

Histidinemia

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Abstract

Histidinemia is an autosomal recessive disorder of histidine metabolism caused by a defect in histidase. The enzyme defect results in elevated urinary excretion of histidine and its metabolites, in high concentration of histidine in blood and cerebrospinal fluid (CSF), and in decreased concentration of urocanic acid in blood and skin. Most reported cases have been identified in newborn screening programs. The incidence of histidinemia in North America is estimated to be 1:12,000 in over 20 million screened newborns. This metabolic disorder seems to be benign in most affected individuals, although, under unusual circumstances, the disorder may be harmful and produce the central nervous system (CNS) disease noted in a few histidinemic patients. Maternal histidinemia is believed to be benign. Low-histidine diet lowers the blood histidine level but seems not to be indicated, at least for most patients, given the apparent lack of consequences of the disorder in many cases. The human histidase gene, histidine ammonia-lyase (HAL), has been localized to chromosome 12q22-q24.1. The molecular characteristics and the precise impairment of histidase in histidinemia have not yet been determined.

Keywords

Histidine metabolisme, histidase deficiency, locus 12q22-q24.1, histidine ammonia-lyase (HAL) gene

Disease name and synonyms

- Histidinemia
- Histidase Deficiency
- Histidine Ammonia-Lyase (HAL) Deficiency
- HAL Deficiency
- HIS Deficiency

Diagnosis criteria/Definition

Histidinemia is an inborn disorder of histidine metabolism caused by a defect in histidase, an

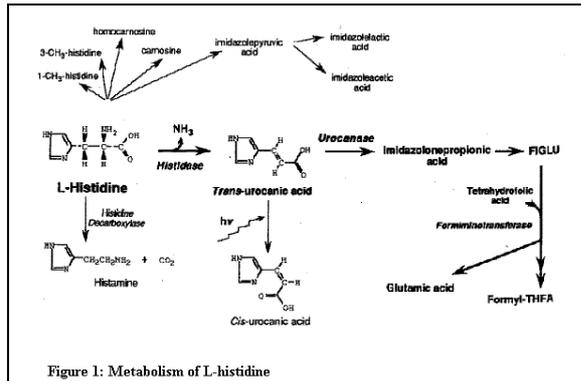
enzyme converting histidine to urocanic acid (**Figure 1**).

The chemical structures of L-histidine, histamine, *trans*-urocanic acid, and *cis*-urocanic acid are shown. Enzyme names are in italics. The major pathway of histidine catabolism is shown in boldface type. Ultraviolet irradiation (270 to 320 nm) is indicated by hv. FIGLU, formiminoglutamic acid; THFA, tetrahydrofolic acid. (Adapted from Taylor *et al.*, 1991a)

The biochemical consequences of the metabolic block include:

- increased concentrations of histidine in blood, urine, and cerebrospinal fluid (CSF);
- increased concentration of histidine metabolites in urine;
- decreased concentration of urocanic acid in blood and skin.

The characteristic finding in histidinemia is the specific increase of blood histidine concentration from 70-120 μM (normal values) to 290-1420 μM .



Frequency

Histidinemia is one of the most frequent inborn errors of metabolism. Reported incidences have ranged from 1:8600 (Québec) to 1:180,000 (New York). The composite frequency derived from these data in screening over 20 million newborns is about 1:12,000. The incidence is particularly high in Japan (1:9600).

Clinical description

Mental retardation and speech difficulties were often reported in the cases identified during the first decade after the discovery of histidinemia (La Du, 1978). In fact, speech problems were so frequently mentioned that this was thought to be a specific clinical feature of the disorder (Witkop and Henry, 1963; Ghadimi and Partington, 1967). The association seemed unlikely, however, since most of those with speech impairment were mentally retarded or had low-normal intelligence (Lott *et al.*, 1970; Gordon, 1970). The absence of mental retardation and speech difficulties in quite a number of cases suggested that these clinical abnormalities were coincidental with rather than due to the metabolic disorder.

Later data supported the view that histidinemia might be benign. In a prospective study carried out in Massachusetts, 20 histidinemic children detected by routine neonatal urine screening and their six histidinemic sibs, identified by family testing, all untreated, showed normal speech, and their mean IQ was essentially the same as that of their nonhistidinemic sibs (107 \pm 12 versus 108 \pm 11) (Levy *et al.*, 1974). Similar conclusions were reached in two follow-up

studies of histidinemic children identified by newborn screening, in Los Angeles (Alfi *et al.*, 1978) and Japan (Tada *et al.*, 1982). Widhalm and Virmani (1994) also reported normal IQ among Austrian children with histidinemia who were identified by newborn screening, including those untreated and those treated with diet during infancy. Retrospective and prospective studies (Rosenmann *et al.*, 1983; Coulombe *et al.*, 1983) together indicated that the prevalence of CNS (central nervous system) disadaptive phenotypes (e.g. impaired intellectual or speech development, seizures, behavioral or learning disorder) in the histidinemia population, is not higher than the frequency of these functional disorders in the non-histidinemia population. On the basis of these data, Scriver and Levy (1983) proposed that histidinemia is not a "disease" in man, although it might be a risk factor for development of an unfavorable CNS phenotype in particular individuals under specific circumstances, such as perinatal hypoxia. The authors also suggested that histidinemia may include more than one form of histidase deficiency -a more frequent benign type and a less frequent disadaptive variant.

Isolated neurologic and somatic abnormalities have also been reported in association with histidinemia (Levy, 1989). These include cerebellar ataxia, hydrocephalus, emotional disturbances, short stature, delayed bone age, seizure disorder, recurrent infections, precocious puberty, congenital hypoplastic anemia, thrombocytopenic purpura and multiple congenital anomalies.

Urocanic acid deficiency in histidinemia could have implications for either or both of two proposed functions of urocanic acid -as an ultraviolet protectant and as a mediator of ultraviolet-induced systemic immunosuppression (Taylor *et al.*, 1991a) -which may affect the incidence of skin disorders in histidinemic patients.

Maternal histidinemia

At least 53 offspring from 21 histidinemic mothers have been reported (Bruckman *et al.*, 1970; Neville *et al.*, 1971; Lyon *et al.*, 1974; Armstrong, 1975; Tada *et al.*, 1982; Matsuda *et al.*, 1983, Levy and Benjamin, 1985). No convincing evidence for an adverse fetal effect from maternal histidinemia has yet emerged.

Management including treatment

Dietary treatment based on low-histidine lowers the blood histidine level. Treatment, however, is rarely a condition since it seems that about 99% of histidinemic patients do not require treatment and that only 1% might benefit (Scriver and

Levy, 1983). Detailed information about treatment can be found in Levy (1989).

If further studies indicate that therapy should be given, this could be facilitated by enzyme replacement. Histidase has been encapsulated within cellulose-nitrate artificial cells for this purpose (Khanna and Chang, 1990). The encapsulation seems to protect histidase activity and to allow for substantial depletion of histidine *in vitro*. Studies of this system *in vivo* have not yet been reported.

Etiology

Biochemical basis:

Deficiency of histidase activity has been identified as the enzyme defect in histidinemia (La Du *et al.*, 1962). The absence of histidase activity in histidinemic patients was demonstrated in samples from liver and skin (stratum corneum), the two tissues that express normally the enzyme (La Du *et al.*, 1962; Auerbach *et al.*, 1967).

Genetic basis:

Histidinemia is an autosomal recessive trait. The human histidase gene (*HAL*) has been localized to chromosome 12q22-q24.1 (Taylor *et al.*, 1991b). Suchi *et al.* (1995) cloned and characterized the *HAL* gene. It is a single-copy gene spanning approximately 25 kb and consisting of 21 exons. Several binding sites for liver and epidermis-specific transcription factors were identified in the 5' flanking region, suggesting that histidase transcription may be regulated in a tissue-specific manner. A polymorphism was identified in exon 16. A tetranucleotide repeat polymorphism in intron 8 has also been described at the *HAL* locus (Maffei *et al.*, 1997).

Some cases of histidinemia involving mental retardation or other abnormalities might result from a contiguous gene syndrome, since they have been reported to be associated with deletions including part of the region 12q22-24.1 (Funderburk *et al.*, 1984; Naccache *et al.*, 1984; Chan *et al.*, 1990). From these cases, it may be concluded that large deletions of the region around the *HAL* locus have occurred, resulting in neurologic deficits, but in no case has a deletion of the *HAL* locus been demonstrated.

Although the molecular characteristics and the precise impairment of histidase in histidinemia have not been determined, there are suggestions that at least in some patients mutations have occurred in the coding region of the *HAL* gene (Kuroda *et al.*, 1982; Shin *et al.*, 1983; Suchi *et al.*, 1996).

Diagnostic methods

The diagnosis of histidinemia is based on finding an elevation of histidine in blood and increased excretion of histidine in the urine. The urinary metabolite imidazolepyruvic acid can usually be detected by the ferric chloride test (La Du, 1978). Further information on the diagnosis of histidinemia is available in Levy (1989).

Newborn screening

Histidinemia has been most frequently identified by routine newborn screening. This screening detected affected infants on the basis of increased histidine in the newborn blood specimen (Alm *et al.*, 1981; Tada *et al.*, 1984; Amador and Carter, 1986) or in a newborn urine specimen (Levy *et al.*, 1972; Lemieux *et al.*, 1988). With the exception of Quebec, where newborn urine screening continues, histidinemia detection is no longer included in newborn screening methods (Levy *et al.* 2003).

Unresolved questions

The molecular characteristics and the precise impairment of histidase in histidinemia remain to be determined.

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