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Histidinaemia: screening, diagnosis, clinical picture, therapy

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The paper presents the data of mass and selective screening on histidinaemia. The results of complex clinical investigation of 16 patients with histidinaemia are demonstrated. Two forms of the disease were differentiated on the basis of evaluation histidine metabolism. The results of morphological examination of liver biopsy specimens obviously demonstrated significant structural and functional disorders of the liver in histidinaemia.

Much of attention attracted by hereditary enzymopathies is devoted to studies concerning histidinaemia. Although the level of the metabolic block and the nature of the enzyme defect and associated metabolic disorders have been elucidated [3, 9, 12, 16], the disease remains inadequately investigated, and diagnosis still poses difficulties. Existing controversy in researchers' opinions concerning clinical manifestations and central nervous system damage increases the complexity of the histidinaemia problem. This engenders radically opposed views on the expediency of active detection of histidinaemia and designing therapeutic modalities.

Survey of literature reports shows that the greater majority of children with histidinaemia have intellectual deficits, speech impairment, seizures or other neurological symptoms, and physical retardation. Early diagnosis and specific pathogenetically relevant therapy are thus necessitated [7, 10, 21, 23, 25]. On the other hand, in opinion of a number of authors [8, 14], histidinaemia may be qualified as a harmless disturbance of amino acid metabolism requiring no special therapy and, consequently, no active detection.

Insufficient number of cases observed by the authors, different approaches to patient evaluation and lack of effective criteria of interpreting identified metabolic disorders may partly account for the discrepant attitudes in histidinaemia-associated problems.

Reviewing 82 case reports of histidinaemia in children led us to the conclusion that a complete evaluation including quantitative determination of skin and liver histidase activity had been performed only in 22 patients [2, 3, 26]. Metabolic disorders were inadequately explored in the rest of the children; moreover, in 19 patients

only urine and blood amino acid assay and the Fölling test were employed [14, 19, 20].

Because of the literature controversies, a purposeful study of histidinaemia seemed to be necessary, recruiting updated objective methods of diagnosis and health evaluation. In addition, it is required that a true, genetically determined histidinaemia be differentiated from other, phenotypically similar conditions.

Materials and Methods

Evaluation of 110 859 newborns (mass screening) and 9843 children with psychomotor retardation (selective screening) has been carried out for detecting patients with histidinaemia.

The diagnostic program was divided into two stages. A semiquantitative amino acid assay using auxotroph strains of *E. coli* K-12 was used at the first stage [11]. At the second stage of the screening, a panel of methods was used, comparising serial determinations of histidine levels in urine and blood with high-voltage electrophoresis, measurement of sweat urocanic acid levels with an enzyme assay [17], L-histidase loading tests, and measurement of skin histidase activity (E.C. 4.3.1.3.) [18].

The major criteria for histidinaemia diagnosis were elevated blood histidine level (normal = 80—135 μmol/l), enhanced urinary histidine excretion (normal = = 350—380 μmol/day), positive Fölling test, reduced sweat urocanic acid levels (normal = 1.0—3.0 μmol/g), abnormal oral histidine loading test, absent or depressed histidase activity in the skin (normal = 1.7—5.3 nmol · g^{-1} · sec^{-1}).

Evaluations of the symptoms of the central nervous system was given a special emphasis in clinical evaluation of the patients.

The range of studies comprised neurological, psychometric (Wechsler test), roentgenological, electro- and echoencephalographic examination.

Evaluation of the liver in individual patient was by morphologic examination of transcutaneous liver biopsy specimens with light and electron microscopy.

Results

Diagnosis of histidinaemia by mass screening of newborns and by selective screening of children. The mass newborn screening and the selective screening of children with psychomotor retardation have been undertaken in order to identify patients with histidinaemia.

The mass screening detected no patients with genetically determined histidinaemia. However, 99 infants (1 : 1,120) were found to have transient hyperhistidinaemia which was interpreted by us as a result of neonatal physiological immaturity of histidase. The delayed histidase maturation seemed to be due to perinatal complications resulting in preterm births, lower birth weights, etc. in 20% of these infants. By its duration, hyperhistidinaemia was classifiable into hyperhistidinaemia of the newborn (66 individuals) with a stable normalization of blood histidine levels at the end of the neonatal period, and hyperhistidinaemia of infancy (22 individuals), with excess blood histidine levels persisiting during 2—6 postnatal months (Fig. 1); this might be related to a slower histidase maturation

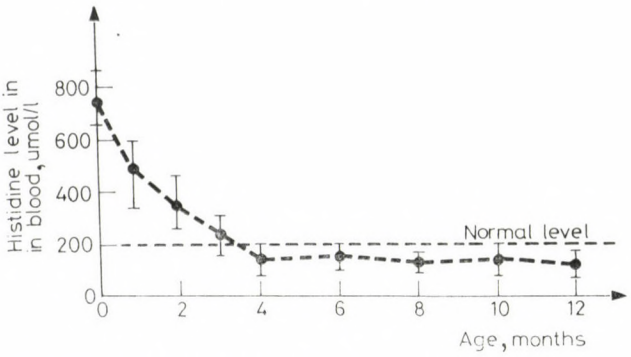

FIG. 1. Dynamic pattern of blood histidine levels in infants with transient histidinaemia during the first year of life

process due to high morbidity of these infants in the first 6 months of life (11 infants could not be examined). Spontaneous reversal of metabolic disorders and good psychomotor development of the infants permitted to withhold dietary correction. This made obvious the inexpediency of mass screening for histidinaemia in the newborn.

During the selective screening, we examined 9843 children with neurodevelopmental disorders. Hyperhistidinaemia was found in 144 children (1: 68). Follow-up of this group and serial testing of urine and blood amino acids showed that hyperhistidinaemia was secondary in 128 patients (1: 77); it was characterized by instability of the abnormalities and their eventual reversal. At the same time diagnosis of genetically determined histidinaemia was confirmed in 16 of 144 children with hyperhistidinaemia (1: 615).

The sixteen children, ranging in age from 1 to 14 years, have been given a detailed examination at the Department of Congenital and Hereditary Diseases (Table I).

Metabolic findings in histidinaemia cases: Table I shows that every of 16 patients had persistently elevated histidine blood level, reduced urocanic acid level in sweat, unrecognizable or significant lowered skin histidase activity, and abnormal response to oral histidine challenge test presenting as a considerable rise and slow decline of blood histidine concentration (Fig. 2). It should be mentioned that enhanced urine histidine excretion and positive Fölling test were seen only in part of children, which might imply unreliability of these tests in histidinaemia diagnosis.

Clinical picture of diagnosed histidinaemia cases: Assessment of clinical and metabolic findings showed that, like many other aminoacidopathies, histidinaemia is characterized by clinical polymorphism.

Two forms of histidinaemia were differentiated on the basis of histidine metabolism: histidinaemia with complete metabolic block (skin histidase activity absent) and that with incomplete metabolic block (skin histidase as

TABLE I

Results of examination of 16 patients with histidinaemia

Patients	Age (yr)	Status of the central nervous system	Metabolic disorders				Fölling test
			Level of histidine in blood (μmol/l)	Level of histidine in urine (μmol/day)	Level of urocanic acid in sweat (μmol/g)	Skin histidase activity (nmol · g^{-1} · sec^{-1})	
1. V. K.	2	Severe mental retardation, linguistic underdevelopment, seizures	970	1,726	0.2	0	+
2. D. K.	2	Same	645	968	0	0	+
3. V. M.	1	Psychomotor retardation	516	395	0.9	0.51	—
4. R. P.	2	Mental retardation, linguistic underdevelopment	280	288	0.1	0.21	—
5. V. P.	2.5	Same	297	210	0.7	0.71	—
6. O. B.	3	Severe mental retardation, symptoms of cerebral palsy, hydrocephalus, seizures	967	813	0.2	0.51	+
7. A. I.	3.5	Mental retardation, linguistic underdevelopment	310	377	0.9	0.24	—
8. A. M.	3.5	Same	380	361	0.4	0.03	—
9. V. M.	3.5	Same	262	281	0.7	0.21	—
10. I. S.	5.5	Same	355	266	0.1	0.31	—
11. V. E.	5.5	Same	510	350	0.4	0.65	—
12. O. K.	8	Same	387	327	0.4	0.50	—
13. M. V.	9	Same	967	1,038	0	0.01	+
14. N. S.	14	Mental retardation, linguistic underdevelopment, seizures	290	493	0.9	0.19	—
15. T. P.	14	Mental retardation, linguistic underdevelopment	580	492	0.4	0.69	—
16. S. P.	14	Same	275	405	0	0.32	—
Mean ± SD			499±67.0	549±120.1	0.5±0.095	0.02±0.065	
Control values			80—135	350—380	1.0—3.0	1.7—5.3	
Mean ± SD					1.8±0.22	3.3±0.66	

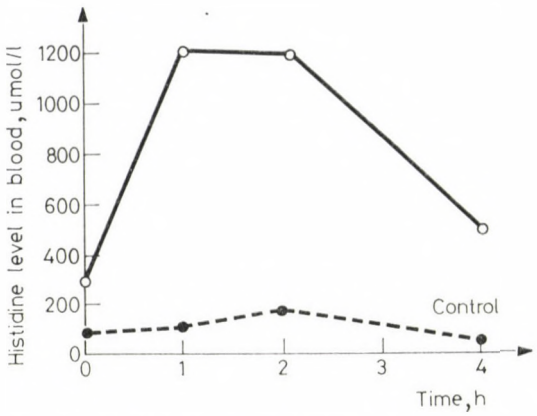

FIG. 2. Loading test with L-histidine in one illustrative histidinaemia patient and in a healthy control

low as 0.01—0.71 $nmol \cdot g^{-1} \cdot sec^{-1}$). Clinical examination revealed prominent phenotypic resemblance of most of patients to PKU patients: fair hair, blue eyes, eczematous skin lesions. Some children displayed bone deformities: spinal and crural curvatures, funnel chest. However, symptoms of the central nervous system damage dominated in the clinical status: severe intellectual deficiency (IQ 60), significant impairment of fine and gross motility, emotional disorders, severe language underdevelopment, convulsive syndrome, and other neurological symptoms indicative of involvement of the cortex and subcortical, brainstem, and cerebellar regions. The disease was progressive, three variants of the progress could be distinguished:

— an early and rapid manifestation in the first six months of life, with seizures and muscular hypotonus clinically prevalent;

— a more gradual onset in the second half-year of life with emerging symptoms of statomotor and mental retardation;

— a late onset of the disease, with initial symptoms of psycho-language retardation appearing in the second year of life.

The severity of cerebral lesions correlated with the degree of histidase defect. Histidinaemia was especially severe in children with complete metabolic block (two patients). It was characterized by a fulminant early onset and predominance of severe nervous system lesions in the clinical picture.

In the majority of histidinaemia patients, the clinical examination revealed secondary metabolic disorders associated with altered protein and lipid metabolism: hyperaminoacidaemia (increased concentrations of 2 to 7 amino acids other than histidine in 13 children), hyperaminoaciduria (enhanced excretion of 2 to 4 amino acids other than histidine in 9 children), hyper-alpha$_2$-globulinaemia (12 chil-

dren), hypo-beta-globulinaemia (10 children), intensified diphenylamine test response (9 children), hypercholesterolaemia (5 children).

Liver biopsy finding of histidinaemia patients: Morphological examination of liver biopsy specimens of patients with histidinaemia demonstrated subtle structural and functional alterations in the liver, generally indicative of impaired protein synthesis and energetic processes in hepatocytes, and moderate destructive-degenerative disorders, probably due to intoxication. The severity of the degenerative disorders correlated with disease duration: they were more pronounced in older children. In particular, light microscopic examination of the liver specimens showed focal dissociation of hepatocytic laminae, granular hepatocyte degeneration, hydropic degeneration of individual cells, local swelling or proliferation of the capillary endothelium.

The most typical ultrastructural hepatocyte abnormalities in histidinaemia included a specific change in appearance of mitochondria and endoplasmic reticulum. Internally re-arranged, rounded mitochondria producing local fusions were commonly seen, especially near to hepatocyte nuclei. The content of such mitochondria was a fine-granulated, moderately osmiophilic material against a light background which showed a few crysts and partially disorganized vesicles disintegrated into chains. The granular endoplasmic reticulum was poorly differentiated, its membranes were well recognizable only in mitochondrion circumferences, suggesting an impairment of protein synthesis. On the other hand, hepatocytes had considerable quantities of glycogen granules which, together with mitochondrial changes, was compatible with a low intensity of redox processes and inadequate detoxication function of the liver.

The prominent ultrastructural abnormalities in hepatocytes of young children were incrased lysosome counts and abundance of bodies containing the membrane material, some of them were outlined by bicontour membranes, and presumably represented disorganized mitochondria.These findings were suggestive of a lack of stability of hepatocyte membrane organelles. Solitary hepatocytes showed sites of partial coagulation necrosis in the cytoplasm. Hyperplasia of intracellular organelles was often observed in the capillary endothelium.

Furthermore, local disorganization and lysis of endoplasmic reticulum membranes and solitary mitochondria were characteristic of hepatocytes of older patients. In addition, there were more diffuse swelling of the endothelial cytoplasm, focal capillary plethora, and moderate expansion of the villous pericapillary spaces filled with the fine granular material.

Results of therapy in histidinaemia: In working out therapeutic measures, a priority was given to designing a special pathogenetically relevant diet [6]. The therapeutic diet was built up by selecting natural foods. The major

principle was restriction of histidine in the patient's diet; its allowance was approximated from the minimum daily requirement which is 34 mg/kg body weight. A final dietary histidine content was established individually, depending on the severity of metabolic defect. Although, the results on the effectivity of the therapy will be published in detail separately, institution of the dietary treatment yielded briefly as follows:

— normal blood histidine levels were achieved within a short period in all patients; however, there were periodical transient elevations of blood histidine levels in individual patients, with no dietary excess;

— the treatment seemed to have a benefical effect on the clinical status of patients with the complete metabolic block, as a reversal of convulsive syndrome previously resistant to anticonvulsants;

— the dietary treatment had a good effect on the mental development of patients with incomplete metabolic block, as reflected by higher IQs.

These results proved the benefical effect of the pathogenetically relevant dietary therapy on histidinaemia progress. The efficacy of the diet was dependent on the degree of the metabolic impairment and on the time of institution.

Examination of 16 parents of affected children revealed elevated fasting histidine blood levels and abnormal oral L-histidine loading test. Reduced urocanic acid levels in sweat were seen only in 3 individuals.

Discussion

Our studies have demonstrated that diagnosis of genetically determined histidinaemia can be established on the basis of the following biochemical findings: hyperhistidinaemia (230 to 970 μmol/l; normal is 80—135 μmol/l), hyperhistidinuria (395 to 1.726 μmol/day; normal is 350—380 μmol/day), absence of urocanic acid from urine, reduced urocanic acid level in sweat (to 0.1—0.09 μmol/g; normal is 1.0—3.0 μmol/g), abnormal response to oral histidine challenge test, absence or reduction of skin histidase activity (0.01—0.71 $nmol \cdot g^{-1} \cdot sec^{-1}$; normal is 1.7—5.3 $nmol \cdot g^{-1} \cdot sec^{-1}$). Application of these diagnostic criteria will clearly distinguish cases of secondary histidinaemia and avoid further input of conflicting evidence concerning the patient's status.

The rather high incidence of transient histidinaemia detected by the mass newborn screening is consistent with the earlier evidence [1, 22], and is a further proof of the needlessness of the neonatal mass screening for histidinaemia. The principal population for the selective screening comprises infants with symptoms of psychomotor retardation.

The variability of clinical-genetic manifestations of histidinaemia is thought to be due to its genetic heterogeneity, existence of several disease variants [2, 3, 13, 15]. Our results have shown that clinical and biochemical abnormalities are to a great extent determined by histidase activity. Two distinct forms are recog-

nizable: histidinaemia with complete and incomplete metabolic block [24].

Exploring the literature, we found no studies dealing with structural-functional evaluation of the liver in histidinaemia. However, the hepatic ultrastructure is known to be significantly altered by another genetic disorder of amino acid metabolism, also associated with cerebral abnormalities, namely by phenylketonuria [4, 5]. It is notable that patients with phenylketonuria develop metabolic disorders, similar to those associated with histidinaemia, e.g. dysproteinaemia, compensated metabolic acidosis. Both diseases are accompanied by acid intoxication, impairment of oxidation processes, lowered protein synthesis.

Analysis of findings of electron microscopy of liver biopsy specimens both similarities and differences of hepatocyte changes in the two diseases. Comparison of hepatic ultrastructural abnormalities shows that histidinaemia with the incomplete metabolic block is accompanied by disorganization and moderate destruction of hepatocyte mitochondria and significant underdevelopment of the granular endoplasmic reticulum, in these conditions cells contain much glycogen and no free lipids. Conversely, the subtle changes of hepatocytes in phenylketonuria are dependent on phenylalanine hydroxylase activity and, in the majority of patients, compensatory hyperplasia rather than mitochondrial degeneration or destruction can be found; with more developed granular endoplasmic reticulum and with free lipids as reserve materials in the cytoplasm.

Thus, it may be asserted that in histidinaemia there occur ultrastructural alterations in hepatocytes and hepatocyte membranes qualitatively different from those in PKU and these are accompanied by a significantly greater impairment of energetic, protein-producing and detoxicating functions of the liver.

The presented findings must compel attention also to the status of the liver in histidinaemia; requiring further study to improve therapeutic modalities. Liver-protecting dietary and medical measures may improve the treatment results in histidinaemia.

References

1. Alm G, Holmgren G, Larsson A, Schimpfessel L: Report of a neonatal screening programme. Clin Genet 20: 229, 1981
2. Anakura M, Matsuda J, Arashima S, Fukushima N, Oka Y: Histidinaemia. Classical and atypical form in siblings. Am J Dis Child 129: 858, 1975
3. Auerbach V, Di George AM, Carpenter CG: Histidinaemia. Direct demonstration of absent histidinase activity in liver and further observations on the histidinaemia disorder. In: Nyhan WL (Ed.) Amino Acid Metabolism and Genetic Variation. McGraw-Hill, New York 1967, 145
4. Barashnev YI, Klembovsky AI, Klyushina LA, Nikolaeva EA, Okatyev VS, Korneichuk VV: Abnormalities of the liver in children with phenylketonuria. Pediatriya (Moscow) 11: 41, 1977
5. Barashnev YI, Korneichuk VV, Klembovsky AI, Klyushina LA: Role of the liver in the pathogenesis of cerebral disorders in phenylketonuria. J Inher Metab Dis 5: 204, 1982
6. Barashneva SM, Nikolaeva EA: Therapeutic diet in histidinaemia. Proceedings of the Institute of Paediatrics and Children' Surgery, "Clinical Genetics", Moscow 1975, 94

7. Berlov BD, Arends R, Harries C: Studies in histidinaemia. Lancet 85: 241, 1965
8. Corner BD, Holton JB, Norman KM, Williams PM: A case of histidinaemia controlled with low histidine diet. Pediatrics 41: 1074, 1968
9. Ghadimi H: Histidinaemia: Emerging clinical picture. In: Nyhan WL (Ed.) Heritable disorders of amino acid metabolism, John Wiley and Sons, New York 1974, 265
10. Ghadimi H: Histidinaemia: Biochemistry and behavior. Am J Dis Chield 135: 210, 1981
11. Goldgarb DM, Nesterova GF, Gukova LA, Kuznetsova VN, Fonstein LA Brikman VG, Belensky GB, Kurnosova LM, Kapustina VM: Auxotroph Escherichia coli strains as indicator of amino acids in human urine and blood. Genetika 5: 88, 1968
12. Hyánek J, Raisová V: Speech and language disorders in histidinemia and other amino acid disturbances. J Inherít. Metab Dis 8: 130, 1985
13. Ito F, Aoki K, Eto Y: Histidinemia. Biochemical parameters for diagnosis. Am J Dis Child 135: 227 1981
14. Kothari PD, Desai AD, Banerjee AP: Histidinemia. Neurol India 22: 141, 1974
15. Kuroda J, Ito M, Ogawa T: A new sensitive mothod for assay of histidase in human skin and detecton of heterozygotes for histidinaemia. Clin Chim Acta 96: 139, 1979
16. La Du BN: Histidinemia. In: Stanbury JB, Wyngaarden JB, Fredrikson DS (Eds) The metabolic basis of inherited disease. McGraw-Hill, New York 1972, 338
17. Likhacheva NY, Burobin VA, Barashnev YI, Nikolaeva EA: Diagnosis of histidinemia by determing urocanic acid in sweat with an enzymic assay Vopr Med Khim 4: 500, 1979
18. Mardashev SR, Babayants RS, Shachmeister IY, Russky LI, Burobin VA: On cutaneous histidine metabolism in selected dermatoses. Vestn Dermatol Venerol 6: 35, 1972
19. Rao SR, Subhash MN, Narayanan HS: Histidinemia. Report of a case. Indian J Pediatr 41: 312, 1974
20. Rostenberg I, Guizar J, Alejandre I, Benitez S, Armendares S: Histidinemia in a consanguineous marriage. J Med Genet 11: 296, 1974
21. Thalhammer O, Scheibenreiter S, Panlitschko M: Histidinemia: Detection by routine newborn screening and biochemical observations on three unrelated cases. Z Kinderheilk 109: 279, 1971
22. Thalhammer O: Histidinemia: Biochemical anomaly or disease? Mschr Kinderheilk 121: 201, 1973
23. Thalhammer O: Histidinemia. Neonatal screening. Excerpta Medica, In Congress Series 606: 98, 1983
24. Veltishchev YE, Barashnev YI, Nikolaeva EA: The problem of histidinemia heterogeneity. Vopr Med Khim 28: 58, 1982
25. Waisman HA: Variations in clinical and laboratory findings in histidinemia. Am J Dis Child 113: 93, 1967
26. Woody NC, Snyder C, Harris LA: Histidinemia. Am J Dis Child 110: 606, 1965

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