Histidinaemia: a benign metabolic disorder

W K Lam, M A Cleary, J E Wraith, J H Walter

Abstract

Histidinaemia is a relatively common inherited metabolic disorder with an incidence similar to phenylketonuria. This paper reports the long term outcome of patients diagnosed by newborn screening in the north west of England. Between 1966 and 1990, 108 infants were diagnosed as having histidinaemia by a regional neonatal screening programme (incidence 1:11 083). A further five children were detected following diagnosis in a sibling. Of the 113, nine were lost to follow up. Infants diagnosed before 1981 (n=47) were placed on a low histidine diet (225 mg/kg/d) for an average period of 21 months (SD 4.5). All patients were reviewed regularly, Griffiths developmental quotients (DQ) were assessed at 2 and 4 years, and WISC-R intelligence quotients (IQ) at 8, 12, and 18 years. IQ data were converted to standard deviation scores (IQ SDS) to account for increasing IQ norms with time. Neither DQ nor IQ correlated with plasma histidine at diagnosis or with the mean plasma histidine throughout life. Growth was normal in all patients. There was no apparent benefit from a low histidine diet in early childhood. In contrast to other studies, there was no excess of clinical symptoms. On the basis of these findings, histidinaemia is a benign metabolic disorder that does not require treatment.

(Arch Dis Child 1996; 74: 343-346)

Keywords: histidinaemia, histidase deficiency, histidine ammonia-lyase deficiency.

Histidinaemia, one of the most common disorders of amino acid metabolism, results from a deficiency in histidase (histidine ammonia-lyase, E.C. 4.3.1.3), an enzyme responsible for the deamination of the essential amino acid histidine to form urocanic acid. In this disorder histidine is transaminated by an alternative pathway to form imidazole derivatives. The biochemical phenotype is characterised by an increase in blood, cerebrospinal fluid (CSF), and urine histidine and by the presence of imidazole metabolites in urine.^{1 2}

Early reports of histidinaemia documented a high frequency of mental retardation and speech delay, but with the introduction of neonatal screening it has become apparent that the majority of affected individuals have developed normally.³⁻⁷ However, concern remains that in some circumstances histidinaemia may cause damage to the central nervous system.⁸⁻¹² A recent study of a large number of children with histidinaemia found various clinical problems in over 20%.¹³

We have undertaken a prospective study in 104 patients with histidinaemia over a 28 year period to determine the impact of histidinaemia on their growth, development, and health, and to establish whether there was any benefit from a low histidine diet given for the first 2 years of life.

Methods

All children diagnosed as having histidinaemia by the Willink Biochemical Genetics Unit between 1966 and 1990 were entered into this study. Most of these were first detected by our newborn amino acid screening programme using paper chromatography. The diagnosis of histidinaemia was based on finding persistently raised plasma histidine concentrations (>0.3 mmol/l) and on the presence of histidine and urine imidazole metabolites in the urine.

LOW HISTIDINE DIET

Until 1981, given the uncertainty of the outcome of the disorder and with the possibility that mental retardation might be linked to high blood histidine levels, this unit's policy was to start patients who were diagnosed on newborn screening on a low histidine diet. The main protein requirement was provided by a synthetic food substitute which was histidine-free (for example, HF2, Cow & Gate), while the daily histidine allowance (225 mg/kg/d) was given either in the form of cow's milk or, after weaning, in exchange portions of certain vegetables or cereals. The diet was usually discontinued after the age of 2 years. After 1981 this policy was abandoned and newborn infants were allowed a normal diet.

GROWTH, DEVELOPMENT AND GENERAL HEALTH

Following diagnosis, patients were seen regularly in our clinic where their growth, general health, and development were monitored. Griffiths developmental assessments were performed at 1, 2, 4, and 6 years, and WISC-R intelligence assessments at 8, 12, and 18 years.

PLASMA HISTIDINE CONCENTRATIONS

Plasma histidine concentrations were measured by amino acid analyser (Waters HPLC system using a lithium cation exchange column, Pickering Laboratories). Measurements were made once or twice yearly, except in children on a low histidine diet in the first 2 years of life, where they were made every 3 months.

Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 4HA
W K Lam
M A Cleary
J E Wraith
J H Walter

Correspondence to:
Dr Walter.

Accepted 14 November 1995

Figure 1 Histidine concentrations from diagnosis plotted against age. Patients in the treated group were given a low histidine diet from diagnosis for a period of mean 21 months (SD 4.5 months). Error bars=SD.

STATISTICAL ANALYSIS

Standard statistical methods were used to compare the data from the intellectual assessments at the various ages with the histidine levels obtained at diagnosis and at the age of testing. In order to compare intellectual performance in histidinaemia patients with that of the general population, IQ scores, obtained from the age of 8 years onwards, were converted to standard deviation scores (SDS) to account for the rise in IQ norms with time.¹⁴ Analyses were carried out to determine whether there was any difference in development or intellectual performance between those given a low histidine diet for the first 2 years and those started on a normal protein intake. Subscores of the developmental assessments were examined to establish whether there was an increased frequency in delayed speech or language development.

Results

Between 1966, when the newborn amino acid disorder screening programme using the Scriver technique started in the Northwest Region of England, and 1990, a total of 1 196

913 infants were screened by the Willink Biochemical Genetics Unit. Histidinaemia was diagnosed in 108 infants, an incidence of 1:11 083. An additional five children were identified following the diagnosis in a sibling on newborn screening. Nine of these 113 patients either moved away from the region or failed to return to the clinic after the initial diagnosis, so were excluded from this study, leaving a total of 104 children, of whom 51 were female and 53 male. The mean age at diagnosis of those patients detected by newborn screening was 11 days (range 9–18). Forty seven patients were placed on a low histidine diet for an average period of 21 (4.5) months.

PLASMA HISTIDINE CONCENTRATIONS

Figure 1 shows the mean plasma histidine concentrations from the time of diagnosis. The histidine concentration at diagnosis was significantly higher in those born before 1981, and who were subsequently treated with a low histidine diet (treated group), than in those begun on a normal diet (non-treated group): 1.29 (0.58) v 0.61 (0.22) mmol/l, $p < 0.001$.

Following the institution of a low histidine diet in the treated group, the mean plasma histidine concentration was maintained at a significantly lower level than that of the non-treated group [0.3 (0.19) v 0.59 (0.23) mmol/l, $p < 0.001$], although histidine concentrations were still much higher than those of the normal population (0.061–0.119 mmol/l). After the diet was stopped, the mean plasma concentration for the treated group rose to 0.52 (0.23) mmol/l, comparable to that of the untreated group ($p = 0.55$).

GROWTH

Mean weight and height were normal for patients at all ages when compared with Tanner and Whitehouse growth charts. There was no statistical significance between the two dietary groups (figs 2–5).

GENERAL HEALTH

We were unable to identify any increased problems in the general health of either group. Two patients had mild asthma, one had an age related behavioural disorder, and one had mild hyperactivity.

DEVELOPMENT AND IQ

Developmental scores and IQ SD scores were normal for both groups at all ages (tables 1 and 2). Concern was raised about the intellectual development of only two patients (1.9%), a brother and sister. The boy, who was treated from birth with a low histidine diet, had a DQ of 86 at 2 years falling to 61 at 7 years. His sister, who was untreated, had a DQ of 87 at 2 years and 78 at 4 years. There were no particular differences, either in their age of diagnosis or in their plasma levels or treatment, to distinguish them from the rest of the patients.

Figure 2 The mean weight of male patients plotted on Tanner and Whitehouse growth charts (97th, 50th, and 3rd centiles). Error bars=SD. There was no significant difference between the two dietary groups.

Only one patient (from the non-diet group) had significant speech delay. This was more likely to have been due to middle ear disease than to histidinaemia, since following tonsillectomy, adenoidectomy, and treatment at a language unit, he was discharged as normal.

Figure 3 The mean height of male patients plotted on Tanner and Whitehouse growth charts (97th, 50th, and 3rd centiles). Error bars=SD. There was no significant difference between the two dietary groups.

Figure 4 The mean weight of female patients plotted on Tanner and Whitehouse growth charts (97th, 50th, and 3rd centiles). Error bars=SD. There was no significant difference between the two dietary groups.

Figure 5 The mean height of female patients plotted on Tanner and Whitehouse growth charts (97th, 50th, and 3rd centiles). Error bars=SD. There was no significant difference between the two dietary groups.

Table 1 Griffiths developmental assessments

Age (years)	DQ mean (SD)		
	Low histidine diet mean (SD)	Normal diet mean (SD)	
2	107 (12) n=45	108 (10) n=31	NS
4	104 (11) n=39	100 (6) n=24	NS

Retesting at 6 years showed that his language subscore had risen from a pretreatment score of 68 to post-treatment score of 86.

No significant difference was found between intellectual performance and mean plasma histidine concentrations at diagnosis or at age of assessment, and there were no statistical differences in the DQ or IQ between the diet and non-diet groups (table 3); however no analyses were made beyond the age of 8 years because of insufficient numbers in the latter group ($n<5$).

Discussion

Most disorders of amino acid catabolism are associated with clinical disease, for example the natural history of untreated phenylketonuria, tyrosinaemia, homocystinuria, hyperglycinaemia, and maple syrup urine disease is particularly severe. There have therefore been concerns that persistently high plasma concentrations of histidine might have a detrimental effect on the developing child.

Following the case report by Ghadimi and Partington,¹⁵ there were several early papers citing speech delay and global mental retardation as part of the clinical spectrum of histidinaemia. However, the validity of these findings has been questioned. Neville *et al*¹⁶ reviewed previously reported cases and commented that 28 of the 42 patients were entirely normal. They accounted for most of the pathological defects that had been reported. LaDu¹⁷ had initially postulated that the speech impairment seen in this disorder could be due to selective damage to the central nervous system. However Gordon,¹⁸ following his own assessment of the reports published at the time, showed that there was no association between speech defects and retarded mental function. He concluded that there might be no direct relation between histidinaemia and brain damage. Others have suggested that histidinaemia may be causally related to myoclonic seizures, liver disease, zinc deficiency, speech disorders, autism, and schizophrenia.^{10 12 19–22} However, further support for the hypothesis that raised plasma histidine is not associated with disease has come from both retrospective and prospective studies of affected children, as well as from evidence that, unlike maternal phenylketonuria, raised histidine concentrations

Table 2 WISC-R assessments. Results are expressed as IQ standard deviation scores

Age (years)	IQ SD score		
	Low histidine diet mean (SD)	Normal diet mean (SD)	
8	0.2 (1) n=34	-0.3 (1.3) n=12	NS
12	0.2 (1) n=21	-	
18	-0.01 (1) n=9	-	

Table 3 Correlation between plasma histidine at diagnosis or at the time of assessment and DQ or IQ

Age (years)	Histidine at diagnosis				Histidine at time of assessment			
	Non-diet group		Diet group		Non-diet group		Diet group	
	Corr	p	Corr	p	Corr	p	Corr	p
2	-0.09	0.57	-0.06	0.81	0.14	0.63	0.18	0.27
4	0.21	0.4	0.12	0.46	-0.49	0.09	-0.09	0.6
8	-0.42	0.19	0.26	0.16	0.14	0.76	0.11	0.6

Corr=correlation coefficient.

during pregnancy do not cause fetal damage. The largest and most recent prospective study by Widhalm and Virmani¹³ included 124 individuals diagnosed on newborn screening. These investigators found that the mean IQ for patients was within the normal range, and that there was no demonstrable effect of treatment with a low histidine diet. Twenty two per cent of the patients, however, had clinical symptoms such as speech defects, behavioural disturbance, motor retardation, and recurrent infections. It is not clear, in the absence of a control group, whether any of these were related to their histidinaemia.

The gene for histidase has been mapped to chromosome 10C2-D1 in mice and 12q22-q24.1 in humans.²³ Although a single mutation has been identified as responsible for murine histidinaemia,²⁴ it is likely that, as with phenylketonuria, several different mutations give rise to human histidinaemia. It is possible that certain of these might be associated with symptoms. This, however, seems unlikely, since in our study we were unable to show any correlation between the level of plasma histidine and any particular clinical problems.

As in the study of Widhalm and Virmani,¹³ we found no benefit from treatment with a low histidine diet. The general health and growth of patients, whether or not on diet, was entirely within the normal range. Analyses comparing histidine levels at the time of diagnosis with IQ or DQ at various ages showed no correlation. Nor was there any significant difference in intellectual performance between the treated and non-treated groups at any age. Finally, we did not find speech impairment to be a problem in our patients.

We conclude that there is no evidence that histidinaemia is detrimental to growth, health,

or intellectual development, or that treatment with a histidine restricted diet in the first years of life confers any benefit for intellectual development. Histidinaemia should be considered a benign condition.

- Imamura I, Watanabe T, Hase Y, *et al.* Histamine metabolism in patients with histidinemia: determination of urinary levels of histamine, N tau-methylhistamine, imidazole acetic acid, and its conjugate(s). *J Biochem Tokyo* 1984; **96**: 1925-9.
- Ito F, Aoki K, Eto Y. Histidinemia: biochemical parameters for diagnosis. *Am J Dis Child* 1981; **135**: 227-9.
- Garvey AM, Gordon N. Histidinaemia and speech disorders. *Br J Disord Commun* 1969; **4**: 146-50.
- Ishikawa M. Developmental disorders in histidinemia - follow-up study of language development in histidinemia. *Acta Paediatr Jpn* 1987; **29**: 224-8.
- Popkin JS, Clow CL, Scriver CR, Grove J. Is hereditary histidinaemia harmful? *Lancet* 1974; **i**: 721-2.
- Hyaneck J, Raisova V. Speech and language disorders in histidinaemia and other amino acid disturbances. *J Inher Metab Dis* 1985; **8** (suppl 2):130.
- Rosenmann A, Scriver CR, Clow CL, Levy HL. Histidinaemia. Part II: Impact; a retrospective study. *J Inher Metab Dis* 1983; **6**: 54-7.
- Duffner PK, Cohen ME. Infantile spasms associated with histidinemia. *Neurology* 1975; **25**: 195-7.
- Dhir SP, Shisiku MW, Krewi A. Ocular involvement in histidinaemia. *Ophthalmic Paediatr Genet* 1987; **8**: 175-6.
- Duncan JS, Brown P, Marsden CD. Progressive myoclonus and histidinaemia. *Mov Disord* 1991; **6**: 87-9.
- Ghadimi HK. Histidinemia: biochemistry and behavior. *Am J Dis Child* 1981; **135**: 210-11.
- Silver AA. Children with autistic behavior in a self-contained unit in the public schools. *J Dev Behav Pediatr* 1986; **7**: 84-92.
- Widhalm K, Virmani K. Long-term follow-up of 58 patients with histidinemia treated with a histidine restricted diet: no effect of therapy. *Pediatrics* 1994; **94**: 861-6.
- Smith I, Beasley MG, Ades AE. Intelligence and quality of dietary treatment in phenylketonuria. *Arch Dis Child* 1990; **65**: 472-8.
- Ghadimi H, Partington MW. Salient features of histidinemia. *Am J Dis Child* 1967; **113**: 83-7.
- Neville BG, Bentovim A, Clayton BE, Shepherd J. Histidinaemia: study of relationship between clinical and biological findings. *Arch Dis Child* 1972; **47**: 190-200.
- La Du BN. Histidinemia. Current status. *Am J Dis Child* 1967; **113**: 88-92.
- Gordon N. Delayed speech and histidinaemia. *Dev Med Child Neurol* 1970; **12**: 104-6.
- Barashnev II, Nikolayeva EA, Klembovsky AI. Histidinaemia: screening, diagnosis, clinical picture, therapy. *Acta Paediatr Hung* 1988; **29**: 343-51.
- Kitano A, Higashi A, Nagata N, Matsuda I, Hase Y, Oura T. Zinc status of untreated histidinemic children. *J Pediatr Gastroenterol Nutr* 1985; **4**: 752-5.
- Pieniazek D, Kubalska J, Pronicka E, Stecko E. Disturbances in histidine metabolism in children with speech abnormalities. *Acta Anthropogenet* 1985; **9**: 117-21.
- Lucca A, Catalano M, Valsasina R, Fara C, Smeraldi E. Biochemical investigation of histidinemia in schizophrenic patients. *Biol Psychiatry* 1990; **27**: 69-75.
- Taylor RG, Garcia Heras J, Sadler SJ, *et al.* Localization of histidase to human chromosome region 12q22-q24.1 and mouse chromosome region 10C2-D1. *Cytogenet Cell Genet* 1991; **56**: 178-81.
- Taylor RG, Grieco D, Clarke GA, McInnes RR, Taylor BA. Identification of the mutation in murine histidinemia (his) and genetic mapping of the murine histidase locus (Hal) on chromosome 10. *Genomics* 1993; **16**: 231-40.