Audit of Organic Acidurias from a Single Centre: Clinical and Metabolic Profile at Presentation with Long Term Outcome

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ABSTRACT

Introduction: Organic Acidurias (OA) accounts between 10% and 40% of confirmed Inborn Errors of Metabolism (IEM) in India. With prompt recognition and management, better survival but adverse neurodevelopmental outcome is reported.

Aim: To study the clinical and metabolic presentation, management with immediate and long term outcome of symptomatic children with confirmed OA.

Materials and Methods: Hospital based study of symptomatic children diagnosed to have OA between 2003 and 2009 and the survivors followed up over next five years. Diagnosis was based on clinical and metabolic presentation and confirmed by spectrometry analyses of urine and blood. Management, immediate outcome, compliance to treatment and recurrence of crises were documented. Neurodevelopmental outcome was assessed in follow up. Mean with Standard Error (Mean ± SE) and frequencies with percentages were calculated.

Results: Of 72 cases suspected to have IEM, 38 (52.8%) were confirmed of (IEM), and out of which 15 (39.5%) had OA. Methyl malonic acidemia, multiple carboxylase deficiency and Propionic Acidemia (PA) constituted the largest proportion. Neurodevelopmental issues (73.3%) and metabolic crisis (53.3%) were common presenting features. Mean ± SE of ammonia was 639.0±424.1 μg/dl and lactate was 33.6±4.9 mg/dl. Mean pH, bicarbonate, and anion gap was 7.27±0.07, 14.1±2.3 and 17.9±2.3 respectively. Management was protocol based. Death was reported in two cases of PA; other morbidities were seen in five. Recurrent crisis (46.7%) complicated the follow up in survivors. Spasticity, extrapyramidal movement disorder, intellectual subnormality, autism spectrum, attention deficit hyperactivity disorder and sensory neural deafness were seen amongst survivors, in spite of compliance to therapy.

Conclusion: OA is part of differential diagnosis in sick children and treatment needs to be prompt and specific. Prognosis is guarded even with long term cofactor supplementation in the symptomatic.

INTRODUCTION

IEM constitute an important and expanding group of monogenic disorders resulting from deficiency of a critical enzyme in the intermediary pathways of carbohydrate, protein and lipid metabolism or deficiency of a cofactor which is responsible for activation of an apoenzyme [1]. They offer formidable challenges to clinicians because of the myriad enzyme defects that exist, complexity of metabolic pathways, diverse clinical and metabolic manifestations, ability to mimic common pediatric illnesses, morbidity and implications in future pregnancies. In India, they occur more frequently because of high birth rate and consanguinity [2,3]. Compared to a decade ago, awareness and availability of specific investigations allow these disorders to be identified at much higher frequency as evidenced by several studies [3-6]. Although it has become imperative to move from an 'at risk' or 'symptomatic sick child' approach to a 'prospective' or 'pre-symptomatic' one, the services are availed by those affordable in the private sector. [7].

OA or organic acid disorders are a subgroup of IEM characterized by excretion of non amino organic acids in urine due to their accumulation in body fluids. Classic presentation of these disorders is with severe metabolic acidosis. Majority of OA are caused by defective catabolism of the three branched chain amino acids namely valine, leucine and isoleucine. OA accounts between 10% to 40% of confirmed IEM in India [8]. They are diagnosed by characteristic organic acid excretion pattern in urine Gas Chromatography Mass Spectrometry (GCMS). Disorders include Maple Syrup Urine Disease (MSUD), Isovaleric Acidemia (IVA), Propionic Acidemia (PA), Multiple

Carboxylase Deficiency (MCD), Methyl Malonic Acidemia (MMA), beta Keto Thiolase (βKT) deficiency, Glutaric Aciduria type 1 (GA1) and others. MCD may result from biotinidase or holocarboxylase synthetase deficiencies with similar urine organic acid metabolites.

Prevention of death or permanent neurologic sequelae in patients with these disorders is dependent on early diagnosis and institution of appropriate therapy [9]. Most of these disorders are amenable to combination of dietary protein restriction, cofactor therapy with megavitamins and removal of toxic metabolites. During critical situation, suspicion as well as emergency treatment including metabolic stabilization will reduce mortality and morbidity. We present our data on the clinical and metabolic presentation, management, mortality and morbidity of symptomatic children confirmed to have OA by urine and blood spectrometry analyses and their five year follow up.

MATERIALS AND METHODS

This is a hospital based study of children diagnosed with OA between 2003 and 2009 before Newborn Screening (NBS) was widely available. The survivors were followed up over the next five years or more. The study was cleared by the Institutional Ethics Committee. Clinical suspicion of an IEM was based on suspect family history, age, presentation, presence of a combination of failure to thrive, developmental delay or regression, recurrent vomiting, abnormal body fluid odours, encephalopathy and organomegaly. The metabolic work up included urine ketones, blood glucose, anion gap, arterial blood gas analysis, blood ammonia and lactate. Diagnosis was

confirmed by urine GCMS for organic acids supplemented by blood tandem Mass Spectrometry (MS/MS). Management, immediate outcome, compliance to treatment and recurrence of crises were documented.

The survivors were prospectively followed up over next five years or more for growth and development, recurrence of symptoms, neurologic sequelae if any and neuroimaging. Failure To Thrive (FTT) was defined as weight, height and weight for age less than 5th centile in WHO growth standards. Developmental delay was defined as development quotient less than 70 and when possible intelligence quotient was assessed by Binet Kamat scale by a clinical psychologist. All children underwent vision and hearing assessment and where indicated brain imaging by Magnetic Resonance (MR).

STATISTICAL ANALYSIS

Statistical analyses included median or Mean±SE for numerical data and frequencies (n) with percentages (%) for categorical data.
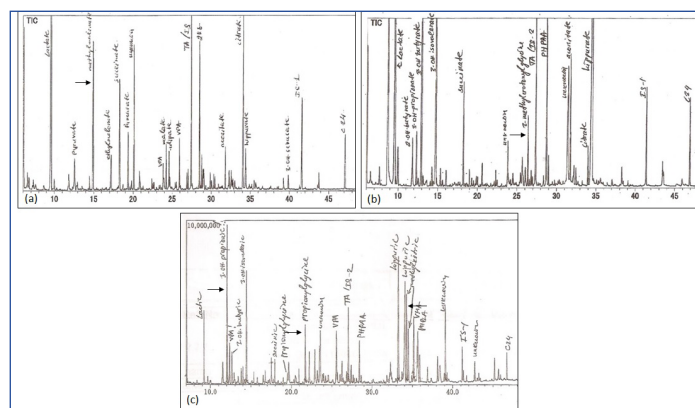
[Table/Fig-1]: Urine gas chromatograph mass spectrometry showing characteristic organic acid excretion pattern: a): Methyl malonic acid in methylmalonic academia; b): 3-methyl crotonyl glycine in multiple carboxylase deficiency; c): 3-hydroxy propionic acid, propionyl glycine and methyl citrate in propionic acidemia. Absence of 3-hydroxy propionic acid and methyl citrate in a) is indicative of presentation without ketoacidosis.
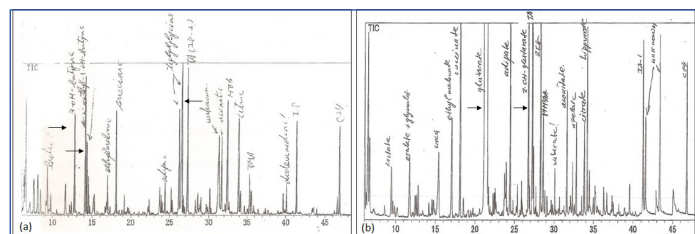
[Table/Fig-2]: Urine gas chromatograph mass spectrometry showing characteristic organic acid excretion pattern: a) 3-OH butyrate, 2-methyl 3-OH butyrate and tiglylglycine in beta ketothiolase deficiency; b) glutaric acid and 3-OH glutaric acid in glutaric aciduria type 1.

RESULTS

A diagnosis of IEM was considered in 72 children on the basis of clinical presentation and metabolic profile. Spectrometry analyses of urine and blood confirmed the same in 38 (52.8%) of which 15 (39.5%) had an OA. Except one child with MMA who was diagnosed at 14 months, all were diagnosed by infancy. The Mean±SE and median ages at diagnosis were 5.6±1.16 and 4 months respectively. Male preponderance was found with a ratio of 2:1. The most common OAs were MMA in 6 (40%) and MCD in 5 (33.3%). Others included two (13.3%) children of PA and one each of GA1 and βKT deficiency. [Table/Fig-1a-c,2a,b] depict the characteristic urine organic acid excretion pattern seen in these children. Consanguinity was seen in one and sibling affected/death in five (33.3%).

Developmental delay was the most common presentation seen in 73.3%. Developmental delay, seizures, alopecia and skin rash were diagnostic of MCD. Three children, one each of developmental delay with microcephaly, failure to thrive with seizures with no ketoacidosis and developmental delay with macrocephaly were confirmed to be MMA, PA and GA1 respectively. More than half (8,53.3%) presented with a metabolic crisis and symptoms at presentation included encephalopathy, seizures and rapid breathing due to metabolic acidosis. One each of MCD and MMA were confirmed by presymptomatic screening in view of sibling history. Two other children presenting as persistent vomiting were evaluated for gastro-oesophageal reflux disease and malrotation in surgical department before a diagnosis of MMA was made. The clinical presentation and metabolic profile at presentation are shown in [Table/Fig-3].

Biochemically, wide anion gap metabolic acidosis, ketosis, lactic acidosis and hyperammonemia prompted the suspicion for diagnosis. The highest ammonia of 5706 µg/dl without ketoacidosis

Clinical	Number(%)	Metabolic	Number(%)
Family history	5 (33.3)	Elevated ammonia	11 (73.3)
Recent weaning	4 (26.7)	Elevated lactate	9 (60.0)
Developmental delay	11 (73.3)	Metabolic acidosis	6 (40.0)
Encephalopathy	8 (53.3)	Wide Anion gap	8 (53.3)
Respiratory distress	7 (46.7)	Respiratory alkalosis	3 (20.0)
Failure to thrive	5 (33.3)	Ketonuria	6 (40.0)
Vomiting	4 (26.7)	Hypoglycaemia	3 (20.0)
Diarrhea	3 (20.0)	Hyperglycaemia	1 (6.7)
Hepatomegaly	8 (53.3)	Hyponatraemia	3 (20.0)
Skin lesions, alopecia	4 (26.7)		
Microcephaly	1(6.7)		
Macrocephaly	1(6.7)		

[Table/Fig-3]: Clinical and metabolic profile of children (n=15) with confirmed organic acidemia at presentation.

Disorder	Age at diagnosis (months)	Presentation and Course	Outcome
Methyl malonic acidemia (1 of 6)	4	Presented as developmental delay, seizures and microcephaly. No metabolic crisis. Unresponsive to B12	Spastic quadriplegia with severe microcephaly (Head circumference at 5 years: 40 cm), severe psycho motor retardation, seizures, severe sensory neural hearing loss, failure to thrive. MR imaging: Gross cerebral atrophy with decreased white matter and profound T2 hyperintensity suggestive of hypomyelination, coronal suture craniosynostosis
Multiple carboxylase deficiency (3 of 5)	2	Metabolic acidosis, alopecia, intertrigo and seizures; no crisis on biotin	Spastic diplegia with attention deficit hyperactivity disorder, moderate intellectual disability; off seizure medication. MR imaging: cerebral atrophy
	4	Alopecia, intertrigo and seizures. No crisis	Catch up in motor milestones, no tone abnormalities, mild intellectual disability, bilateral severe to profound sensory neural hearing loss with no language development; off seizure medication
	8	Metabolic acidosis in addition to alopecia, intertrigo and seizures; Poor compliance to therapy with recurrent crisis and seizures	Catch up in motor milestones, no tone abnormalities; complex partial seizures with autism like and attention deficit hyperactivity disorder, moderate intellectual disability, bilateral moderate sensorineural hearing loss; complex partial seizures on therapy. MR imaging: Normal
Beta keto thiolase deficiency (1)	6	Metabolic acidosis, hyperglycaemia and encephalopathy; recurrent crisis	Extra pyramidal movement disorder, moderate intellectual disability; off seizure medications. MR imaging: Normal

[Table/Fig-4]: Summary of children with confirmed organic acidemia and adverse neurodevelopment outcome.

was seen in a child with PA [10]. The Mean ±SE ammonia level observed was 639.0±424.1 μg/dl (median 196 μg/dl) and lactate was 33.6±4.9 mg/dl. Mean pH was 7.27±0.07, arterial bicarbonate 14.1±2.3, base deficit 14.9±3.4 and anion gap 17.9±2.3. Neuroimaging (NI) was diagnostic in GA1 with bilateral widening of sylvian fissure and cerebrospinal fluid space anterior to temporal lobe (bat-wing appearance).

Empiric management in crisis included dehydration correction, megavitamins, carnitine, sodium benzoate when indicated, intravenous sodium bicarbonate based on base deficit in blood gases, broad spectrum antibiotics. Specific management after GCMS and MS/MS reports were available included protein restriction, cofactor supplementation like biotin for MCD and PA; vitamin B12 for MMA and riboflavin for GA1. The course was complicated by multiple crisis in 7 (46.7%) precipitated by infection. Poor compliance was noted only in one. The overall mortality observed was both of PA. Adverse outcome was seen in one of six MMA, three of five MCD and βKT deficiency. [Table/Fig-4] gives the adverse neurodevelopmental outcome in survivors of various categories of OA. Spasticity, extrapyramidal movement disorder, intellectual subnormality, autism spectrum, Attention Deficit Hyperactivity Disorder (ADHD) and sensory neural deafness were seen amongst survivors, in spite of compliance to therapy.

DISCUSSION

In our study, OA contributed to 20.8% of all children investigated and 39.5% of confirmed IEM. Among high risk children screened for IEM, Nagaraja D et al., and Narayanan MP et al., from Southern India have reported OA in 41.6 and 10.7% respectively [6,11]. Prevalence data of IEM in general and OA in particular from India is limited due to difficulties in establishing the diagnosis in an acutely sick child. Najafi R et al., have documented a high consanguinity rate of 84.7% in Mid-West [12]. In our study, though we did not have significant positive consanguinity, familial pattern in two suggested recessive inheritance pattern. High occurrence of MMA over other OA has been reported by other authors. Narayanan MP et al., and Najafi R et al., in their study report that MMA contributes to 34% and 33% of OA respectively [11,12]. Some of the unusual presentations in our children and reported as well, included PA masquerading as urea cycle disorder and βKT deficiency as diabetic ketoacidosis [10,13-17]. NI is highly useful in the diagnosis of GA1, as these children can have a subacute course and may present only with developmental delay and macrocephaly [18,19].

Neuropsychiatric manifestations occur in IEM either at presentation or as sequelae. It is thought to be due to disruption of normal late neurodevelopment or monoaminergic neurotransmitter systems [20]. A disturbance in mitochondrial function which is the final common pathway of all intermediary metabolisms may also be contributory. Autism spectrum disorder has been described in OA specifically PA, methylcrotonyl-CoA and biotinidase deficiencies [21-24]. The relation between ADHD and phenylketonuria is well documented [25]. ADHD is also associated with urea cycle disorders, maple syrup urine disease and homocystinuria. The autism and ADHD seen in our children with MCD may be part of moderate intellectual disability. NI was normal in this group.

Sensorineural hearing loss and optic atrophy are reported in untreated children with biotinidase deficiency [26-28]. It is proposed that accumulation of biocytin or small biotiny peptides may mediate neuronal injury in these children. Weber P et al., reported that vision and hearing abnormalities were none in infants diagnosed by NBS compared to children where treatment was initiated after onset of symptoms [26]. Wolf B et al., reports that more than three-fourths of symptomatic children have sensorineural hearing loss which does not seem to resolve or improve with biotin treatment [29]. Of the seven children with symptomatic biotinidase deficiency,

Venkataraman V et al., report neurological deficit in one and deafness in none [30]. The variable prognosis in our series could be best explained by age and developmental period at diagnosis, severity of enzyme defect as well as phenotypic variations, recurrent metabolic decompensations, response and compliance to cofactor therapy.

CONCLUSION

Until NBS is a reality, OA should be part of the differential diagnosis in any sick neonate or infant with a negative sepsis screen, persistent metabolic acidosis and ketosis as well as in any infant with unexplained neurological deterioration even in the absence of ketoacidosis. Prognosis is guarded even with prompt institution of emergency treatment and long term cofactor supplementation.

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