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ORIGINAL ARTICLE

Clinical Spectrum of Inherited Disorders of Metabolism

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Abstract

Objective To study the clinical profile and outcome of children with Inborn errors of metabolism.

Methods Thirty one newly diagnosed children with Inborn errors of metabolism over a 1 y period were studied for their relevant clinical, biochemical, diagnosis, treatment and follow-up details.

Results Inborn errors of metabolism accounted for 2% of hospital admissions. Sixty five percent were born to parents of consanguineous marriage. Of the 31 children with Inborn errors of metabolism, 16 (51%) had lysosomal storage disorders, 8 (26%) had disorders of amino acid metabolism, 2 (6%) each had disorders of carbohydrate and bile acid metabolism, 1 (3%) each had disorders of fatty acid oxidation, mitochondrial and peroxisome metabolism. Acrodermatitis dysmetabolica, as a complication was observed in one child and the overall mortality rate in this series was 10%.

Conclusions Lysosomal storage disorders constituted the majority of Inborn errors of metabolism in this series and amino acidopathies/organic acidemias were successfully treated with special formulas.

Keywords Metabolism · Lysosomes · Organic acidemias · Children

Introduction

Inborn errors of metabolism (IEM) are individually rare, but collectively numerous. Their protean clinical presentations in children with substantial morbidity and mortality pose a formidable challange to the practicing Pediatrician [1]. The recent availability of Tandem mass spectrometry and Gas chromatography has enabled the diagnosis of amino acid disorders, organic acidemias and fatty acid oxidation disorders to a greater extent. In India, the reported prevalance of IEM is 1 in 2497 newborns [2] although the true pan India prevalence still remains unknown [3]. To get a better estimate of number of patients with rare disorders, ICMR has launched the "The Indian Rare disease Registry" in 2017. India having a relatively high birth rate of approximately 25 million babies born every year and also a higher prevalence of consanguineous marriages across the country, the occurrence of IEM may be even higher. There is paucity of data from south India with regard to the clinical spectrum of IEM except for a few isolated case reports/series and hence authors studied the clinical spectrum and outcome of IEM in children.

Material and Methods

This prospective study was conducted in the Metabolic Clinic of Kanchi Kamakoti CHILDS Trust Hospital, Chennai during the period June 2017 till May 2018 and the study was approved by the Institutional Ethics Committee. During this period, 31 children aged from newborn to eighteen years in whom the diagnosis of IEM was newly established were included for the study. Their relevant clinical, biochemical, imaging, molecular genetic, treatment and follow-up details were analysed. Children with suspected IEM, sepsis and in whom the diagnosis was not established during the said period were excluded.

The data collected were tabulated and analysed by using the Microsoft office excel 2007. The data are expressed in form of numbers and percentages.

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Table 1 Clinico laboratory profile of children with IEM

S.no	IEM groups	No. of cases	Age at presentation	Sex	Clinical features at presentation	Salient specific investigations	Diagnosis	Treatment
1	Amino acid and peptide metabolism	1	3 d	F	Vomiting, lethargy	PAA – Elevated citrulline, UOA – Elevated orotic acid *Genetic testing*: A homozygous 1 Bp deletion [c.478del] in exon 7 of ASL gene resulting in frameshift & premature truncation of protein 15 aminoacids downstream to codon 160(p.HisIlefsTer15).	ASL deficiency	Special formula – Non essential amino acid free formula, Other drugs – Sodium benzoate (250 mg/kg/d), L-arginine (250 mg/kg/d), Developmentally normal till 1 y of follow-up.
		5	3 mo	F	*Patient 1:* Irritability, abnormal body odor	*Patient 1:* PAA – Leucine/isoleucine – 4267 μmol/L (26–262), valine – 871.15 μmol/L (41–233).	*Patient 1:* MSUD	*MSUD*: Branched chain amino acid free formula, Thiamine (50 mg/d)
			7 mo	M	*Patient 2:* Irritability, seizures, abnormal body odor, dystonic movements	*Patient 2:* PAA: Leucine/isoleucine – 3233 μmol/L (26–262), valine – 723 μmol/L (41–233).	*Patient 2:* MSUD	*MSUD*: Branched chain amino acid free formula, Thiamine (50 mg/d)
			6 mo	F	*Patient 3:* Lethargy, poor feeding, acidotic breathing	*Patient 3:* PAA – Normal ACP: Reduced carnitine & Acyl carnitine level, UOA: Elevated MMA Elevated plasma MMA – 15.94 μmol/L (0–4.7), Reduced plasma homocysteine – 1.79 μmol/L (415 μmol/L)	*Patient 3:* MMA	*MMA*: Methionine & valine free formula, Carnitine (100 mg/kg/d), Vit B12
			1 mo	M	*Patient 4:* Lethargy, poor feeding	*Patient* 4: PAA – Elevated glycine – 524.43 μmol/L (<505), ACP – Elevated propionyl carnitine – 11.38 μmol/L (<6), UOA – Elevated 3 hydroxy propionic acid – 19.34% (0.2%).	*Patient 4:* Propionic acidemia	*Propionic acidemia:* Methionine & valine free formula, Carnitine (100 mg/kg/d)
			7 mo	F	*Patient 5:* Seizures, dystonia, macrocephaly	*Patient 5:* TMS – Elevated Glutaryl carnitine level. Genetic testing of GCDH gene showed pathogenic homozygous mutation in exon 8 [c.769c>T,p.R257W].	*Patient 5:* Glutaric aciduria type 1	*Glutaric aciduria:* Lysine & tryptophan free formula, diet free in lysine with reduced tryptophan, Riboflavin (200 mg/d), Carnitine (100 mg/kg/d)
		1	11 mo	M	Seizures	PAA: Glycine – 524 μmol/L (81–436), CSF glycine – 136 μmol/L (up to 38), CSF/plasma glycine ratio = 0.25 (>0.08), UOA and plasma ACP – Normal	Nonketotic hyperglycine-mia	Dextromethorphan (10 mg/kg/d), Carnitine (100 mg/kg/d), Sodium benzoate (250 mg/kg/d), Protein free formula
		1	19 mo	M	Blackish discoloration of urine	Urine for homogentisic acid (quantitative) = elevation factor of 456 (Reference range 1%)	Alkaptonuria	High dose Vit-C (500 mg/d)
2	Carbohydrate metabolism	2	4 mo	M	*Patient 1:* Floppiness, developmental delay, fast breathing	*Patient 1:* Alpha glucosidase: 3.3 nmol/h/blood [15.5–92.2]	Pompe disease	*Patient 1:* Antifailure drugs, aspirin (5 mg/kg/d), carnitine (100 mg/kg/d), died at 16 mo
			8 mo	F	*Patient 2:* Developmental delay, hypotonia	*Patient 2:* Alpha glucosidase: 4.05 nmol/h/blood [10–60] *Genetic analysis: E*xon 13 GAA+,C.1826 dup A -variant, GSD II	Pompe disease	*Patient 2:* Registered for alglucosidase alfa enzyme replacement therapy
3	Fatty acid and ketone body metabolism	1	1.2 y	M	Vomiting, lethargy, acidotic breathing	PAA – Normal, ACP – C2 = 3.04, C16 = 4.07, C18:1 = 2.16, [C16 + C18: 1/C2] = 2.05 (Ref <0.43)-- > CPT II deficiency	CPT 2 deficiency	Diet: High carbohydrate and low fat diet, avoidance of prolonged fasting, Carnitine (100 mg/kg/d)
4	Lysosomal storage disorders	6	1 y	M	*Patient 1:* Abdomen distension, hepatosplenomegaly	*Patient 1:* Beta glucosidase levels: 1.5 nmol/ml/h (Normal range: 2.3–14.1).	Gaucher disease	Registered for imiglucerase enzyme replacement therapy
			1.2 y	M	*Patient 2:* Abdomen distension, splenohepatomegaly	*Patient 2:* Beta glucosidase levels: 1.67 nmol/ml/h (Normal range: 2.3–14.1). *Genetic analysis*: c.[1448T>C];[1448T>C] (p.[Leu483Pro];[Leu483Pro]) – *Gaucher disease*	Gaucher disease	Registered for imiglucerase enzyme replacement therapy
			2 y	M	*Patient 3:* Abdomen distension, pallor, splenohepatomegaly, B/L lateral rectus palsy	*Patient 3:* Beta glucosidase levels: 0.87 nmol/ml/h (Normal range: 2.3–14.1)	Gaucher disease	Registered for imiglucerase enzyme replacement therapy

Table 1 (continued)

S.no	IEM groups	No. of cases	Age at presentation	Sex	Clinical features at presentation	Salient specific investigations	Diagnosis	Treatment
			1.2 y	F	*Patient 4:* Developmental delay floppiness, abdomen distension, hepatosplenomegaly, cherry red spot	*Patient 4:* Acid sphingomyelinase levels: 2.02 nmol/ml/h (Normal: 9.5–58)	Niemann-Pick disease	Physiotherapy & counseling
			9 y	M	*Patient 5:* Developmental delay, abdomen distension, splenohepatomegaly, cherry red spot	*Patient 5:* Acid sphingomyelinase levels: 1.05 nmol/ml/h (Normal: 2.4–3.9)	Niemann-Pick disease	Physiotherapy & counseling
			6 mo	F	*Patient 6:* Seizures irritability, hypertonia, optic atrophy	*Patient 6:* MRI brain: Demyelination in parieto-occipital regions with cortical atrophy. Beta Galactocerebrosidase levels: 6.4 nmol/17 h/mg (normal: 18–84)	Krabbe disease	Physiotherapy and counseling
		10			Short stature (70%), developmental delay (60%), bony deformities (60%), cognitive impairment (30%), coarse facies (100%), corneal clouding (60%), hepatomegaly (40%)	**Galactosamine 6 sulfatase (low in 7) – Morquio IV-A** [*Patient 1:* 2 y/M, 2.1 nmol/17 h/mg, *Patient 2:* 1 y/M, 2.3 nmol/17 h/mg, *Patient 3:* 8 y/M, 2.8 nmol/17 h/mg, *Patient 4:* 2 y/F, 3.6 nmol/17 h/mg, *Patient 5:* 3 y/M, 2.4 nmol/17 h/mg, *Patient 6:* 6 y/M, 3.2 nmol/17 h/mg, *Patient 7:* 2 y/M, 2.3 nmol/17 h/mg, Normal range (30–170)]	Morquio A (7)	Supportive treatment & genetic counseling
						Alpha iduronidase (low in 1): Hurler [*Patient 1:* 2 y/F, 0.068 nmol/h/ml (2.4–12)]	Hurler (1)	Registered for laronidase enzyme replacement therapy
						Alpha N-acetyl glucosaminidase (low in 2) – Sanfillipo Type B [*Patient 1:* 4 y/M, 1 nmol/ml/h; *Patient 2:* 3 y/F, 0.03 nmol/ml/h (6–20)]	Sanfillipo type B(2)	Supportive treatment & genetic counseling
5	Peroxisomal	1	53 d	F	Cholestatic jaundice, dysmorphic facies, icterus, B/L cataract, nystagmus, poor weight gain, hepatomegaly, hypotonia	Very long chain fatty acids (VLCFA) – Phytanic acid – 4.24 μmol/L (0.37–3.46), hexacosanoic acid – 18.45 μmol/L (<=0.68), C24/C22 = 2.32(0.67–0.87), C26/C22 = 0.69(0.002–0.01)-- > increased. A homozygous two base pair deletion in exon 1 of the PEX6 gene	Zellweger syndrome	UDCA (20 mg/kg/d), vitamin supplementation (A, D, E, K, B, C), Simyl MCT oil. Died at 3 mo of age.
6	Bile acid metabolism and transport	2	8 y	F	Intermittant jaundice, hepatomegaly	*Genetic analysis*: Both patients were homozygous for A $(TA)_7$ TAA allele in the promoter region of UGT1A1 gene.	Gilbert	Reassurance
			4 y	F	Recurrent jaundice, mild hepatomegaly		Gilbert	
7	Mitochondrial disorders	1	8 mo	M	Vomiting, irritability, fast breathing, acidotic breathing, spasticity, nystagmus	*Genetic analysis:* A homozygous nonsense variation in exon 4 of the LYRM7 gene (chr5:130522772; C > T; c.214C>T), mitochondrial complex III deficiency, nuclear type 8	Nuclear mitochondrial complex 3 deficiency	Thiamine (100 mg/d), Co-enzyme Q (10 mg/kg/d), carnitine (100 mg/kg/d), physiotherapy. Died at 13 mo of age.

ACP Acyl carnitine profile, *ASL* Arginosuccinate lyase, *B/L* Bilateral, *CPT* Carnitine palmitoyl transferase, *CSF* Cerebrospinal fluid, *F* Female, *IEM* Inborn error of metabolism, *M* Male, *MCT* Medium chain triglycerides, *MMA* Methyl melonic acidemia, *MSUD* Maple syrup urine disease, *PAA* Plasma amino acid (by high performance liquid chromatography), *TMS* Tandem mass spectrometry, *UDCA* Ursodeoxycholic acid, *UOA* Urine organic acid

Results

During this period, 31 children were diagnosed with IEM out of 1539 hospital admissions, accounting for 2% of hospital admissions. Of the 31 children, 3 were admitted in to ICU and the rest were admitted in ward either for diagnoses or treatment. Of the 31 children, 18 (58%) were boys and 13 (42%) were girls and the male: famale ratio was 1.3: 1. Twenty children (65%) were born to parents of consanguineous marriage and sibling death due to a similar illness was seen in 3 (10%). Of the 31 children with IEM, 16 (51%) had lysosomal storage disorders, 8 (26%) had disorders of amino acid metabolism, 2 (6%) each had disorders of carbohydrate and bile acid metabolism, 1 (3%) each had disorders of fatty acid oxidation, mitochondrial and peroxisome metabolism. Their mean age at onset of symptoms/diagnosis, salient specific investigations and treatment details are shown in Table 1. Children with Gaucher disease, Pompe disease and Hurler disease were referred and registered for specific enzyme replacement therapy and children with amino acidemias and organic acidemias (OA) were treated with special formulas in addition to the appropriate dietary interventions. Others were offered symptomatic and supportive care. A 5-mo-old infant with Maple syrup urine disease (MSUD) developed erythematous lesions in the perioral, perianal and in both cubital fossa within 6 wk of initiating Branched chain amino acid (BCAA) free formula. Her plasma isoleucine, leucine and valine levels were low. She was diagnosed as acrodermatitis dysmetabolica due to isoleucine deficiency and initiated on breast feeds along with BCAA formula in the ratio of 40:60 and isoleucine sachets @ 100 mg/kg/d for 5 d following which her skin lesions resolved completely. Of the 31 children with IEM, 3 died (Multifocal cystic leukoencephalopathy due to *LYRM7* gene mutation, Pompe disease and Zellweger syndrome respectively) and the rest are under follow-up. The overall mortality rate in this series was 10%.

Discussion

IEM have a varied clinical presentation and hence a high index of suspicion is needed to make a diagnosis in a given case. Early newborn screening might reduce the morbidity and mortality in select IEMs [4]. Consanguinity was seen in two-third (65%) of children in the present study, whereas Choudhry et al. [5] and Arif et al. [6] had reported consanguinity in 100% and 9.9% of their cases respectively. Non ketotic hyperglycinemia and disorders of amino acid metabolism were the commonest IEMs identified by Choudhry et al. [5] and Arif et al. [6] whereas in this study, lysosomal storage disorders (LSD) (51%) were the commonest IEM identified. Metachromatic leukodystrophy and Gauchers disease were the predominant LSD reported by Verma et al. [7]. Gaucher disease (31.93%) followed by mucopolysaccharidoses (20.16%) were the predominant LSD reported by Agarwal et al. [8]. In the present study, mucopolysaccharidoses especially type IV (Morquio A) was the commonest LSD seen. The above discrepancies with regard to the type of IEM reported might be due to the small sample sizes from the various series.

Enzyme replacement therapy (ERT) is currently approved for ten LSDs (Gaucher disease, Pompe disease, Fabry disease, lysosomal acid lipase deficiency, alpha mannosidosis and mucopolysaccharidoses types I, II, IVA, VI and VII) and neuronal ceroid lipofuscinosis type 2. As the cost of ERT is prohibitive, access has been facilitated for Indian patients through a charitable access program run by a pharmaceutical company, INCAP for 4 LSD namely Gaucher, Pompe, Fabry and MPS I disease.

Methyl malonic caidemia (40%) was the commonest organic acidemia (OA) reported by Sindgikar et al. [9] in their series whereas in present series MSUD was the commonest OA observed. Recently Food Safety and Standards Authority of India (FSSAI) has allowed the import of special formulas for inborn errors of metabolism [10] and the present patients with amino acid disorders were treated with these special formulas in addition to the appropriate dietary interventions. As there is limited literature available on IEM from our country, the present study highlights the burden of IEM from a single center over a 1 y period. IEM if diagnosed and treated early, not only has a better prognosis, but also one can offer appropriate genetic counseling and prenatal diagnosis for their families.

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Authors' Contribution RA collected the data. RA and RG reviewed the literature and drafted the manuscript. RG and LJ were involved in patient management and reviewed the manuscript for intellectual content. RG will act as the guarantor for this article.

Compliance with Ethical Standards

Conflict of Interest None.

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