Hyperammonaemia in 20 families

Biochemical and genetical survey, including investigations in 3 new families

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Palmer, T., Oberholzer, V. G., Burgess, E. A., Butler, L. J., and Levin, B. (1974). *Archives of Disease in Childhood*, **49**, 443. **Hyperammonaemia in 20 families: biochemical and genetical survey, including investigations in 3 new families.** Investigations have been made in 3 new and 2 previously reported families with ornithine transcarbamylase defects and the results are reported. The biochemical findings relevant to the diagnosis of hyperammonaemia in these and the 15 other families known to be affected are tabulated. In 2 families where the *propositus* appears to have a variant type of ornithine transcarbamylase defect, the mode of inheritance is uncertain. In the other 18 families, while it cannot be assumed that all affected cases are suffering from the results of an identical mutation, there is good evidence for an X-linked dominant mode of inheritance, and no positive evidence in any family for a different mode of inheritance.

Hyperammonaemia due to a deficiency of hepatic ornithine transcarbamylase (OTC) activity was first described by Russell *et al.* (1962) and the clinical and biochemical features in several patients have been reviewed (Levin, 1971; Shih and Efron, 1972). Together with other urea cycle defects, it may be indicated by mental and physical retardation coupled with protein intolerance, raised plasma levels of ammonia, glutamine, and sometimes alanine, and increased urinary excretion of ammonia and pyrimidine metabolites (Levin, 1971; Palmer, 1973). Though distinguishable from the other diseases of the urea cycle by the failure to find raised quantities of citrulline, argininosuccinic acid, or arginine in the plasma or urine, hyperammonaemia can only be diagnosed with certainty by assay of the liver enzymes of the urea cycle.

In addition to the 13 families included in the recent review of Short *et al.* (1973), 7 further families are now known to be affected (references—see Table I). Investigations into 3 of these are described here, together with further studies on 2 previously documented ones. The mode of inheritance is discussed in the light of the new results.

The form of hyperammonaemia caused solely by a carbamyl phosphate synthetase (CPS) deficiency (Freeman *et al.*, 1970; Odièvre *et al.*, 1973) is a separate topic and will not be considered here.

Methods

The methods used for the detection of hyperammonaemia have been previously described (Levin *et al.*, 1969a, b, c). Blood for amino acid determinations was collected in each case before and after a protein load ingested during the morning (Palmer *et al.*, 1973). Protein was given as a stress to the urea cycle.

Summary of present results and previously reported findings

The biochemical findings relevant to the diagnosis of hyperammonaemia in all members of families known to be affected are summarized in Table I.

Plasma levels of ammonia above the upper limit of normal, including high levels found only after a protein load, are indicated by +, normal ammonia levels and/or a normal response by —. Raised and normal plasma glutamine levels are similarly indicated, though this important amino acid was not estimated in the majority of the subjects. In those cases where the plasma glutamine had decayed before it could be estimated, the probability of a raised or normal initial glutamine level was deduced

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Summary of relevant findings in families with 1 or more members having

Group	A (mothers affected)												
Family no.	1a				1b (mothers in families 1a and 1b are sisters)			2					
References	Russell <i>et al.</i> (1962) Levin, Oberholzer, and Sinclair (1969c) Palmer (1973)				Russell <i>et al.</i> (1962) Levin <i>et al.</i> (1969c) Palmer (1973)			Levin <i>et al.</i> (1969a) Palmer (1973)					
Initials Relationship to propositus	MB	DB Twin	Mrs.B Mother	Mr.B Father	JM	Mrs.M Mother	Mr.M Father	JW	Mrs.W Mother	Mr.W Father	DM Maternal uncle	MM Maternal aunt	Ms.M Maternal grandmother
Sex	F	F	F	M	F	F	M	F	F	M	M	F	F
Raised plasma ammonia	+	+	+		+	+	—	+	+	+			+
Raised plasma glutamine	(+)	+	+	(—)	(+)	(+)	(—)	+	+	+	+	—	+
Liver OTC pH 7	7				5			8	8	66			
Liver OTC pH 7.7-8.5								18	40	98			
Liver CPS	62				35			48	48	57			
Other members of family and relationship to propositus	1 sister (normal ammonia levels)				1 sister (normal ammonia levels)			1 maternal uncle and 1 paternal uncle died as neonates					
Clinically normal													
Abnormal													

TABLE I-

Group	B (mothers unaffected)													
Family no. References	7 Short <i>et al.</i> (1972) Short <i>et al.</i> (1973)			8 Short <i>et al.</i> (1972) Short <i>et al.</i> (1973)			9 Palmer (1973)		10 Sunshine <i>et al.</i> (1972)		11 Corbeel <i>et al.</i> (1969)		12 Nagayama <i>et al.</i> (1970)	
Initials	P	Mrs.P Mother	Mr.P Father	L	Mrs.L Mother	Mr.L Father	JK	Mrs.K Mother	JJ	J Both parents	?	? Both parents	MO	Both parent
Relationship to propositus	F	F	M	F	F	M	F	F	F		F		F	
Sex	F	F	M	F	F	M	F	F	F		F		F	
Raised plasma ammonia	+	-	-	+	-	-	+	-	+	-	+	-	+	
Raised plasma glutamine							+	-	+				+	
Liver OTC pH 7							10				30		14	
Liver OTC pH 7.7-8.5	19	105	125	26	130	118	11		6				11	
Liver CPS	91	114	144	70	113	108	35						89	
Other members of family and relationship to propositus	1 brother								2 brothers		2 sisters		2 maternal uncles died as neonates	
Clinically normal														
Abnormal														

Note: Enzyme activities expressed as a percentage of the normal mean. *Neonatal death. CPS, carbamyl phosphate synthetase.

deficiency of liver ornithine transcarbamylase activity (OTC)

affected)

3				4					5			6		
Campbell <i>et al.</i> (1971) Campbell <i>et al.</i> (1973) Short <i>et al.</i> (1973)				Short <i>et al.</i> (1972) Short <i>et al.</i> (1973)					Cathelineau <i>et al.</i> (1972)			Salle <i>et al.</i> (1972) Palmer (1973)		
M*	M* Brother	Mrs.M Mother	Mr.M Father	C	C* Brother	Mrs.C Mother	Mr.C Father	? Maternal aunt	VL	Mrs.L Mother	Mr.L Father	EM	Mrs.M Mother	Mr.M Father
M	M	F	M	F	M	F	M	F	F	F	M	F	F	M
+	+	+	—	+	+	+	—	+	+	+	—	+	+	+
0.4 210	0.1 110	98 81	103 91	23	11.0 147	39 102	99 152	63	12 73	43 59		36 10		
1 brother died as neonate; another stillborn				3 brothers, 1 sister 1 brother and 3 maternal uncles died as neonates					1 brother, 1 sister 1 sister died at 4 yr			1 sister 1 brother died as neonate		

continued

C (mothers undiagnosed)								D (variant cases)				
13 Saudubray <i>et al.</i> (1973)	14 Levin (1971) Palmer (1973)		15 Hopkins <i>et al.</i> (1969)	16 MacLeod, MacKenzie, and Scriver (1972)	17 Kang, Snodgrass, and Gerald (1973)		18	19 Levin <i>et al.</i> (1969b) Palmer (1973)				20 Matsuda <i>et al.</i> (1971)
CP*	JM	BM* Brother	?	?*	?*	?* Brother	NH	PL	Mrs.L Mother	Mr.L Father	BL Brother	?
M	F	M	F	M	M	M	F	M	F	M	M	F
+	+		+	+		+	+	+	—		—	+
+	+				+		+	+	—	—		
2 97	16 34	0.7 38	4	5	0 280	0.3 150	22 88	25 78				25 70 123
1 brother 2 brothers and 2 maternal uncles died as neonates; 1 brother and 1 maternal uncle stillborn	3 other brothers died as neonates											

from the observed glutamic acid level (Palmer, 1973) and indicated in Table I by (+) and (-), respectively. Also included are the liver OTC activities at pH 7 and 7.7-8.5 and liver CPS activities. OTC activities measured between pH 7.7 and 8.5 have been grouped together, though results do vary with the different buffers which have been used by various investigators. For better comparison, the activities have been expressed in Table I as a percentage of the mean activity obtained in controls by the same investigators under the same conditions. In the controls investigated by us, the lowest OTC activity was 76% of the mean at pH 7, and 67% of the mean at pH 8. The lowest CPS activity was 57% of the mean.

Most of the information in Table I has been compiled from data published in detail. Relevant references are given. However, there are 5 families in which some or all of the investigations have not previously been published, and results of these are reported here.

Present investigations.

Family 2 (Table I). This is the family in which hyperammonaemia in mother and child was first reported (Levin *et al.*, 1969a). Amino acid levels in plasma and urine from 3 members of the family have now been determined. Both the maternal grandmother and maternal uncle of the proband had high plasma and urine glutamine levels, but those of a maternal aunt were normal (Table IV; Palmer, 1973). The father of the proband was examined on two occasions and on each he had slightly raised fasting plasma glutamine levels, 14.0 and 13.8 mg/100 ml. Corresponding plasma ammonia levels were also raised, 63 and 67 $\mu\text{g NH}_3\text{-N}/100\text{ ml}$.

Family 9 (Table I). The proband, J.K., was a 4-year-old Yugoslav girl who also had unexplained ketosis. A biopsy specimen of her liver had a low

OTC activity (Table II). Amino acid levels in plasma collected fasting and 3 hours after a protein load from the patient and her mother are given in Tables III and IV, respectively. Raised plasma glutamine levels were found in both specimens from the child, while those from the mother were normal. All other plasma amino acid levels were within normal limits for both subjects. The corresponding plasma ammonia levels of the affected girl were also high, 185 and 400 $\mu\text{g NH}_3\text{-N}/100\text{ ml}$ respectively, whereas the fasting level of the mother was normal, 39 $\mu\text{g NH}_3\text{-N}/100\text{ ml}$.

Family 14 (Table I). The proband, J.M., was a 2-year-old West German girl. The OTC activity in a biopsy liver specimen was low (Table II). Plasma, urine, and CSF amino acid levels have been given in an earlier review (Levin, 1971, Table 6). 4 of her brothers died as neonates, and the liver OTC activity in a necropsy specimen from one, B.M., was found to be low (Table II).

Family 18 (Table I). The proband, N.H., a girl, died at the age of 5 years, a few months after the onset of symptoms. Hyperammonaemia was diagnosed at the Willink Biochemical Genetics Laboratory, Royal Manchester Children's Hospital, and an OTC defect was shown in a necropsy liver specimen at our laboratory (Table II).

Family 19 (Table I). Levels of all plasma amino acids, including glutamine, of the father and younger brother of a boy, P.L., described as having a variant type of OTC defect (Levin *et al.*, 1969b), were normal (Palmer, 1973). Plasma ammonia was determined in the brother of the proband and was also found to be normal. The plasma glutamine level of P.L. has been consistently high in spite of treatment by low protein intake, and when last measured at the age of 5 years it was 18.5 mg/100 ml.

TABLE II
Hepatic urea cycle enzyme activities ($\mu\text{mol/hr per g wet weight}$)

	OTC		CPS	ASS	ASL	A
	pH 7.0	pH 8.0				
JK (family 9)	528	622	111	12	176	24,500
JM (family 14)	308	950	108			26,400
BM (family 14)	36	2200		9	14	25,600
NH (family 18)	171	1315	280	29	109	15,100
Controls						
Lowest	3950	3900	182	21	100	24,600
Highest	6650	9090	615	41	177	56,300

OTC, ornithine transcarbamylase; CPS, carbamyl phosphate synthetase; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase; A, arginase.

TABLE III

Plasma levels (mg/100 ml) of some amino acids before and after protein meals (1 g protein/kg body weight) in a girl with hyperammonaemia and in controls

	JK (4 yr) (Table I, family 9)		6 controls (4 mth-4 yr) (Palmer, 1973)			
	Fasting	3 hr	Fasting		2 hr	
			Mean	SD	Mean	SD
Glutamine	24.4	25.6	9.0	0.9	9.8	0.8
Glutamic acid	0.51	0.80	1.0	0.35	1.30	0.60
Citrulline	0.12	0.22	0.38	0.15	0.45	0.12
Glycine	1.05	0.98	1.35	0.35	1.10	0.20
Alanine	1.55	2.2	1.70	0.25	2.15	0.35
Leucine	0.80	1.7	1.35	0.25	2.60	0.50
Ornithine	0.50	0.73	0.56	0.09	0.90	0.20
Lysine	1.55	2.4	1.85	0.30	2.95	0.15
Arginine	0.53	0.47	0.96	0.10	1.20	0.10

TABLE IV

Plasma levels (mg/100 ml) of some amino acids before and after protein meals (0.65-0.85 g protein/kg body weight) in adult members of affected families and in controls

	Mrs. K (Table I, family 9)		Mrs. M (Table I, family 2)		MM (Table I, family 2)		DM (Table I, family 2)		7 adult controls (Palmer, 1973)			
	Fasting	3 hr	Fasting	3 hr	Fasting	3 hr	Fasting	3 hr	Fasting		2 hr	
									Mean	SD	Mean	SD
Glutamine	10.0	11.1	15.5	17.0	9.7	12.2	15.0	17.0	9.9	1.5	12.2	1.3
Glutamic acid	0.71	1.1	0.43	0.96	0.38	1.2	0.64	1.1	0.72	0.25	0.88	0.12
Citrulline	0.07	0.14	0.54	0.44	0.36	0.39	0.56	0.69	0.44	0.14	0.50	0.12
Glycine	1.9	2.0	1.9	2.2	1.7	2.0	2.2	2.9	1.60	0.20	2.00	0.35
Alanine	1.95	2.85	3.5	3.7	2.8	3.8	3.2	4.7	2.80	0.55	3.60	0.50
Leucine	0.96	3.2	1.0	1.9	0.97	2.2	1.3	2.0	1.35	0.20	3.05	0.50
Ornithine	0.43	0.94	0.72	1.0	0.51	0.86	0.95	1.1	0.62	0.12	1.00	0.10
Lysine	1.85	4.55	2.2	2.9	2.0	3.1	2.3	3.6	2.50	0.45	5.05	0.65
Arginine	0.77	2.3	1.1	1.7	1.7	2.4	1.7	2.9	1.45	0.25	2.80	0.50

Classification of families in Table I. In all affected members of families 1-18, the liver OTC activities at both pH 7 and 7.7-8.5, where measured, were found to be conspicuously low. However, it does not necessarily follow that they are all suffering from an identical genetic defect. On the basis of the diagnostic features discussed above, the fathers of affected cases, with possibly two exceptions to be discussed later, appear to be normal, while the mothers are clearly affected in some families but not in others. The 18 families have therefore been grouped into those where the mother is affected (group A), those where she appears to be unaffected (group B), and those where the situation is unknown (group C). Group A includes one instance (family 3) in which a biopsy liver specimen from the mother had a normal OTC activity. However, she had high plasma ammonia

levels and was considered by the investigators (Short *et al.*, 1973) to be affected.

The *propositi* in families 19 and 20 had conspicuously reduced liver OTC activities at pH 7, but activities at pH 7.7-8.5 were near the lower limit of normal. These 2 children were thus considered to have a variant form of OTC deficiency, and they have here been placed in a separate group (group D).

From Table I, it can be seen that liver CPS activities in affected females tended to be low, and this was very conspicuous in 1 case (family 6). In contrast, the CPS activities in affected males were never low, and, in fact, raised levels were seen in some cases. The significance of this is not known.

Raised fasting plasma glutamine levels were found in all the affected patients where this was accurately measured. Thus it seems that hyperammonaemia can always be indicated by an abnormal fasting

glutamine level, without the necessity of performing protein loading tests.

Inheritance of hyperammonaemia

In the first family to be reported (Table I, families 1a and 1b) the 3 affected children were all girls. Their mothers, who were sisters, appeared to be similarly affected for they had raised plasma levels of glutamine and ammonia, and a reduced OTC activity was found in the jejunal mucosa of one of them. No abnormality was detected in the fathers. A dominant mode of inheritance was considered to fit these observations more closely than a recessive mode, for the latter would require that two sisters, both heterozygous for the disease gene, had married 2 unrelated heterozygous male carriers and that the heterozygous state was only detectable in females. Furthermore, apart from 1 male who had a variant form of the disease, the first 10 cases were all female. It was therefore concluded that the disease was not only dominant but possibly sex-limited also, and that the expression in males might be lethal (Levin *et al.*, 1969a, c; Levin, 1971). In support of this suggestion a boy was later found to have an almost complete absence of liver OTC (Table I, family 3) and he died in the neonatal period. After a study of this and other families, Short *et al.* (1972, 1973) suggested that the disease might be X-linked, with affected males having a total defect of liver OTC and affected females only a partial defect with a mean activity of 25%. The same conclusion was reached by Saudubray *et al.* (1973).

From the data now available (Table I), only the families in group A provide definite information concerning the mode of inheritance. In group B and the variant group D, where the parents were normal, the occurrence of sibships containing only a single affected individual makes it impossible to distinguish between a recessive mode and a fresh mutation, while in group C the parents were not investigated.

Direct transmission from affected mothers to their offspring, shown in group A families, indicates a dominant mode of inheritance. For X-linkage to be present a number of factors must be satisfied. First, not only should both sexes be affected but the effects of random X-inactivation by Lyonization (Lyon, 1962) should produce a more variable and therefore generally less severe disease in the heterozygous females than in the hemizygous males whose single X containing the mutant gene is always active. Secondly, equal groups of offspring, normal and abnormal, for each sex, should be produced by female carriers, assuming regular segregation of the X chromosomes. Thirdly, there should be no

transmission of the disease from hemizygous fathers to their sons. However, males with hyperammonaemia appear to be so severely affected that they die in the neonatal period and never procreate, so that this consequence of X-linked inheritance from affected fathers cannot be shown.

Obviously the number of individuals listed in group A of Table I who are the progeny of females known or assumed to be affected is too small for a detailed statistical analysis or for any sib corrections to be made for ascertainment bias. Nevertheless, if one assumes that all neonatal deaths among males in this group were due to the disease, then equal numbers of affected males and females, 11 of each, have occurred, and also nearly equal numbers of normal children of the two sexes, 4 males and 6 females. However, the numbers of normals and abnormals are not equal, for there are twice as many in the affected group compared with the normal group.

The main evidence for the hypothesis that inheritance is X-linked and dominant is the very different nature of the disease in the two sexes. Except in the variant group D, males are very severely affected, with enzyme activities close to zero. Females, on the other hand, have a range of enzyme activities from 4% of the normal mean up to normal values. This is consistent with random inactivation of the X chromosome (Lyonization).

The fathers of affected children appear to be normal, except in 2 families. In 1 (family 2), the father of the proband had slightly raised plasma levels of glutamine and ammonia. His liver OTC activity at pH 8 was normal, but at pH 7 it was slightly low, and the enzyme was shown to have an abnormal K_m to carbamyl phosphate. Thus, he may carry a gene for a variant type of hyperammonaemia, and the severity of his daughter's illness might have been due to the inheritance of a different type of hyperammonaemia from each parent. Also in family 2, the maternal uncle showed high glutamine levels in the only plasma specimens available, collected before and after a protein load, whereas similar specimens from the maternal aunt were found to be normal. In view of the limited studies made and the possibility of a labelling or other error before the arrival of the samples at our laboratory, these findings have to be treated with caution until they can be confirmed.

In the other family (family 6), the father may have had a slightly raised plasma glutamine level after a meal, but the result was equivocal since it was not known how much protein he had ingested. The proband had very low hepatic activities of both OTC and CPS, so a variant disease with a recessive

inheritance pattern might be involved in this case. However, the mother was clearly affected, with raised glutamine and alanine levels, and without more evidence this family cannot be considered different from the others in group A.

In conclusion, though it is impossible to satisfy all the criteria with the data available, there is strong evidence in many affected families for an X-linked dominant mode of inheritance for OTC deficiency, and while it cannot be assumed that all affected cases are suffering from an identical genetic defect, there is so far no positive evidence in any family for a different mode of inheritance.

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Addendum

Three more cases of OTC deficiency have come to our notice. The first is a 3-year-old girl (Dr. M. M. Liberman, Northwick Park Hospital, Harrow) who has 22% of the normal hepatic OTC activity in pH 7 buffer and 33% in pH 8 buffer. Her 3 brothers, 2 sisters, and both parents had normal fasting plasma glutamine levels. The second is a boy (Professor J.-P. Farriaux, Lille, France) who has only 0.8% of the normal liver OTC activity in pH 7 buffer, but has 30% of the normal activity in pH 8 buffer. OTC activity has been assayed in intestinal biopsies from the parents. The mother's activity was 50% of normal while the father's intestine showed a normal activity. There are no sibs. The third case, described by Krebs, Hems, and Lund (1973), was a 13-month-old girl with a liver OTC activity 2% of normal. 2 brothers had died as infants and a sister died at 9 months of age. Another sister was normal. These cases do not change our conclusions as to the mode of inheritance of hyperammonaemia.

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- Krebs, H. A., Hems, R., and Lund, P. (1973). Regulatory mechanisms in the synthesis of urea. In *Inborn Errors of Metabolism*, p. 201. Ed. by F. A. Hommes and C. J. Van Den Berg. Academic Press, London and New York.