Neonates with inborn errors of metabolism: spectrum and short-term outcomes at a tertiary care hospital

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We aimed to evaluate the neonates diagnosed as IEM in our neonatal intensive care unit and their outcomes. Among 2994 neonates hospitalized, 51 were diagnosed as IEM (1.7%). Admission complaints were poor feeding, decreased activity, jaundice, seizures, abnormal screening and respiratory problems. Phenylketonuria (11), organic acidemias (8), maple syrup urine disease (5), citrullinemia (5), galactosemia (4), nonketotic hyperglycinemia (4) and tyrosinemia (2) were the most commonly diagnosed IEMs. The follow-up period was 2.5-43 months. Among the 33 neonates followed, 19 had normal development, 9 had developmental delays and 5 had cerebral palsy according to the Guide for Monitoring Child Development. Postnatal age on admission, Apgar score at 5 minutes, being transferred, peritoneal dialysis, cranial ultrasonographic findings, consanguinity and sibling history had significant effects on outcome.

Early diagnosis through expanded neonatal screening in countries with high rates of consanguinity, enabling the initiation of early treatment, is essential for achieving low mortality rates and good prognoses.

Key words: inborn errors of metabolism, neonate, outcome.

Inborn errors of metabolism (IEMs) often present around the time of birth. They are responsible for some cases of hydrops fetalis and a number of dysmorphic syndromes. However, most affected neonates appear normal at birth and subsequently deteriorate due to hypoglycemia, metabolic acidosis, neurological or cardiac problems, or liver disease[1-4]. Patients with an IEM may also present at (or shortly after) birth with seizures or severe hypotonia[5,6]. An IEM can easily be misdiagnosed as a condition such as sepsis or birth asphyxia in the newborn period[7]. Physicians should be aware of the importance of prompt detection, and early measurements of biochemical markers such as plasma ammonia should be monitored[8]. For a good prognosis and outcome, there should be no delay in obtaining a definitive diagnosis. Treatment often involves measures to reduce catabolism and to remove toxic metabolites[9]. During the neonatal period, IEMs most often present with an overwhelming illness requiring prompt diagnosis and both supportive and specific treatments[10]. The most frequent disorders are organic acidurias that present with ketoacidosis and urea cycle defects characterized by hyperammonemia[11]. Toxin removal procedures and nutritional support with a protein-free, high-energy diet are essential treatments for both situations[10]. In patients presenting with hypoglycemia, blood glucose levels must be corrected, and high-glucose infusion is required[1-4]. Glycogen storage diseases and gluconeogenesis defects are easily treated with a permanent glucose provision, while hypoglycemia may quickly recur. In patients with galactosemia, hereditary fructose intolerance or tyrosinemia type I, liver failure requiring galactose and fructose exclusion in association with a low-protein

diet is the leading type of presentation. For patients presenting with easily corrected hypoglycemia, beta-oxidation defects should be kept in mind[9,10,12]. Patients who do well in the first few weeks of life may develop cardiac failure, arrhythmia and/or liver failure, and the precise diagnosis can easily be missed[1-6]. In infants presenting with intractable convulsions, vitamin responsiveness to biotin, pyridoxine and folate must be considered[13].

In this study, we aimed to determine the ratio and outcomes of neonates with IEMs hospitalized in our neonatal intensive care unit (NICU), and to evaluate the patients' admission complaints and clinical and laboratory findings. We also compared our results with the literature and the results of infants treated in other NICUs.

Material and Methods

A clinical study was designed to identify the neonates hospitalized in our NICU with the diagnosis of IEM between January 2010 and June 2013, and to assess their outcomes. We recorded the clinical findings and laboratory results of neonates diagnosed as IEM. The patients' diagnoses, complications, treatments, other therapies and outcomes were noted. The neonates were followed up regularly in the outpatient neonatology, developmental pediatrics, endocrinology, nutrition and metabolism clinics. Their physical and neurological findings were determined by a pediatrician that was unaware of the study. They were also examined by a developmental pediatrics specialist on the basis of the Guide for Monitoring Child Development[14].

IEM was suspected initially as a possible diagnosis by our NICU team. Neonates with unexpected and prolonged hypoglycemia, resistant metabolic acidosis, prolonged jaundice, feeding intolerance, dysmorphic findings, unexplained hypotonia, hepatic failure of probable metabolic origin and neonatal encephalopathy were suspected to be IEM cases and referred to the nutrition and metabolism division. In cases where there was a strong suspicion of IEM, the patients were screened in our hospital using standard laboratory methods. Plasma ammonia levels were determined in EDTA plasma using glutamate dehydrogenase. Plasma amino acids were measured by automated ion-exchange chromatography with ninhydrin. Urinary organic acids were analyzed by gas chromatography-mass spectrometry. The diagnosis was later confirmed by enzymatic studies of cultured fibroblasts or liver tissue of the patients or by molecular analysis.

If the neonate had neonatal encephalopathy due to toxic metabolite accumulation, resistant metabolic acidosis or feeding intolerance, protein intake was discontinued entirely for the first 24 hours and hypercaloric parenteral nutrition was started, with a high dose of glucose infusion to prevent hypoglycemia. In those neonates with prolonged jaundice and positive urine-reducing substances, enteral nutrition was discontinued. Depending on the underlying disease, appropriate pharmacological therapy and formula feeding were given. Acute metabolic crisis in a patient was considered an indication for emergency peritoneal dialysis (PD).

Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) program (version 13.0), with the chi-square test used to determine the factors affecting outcome. Statistical significance was defined as a P value < 0.05.

Results

During 3.5-year study period, 2994 neonates were hospitalized in our NICU. Of these, 51 were diagnosed with an IEM during hospitalization; thus, the ratio of neonates in our unit with an IEM was 1.7%. All of the patients had had an uneventful prenatal course. There were 4 cases with an Apgar score below 6 at 5 minutes. The mean birth weight was 2960±631 g (1000-4300), mean gestational age was 38.2±2.9 weeks (28-41), and mean age on admission was 11.8±10.5 days (0-45). The rate of consanguinity was 70.6%, and that of sibling history, 33.3%. Among the 51 neonates diagnosed with an IEM, 35 (68.6%) had been transferred from another NICU for further evaluation, and 16 (31.4%) had been admitted to our emergency department. The patients' complaints, along with demographic characteristics of the infants and their mothers, are summarized in Table I.

The indications for hospitalization were suspected septicemia (22), abnormal neonatal screening result (11), prolonged jaundice

Table I. Clinical and Demographic Characteristics of Patients with Inborn Errors of Metabolism

Characteristic	Data
Mother's age (mean±st dev, min-max)	28.1±6.4 years (19-43)
Delivery route (vaginal/cesarean section)	22/29 (0.76)
Gender (female/male)	23/28 (0.82)
Admission complaints of parents (n, %)	
Poor feeding and/or inactivity	19 (37.3)
Guthrie abnormalities	11 (21.6)
Jaundice	6 (11.8)
Respiratory problems	5 (9.8)
Vomiting	3 (5.9)
Seizure	3 (5.9)
History of another sibling with IEM	2 (3.9)
Fever	1 (2)
Nonimmune hydrops fetalis	1 (2)
Dysmorphic findings (n, %)	
Major	1 (2)
Minor	4 (7.8)
Duration of hospitalization (mean±st dev, min-max)	26.5±20 days (3-90)
Liver failure (n, %)	20 (39.2)
Disseminated intravascular coagulation (n, %)	19 (37.3)
Resistant hypoglycemia (n, %)	15 (29.4)
Lactate elevation (n, %)	13 (25.5)
Resistant metabolic acidosis (n, %)	11 (21.6)
Mechanical ventilation (n, %)	29 (56.9)
Neonates receiving PD (n, %)	15 (29.4)
Duration of PD (mean±stn. dev, min-max)	1.5±2.6 days (1-12)
Inotropic support (n, %)	
One drug	16 (32)
Multiple drugs	9 (18)
Rehospitalization (n, %)	
None	32 (62.7)
<3	9 (18)
≥3	8 (15.7)
Cranial ultrasonography (n, %)	
Normal	18 (35.3)
Brain edema	9 (17.6)
Hemorrhage	4 (7.8)
Other	8 (15.7)

* IEM: inborn errors of metabolism, PD: peritoneal dialysis.

(5), perinatal asphyxia and/or neonatal encephalopathy (4), poor feeding and/or hypotonia (2), hypoglycemia (2), vomiting (2), hydrops fetalis (1), sibling history (1) and dysmorphic findings (1). There were 15 neonates (29.4%) who were started on acute peritoneal dialysis (PD), as hemodialysis is not available in our NICU. The distribution of the various IEMs diagnosed in our NICU is shown in Table II. The mortality rate was 27.5% (n=14), with the diagnoses of the infants who died being as follows: citrullinemia (5), maple syrup urine disease (MSUD) (2), propionic acidemia (PA) (2), pyruvate carboxylase deficiency (1), phenylketonuria (PKU) in an extremely low-birth weight (ELBW) infant (birth weight 1000 g, died secondary to sepsis on postnatal day 25) (1), Zellweger syndrome (1), Wolman disease (1) and probable urea cycle disorder (UCD) without molecular analysis (1).

Forty neonates were discharged to home, but

Table II. Spectrum of Inborn Errors of Metabolism Diagnosed in Our Neonatal Intensive Care Unit

Inborn errors of metabolism	n	%
Amino acid disorders	22	43.1
Phenylketonuria	11	21.6
Maple syrup urine disease	5	9.8
Nonketotic hyperglycinemia	4	7.8
Tyrosinemia	2	3.9
Organic acidemias	8	15.7
Propionic acidemia	5	9.8
Methylmalonic acidemia	2	3.9
Glutaric aciduria type 2	1	2
Disorders of the urea cycle	6	11.8
Citrullinemia	5	9.8
Other	2	3.9
Sugar intolerances		
Galactosemia	4	7.8
Mitochondrial disorders	3	5.9
Pyruvate carboxylase deficiency	2	3.9
Pyruvate dehydrogenase deficiency	1	2
Complex molecules synthesis/catabolism defects		
GM_1 gangliosidosis	1	2
Zellweger syndrome	1	2
Ketolysis defect		
SCOT deficiency	1	2
Molybdenum cofactor deficiency	1	2
Transcobalamin deficiency	1	2
Congenital disorders of glycosylation type 1a	1	2
Wolman disease	1	2
Congenital lactic acidosis	1	2
Total	51	100

* SCOT deficiency: succinyl-CoA:3-ketoacid CoA transferase deficiency.

3 of them died during follow-up. Among 32 infants who were regularly followed (Table III), the physical parameters (weight, height and head circumference) of 24 cases were in the 3rd-97th percentiles. There were 5 infants with head circumference below the 3rd percentile. We found severe neurologic impairment according to the Guide for Monitoring Child Development in 5 neonates, who were diagnosed as MSUD, UCD, tyrosinemia, nonketotic hyperglycinemia (NKHG) and PA. Normal neurodevelopment was observed in cases with PKU (10),

Table III. Outcomes of Neonates with Inborn Errors of Metabolism

Outcome	n	%
Lost to follow-up	3	5.9
Followed by local unit	2	3.9
Exitus	14	27.5
Normal	18	35.3
Developmental delay	9	17.6
Cerebral palsy	5	9.8
Total	51	100

Table IV. Neurodevelopmental Outcomes of Infants Diagnosed with Inborn Errors of Metabolism

No	BW (gr)	GA (weeks)	Admission age (days)	Diagnosis	Age at follow-up (months)	Weight %	Length %	Head size %	Outcome
1	2930	36.0	5	PA	43	50-75	10	<3	CP
2	3350	39.0	4	NKHG	24	<3	<3	<3	Developmental delay
3	2730	38.0	17	PKU	37	50	10-25	10-25	Normal
4	3800	40.0	6	MSUD	37	10-25	10	3-10	CP
5	3000	38.0	20	PKU	35	25	25-50	25	Developmental delay
6	3120	38.0	26	Transcobalamin defic.	22	75	50	3	Developmental delay
7	3000	40.0	3	MMA	11.5	75	50	<3	Normal
8	1900	35.0	14	UCD	21	<3	<3	<3	CP
9	2900	39.0	13	PKU	31	3-10	3-10	3-10	Normal
10	3160	41.0	23	PKU	30	75	25	3-10	Normal
11	3160	32.0	35	Tyrosinemia	30	<3	<3	<3	CP
12	3200	40.0	6	Galactosemia	29	10	10-25	10	Developmental delay
13	3400	40.0	6	Galactosemia	26.5	<3	25	50	Normal
14	2800	40.0	12	PA	22	10-25	25	25	Developmental delay
15	2880	38.0	14	MSUD	20.5	50	3-10	3	Developmental delay
16	3300	39.0	20	PKU	4	25-50	25-50	25	Normal
17	2840	40.0	3	NKHG	14.5	25-50	25-50	10	Developmental delay
18	4300	40.0	3	NKHG	12.5	50	75	75	Developmental delay
19	3000	39.0	12	MSUD	3.5	50	50	50	Normal
20	3700	41.0	2	NKHG	2.5	50	50	75	Normal
21	3400	40.0	3	Galactosemia	6.5	75	50	25	Normal
22	1540	31.0	30	Glutaric aciduria II	18	<3	10	3-10	Normal
23	3000	40.0	11	CDG type 1a	15	<3	<3	25	Developmental delay
24	2500	37.0	2	MMA	13	10-25	25-50	10-25	Normal
25	3200	40.0	7	Molybdenum cofactor deficiency	9.5	3-10	10	3	Developmental delay
26	3350	40.0	16	PKU	3.5	25-50	25	10-25	Normal
27	2900	39.0	16	PKU	3.5	10	3-10	10	Normal
28	4100	39.0	2	SCOT deficiency	9.5	75-90	50-75	75	Normal
29	3020	40.0	16	PKU	9.0	10	10	10	Normal
30	2950	37.0	13	PKU	4	50-75	50-75	25-50	Normal
31	2600	35.0	15	PKU	3	25-50	25-50	25	Normal
32	3700	41.0	28	CLA	2.5	50-75	50-75	50-75	CP

* BW: birth weight, CDG: congenital disorders of glycosylation, CLA: congenital lactic acidosis, CP: cerebral palsy, GA: gestational age, MMA: methylmalonic acidemia, MSUD: maple syrup urine disease, NKHG: nonketotic hyperglycinemia, PA: propionic acidemia, PKU: phenylketonuria, UCD: urea cycle disorders, SCOT deficiency: succinyl-CoA:3-ketoacid CoA transferase deficiency.

galactosemia (3), PA (1), MSUD (1), succinyl-CoA:3-ketoacid CoA transferase deficiency (1), transcobalamin defect (1) and glutaric aciduria type 2 (1). All the patients with PKU had received early diagnosis following abnormal neonatal screening. Factors affecting prognosis were postnatal age on admission, Apgar score at 5 minutes, PD therapy, being transferred from another NICU, findings on cranial ultrasonography (USG), consanguinity and sibling history ($p<0.05$).

Discussion

IEMs are a very heterogeneous group of inherited diseases that are being increasingly identified; they are responsible for significant morbidity and mortality[1-3]. Up to now, the reported ratios and incidences of neonates with IEMs in NICUs have varied. Couce et al.[15] reported 31 neonates with IEMs during an 8-year study period in Italy. Tu et al.[16] diagnosed IEMs in 8 neonates during an 11-month period; the incidence of IEMs in their ICU was found to be 1.1%. Kamate et al.[17] reported 11 infants with IEMs in their pediatric intensive care unit (PICU) during a 14-month period. Jouvet et al.[18] found an IEM ratio of 2.2% in their PICU, with 33 infants diagnosed as IEM during a period of 5 years. We found 51 neonates with IEMs during a 3.5-year study period, and thus an incidence of 1.7% in our NICU. As far as we can determine, this is among the highest ratios reported in the literature for a NICU.

Diagnosis and management of IEMs in the newborn period vary, as a consequence of the atypical and variable presentations of these disorders during that stage of life[1-3]. The diagnosis often needs to be established quickly and treatment commenced without delay in order to prevent death or permanent neurological sequelae. This should be carried out in collaboration with a specialized unit[9,10]. In the present study, there was a wide range of presentations, as well as types of IEM (Tables I and II), and a very high rate of consanguinity (70.6%); the ratio of patients with sibling history of IEM was 33.3%. One of our patients weighed only 1000 g and was diagnosed as PKU by means of early neonatal screening; however, the patient died secondary to septicemia on postnatal day 25. We propose that newborn screening should be expanded, especially in countries with significant risk factors such as a high rate of consanguinity, and should include even ELBW infants. Delay in screening for critically ill and premature infants places the NICU population at high risk for devastating side effects of untreated or late-treated metabolic diseases.

Patients with an IEM commonly present around the time of birth. Although most affected neonates are born healthy and subsequently deteriorate, some disorders may present at (or shortly after) birth, and a few may be detected by antenatal USG[1-3,7] The mean admission day of our patients was 11.8±10.5 days (0-45) postnatally. We consider our patients to have had late referral. In developing countries, low awareness of IEMs among parents and medical specialists and delayed transfer of patients to specialized units often lead to delayed diagnosis or treatment. Careful taking of family histories and provision of genetic counseling are of great importance; moreover, without expanded newborn screening using tandem mass spectrometry (MS/MS), IEMs are underdiagnosed[19]. Expanded newborn screening is able to diagnose over 20 additional rare, treatable IEMs based on the further analysis of the Guthrie card blood sample[20]. Over the past decade, MS/MS has become a key technology, replacing classic one-analysis, one-metabolite, one-disease screening techniques with a one-analysis, many-metabolites, many-diseases method[21].

Recognition and investigation of neonates in whom an IEM may be present is of utmost importance[1-8]. Pediatricians and neonatologists play a significant role in identifying which infants should be investigated[22,23]. Although we did not determine how many neonates were investigated for IEMs, patients with unexpected and prolonged hypoglycemia, resistant metabolic acidosis, prolonged jaundice, dysmorphic findings, feeding intolerance, unexplained hypotonia, hepatic failure of probable metabolic origin and neonatal encephalopathy were suspected of having possible IEMs and consequently referred to the metabolism and nutrition division. We found that 16 (31.4%) of our neonates had been admitted to the emergency department, and 35 (68.6%) of them had been transferred from another NICU for further evaluation due to

suspicious clinical and laboratory abnormalities. We had only one case of nonimmune hydrops fetalis, one case with a major anomaly (Zellweger syndrome) and six cases with dysmorphic findings. As we possess in our hospital the means to investigate patients with a suspected IEM through laboratory analysis, they were diagnosed as soon as possible following admission to our NICU. The appropriate collection of urine and blood samples is another serious issue in the diagnosis of IEM[1,24]. The samples should be obtained during the period of acute crisis, preferably before initiating therapy[24]. Physicians should transport the samples to the laboratory as soon as possible. Following achievement of metabolic stability and diagnosis of IEM, management by a dietitian or nutritionist experienced in dealing with IEMs is necessary[1,10,24]. In the case of disorders lacking an effective treatment, early diagnosis can lead to appropriate genetic counseling of the parents and reliable prenatal diagnosis of future pregnancies[25].

More than 400 biochemically diverse IEMs have been identified[7]. In the literature, the ones presenting most frequently during the newborn period have been identified as PKU, MSUD, tyrosinemia, PA, galactosemia, and Zellweger syndrome[15-17,24]. In the present study, the most common IEMs were PKU, MSUD, PA, citrullinemia, galactosemia, NKHG, and tyrosinemia (Table II), consistent with the literature. Some rarely seen IEMs, such as CDG type 1a, Wolman disease and GM1 gangliosidosis, were also diagnosed by genetic analysis in our NICU. High rates of consanguinity and involvement of multiple siblings in the same family are likely to be the reason for that.

Although recent advances in the diagnosis and treatment of IEMs have substantially improved the situation, many IEMs are responsible for significant pediatric and neonatal morbidity and mortality. Although there are a number of factors affecting prognosis, mortality and morbidity rates nonetheless remain higher in neonates[19,25]. Kamate et al.[17] diagnosed IEMs in 11 children in a PICU during 2007-2008, with 36% mortality. In this study, the mortality rate of 27.5% looks high, but we suggest late referral of the patients to be the reason for the high mortality rate and relatively poor prognosis. In addition, an expanded neonatal screening program is not in place in our country. Couce et al.[15] reported 31 infants with IEMs during an 8-year period and suggested there was a better outcome in those infants who were diagnosed by early neonatal screening and in whom early therapy was initiated. In IEM, early diagnosis and immediate treatment significantly affects prognosis. In addition, most studies report that the type of metabolic disorder may have a primary effect on prognosis; i.e., prognosis for organic acidemias is better than that for UCD[26]. We saw a better outcome in those infants with PKU who were diagnosed early by neonatal screening. In this study, postnatal age of infants on admission, Apgar score at 5 minutes, being transferred, cranial USG findings, PD, consanguinity and sibling history had a significant effect on the outcomes, including morbidity and mortality. PD might also have played a role in the poor prognosis of patients in our study, as hemodialysis is the ideal therapy for toxin removal. We suggest that late admission and delay in initiating appropriate therapy might be associated with poorer outcomes. In this study, the follow-up period is relatively short. It is obvious that any manifestation of CNS injury will become more distinct as the infant grows.

Consequently, early diagnosis and treatment is essential for reduction of mortality and morbidity related to IEMs. The first step is early diagnosis, followed by immediate referral of the patient to an appropriate center, performance of specific laboratory analysis as soon as possible, commencement of pharmacological and dietary therapies without delay and, if needed, dialysis therapy, preferably hemodialysis. We want to emphasize the importance of expanded early neonatal screening, especially in countries such as ours with high rates of consanguinity. Early diagnosis and treatment are likely to result in better neurodevelopmental outcomes and lower mortality rates.

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