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Inherited metabolic disorders in Pakistan: Presentation, diagnosis and outcome of congenital hyperammonemias

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Inherited Metabolic Disorders in Pakistan: Presentation, Diagnosis and Outcome of Congenital Hyperammonemias

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Abstract

A total of 21 patients were admitted to Aga Khan University Hospital with suspected congenital hyperammonemias during the period 1989 to 1992. There were 11 patients with acidosis and 10 patients were without acidosis. Prominent clinical manifestations included positive family history (76%), onset in the first week of life (67%) and neurological manifestations (76%). Of patients with hyperammonemia and acidosis, 4 had severe metabolic acidosis with anion gap of 3OmEq/L and above. Of patients with hyperammonemia without acidosis, 4 had ammonia level ranging from 1600-2000 mg/dl. Diagnosis was confirmed in only 1 patient and that was also done abroad. Overall mortality was 71%. In conclusion, these disorders are not uncommon in our country and should be suspected in all infants with above clinical or biochemical abnormalities (JPMA 44: 229,1994).

Introduction

In born errors of metabolism are group of disorders which result from partial or complete absence of enzymes involved in biochemical reactions within the cells. This leads to both abnormal synthesis as well as ketabolism of metabolites. Most of these metabolites are neurotoxic and may cause death in early neonatal period or severe neurological disability. There are about 60 inherited metabolic disorders which can present in the neonatal period[1,9]. Number of these can be treated successfully if suspected and diagnosed early. Galactosemia[2], pheny lketonuria[3], homocystinuria[4,8]. methylmalonic aciduria[5,8] and congenital hyperammonemia[6,7,11] are groups of disorders for which treatment is available. The incidence of each of these conditions is rare, but as a group they are not infrequent cause of disease in neonatal period. Since most of inborn errors of metabolism are inherited as autosomal recessive traits, incidence is expected to be high in Pakistan because of increased frequency of consanguinity in muslim couples. Over the last 7 years we have seen a number of inherited metabolic disorders. Though the facilities for diagnosis are limited, it has been possible for us to suspect disorders of hyperammonemia with or without metabolic acidosis on clinical and biochemical evaluation. The present study will focus on this particular group of disease. Our objectives are to describe different types of disorders with hyperammonemia, to evaluate their clinical manifestation and outcome at this hospital and increase awareness of this problem among the pediatricians in this country.

Methodology

A review of charts was conducted from January, 1989 to December, 1992 (Table 1).

Appendix A. Clinical Manifestations suggestive of Inborn Errors of Metabolism.

- Positive family history of unexplained siblings death in neonatal period.
- Tachypnoea in absence of pulmonary or cardiac disease.
- Persistent vomiting.
- Sepsis like symptoms of lethargy poor suck and poor feeding which cannot be explained otherwise.
- Presence of encephalopathy seizures, hypotonia, hypertonia level of consciousness and coma.

Presence of peculiar odour: Maple syrup, sweaty feet etc.

Table I. Inherited Metabolic Disorders at AKU: January, 1985- June, 1992.

Adrenogenital Syndrome (CAH)	32
Leukodystrophies	13
Lipid Storage Gaucher	1
Glycogen Storage disease	3
Galactosemia	4
Mucopolysaccharidosis	3
Porphyria	6
Crigler Najjar Syndrome	1
Vit. D resistant rickets	1
Cystic Fibrosis	7
Aminoacid disorders	22
Total	93

All infants whose laboratory evaluation or clinical manifestation were suggestive of congenital hyperainmonemias were included in the study.

Appendix B. Laboratory Investigations for Suspect Inborn Errors of Metabolism.

I.	Biochemical/Hematological Tests
-	Complete Blood Picture.
-	Electrolytes, Anion gap, ABG's.
-	Blood Glucose.
-	Urine for Ketones and reducing substance.
II.	Metabolic Screen
-	Urine aminoacid chromatography.
-	*Qualitative and quantitative analysis of serum aminoacid.
-	Serum lactate.
-	Serum Ammonia.
-	Plasma Carnitine level*.
-	Urine for ferric chloride or Dinitrophenylhydrazine test.
III.	*Specific Studies Tissue Biopsies: Muscle, Skin and Liver. Histology and enzyme assay and DNA analysis: Requires snap freezing at -70°C (excluding skin).
IV.	If blood or urine specimen is to be stored, it should be collected before any IV treatment. Collect 5 ml of blood in lithium heparinized tube-centrifuge in store packed cells and plasma separately at -20°C. Take another 1 ml of blood in fluoride tube. Centrifuge it. Discard red cells but store plasma at -20°C. Take 10 ml of urine ; store it at -20°C..

* Laboratory investigation not available at AKU or elsewhere in the country.

Clinical manifestations which helped to suspect and diagnose are shown in Appendix A[1,9,12]. Step wise approach was used for laboratory evaluation, (Appendix B)[10,12,13].

Results

There were total of 21 patients suspected of having hyperammonemia with and without metabolic acidosis (Table II).

Table II. Disorders with congenital hyperammonemia admitted to AKU from 1989-1992.

1. Associated with metabolic acidosis, ↑ anion gap and hyperammonemia	
Maple syrup urine disease	3
Ketotic hyperglycinemia	1
Isovaleric acidemia	1
Suspected	6
2. Without acidosis and hyperammonemia	
Urea cycle defect	6
Suspected urea cycle defect	3
Non-ketotic hyperglycinemia	1
Total	21

There were 11 patients with acidosis and 10 without acidosis.

Appendix C. Treatment protocol for patients suspected of congenital hyperammonemia with or without acidosis.

1.	Admission to neonatal intensive care/intensive care unit.		
2.	Mechanical ventilation indicated for severely ill infants.		
3.	Sodium bicarbonate infusion (continuous infusion) indicated in treatment of organic acidemias.		
4.	15-20% dextrose infusion with insulin 0.05 u/kg/h and intravenous lipid to be given through central line.		
5.	Megavitamin cocktail indicated for vitamin responsive organic.		
-	Vitamin B_{12}	-	1 mg/day*
-	Biotin	-	100 mg/day**
-	Thiamine	-	50 mg/day**
-	Riboflavin	-	50 mg/day**
-	Nicotinamide	-	600 mg/day**
-	Pyridoxine	-	100 mg/day*
6.	Peritoneal dialysis	-	For removal of toxic metabolites
7.	Exchange Transfusion	-	If access to immediate peritoneal dialysis is not available
8.	Sodium Benzoate infusion (indicated for removal of ammonia urea cycle defect). Phenylactate infusions (not available in Pakistan) can also be used for the same purpose.		
9.	Glycine Supplementation 250 mg/kg od p.o. (indicated in ISOVAL Acidemia)		
10.	Dietary Management.		
-	Protein restriction - 1-1.5 gm/kg/day		
-	Protein free diet powder to be used with low protein diet contains vitamins, minerals, fat and carbohydrate (available through Mead Johnson, Pakistan).		
-	MSUD Formula	-	Available through Mead Johnson, Ross Laboratories& Milupa Co.
-	UCD-1 (for urea cycle defect)	-	Supplied by Milupa Co. Germany.
-	S-14 Lower protein formula	-	Supplied by Wyeth Lab.Ltd. This is supplied to our patients free of cost by Wyeth Lab. Ltd.

* Available in Pakistan.

** Not available in Pakistan.

Patients with isovaleric acidemia and non-ketotic hyperglycinemia were diagnosed elsewhere but were followed at AKU. All infants were admitted to neonatal intensive care unitlintensive care unit. Appendix C[6,7,11,12,14,15] shows the overall treatment given to infants with congenital hyperammonemia.

Table III. Major clinical manifestation of disorders with congenital hyperammonemia.

	N=21	% of Total
Family History: Sibling deaths consanguinity	16	76
Onset in first week	14	67
Lethargy↓responsiveness and poor suck	16	76
Hypotonia	16	76
Hypertonia	1	5
Seizures	9	43
Coma	5	2
Vomiting	4	19
Intermittent loss of consciousness/lethargy	2	9.5

Table III shows major clinical manifestation. Prominent features included positive family history (76%), onset in the first week of life (67%) and neurological manifestation (76%). Tables IV and V show laboratory evaluations of patients with hyperammonemia. All 3 patients suspected of having There were total of 21 patients suspected of having hyperammonemia with and without metabolic acidosis (Table II). There were 11 patients with acidosis and 10 without acidosis. Patients with isovaleric acidemia and non-ketotic hyperglycinemia were diagnosed elsewhere but were followed at AKU. All infants were admitted to neonatal intensive care unitlintensive care unit. Appendix C6,7,11,12,14,15 shows the overall treatment given to infants with congenital hyperammonemia. Table III shows major clinical manifestation. Prominent features included positive family history (76%), onset in the first week of life (67%) and neurological manifestation (76%).

Table IV. Disorders with congenital hyperammonemia and acidosis.

Pat. #	Diagnosis	pH	↑AG$	Hypo-glycemia	↑NH_3 µg/dl	Ketonuria	DNPH* test	UC**	↓WBC	↓Plat.	Culture
1.	MSUD	7.38	-	N	-	+ve	+ve	Isoleucine	-	-	-
2.	MSUD	7.5	-	N	-	+ve	+ve	Isoleucine	-	77	Salmonella paratyphi
3.	MSUD	7.42	18	N	246	-	-ve	Isoleucine	7.0	-	-
4.	Isoval***	7.42	20.1	?	303	-	-	N	4.2	69	-
5.	Ketotic Hyper-glycinemia	7.1	?	N	155	+ve	-	glycine	N	N	-
6.	OA****	7.0	33	N	727	+ve	-	N	-	-	-
7.	OA	7.36	8	N	361	-ve	-	N	4.7	114	Klebsiella species
8.	OA	6.9	30	N	Not done	-	-	Not done	N	N	-
9.	OA	7.3	24	11	970	+ve	-	N	↑	15	-
10.	OA	6.9	41.6	7	454	-ve	-	N	↑	100,000	-
11.	OA	6.9	41.4	N	727	-ve	-	Generalized Aminoacid	N	N	-

* = Dinitrophenyl hydrazine
** = Urine Chromatography
*** = Diagnosed in U.K
**** = Organic acedemias - Patients in whom we were unable to specify diagnosis
$ = Aniongap

Table V. Disorders with congenital hyperammonemia without acidosis.

Pat. #	Diagnosis	pH	↑AG	Hypo-glycemia	↑NH_3 µg/dl	Ketonuria	DNPH test	UC	↓WBC	↓Plat.	Culture
12.	Nonketotic* hperglycine	7.1	- 19.8	12	N	-ve	-	-	N	N	-
13.	Urea cycle defect	7.4	14	N	132	-ve	-	N	N	N	-
14.	Urea cycle defect	7.36	22.4	N	1804	-ve	-	N	N	N	-
15.	Urea cycle defect	N	?	N	303	-	-	?	N	N	-
16.	Urea cycle defect	6.97	25	N	1970	-	-	N	N	N	-
17.	Urea cycle defect	(RA) 7.62	16	N	1606	-ve	-	N	N	N	-
18.	Urea cycle defect	7.34	6	N	181	-ve	-	N	N	N	-
19.	Urea cycle defect	N	6.7	N	151	-	-	?	N	N	-
20.	Urea cycle defect	7.4	12.4	N	727	+ve	-	N	N	N	-
21.	Urea cycle defect	7.3	?	N	1212	-ve	-	↑cystine	N	N	-

*Diagnosed in India.

Tables IV and V show laboratory evaluations of patients with hyperammonemia. All 3 patients suspected of having Maple syrup urine disease (MSUD) had abnonnal excretion of isoleucine. 1/3 infants also bad Maple syrup body odour. Ammonia level was normal in 2/3 infants. Of 6 patients suspected of organic acidemia, five died. Four had severe metabolic acidosis with Anion gap of >30mEq/L. Patient #7 was included in the study because there was strong family history of sibling deaths, compensated metabolic acidosis and high ammonia level. He also had Klebsiella sepsis. This infant is alive and thriving. Urinary chromatography was not helpful in any of these cases. Among infants with hyperammonemia without acidosis, 4 had ammonia level ranging from 1600-nearly 2000 mg/dl. One of these infants also had tenninal metabolic acidosis with pH of 6.9 and and anion gap of 25 mEq/L (Patients # 14, 16, 17,21). Patient #21 was first seen at 8 months of age with recurrent episodes of intermittent vomitingand drowsiness andthenatoneyearofage. This time his drowsiness progressed to

coma. Ammonia level prior to death was 727 ug/dl. We suspected urea cycle defect in all 5 infants. The other 4 infants were also suspected of having urea cycle defect. Patient # 13 was twin brother of Patient# 16. He died at 2 months of age in a comatosed state. Unfortunately NH3 level was not documented at this time. Patient # 18 presented to us with failure to thrive, vomiting and diarrhoea. His weight was 1.9 kg at 2 months of age. This child was lost to follow up. Patient# 19 developed seizures at 1 month of age.

Three of her siblints died of similar complaints. Patient # 14 was an older child of 4 years of age who had intermittent episodes of unconsciousness. This child was also lost to follow-up. Infant with non-ketotic hyperglycinemia was 2 years old female who presented to ER with hypoglycemic coma. She died on the same day of admission.

Table VI. Outcome of Infants with Hyperammonemia.

Patient #	Diagnosis	Outcome
1.	MSUD	Expired
2.	MSUD	Expired
3.	MSUD	Expired
4.	Isovaleric acidemia	Alive
5.	Ketotic hyperglycinemia	Expired
6.	Organic acidemia	Lost to follow up
7.	Organic acidemia	Alive
8.	Organic acidemia	Expired
9.	Organic acidemia	Expired
10.	Organic acidemia	Expired
11.	Organic acidemia	Expired
12.	Nonketotic hyperglycinemia	Expired
13.	Urea cycle defect (twin II)	Expired
14.	Urea cycle defect	Expired
15.	Urea cycle defect	Lost to follow-up
16.	Urea cycle defect (twin I)	Expired
17.	Urea cycle defect	Expired
18.	Urea cycle defect	Lost to follow-up
19.	Urea cycle defect	Alive
20.	Urea cycle defect	Expired
21.	Urea cycle defect	Expired

Table VI shows the outcome. 15/21(7 1%) infants died. Three infants were lost to followup.

Discussion

This is undoubtedly large group of patients with congenital hyperam.monemia seen at AKU which is

one of the largest teaching hospitals in this country. One of the major problems we encountered here was confirmation of diagnosis which could not be done because of non existence of diagnostic facilities needed for this purpose. However, inspite of this, these conditions were suspected on clinical symptom and tests described in Appendix B. Overall mortality was extremely high. In patients with less severe clinical presentation proper management led to improvement. We feel that because of consanguineous marriages in this country these problems are not uncommon and there is a great need of establishing diagnostic facilities to confirm diagnosis, institute early treatment for better outcome and counselling parents. It is important to make the diagnosis for the sake of parents who have every right to know why their in fant had died and for the purpose of genetic counselling.

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