysis of blood histidine and urine ferric chloride test in order to overlook the patients with this condition.

5.9 Specimen Collection

Test	Preconditions	Material	Handling	Pitfalls
His (B)	Free diet	Serum/plasma	Frozen (−20 °C)	Very unstable, not excreted until several months of age
His (U)	Free diet	Random urine	Frozen (−20 °C)	
IPyA (U)	Free diet	Random urine	Frozen (−20 °C)	
UroA (U)	Free diet	Random urine	Frozen (−20 °C)	Is usually accompanied by urocanolyglycine and imidazolepropionic acid
UroA (skin)	Free diet	Cuticle	Frozen (−20 °C)	Alkaline pH will result in decomposition, leading to the formation of glutamic acid
Histidase (skin)	Free diet	Cuticle	Frozen (−20 °C)	
Urocanase (liver)	Free diet	Liver	Frozen (−20 °C)	
Figlu (U)	Free diet	Urine	Frozen (−20 °C)	

5.10 Prenatal Diagnosis

Prenatal diagnosis is not indicated for histidinemia and urocanase deficiency because these disorders are probably harmless.

5.11 DNA Analysis

Although cDNAs encoding human histidase and formiminotransferase have already been cloned, mutation analysis is not performed in patients with histidinemia and formiminotransferase deficiency. cDNA for human urocanase is not cloned.

5.12 Initial Treatment (Management while Awaiting Results)

Restricting dietary histidine will bring the blood histidine level back to normal and eliminates the urinary imidazole metabolites in patients with histidinemia and urocanase deficiency. However, no urgent treatment is required because of the benign nature of this condition.

5.13 Summary/Comments

Histidinemia is one of the most frequent of the inborn errors of metabolism, whereas urocanase deficiency is rare. Histidinemia is easily diagnosed on the basis of an elevation of histidine in the blood and/or increased excretion of imidazolepyruvic acid in the urine, detected by the simple ferric chloride test. On the other hand, it is feasible to find patients with urocanase deficiency by selective screening for inborn errors of metabolism, using chromatographic system that picks up UV-positive substance. Formiminotransferase deficiency is diagnosed by finding glutamic acid (from the decomposition of Figlu) and hydantoin-5-propionic acid in the urine. Probably, none of the defects requires treatment.

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