Profile and outcome of children with inborn errors of metabolism in a tertiary pediatric intensive care unit in South India

Rajakumar Padur Sivaraman[1], Umamaheswari Balakrishnan[2], Sathya Chidhambaram[3], Shruthi Tarikare[1], Shuba Sankaranarayanan[4]

From [1]Associate Professor, [3]PG Student, [4]Professor, Department of Pediatrics, [2]Associate Professor, Department of Neonatology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India

Correspondence to: Dr. Umamaheswari Balakrishnan, Department of Neonatology, Sri Ramachandra Institute of Higher Education and Research, Chennai - 600 116, Tamil Nadu, India. E-mail: drumarajakumar@gmail.com

ABSTRACT

Introduction: Inborn errors of metabolism (IEM) can present as acute metabolic emergencies resulting in significant morbidity or death. Good intensive care supportive management and specific metabolic crisis treatment by tertiary pediatric intensive care unit (PICU) play a crucial role in optimizing the outcomes. **Objectives:** We aimed to study the clinical profile and outcome of children with IEM presenting as an acute metabolic crisis in a tertiary PICU. **Methods:** This retrospective descriptive study was conducted in a tertiary care center in south India between June 2016 and December 2018. We included children admitted in PICU as medical emergency and diagnosed to have IEM either earlier or at the time of PICU presentation by biochemical testing (basic testing and tandem mass spectrometry [TMS], gas chromatography-mass spectrometry [GCMS] and high-performance liquid chromatography [HPLC], and/or specialized testing) and/or molecular analysis. Clinical profile, details of diagnostic workup, and outcome were collected and analyzed. **Results:** Out of 2815 children admitted in PICU, 15 had IEM (0.9%). Median (interquartile range) age of presentation was 15 months (10–30 months). Consanguinity was found in 80%. The most common disorder was protein metabolic disorder. Seven patients were diagnosed in the newborn period, five during evaluation for developmental delay before PICU admission, and three were newly diagnosed during PICU admission. Supportive therapy of invasive/non-invasive ventilation and peritoneal dialysis was initiated in 10 and 4, respectively. Special formula was started in nine patients. Five (33%) died in spite of intensive care management. TMS, GCMS, and HPLC yielded definitive diagnosis in 12 (80%) patients. Molecular analysis was done in 12 patients. **Conclusion:** The most common cause for metabolic crisis in PICU is due to protein metabolic disorder. Aggressive intensive care and IEM directed therapy can be lifesaving, but still, the mortality is high.

Key words: *Inborn errors of metabolism, Inborn errors of metabolism, India, Outcome, Pediatric intensive care unit, Pediatric*

Inborn errors of metabolism (IEM) are individually rare but collectively common accounting for about 20% deaths from genetic disorders and nearly more than one-third of inherited neurological condition [1]. IEM are heterogeneous group of the disorder occurring due to a defect in the synthesis of enzyme or cofactor, transport of chemicals involving intermediary metabolites of carbohydrate, protein, or lipid. IEM presents as intoxication, which occurs due to the accumulation of intermediary metabolites, or as energy failure due to the failure of energy production or utilization or as storage of complex molecule resulting in storage disorders. Most of the disorders are of autosomal recessive inheritance.

Presentation occurs in the neonatal period or subsequently in the pediatric age group. The possibility of IEM should always be considered in a child with an unexplained, recurrent, or refractory illness. In those presenting in the pediatric age group, it is either the first manifestation precipitated by exercise, infection, excess protein intake or after prolonged fasting or the recurrence of the

same signs which occurred during the neonatal period [2]. IEM can present as acute metabolic emergencies resulting in significant morbidity, progressive neurological injury, or death. Optimal outcome for children with IEM depends on recognition of signs and symptoms of the metabolic disease, prompt evaluation, and referral to a center familiar with evaluation and management of these disorders [3]. Good intensive care supportive management and specific metabolic crisis treatment by tertiary pediatric intensive care unit (PICU) play a crucial role in optimizing the outcomes.

Metabolic disorders should be recognized as one of the important etiologies in any child with the unexplained crisis with the background of consanguinity in pediatric ICU, especially with decreasing trends of infective etiology. The increasing availability of diagnostic biochemical testing in India enables definitive diagnosis of these rare inherited genetic condition [4]. The utility of the biochemical testing in the PICU setting has not been well studied. Furthermore, the data on these metabolic

disorders presenting as a medical emergency or as the metabolic crisis is sparse in India. Hence, we undertook this retrospective study with the aim to study the clinical profile, and outcome of children with IEM admitted in a tertiary PICU with an acute metabolic emergency.

METHODS

This retrospective descriptive study was conducted in a tertiary care center in South India between June 2016 and December 2018. Our PICU is an accredited level III referral unit with an average annual admission of 1000 children. The metabolic clinic was started in our hospital in November 2014 and follow-up of metabolic patients take place in the metabolic clinic.

Children between 1 month and 18 years admitted in PICU with metabolic emergency and diagnosed to have IEM were included in the study. We included children diagnosed for the first time as IEM during the PICU stay and those who were diagnosed earlier either during newborn period or in the metabolic clinic. Children without a definitive diagnosis at the time of discharge or death were excluded from the study. Diagnosis of IEM was based on biochemical and/or molecular analysis. Biochemical testing done to confirm IEM include tandem mass spectrometry (TMS) for detecting abnormality in acylcarnitine profile and amino acid profile, and urinary gas chromatography-mass spectrometry (GC-MS) for detecting abnormality inorganic acids and plasma high-performance liquid chromatography (HPLC) for detecting abnormality in amino acid levels or other specific tests such as plasma very long chain fatty acid, cerebrospinal fluid, urine and plasma α-amino adipic semialdehyde (AASA), and pipecolic acid. Molecular analysis was done by utilizing next-generation sequencing and further validated by Sanger Squencing.

Data were collected retrospectively from the PICU register, case sheet from the medical record department and metabolic register. Clinical parameters collected include the age of presentation as a crisis, newly diagnosed or known entity, and age of initial diagnosis, sex, consanguinity, clinical signs and symptoms during the presentation, diagnosis, treatment, the outcome in terms of death, or discharge. Management details done including the specific measures for substrate reduction, supplementation of cofactors, removal of toxic metabolites, and supportive measures were collected. Details on biochemical tests done and the molecular analysis carried on these patients were studied. We included molecular testing done either immediately after the diagnosis or later from stored DNA. IEM were categorized as protein, lipid or carbohydrate metabolic disorder, vitamin responsive disorder, and peroxisomal or lysosomal storage disorder. Institutional Ethics Committee approval was obtained.

Categorical data were expressed as number and percentage and numerical data as median and interquartile range (IQR).

RESULTS

There were a total of 2815 children admitted in PICU in our hospital during the study period; out of which, 19 patients presented as a metabolic crisis or as a medical emergency and 15 children (0.53%) had IEM. Almost half of them (7/15) had been diagnosed in the neonatal period, five during evaluation for developmental delay before PICU admission, and three were diagnosed for the first time in PICU. Median (IQR) age of presentation in PICU was 15 months (10–30 months). Ten patients had more than one admission. Forty percent (6/15) were male. The majority (12/15) was born out of consanguineous marriage.

Spectrum of IEM presenting in PICU were as follows: Protein metabolic disorder-maple syrup urine disease (MSUD), propionic acidemia (PA), methylmalonic acidemia (MMA), citrullinemia type I and arginosuccinic aciduria (ASA);Fat metabolic disorder- HMG Co-A lyase deficiency, Succinyl CoA 3 oxoacid CoA transferase (SCOT) deficiency (ketolytic defect); Vitamin responsive disorders – Pyridoxine-dependent seizures (PDS), multiple carboxylase deficiency (MCD); Peroxisomal disorder- Zellwegar biogenesis defect and Lysosomal storage disorder- glycogen storage disorder (GSD) type III. The number of children in each category has been depicted in Fig. 1. The conditions diagnosed for the first time in PICU were MMA, SCOT deficiency, and Zellweger biogenesis defect.

Details of the patients in terms of clinical presentation, medical management, and supportive care are depicted in Table 1. An emergency medical management plan was executed including initiation of high dextrose with GIR of 8–10 mg/kg/min with or without intralipid infusion of 1–2 g/kg/day in all diagnosed protein metabolic disorder patients. Further protein free formula was introduced followed by special formula and breastfeeding. Supportive care given during PICU stay was as follows: Six children required ventilator support and four managed with high flow nasal cannula support. Specific treatment includes the following: Four needed peritoneal dialysis (PD); nine needed special formulas, and seven of protein metabolic disorders needed specific vitamin cofactors as additional therapy. PDS and MCD were treated with pyridoxine and high dose biotin (80–100 mg/day), respectively.
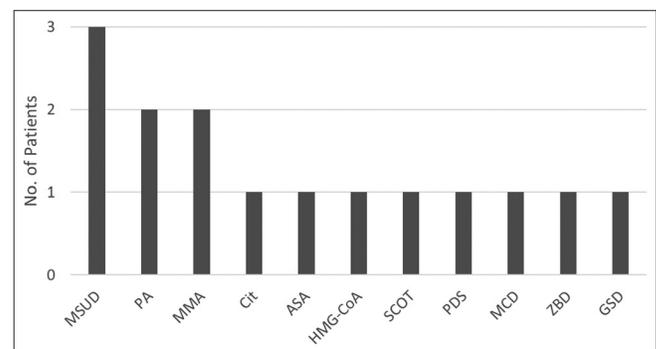
Figure 1: Spectrum of inborn error of metabolism presenting in the pediatric intensive care unit. MSUD: Maple syrup urine disorder, PA: Propionic acidemia, MMA: Methylmalonic acidemia, Cit: Citrullinemia Type I, ASA: Argino succinic aciduria, HMG CoA: HMG Co A lyase deficiency, SCOT: Succinyl CoA 3 oxoacid CoA transferase deficiency, PDS: Pyridoxine dependent seizures, MCD: Multiple carboxylase deficiency, ZBD: Zellweger biogenesis disorder, GSD: Glycogen storage disorder type III

Table 1: Clinical presentation, management, and outcome of patients with IEM

Case No.	Diagnosis	Age# (month)	Age* (month)	Clinical presentation	Investigation (baseline)	Medical management	Intervention	Outcome
1	MSUD	10	18	Generalized tonic clonic seizures	Hypoglycemia lactic acidosis elevated lactates	Thiamine, levitracetam, phenytoin	Invasive ventilator support	Died
2	MSUD	8	10	Fever respiratory distress	Lactic acidosis	Thiamine	HFNC support	Discharged
3	MSUD	Neonatal period	10	Seizures failure to thrive	Hypokalemia lactic acidosis hyperammonemia	Thiamine, carnitine, clonazepam	Invasive ventilator support	Died
4	Propionic acidemia	5	11	Cough fever, lethargy dehydration	Hyperammonemia hypoglycemia metabolic acidosis ketosis	L carnitine Low protein diet	Ventilated, PD	Died
5	Propionic acidemia	Neonatal period	24	Lethargy, extrapyramidal movement	Hyperammonemia hypoglycemia metabolic acidosis ketosis	L carnitine low protein diet	HFNC, PD	Discharged
6	Methylmalonic acidemia	8	8	Seizures vomiting, tachypnea refusal to feed	High anion gap metabolic acidosis hyperammonemia	Vitamin B12 L Carnitine	HFNC support	Discharged
7	Methyl melonic acidemia	24	36	Vomiting, refusal to feed	Hyperammonemia metabolic acidosis	Vitamin B12 L Carnitine	HFNC support	Discharged
8	Citrullinemia	Neonatal period	13	One episode of seizure loss of consciousness	Hyperammonemia	Protein restricted diet	Invasive ventilatory support, PD	Died
9	Arginosuccinicaciduria	Neonatal period	18	Seizures, fever	Hyperammonemia	Protein restricted diet	Supportive care	Discharged
10	SCOT deficiency	96	96	One episode of GTCS, encephalopathy, Flu-like symptoms	Ketosis, high anion gap metabolic acidosis	High dextrose	Ventilatory support	Died
11	HMG CoA lyase deficiency	Neonatal period	15	Reduced activity reduced oral intake	Hypoglycemia ketone negative	High dextrose	Supportive care	Discharged
12	Multiple carboxylase deficiencies	Neonatal period	30	One episode of GTCS	Hyperammonemia, metabolic acidosis	High dose Biotin	PD, ventilated	Discharged
13	Pyridoxine-dependent seizures	Neonatal period	3	Seizures, reduced activity	Baseline investigations normal	Pyridoxine, folinic acid	Supportive care	Discharged
14	Zellweger spectrum disorder	8	8	Seizures- infantile spasms, reduced activity	Baseline investigations normal	Fat soluble vitamin supplements	Supportive care fat soluble vitamins, steroids	Discharged
15	GSD type III	54	60	Lethargy poor feeding	Hypoglycemia elevated ketones	Concentrated dextrose	Supportive care corn starch diet	Discharged

Age #at diagnosis of IEM, *age at the time of last PICU admission, MSUD Maple syrup urine disease, GSD: Glycogen storage disorder, PD: Peritoneal dialysis, MSUD: Maple syrup urine disease, SCOT: Succinyl CoA 3 oxoacid CoA transferase, IEM: Inborn errors of metabolism, PICU: Pediatric intensive care unit, HFNC: High flow nasal cannula

Five children died either during first or subsequent crisis admission despite adequate medical management with a mortality of 33% during the ICU stay. Among six patients who needed mechanical ventilation, five died. Ten children were discharged and advised for regular follow-up in the metabolic clinic. A future emergency crisis management plan was modified taking into account the current status and handed over to the parents before discharge.

The results and the findings of biochemical testing done during PICU stay or earlier, aiding in the diagnosis of the individual condition, have been described in Table 2. Genetic counseling

was done for all the parents. Molecular confirmation was done in 12 patients and is depicted in Table 3. Subsequent prenatal diagnosis was done for six mothers.

DISCUSSION

We present the cases of IEM presented in our PICU either as a metabolic emergency or as a crisis during a 2½ years period. IEM could potentially be underdiagnosed and high index of suspicion, and team effort is essential to diagnose IEM. Considering IEM in parallel with other common conditions is essential in the PICU

Table 2: Biochemical analysis which aided in definite diagnosis

Case No.	Diagnosis	TMS	GCMS	HPLC	Other specialized tests
1,2,3	MSUD	↑ Leucine/ Isoleucine	2 OH, valeric acid, 2 OH 3 Methyl valeric acid N-Ac- leucine	↑ branched chain amino acids	-
4,5	Propionic acidemia	↑ C3 and C3/C2	OH propionic acid, propionyl glycine, tiglylglycine	↑ glycine	-
6,7	Methylmalonic Acidemia	↑ C3 and C3/C2	Methylmalonic acid	Normal	Quantitative elevation of MMA
8	Citrullinemia type I	↑ citrulline	Normal	↑ Citrulline and low arginine	Low ASA
9	Arginosuccinic aciduria	↑ citrulline	Normal	↑ Citrulline and ↑ Glutamic acid ↓ Arginine	Elevated ASA
10	Succinyl CoA 3 oxoacid CoA transferase (SCOT) deficiency	↑ C4OH and C4OH/C2	Elevated lactic acid, 2-OHbutric acid, 3-OHbutric acid	Non-specific elevation of multiple amino acids	-
11	HMG CoA lyase deficiency	↑ C5OH	3 Oh isovaleric acid, three methyl glutaconic acid, three OH Methyl glutaric acid	Normal	-
12	Multiple carboxylase deficiencies	↑ C5OH	3 methyl crotonyl glycine, methyl citrate	Normal	-
13	Pyridoxine-dependent seizures	Normal	Normal	Normal	Elevated AASA and pipecolic acid in plasma and urine
14	ZBD	Normal	Normal	Normal	Elevated VLCFA and low plasmologen

TMS: Tandem mass spectrometry, GCMS: Gas chromatography-mass spectrometry, HPLC: High-performance liquid chromatography, MSUD: Maple syrup urine disease; MMA: Methylmalonic acid, ASA: Arginosuccinic aciduria, AASA: α-aminoadipic semialdehyde, VLCFA: Very long chain fatty acid, ZBD: Zellweger biogenesis disorder

setting. Availability of advanced biochemical testing helped in the definitive diagnosis.

The most common IEM in our study was protein metabolic disorder accounting for 60% of the total IEM. Protein metabolic disorder including amino acid disorders, organic acidemia, and Urea cycle disorders (UCD) is known to present as metabolic crisis and that could be the possible reason for this being the most common disorder in PICU. A study done in Hyderabad where newborns were screened for IEM also found amino acid disorders to be as common as 1 in 3600 newborns [5]. It is possible that the same has been reflected in the PICU setting as well. We had three children with newly diagnosed conditions during the PICU admission. This is, in contrast, to the study by Kamate *et al.*, where all 11 cases presented in PICU were newly diagnosed [6]. In our study, almost half have been diagnosed in the neonatal period itself, which is most likely to indicate a more severe spectrum of IEM. This could be due to the facility in our center to diagnose in the neonatal period itself with regular follow-up of these children in the metabolic clinic. Any child presenting with unexplained encephalopathy should have basic investigations including ammonia [7]. This simple test helps in picking up protein metabolic disorders including UCD and organic acidemia. We had one such newly diagnosed MMA in our study, presenting with hyperammonemia at 8 months of age which made us do detailed biochemical testing confirming the diagnosis of MMA.

In developed countries, newborn screening is being done widely for varying metabolic disorders. The conditions screened are 6, 29, and 23 conditions, in the UK, USA, and Australia, respectively [8]. Among the patients who presented for the first time, MMA could have been potentially picked up by NBS. Even in countries where screening is a part, van Karnebeek and Stockler, in a systematic review identified 81 treatable disorders as an etiology for intellectual disability [8]. In our study, we identified IEM in five children during the evaluation of developmental delay. There are few disorders which cannot be picked up by newborn screening. This includes disorders such as PDS, Zellweger biogenesis disorder (ZBD), and GSD. As expected, the yield of baseline investigation as well as TMS, GCMS, and HPLC was low in detecting PDS and ZBD even in our study. Although PDS typically presents in the neonatal period (within a month), it can present atypically up to 3 years of age [9]. Any seizures which are refractory presenting in this age group warrant a trial of pyridoxine. In our study, the PDS was diagnosed in the neonatal period itself.

Treatment modalities of any IEM include a reduction in substrate availability, supplementation with enzyme or cofactors, providing deficient metabolite and removal of a toxic metabolite [3,10-12]. The same strategy was utilized in treating our patients admitted in PICU. Although hemodialysis is more efficient in clearing the toxic metabolite, the ease and cost-effectiveness

Table 3: Molecular analysis for the study population

Cases	Diagnosis	Gene	Variant	Zygosity	Variant
Case 1	MSUD	BCKDHB	Exon 1 c. 3G>A; Exon 5 c. 484A>G	Compound heterozygous	Pathogenic
Case 2	MSUD	BCKDHA	Exon 9 c. 1312T >C	Homozygous	Pathogenic
Case 3	MSUD	BCKDHB	Exon 4 c. 410C >T	Homozygous	Pathogenic
Case 4	Propionic acidemia	PCCA	Exon 13 c. 1195C >T	Homozygous	Pathogenic
Case 5	Propionic acidemia	PCCA	Exon 12 c. 937C >T	Homozygous	Pathogenic
Case 6	Methylmalonic acidemia	MUT(-)	Exon 3 c. 643G >T	Homozygous	Pathogenic
Case 8	Citrullinemia Type I	ASS1	Exon 15 c. 1168G >A	Homozygous	Pathogenic
Case 9	Arginosuccinicaciduria	ASL	Intron 11 c. 918+5G >A	Homozygous	Pathogenic
Case 12	HMG CoA lyase deficiency	HMGCL	Exon 7 c. 602C >A	Homozygous	Pathogenic
Case 13	Pyridoxine-dependent seizures	ALDH7A1	Exon 9 c. 841C >T	Homozygous	Pathogenic
Case 14	ZBD- I B	PEX1	Exon 5 c. 1108del A	Homozygous	Pathogenic
Case 15	GSD type III	AGL	Exon 31: c. 4256dup	Homozygous	Pathogenic

MSUD: Maple syrup urine disease, GSD: Glycogen storage disorder, ZBD: Zellweger biogenesis disorder

make PD ASA- as a useful modality. Among the four patients who underwent PD, two survived. Administration of vitamins like pyridoxine could be the only treatment for PDS, whereas giving biotin and other factors would generally form an additional modality for conditions like PA. Carnitine either as parenteral or oral therapy also help in the removal of toxic metabolite especially in organic acidemias and we promptly initiated that in needed children. Special formula was used to provide deficient metabolite and to reduce the substrate availability. After the acute crisis, breastfeeding was encouraged along with special formula in protein metabolic disorders as an amino acid load of breastmilk is low [13]. Low protein diet was initiated in older children with protein metabolic conditions at the time of discharge. As a patient with GSD is more prone for hypoglycemia, especially after moderate fasting, uncooked corn starch which is a form of complex carbohydrate was started to prevent further hypoglycemia.

In our study, biochemical testing which helped in arriving at specific diagnosis was elaborated. It is important to request for GCMS and HPLC along with TMS, as TMS alone would act only as a screening tool and not a diagnostic tool. All the information got from the test results have to be taken holistically to arrive at a specific diagnosis. TMS, GCMS, and HPLC are the most common diagnostic modality to aid in definitive diagnosis [1,8]. Very long fatty acid assay, plasma and urine AASA, and pipecolic acid are some of the specialized metabolic testing utilized in our study cohort.

Molecular testing was done in 80% of the study cohort. We could confirm using molecular analysis in a higher proportion as we included testing done from stored DNA. It is a good practice to store DNA even when the testing cannot be done at an acute state during PICU admission. As all the conditions in the present study are inherited in an autosomal recessive manner, we got 92% (11/12) of a pathogenic variant in homozygous status and only 8% (1/12) as compound heterozygous. In India due to the high prevalence of consanguineous marriage and endogamous population [14], there is a high chance of these condition occurring in the homozygous state rather than the compound heterozygous state. Notably, GSD type III was made only using the molecular method. In the present genomic era, next-generation sequencing is the most common test utilized to detect single gene disorder. This could be due to the genetic heterogeneity of many of the IEM where >1 gene is responsible for the same phenotype. Exome sequencing is an effective technology for diagnosing metabolic disorders [15]. We also got one intronic variant, which would have been missed if exome sequencing alone is done. Molecular analysis has not only helped the index child but also in prenatal diagnosis in 50% of the families.

Mortality occurred in five patients out of 15. Mortality is similar to that of the previous PICU study done in India [6]. One of the patients who died was diagnosed to have H3N2 influenza infection. He was an 8-year-old boy who was otherwise normal presenting with ketoacidosis and diagnosed to have SCOT

deficiency by biochemical testing. This reiterates the fact that metabolic disorders can be precipitated by infection. A previous case report describes another ketolytic defect, namely beta-ketothiolase deficiency presenting as metabolic encephalopathy at 11 months of age [16]. Whenever there is ketoacidosis, intensivists apart from diabetic ketoacidosis should suspectketolytic defect especially when there is no hyperglycemia or glycosuria. Need for mechanical ventilation is associated with high mortality in our study.

As this study describes only the short-term outcome, it is not taking into account the death that could potentially happen outside the study period or which could happen at a different hospital or home. This is one of the limitations of the study. Strengths of our study are a detailed description of biochemical testing aiding the definitive diagnosis and high proportion (80%) of a patient having molecular confirmation.

CONCLUSION

The most common cause for metabolic crisis in PICU is due to protein metabolic disorder. Aggressive intensive care and IEM directed therapy can be lifesaving, but still, the mortality is high. Need for mechanical ventilation is associated with poor prognosis. As IEM occurred uncommonly in PICU, a centralized database with inputs from all tertiary care centers would give a better insight about the individual conditions.

REFERENCES

1. Dherai AJ. Inborn errors of metabolism and their status in India. Clin Lab Med 2012;32:263-79.
2. Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: An overview. Semin Neonatol 2002; 7:3-15.
3. Champion MP. An approach to the diagnosis of inherited metabolic disease. Arch Dis Child Educ Pract Ed 2010;95:40-6.
4. Rao AN, Kavitha J, Koch M, Suresh Kumar V. Inborn errors of metabolism: Review and data from a tertiary care center. Indian J Clin Biochem 2009; 24:215-22.
5. Rama Devi AR, Naushad SM. Newborn screening in India. Indian J Pediatr 2004;71:157-60.
6. Kamate M, Chetal V, Kulgod V, Patil V, Christopher R. Profile of inborn errors of metabolism in a tertiary care centre PICU. Indian J Pediatr 2010; 77:57-60.
7. Häberle J. Clinical practice: The management of hyperammonemia. Eur J Pediatr 2011;170:21-34.
8. van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: A systematic literature review. Mol Genet Metab 2012;105:368-81.
9. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child 1999;81:431-3.
10. Kumta NB. Inborn errors of metabolism (IEM) an Indian perspective. Indian J Pediatr 2005;72:325-32.
11. Shennar HK, Al-Asmar D, Kaddoura A, Al-Fahoum S. Diagnosis and clinical features of organic acidemias: A hospital-based study in a single center in Damascus, Syria. Qatar Med J 2015;2015:9.
12. Alfadhel M, Mutairi FA, Makhseed N, Jasmi FA, Al-Thihli K, Al-Jishi E, *et al.* Guidelines for acute management of hyperammonemia in the middle east region. Ther Clin Risk Manag 2016;12:479-87.
13. MacDonald A, Depondt E, Evans S, Daly A, Hendriksz C, Chakrapani AA, *et al.* Breast feeding in IMD. J Inherit Metab Dis 2006;29:299-303.
14. Verma IC. Burden of genetic disorders in India. Indian J Pediatr 2000; 67:893-8.
15. Shakiba M, Keramatipour M. Effect of whole exome sequencing in diagnosis of inborn errors of metabolism and neurogenetic disorders. Iran J Child Neurol 2018;12:7-15.
16. Akella RR, Aoyama Y, Mori C, Lingappa L, Cariappa R, Fukao T, *et al.* Metabolic encephalopathy in beta-ketothiolase deficiency: The first report from India. Brain Dev 2014;36:537-40.