

# Clinical outcome of major organic acidemias – A three years follow-up study

Mundakkassery Pullurmanan Narayanan\*, Kannan Vaidyanathan and Damodaran Madhavi Vasudevan  
*Metabolic Disorders Laboratory, Department of Biochemistry, Amrita Institute of Medical Sciences and Research Centre, Kerala, India*

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**Abstract.** The term “organic acidemia” or “organic aciduria” (OA) applies to inborn errors of metabolism (IEM) in which organic acids accumulate in tissues and biological fluids. Classical organic acidurias include methylmalonic aciduria (MMA), propionic aciduria (PA), isovaleric aciduria (IVA) and maple syrup urine disease (MSUD). Aminoacidurias like phenylketonuria are common in the western population. Organic acidemias like MMA, PA and MSUD are more common in Asian countries, especially in India compared with the west. This study was conducted to determine the prevalence and treatment outcome of organic acidemias in a study population in India. Four hundred and twenty suspected cases of organic acidemias with an upper age limit of twelve years were enrolled over a two years period between January, 2007 and December, 2008, with a three years patient follow-up. Screening tests and thin layer chromatography followed by quantification of organic acids in urine and quantification of amino acids in blood by high performance liquid chromatography were done for detection of organic acidemias. Out of 420 patients, 45 patients (10.7%) were found to have organic acidemias, 15 cases of MMA, 16 cases of PA, 13 cases of MSUD, and one case of IVA were identified. Fifteen patients (33.3%) died during the course and remaining 30 are under therapeutic regimen and showed marked clinical improvement. Therapeutic regimens based on protein restriction, sodium bicarbonate (to correct acidosis), L-carnitine and vitamins were given to the patients. Prompt diagnosis helped to provide specific treatment to majority of these patients with rapid improvement in symptomatology.

**Keywords:** Organic acidemias, maple syrup urine disease, methylmalonic aciduria, propionic aciduria, isovaleric aciduria, tandem mass spectrometry

## 1. Introduction

Organic acidurias (OAs) arise due to alterations of the intermediary metabolism that lead to the accumulation of organic acids in the tissues, metabolic acidosis and intracellular biochemical alterations [1]. Organic acid disorders (OAD) are considered the most frequent inherited metabolic disorders among severely ill chil-

dren [2–4], and together with the aminoacidopathies constitute the most prevalent groups of inborn errors of metabolism in high risk populations [5]. There are a wide range of clinical manifestations in organic acidemias affecting multiple organ systems with the predominant manifestations being of the central nervous system [6,7]. The diagnosis of OAs requires identification of an abnormal pattern of organic acids in biological fluids, especially urine, by gas chromatography or high performance liquid chromatography (HPLC). Effective treatment for many organic acidemias has improved during the last decade, which renders their prompt diagnosis critical. The prevalence of organic acidemias is high in India [8,9]. Therefore this study

\*Corresponding author: Mundakkassery Pullurmanan Narayanan, Senior Research Fellow, Metabolic Disorders Laboratory, Department of Biochemistry, Amrita Institute of Medical Sciences and Research Centre, AIMS-Ponekkara (PO) Kochi-682041, Kerala, India. Tel.: +91 9497274495; Fax: +91 0484 2802020; E-mail: omnarayananmp@gmail.com.

has been conducted to find out the prevalence and treatment effectiveness of organic acidemias in a study population in India.

Most organic acidemias result from deficient enzyme activity due to genetic mutations and are inherited in an autosomal recessive manner. A neonate affected with an OA is generally well at the time of birth and for the first few days of its life. The usual clinical presentation is that of toxic encephalopathy which includes vomiting, poor feeding, neurologic symptoms such as seizures, abnormal tone, lethargy and coma. The clinical outcome is improved when a diagnosis is made and treatment is instituted in the first ten days of life. In the older child or adolescent, variants OAs can present with loss of intellectual function, ataxia or other focal neurologic signs, Reye syndrome, recurrent ketoacidosis, or psychiatric symptoms. Issues pertaining to the diagnosis and management of OAs in India included lack of awareness of atypical and variable presentations, absence of reliable population data and involvement of multiple siblings in the same family due to consanguinity. The importance of careful family history taking and genetic counseling are emphasized [10].

The aim of therapy is to restore biochemical and physiologic homeostasis [11–13]. The treatments, though similar in principle, depend on the specific biochemical lesion and are based on the position of the metabolic block and the effects of the toxic compounds. Treatment strategies include dietary restriction of the precursor amino acids and use of adjunctive compounds to dispose of toxic metabolites or to increase the activity of deficient enzymes. Three steps are extremely important in emergency management (awaiting diagnosis) of organic acidurias. The first step is to obtain adequate samples (blood and urine) before treatment is initiated. The second step is to begin parenteral and/or enteral nutrition with a protein-free solution. The third step is to treat with cofactors. It is critical to carry out this strategy quickly with each suspect case of an inborn error of metabolism [14]. Specific management of organic acidurias includes pharmacological doses of L-carnitine and dietary protein restriction. Metabolic decompensation must also be treated vigorously to avoid permanent brain damage [15]. Toxin removal with a dialytic therapy or exchange transfusion may also be required.

Dietary therapy is the major basis of treatment in maple syrup urine disease. Other organic acidemias require dietary modification in addition to other modalities. Certain basic principles of dietary management should clearly be understood for proper management of

these disorders. Commercially available diets are very expensive. Modification of a routine Indian diet may be tried based on content of different nutrients but proper metabolic control may not be achieved [16].

Diagnosis and therapy should be aggressive, since prognosis of many disorders is related to early diagnosis and specific therapeutic measures. These include long term management with protein restriction, supplementation with special amino acid mixtures and carnitine. Continuous arteriovenous hemofiltration has turned out to be a very effective detoxification method during acute metabolic crisis of the newborn. Long term follow-up and therapy is very important for improving the outcome of the patients. Measurement of odd long chain fatty acids (OLCFA) in erythrocyte membranes has proven to be a good marker of metabolic control in children with disorders of the branched-chain amino acid metabolism [17].

## 2. Materials and methods

This study was conducted in 420 consecutive high-risk children from Amrita Institute of Medical Sciences with a suspicion of inborn errors of metabolism (IEM), especially organic acidemia between January, 2007 to December, 2008. During the study period 4899 patients were screened for IEM. An age limit of less than thirteen-years was an inclusion criteria. Informed consent was obtained prior to collecting laboratory samples. The study protocol conformed to the ethical guidelines of the "World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, in June 1964, as revised in Tokyo in 2004. The study was approved by the ethical review committee of the institution. As a part of the study, a fresh random urine sample (20 ml) was collected without preservatives and a blood specimen was collected with EDTA as the anticoagulant. Clinical features at presentation, age at diagnosis, sex, parental consanguinity, family history of IEM and unexpected deaths were recorded. Urine screening tests, thin layer chromatography, HPLC of plasma amino acids and urine organic acids were performed as previously reported [9].

### 2.1. Treatment and follow-up

#### 2.1.1. Maple syrup urine disease (MSUD)

The serum levels of branched-chain amino acids (BCAA) were normalized by limiting the dietary in-

take of BCAA while simultaneously providing adequate nutrition to maintain growth and development. Thiamine was administered at a dose of 50–300 mg per day for at least three weeks to determine thiamine responsiveness. The optimal intake of BCAA for MSUD patient was individualized and was usually 2/3 to 1/2 of the RDA for normal children. A treatment protocol for MSUD was designed to i) inhibit endogenous protein catabolism, ii) sustain protein synthesis, iii) prevent deficiencies of essential amino acids, and iv) maintain normal serum osmolarity. The effective treatment requires life-long dietary restriction and proper monitoring of branched-chain amino acids to avoid brain injury. Branched-chain ketoacid excretion and branched-chain amino acid levels were measured at the time of a routine clinic visit, allowing immediate diagnosis and treatment of metabolic derangements. Home monitoring of branched-chain ketoacids (BCKA) by DNPH test was recommended to the patient's parents or guardians. In classic MSUD, rapid leucine accumulation in brain displaces other essential amino acids resulting in neurotransmitter depletion and disruption of normal brain growth and development [18]. The three aspects of management of the metabolic crisis are, a) Rapid removal of the toxic metabolite by peritoneal dialysis, b) Nutritional support by BCAA free L-amino acids mixtures in combination with glucose, lipid, electrolytes and vitamins and c) The therapeutic approach to the treatment of catabolic stress is to stimulate anabolism with insulin [19].

#### 2.1.2. Methylmalonic acidemia (MMA)

Critically ill patients are stabilized by restoring volume status and acid-base balance; reducing or eliminating protein intake; providing increased calories via high glucose-containing fluids, and insulin to arrest catabolism. Proper monitoring of serum electrolytes, ammonia, arterial blood gases, and urine output is also required. Management of MMA includes a high-calorie diet restricted in amino acid precursors of methylmalonate; hydroxocobalamin intramuscular injections (1–2 mg daily for several days); carnitine supplementation; antibiotics such as neomycin or metronidazole to reduce propionate production from gut flora; gastrostomy tube placement as needed; and treatment of infections [19]. In cobalamin-responsive patients ( $N = 7$ ), hydroxocobalamin (1–14 mg per week i.m. or 5–20 mg per week orally) was used. All cobalamin-nonresponsive patients and all cobalamin-responsive patients ( $N = 15$ ) were supplemented with L-carnitine (50–100 mg per kg per day) and intestinal decontami-

nation by antibiotic therapy. MMA patients improved in alertness and appetite following brief metronidazole therapy.

#### 2.1.3. Propionic acidemia (PA)

A low protein diet (0.5–1.5 g per kg per day) which is selectively reduced in propionate precursors was given to the patients. Attacks of ketoacidosis should be vigorously treated by withdrawing all dietary protein and administering sodium bicarbonate parenterally, glucose is also required to avoid catabolism. Since propionyl CoA carboxylase requires biotin as coenzyme; certain patients could improve on biotin and L-carnitine supplements. Gut bacteria may contribute significantly to propionate production, specific antimicrobial therapy may reduce the total amount of propionate in serum and tissues. Metronidazole (10 mg per day) was used to reduce propionate levels.

#### 2.1.4. Isovaleric acidemia (IVA)

Treatment during acute episodes included a glucose infusion to provide calories and to reduce endogenous protein catabolism and a bicarbonate infusion to control acidosis. Treatment during recovery and remission consisted of restriction of natural dietary protein to age adjusted leucine requirements and supplementation of a leucine free medical food as a source of other amino acids. Glycine and carnitine were administered to remove isovaleryl CoA as nontoxic readily excreted products such as isovaleryl glycine and isovaleryl carnitine. One hundred and fifty mg per kg per day of glycine was administered when patients were on a stable leucine restricted diet, with the dose being increased to as much as 600 mg per kg per day when isovaleric acid level were elevated [19].

### 3. Results

We analyzed urine samples from 420 high-risk children and identified 45 (10.7%) children whose pattern of urine organic acid excretion was abnormal on two occasions. The OA's diagnosed were 15 cases of methylmalonic aciduria, 16 cases of propionic aciduria, 13 cases of MSUD, and one case of isovaleric aciduria. Among the high-risk cases, 179 (42.6%) were females and 241 (57.4%) were males. Out of the 15 cases with methylmalonic aciduria, seven cases had vitamin B12 deficiency. Figures 2 and 3 describe the clinical features and the major neurological abnormalities of patients with organic

Table 1  
Serial levels of branched-chain amino acids in patient 1 diagnosed with MSUD

	Valine ( $\mu\text{mol/L}$ ) Normal level < 255 $\mu\text{mol/L}$	Leucine ( $\mu\text{mol/L}$ ) Normal level < 150 $\mu\text{mol/L}$	Isoleucine ( $\mu\text{mol/L}$ ) Normal level < 80 $\mu\text{mol/L}$
11.04.2009	518	3020	437
25.07.2009	194	1708	350
15.03.2010	98	424	166
06.08.2010	135	479	69

acidemias respectively. Neurological abnormalities (60%) were found to be the most frequent presenting feature, followed by metabolic acidosis (42%), hyperammonemia (30%), feeding difficulties (26%), hypoglycemia (26%), vomiting (25%), skin rashes (20%), lactic acidemia (20%), hepatomegaly (16%), failure to thrive (16%), hypo/hyper/dystonia (12%), ketosis/ketonuria (8%) and dysmorphies (6%). Psychomotor delay/mental retardation (55.5%), seizures (40%), coma (15.5%), ataxia (11.1%), lethargy (24.6%), encephalitis/encephalopathy (6.6%), extra pyramidal syndrome (2.2%), visual deficiency (2.2%), speech delay (1.1%), hyperactivity (1.1%), were the major neurological signs. Figure 4 describes the major laboratory findings and Fig. 5 the Magnetic Resonance Image (MRI) abnormalities of these patients. Abnormal MRI findings were found in 11 patients. Macrocephaly (15.5%), cerebral atrophy (6.6%) and cerebral edema (2.2%) were the major MRI changes, among those detected to be abnormal.

The frequency of these disorders found in our population was similar to those found in other countries [20–25]. There was a family history of neonatal or infant death in 14 cases (31.1%), and first-degree consanguinity occurred in 16 (35%) cases.

Treatment regimens consisting of protein restriction (1.5–2.0 g protein per kg per day), sodium bicarbonate (to correct acidosis), L-carnitine, and vitamins were given for patients with MSUD, MMA, PA and IVA. Prompt diagnosis allowed specific treatment in the majority of patients with rapid improvement in symptomatology in 20 (44%) and moderate improvement in 10 (22%), indicating the importance of a prompt diagnosis. The patients who responded best to treatment were those affected with MMA and PA, whereas children affected by MSUD did not respond as well to therapy. There was a minimum of three years follow up for all patients. Both long term nutritional therapy and acute-phase management considerably reduced morbidity, mortality and length of hospitalization. A team work approach to management of the disease with parental understanding and cooperation was essential for successful metabolic control.

In this study, 15 patients (33.3%) died and there was a delay in the proper diagnosis in eight cases which prevented therapy from being instituted. When a diagnosis of OA is made late, the symptoms are often severe and outcome poor. The relatively high mortality of our patients may be possibly explained by the delay between age at presentation and age at diagnosis. Four patients with classic MSUD died due to acute complications precipitated by infections. Fatal cerebellar edema occurred in patients with acute metabolic crisis and in the recovery phase.

Patient 1 with MSUD presented at day 12 with metabolic acidosis, abnormal urine odor, ketonuria and hepatosplenomegaly. Blood and urine studies revealed the diagnosis of MSUD and aggressive treatment was started promptly including a branched-chain amino acid restricted diet and supplementation. The patient is now three years of age had no further exacerbations. The levels of leucine, isoleucine and valine all came down to normal levels (Table 1). In patient 2 with MSUD the diagnosis was delayed and hence treatment was not instituted and the baby died. Abnormal levels of BCAA are reported in Fig. 1.

Most surviving patients had a poor nutritional status with growth retardation or neurological impairment on longterm follow up. Patients with MMA and PA had cognitive developmental delays with 60% having and IQ less than 75. Most of these patients required special education.

#### 4. Discussion

The present report is a comprehensive study on the diagnosis and follow-up of common disorders of organic acid metabolism in high-risk patients over three years. Management for patients with OA requires that nurses increase their familiarity with metabolic genetics and develop a better understanding of proper medical and nursing management while research continues to determine the appropriate treatment and long-term management methods. Neonates affected with OAs require emergency diagnosis and treatment depending

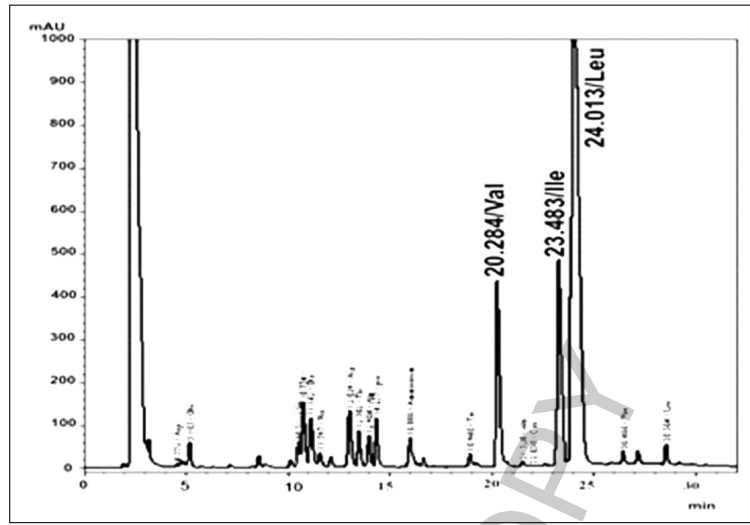


Fig. 1. Chromatogram of patient 2 (Leucine 2240  $\mu\text{mol/L}$ , Valine 411  $\mu\text{mol/L}$ , Isoleucine 180  $\mu\text{mol/L}$ ; Normal levels Leu < 150, Val < 255 and Ile < 80  $\mu\text{mol/L}$ ).

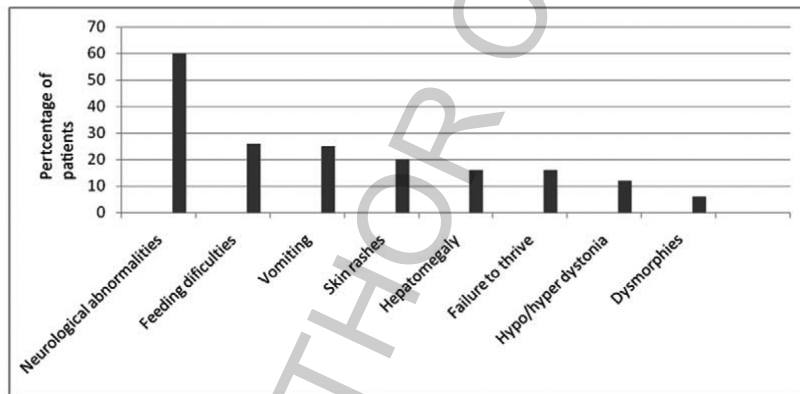


Fig. 2. Major clinical findings at diagnosis in patients with organic acidemias ( $N = 45$ ).

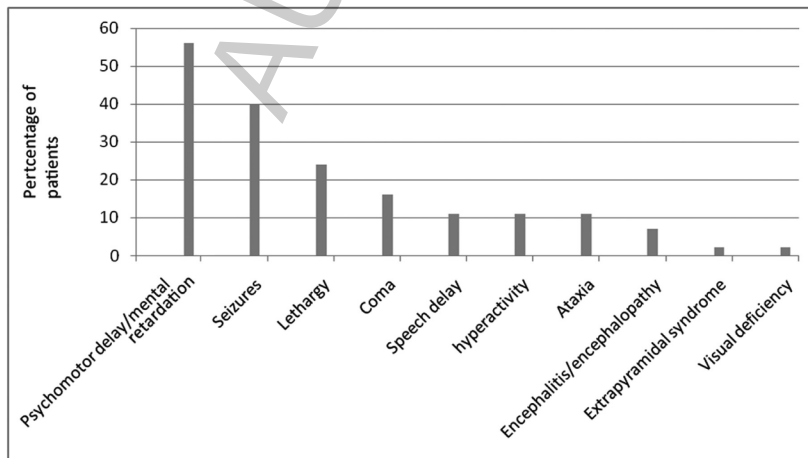


Fig. 3. Neurological abnormalities in patients with organic acidemias ( $N = 45$ ).

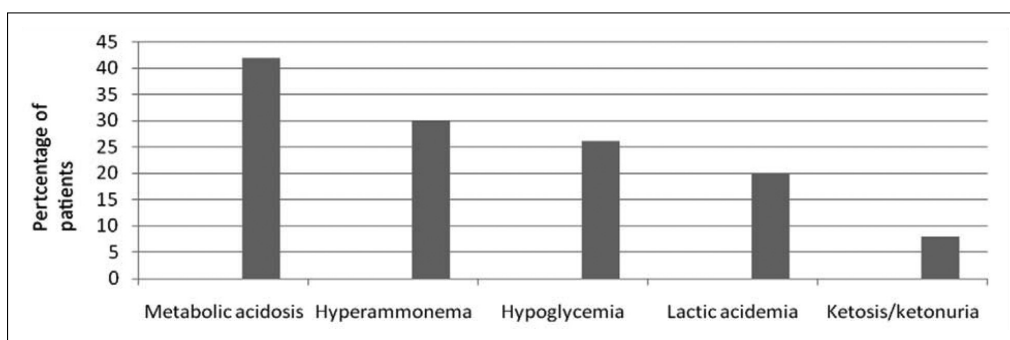


Fig. 4. Major laboratory findings at diagnosis in patients with organic acidemias ( $N = 45$ ).

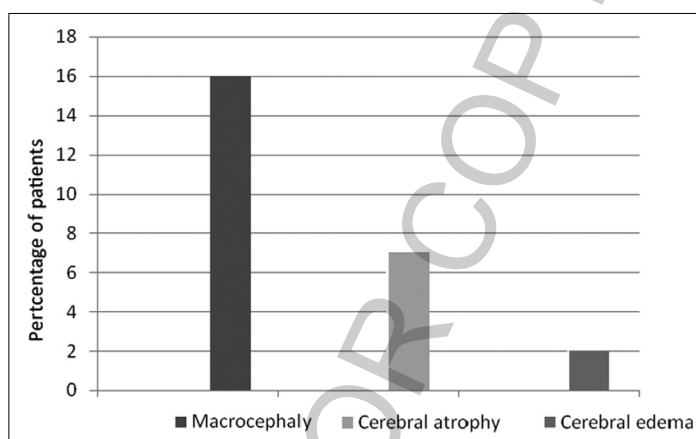


Fig. 5. MRI findings in patients with organic acidemias ( $N = 45$ ).

on the position of the metabolic block, and the effects of the toxic compounds. The majority of organic acidemias may be treated by limiting the source of or removing the toxic intermediary metabolites. Adjunctive compounds are used to dispose of toxic metabolites or to increase the activity of deficient enzymes. Frequent monitoring of growth, development, and biochemical parameters is essential. Decompensation caused by catabolic stress (e.g., from vomiting, diarrhea, febrile illness, and decreased oral intake) requires prompt and aggressive intervention. During this period we diagnosed 14 cases of urea cycle disorders also and they are not included in this paper.

The emergency treatment of organic acidurias in the neonate has two main goals: toxin removal and anabolism. Anabolism is always promoted by early diet therapy. The best method of toxin removal depends on the nature of the defect; peritoneal dialysis with exchange transfusions or multiple or prolonged exchange transfusions in MSUD and in PA, diuresis and exchange transfusions in MMA and glycine supplementation in

IVA. Vitamin supplementation (thiamine 20 mg, biotin 10 mg, B<sub>12</sub> 2 mg and riboflavin 100 mg) should be tried in all cases although the neonatal forms of these defects are very rarely vitamin responsive. Additional treatments such as carnitine or insulin may prove to be useful [26].

Adjunctive measures to dispose of toxic metabolites include use of thiamine to treat thiamine-responsive MSUD and hydroxocobalamin (but usually not cyanocobalamin) to treat methylmalonic acidemia. For the disorders of propionate metabolism, intermittent administration of non-absorbed antibiotics can be used to reduce the production of propionate by gut bacteria. Appropriate management does not guarantee a good outcome in organic acidemias, as individuals affected are medically fragile [27].

Rousson et al. recorded poor overall prognosis and the slow improvement in the outcome of OAs over a period of fifteen years. In MSUD, while early diagnosis and early management remain a basic requirement, intellectual development did not improve as much as

expected. In PA and MMA modern treatment does not prevent a fatal outcome in the classical neonatal forms. It should be also emphasized that in the rare cases where a coenzyme deficiency has been demonstrated, vitamin therapy is very often ineffective *in vivo* [28].

Outcome is enhanced by diagnosis of organic acidemias in the first ten days of life [11–13,29]. Even with appropriate management, individuals with organic acidemias have a greater risk of infection and a higher incidence of pancreatitis, which can be fatal [30]. Methylmalonic acidemia is associated with an increased frequency of renal failure and the cblC variant of methylmalonic acidemia is associated with pigmentary retinopathy and poor developmental outcome in the early-onset form [31–34].

Classic MSUD starts in the first week of life. It is characterized by convulsions, severe mental retardation, vomiting, acidosis, coma and death within the first year of life. Urine contains branched-chain keto acids, valine, leucine and isoleucine. Rothera's test is positive, but unlike in cases of ketoacidosis, even boiled and cooled urine will give the test. Diagnosis depends on enzyme analysis in cells. Diagnosis should be done prior to 1 week after birth, giving a diet low in branched-chain amino acids. A mild variant is called intermittent branched-chain ketonuria. This form of disease will respond to high doses of thiamine because the decarboxylation of the BCKA requires thiamine. Dietary treatment should continue throughout the patient's life. Snyderman et al. developed a synthetic formula in which the protein requirement was supplied in the form of a mixture of 18 amino acids based on the amino acid composition of the breast milk [35]. Carbohydrates, fats, minerals and vitamins were employed to supply the remaining nutrients. This diet made it possible to adjust the intake of each BCAA guided by the patient's plasma levels [19]. Brunetti-Pierri et al. [36] report successful use of phenylbutyrate in bringing down branched-chain amino acid levels in MSUD. Strauss et al. [37] has suggested novel therapeutic modalities in the management of MSUD based on their experience in treating 79 patients over 20 years.

The use of specific metabolic food (formulas) deficient in the particular precursor amino acids for each disorder is a critical part of management as it provides the essential amino acids in an otherwise protein-deficient diet. Adequate calories to inhibit catabolism are supplied as carbohydrate and fat and appropriate protein must be supplied to support anabolism. Total parenteral nutrition has been used during gastrointestinal illness or surgery but must be monitored with careful

attention to biochemical parameters. Hyperammonemia is a true neonatal emergency with high mortality and neurological complications in most survivors. It requires a rapid and vigorous treatment in order to normalize the ammonia concentration as fast as possible. N-carbamylglutamate, added to the classic treatment, quickly normalized plasma ammonia levels in patients and avoids the need of hemodialysis or peritoneal dialysis. A particularly sudden fall of ammonia was achieved in patients following the start of N-carbamylglutamate treatment [38]. A treatment approach with carglumic acid, the structural analogue of N-acetyl-glutamate, has been proposed to decrease high ammonia levels encountered in MMA and PA crises [39].

## 5. Conclusion

The study evaluates the epidemiology and effectiveness of treatment in organic acidemias in a large patient population in India. The results of the study indicate the importance of early diagnosis of organic acidemias in developing countries particularly in severely ill patients. Outcomes are improved with adequate treatment and proper follow-up of these patients. Availability of therapy for many of these disorders and treatment control of affected individuals by serial analysis of urine and blood is also important and this prevents further morbidity and reduces mortality rates.

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