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, 11 with acidosis and 10 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 1600-2000ug/dl. Diagnosis was confirmed in only 1 patient and that was also done abroad. Overall mortality was 71%. These disorders are not uncommon in our country and should be suspected in all Infants with above clinical or biochemical abnormalities (JPMA 43:232, 1993).

Introduction

Inborn errors of metabolism are a 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[1,2]. Number of these can be treated successfully if suspected and diagnosed early. Galactosemia[3], phenylketonuria[4], homocystinuria[5,6], methylmalonic aciduria[6,7] and congenital hyperammonemia[8-10] are group of disorders for which treatment is available. This study reports different types of disorders with hyperammonemia, their clinical manifestation and outcome.

Methodology

From January, 1989 to December, 1992, a review of charts of all infants whose laboratory evaluation or clinical manifestation were suggestive of congenital hyper ammonemias were included in the study. Clinical manifestations and laboratory evaluation, which helped in the diagnosis are shown in Tables I and II[1,2,11-13].

Table I. 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 II. 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 it 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.

Results

Twenty one (11 with and 10 without metabolic acidosis) patients, suspected of having hyperammonemia (Table III).

TABLE III. Disorders with congenital hyperammonemia admitted to AKU from 1989-1992.

I. Associated with Metabolic Acidosis, ↑ Aniongap & Hyperammonemia		
Maple syrup urine disease	-	3
Ketotic hyperglycinemia	-	1
Isovaleric acidemia	-	1
Suspected	-	6
II. Without Acidosis & Hyperammonemia		
Urea cycle defect	-	6
Suspected urea cycle defect	-	3
Non ketotic hyperglycinemia -	-	1
Total		21

Patients with isovaleric acidemia and nonketotic hyperglycinemia diagnosed elsewhere were followed at AKU. Ml infants were admitted to neonatal intensive care unit/intensive care unit.

Table IV. 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 acidemias.	
Vitamin B12	1mg/day (available in Pakistan)
Biotin	100 mg/day (not available in Pakistan)
Thiamine	50 mg/day "
Riboflavin	50 mg/day "
Nicotinamide	600 mg/day "
Pyridoxine	100 mg/day (available in Pakistan).
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). Phenylacetate infusions (not available in Pakistan) can also be used for the same purpose.	
9. Glycine Supplementation (indicated in ISOVAL Acidemia)	250 mg/kg od p.o.
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.	

Table IV shows the treatment given to these infants.[8,10,12,14,15]

TABLE V. Major Clinical manifestations 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	24
Vomiting	4	19
Intermittent loss of consciousness/lethargy	2	9.5

Table V shows major clinical manifestation. Prominent fntures included positive family history (76%), onset n the first week of life (67%) and neurological manifestation (76%).

Table VI. Disorders with congenital hyperammonemia and acidosis.

Pat No.	Diagnosis	pH	↑ AG ****	Hypo-glycemia	↑ NH3 ug/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	S. paratyphi
3	MSUD	7.42	18	N	246	-	Neg	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	*14	Klebsiella sepsis
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	-

* Dinitrophynyl hydrazine
** Urine chromatography
***Diagnosed in U.K.
**** Organic acedemias - Patients in whom we were unable to specify diagnosis.

Table VII. Disorders with congenital hyperammonemia without acidosis.

Pat No.	Diagnosis	pH	↑Ag	Hypo-glycemia	↑NH3 ug/dl	Ketonuria	DNPH test	UC	↓ WBC	↓PLAT	Culture
12	Nonketotic* hyperglycine	7.1 19.8	-	12	N	-ve	-	-	N	N	-
13	Urea cycle defect	7.4	14	N	132	Neg	-	N	N	N	-
14	Urea cycle defect	7.36	22.4	N	1804	Neg	-	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) defect	7.62	16	N	1606	Neg	-	N	N	N	-
18	Urea cycle defect	7.34	6	N	181	Neg	-	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.

Table VI and VII show laboratory evaluations of these patients. All 3 patients suspected of having Maple syrup urine disease (MSUD) had abnormal excretion of isoleucine. 1/3 infants also had 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 aniongap of> 3OmEaJl. Patient # 7 was included in the study because there was strong family history of sibling deaths, compensated metabolic acidosis and high 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 ug/dl. One of these infants also had terminal metabolic acidosis with pH of 6.9 and an aniongap of 25 mEq/I (Patient # 14,16,17,21). Patient # 21 was first seen at 8 months of age with recurrent episodes of intermittent vomiting and drowsiness and then at one year of age. This time his drowsiness progressed to coma. Ammonia level prior to death was 727 ug/dl. Urea cycle defect was suspected 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 with failure to thrive. vomiting and diarrhoea. He weighed 1.9 kg at 2 months of age. This child was lost to follow-up. Patient # 19 developed seizures at I month of age. Three of her siblings died of similar complaints. Patient # 14 was aged 4 years who had intermittent episodes of unconsciousness, was lost to follow-up. Infant with non-ketotic hyperglycinemia was 2 year old female who presented to ER with hypoglycemic coma, and died on the same day.

Table VIII. Outcome of infants with hyperammonemia.

Patient No.	Diagnosis	Outcome
1	MSUD	Expired
2	MSUD	Expired
3	MSUD	Expired
4	Isovaleric acidemia	Alive
5	Ketotic hyperglycinemia	Expired
6	Organic acidemia	Lost to followup
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 followup
16	Urea cycle defect (twin I)	Expired
17	Urea cycle defect	Expired
18	Urea cycle defect	Lost to followup
19	Urea cycle defect	Alive
20	Urea cycle defect	Expired
21	Urea cycle defect	Expired

Table VIII shows the outcome. 15/21 (7 1%) infants died. Three infants were lost to follow-up.

Discussion

This is undoubtedly large group of patients with congenital hyperammonemia seen at AKU which is one of the largest teaching hospitals in this country. One of the major problems 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 Table II. Overall mortality was extremely high. In patients with less severe clinical presentation proper management led to improvement. It is felt that because of consanguineous marriages in this country these problems may not be infrequent and there is a great need for 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 infants had died and for the purpose of genetic counselling.

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