

Organic Acidurias: An Updated Review

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Abstract Organic acidurias are an important class of inherited metabolic disorders arising due to defect in intermediary metabolic pathways of carbohydrate, amino acids and fatty acid oxidation. This review summarizes the current knowledge about the important organic acidurias in the Indian population. Specifically, diagnosis and principles of treatment of organic acidurias are covered. The salient features of common organic acidurias as well as their prevalence in various parts of the world are reviewed in some detail.

Keywords Organic acidurias · Maple syrup urine disease · Methylmalonic aciduria · Propionic aciduria · Isovaleric aciduria · Tandem mass spectrometry

Introduction

Organic acidurias (Organic acid disorders, OADs) are an important class of inherited metabolic disorders (IMD) arising due to defect in intermediary metabolic pathways of carbohydrate, amino acids and fatty acid oxidation. It leads to accumulation of organic acids in tissues and their subsequent excretion in urine [1]. It is now known that along with amino acidurias, organic acidurias form the most important class of IMD in high-risk population and among

severely-ill children [2–5]. Although individually rare, the conjunct frequency of OAD in preselected high-risk group may be up to 200 times higher than that identified in the general population [6]. Several studies have pointed out the main clinical and laboratory characteristics that lead to the suspicion of inborn error of metabolism especially OAD in critically ill children [7, 8].

In Western countries, aminoacidurias, especially phenylketonuria, are the most common IMD. PKU is very common in USA, China, Taiwan, Turkey, Ireland, Italy, UK, British Columbia and other parts of Europe, whereas it is rare in India [9–15]. However organic acidurias are comparatively rare in UK, USA and other Western countries [13]. In our previous paper, we have showed that organic acidurias (OAD) are quite common in our part of the world [16]. There are also other studies which report a higher prevalence of OAD in India (Please see details mentioned below). OADs were seen in some Western countries, for example in North Carolina, as reported by Frazier et al. [17].

There is an accelerating demographic switch from communicable diseases to genetic disorders. India is a country with a very high birth-rate and the number of children born with IMD is also very high making it a problem of tremendous importance. In one of the earlier studies in India, biochemical screening of 4400 cases of mental retardation revealed that 5.75% (256 cases) were due to various inherited metabolic disorders [18, 19]. There is no sex difference reported in the incidence of IMD [20]. Age of clinical presentation varies from child to child and the form of presentation is also variable according to age. It also depends upon the degree of accumulation of toxic substances before the metabolic block. Environmental factors may trigger the onset and severity of disease. e.g. diet, intercurrent infections, fasting, drugs etc.

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Common Organic Acidurias: Basic Considerations

Important organic acidurias (See Table 1) include propionic acidurias (PA), methyl malonic acidurias (MMA), branched chain organic acidurias (which includes isovaleric aciduria), glutaric aciduria Type I, multiple carboxylase deficiency (which is due to deficiency of 4 biotin dependent enzymes) etc. Rarer OADs are summarized in Table 3. Maple syrup urine disease (MSUD) is due to elevated branched chain amino acids (valine, leucine and isoleucine) and is considered as branched chain aminoaciduria; it is also referred to as organic aciduria. Propionic aciduria, methyl malonic aciduria, MSUD and isovaleric aciduria are sometimes referred to as classical organic acidurias. All organic acidurias are inherited as autosomal recessive conditions.

Diagnosis of Organic Acidurias

Organic acidurias generally present with hyperammonemia and high anion gap metabolic acidosis. Additional biochemical features include hypoglycemia, ketonuria etc. The major clinical features are developmental delay/mental retardation, seizures, lethargy, coma, hypotonia, vomiting, failure to thrive, hepatomegaly, respiratory distress, and cardiac dysfunction. The symptoms worsen in the absence of supporting care and can proceed to coma/death. A diagnosis in the first 24–48 h is vital and can prevent chronic sequel including physical/mental retardation. The prevalence of organic acidurias is high in India, a rapidly

developing country with a high birth rate and relatively frequent occurrence of consanguineous marriages.

There is a clinically well demarcated sub-group of OAD known as ‘cerebral’ OADs where neurological manifestations are predominant or sometimes even exclusive [21].

Analysis of organic acids in urine is of paramount importance for the diagnosis of organic acidurias. More than 100 different organic acids are excreted in urine in these conditions (See Table 2). Confirmatory diagnosis of organic acidurias require expensive instruments like HPLC, GC/MS or tandem mass spectrometry and enzyme assays/DNA analysis. High-field proton NMR is a promising technique for the diagnosis of OAD. Screening tests like DNPH test (Di nitro phenyl hydrazine test) and thin layer chromatography are also employed when these are not available, but they do not confirm the diagnosis. A flow chart for the laboratory diagnosis of common organic acidurias is given in Fig. 1.

Treatment

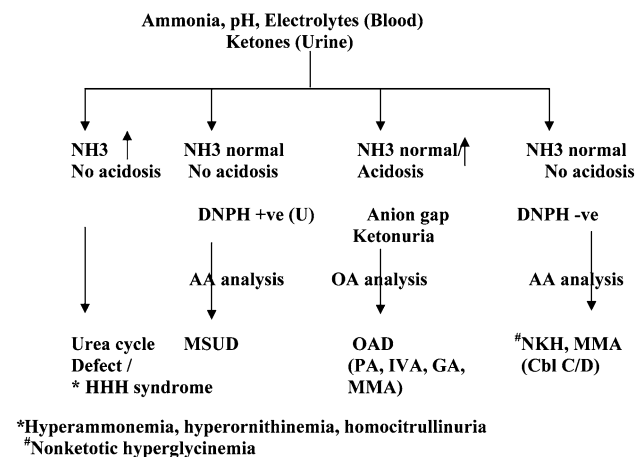
Most of the common organic acidurias can be effectively treated; therefore diagnosis becomes much more important. Amino acid based formulas provide energy, nitrogen, vitamins and minerals which can promote anabolism and growth. Goal of nutritional therapy is to provide all essential nutrients to promote physical and mental development [23]. Synthetic amino acid based formulas should provide approximately 50% of daily protein requirement. At the same time, the offending dietary precursor amino

Table 1 Common organic acidurias

Organic aciduria	Enzyme deficiency	Salient clinical features	Incidence
Methyl malonic acidurias	Methyl malonyl CoA mutase	Neonatal or infantile metabolic ketoacidosis, failure to thrive, developmental retardation, megaloblastic anemia and macrocytosis	1:50,000 (USA)
Propionic aciduria	Propionyl CoA carboxylase	Severe metabolic ketoacidosis in neonatal period, elevated 3 hydroxy propionate, methyl citrate, tiglyl Glycine, and unusual ketone bodies in urine	1:3000 (Saudi Arabia)–1:35,000 (USA)
Isovaleric aciduria	Isovaleryl CoA dehydrogenase	Acute episode of severe metabolic acidosis and moderate ketosis with vomiting, coma and death, odor of sweaty feet. Chronic, intermittent form with episodes of metabolic acidosis	1:250,000 (USA)
Maple syrup urine disease (MSUD)	Branched chain ketoacid dehydrogenase complex (BCKAD complex)	Burnt sugar odor to urine, convulsions, severe mental retardation, vomiting, acidosis, coma and death within the first year of life (Classic form)	1:100,000 (Higher prevalence in certain populations)
Glutaric aciduria Type I	Glutaryl CoA dehydrogenase	Dystonia, dyskinesia, excretion of glutaric and 3 hydroxy glutaric acids in urine, neuronal degeneration	1:75,000 (USA)
Multiple carboxylase deficiency	Acetyl CoA carboxylase, propionyl CoA carboxylase, 3 methyl crotonyl CoA carboxylase, pyruvate carboxylase (Biotin dependent enzymes)	Ketoacidosis, diffuse erythematous skin rash, alopecia, seizures, hypotonia, developmental retardation	1:100,000 (USA)

Table 2 Organic acids excreted in urine in different organic acidurias [22]

Organic acidurias	Organic acids excreted in urine
Maple syrup urine disease	2 hydroxy 3 methyl valerate, 2 hydroxy isocaproate, 2 hydroxy isovalerate, 2 keto 3 methyl valerate, 2 ketoisocaproate, 2 ketoisovalerate
Methyl malonic aciduria	2 methyl glutaconate, 3 hydroxy propionate, 3 keto 2 methyl butyrate, 3 keto 2 methyl valerate, methyl citrate, methyl malonate, 3 hydroxy butyrate, propionyl glycine, lactate and pyruvate
Propionic acidurias	2 methyl glutaconate, 3 hydroxy 2 ethyl glutarate, 3 hydroxy propionate, 3 keto 2 methyl butyrate, 3 keto 2 methyl valerate, methyl citrate, tiglyl glycine, 3 hydroxy butyrate, propionyl glycine, lactate and pyruvate
Isovaleric acidurias	3 hydroxy isovalerate, 4 hydroxy isovalerate, isovaleryl glycine, 3 hydroxy butyrate, isovaleryl carnitine, isovaleryl glucuronide, lactate and pyruvate
Glutaric aciduria Type I	Glutaconate, 3 hydroxy glutarate, glutarate, 3 hydroxy butyrate, 2 hydroxy butyrate, 2 keto glutarate
Multiple carboxylase deficiency	3 hydroxy butyrate, methyl citrate, 3 methyl crotonyl glycine, 3 hydroxy propionate, tiglyl glycine, lactate and pyruvate

**Fig. 1** Flow chart for diagnosis of organic acidurias

acid has to be restricted. Fasting also has to be avoided [24]. Secondary carnitine deficiency is common and hence L-Carnitine (as well as biotin) is also given [25]. Metronidazole is given to reduce endogenous gut propionate. Treatment of the acute case includes dialysis, correction of fluid and electrolyte imbalances, correction of acidosis as well as maintenance of cerebral function with adequate perfusion, oxygen and glucose as the case demands. Selective detoxificants like glycine and carnitine are given in some cases.

Sometimes, patients with OAD present in a critical condition, with eventual death. Even when the treatment is not available, the identification of OAD is important for the genetic counseling and for making the pre-natal diagnosis possible in a future gestation [26].

Indian Studies

In the multicentric Indian Council of Medical Research (ICMR) study, 4.9% of the genetic causes of mental retardation were due

to metabolic disorders. Screening of mentally retarded children in India revealed that 0.5–2.4% of children had amino acid disorders [27]. In a multi-centric study by ICMR in 1991 on 1314 children, 5% were found to have a metabolic defect. In a hospital based study in India biochemical screening of 4400 cases of mental retardation revealed that 256 (5.75%) cases were due to metabolic disorders [18, 19, 28].

Other studies from South India reported the presence of disorders of amino acid metabolism among 0.66–2.4% of children with mental retardation [27, 29–31]. Kaur et al. [32] screened 2560 cases for IMD and 62 positive cases were reported. The frequency pattern of the various amino acid disorders in North India was found to be remarkably different from that observed in Western countries.

Swarna et al. [33] detected 41 cases of IMD among 4500 children screened from Andhra Pradesh. Uma et al. [34] also reported a new entity, threoninaemia from Andhra Pradesh.

Screening is a basic tool for clinically suspected cases of inborn metabolic disease by a simple economical and effective technique like paper chromatography, TLC and some biochemical tests. However, it is not reasonable to make firm decision on the basis of screening test. HPLC is an acceptable technique to analyze and quantification of amino acids, organic acids and metabolites from biological fluids [35]. It is speculated that late suspicion was an obstacle for early diagnosis of OA [36].

Nagaraja et al. [37] identified 47 cases of organic acidurias and 61 cases of amino acidurias in a total of 113 children with IMD. Study conducted by Mamta et al. [38] on the incidence of organic acidurias in India found out that out of 365 patients with IEM diagnosed over a period of 20 years, organic aciduria accounted for 27% of cases (MMA 18%, PA 9.2%).

In our own study published in the previous issue of IJCB, we had screened 420 high-risk children and identified 45 children (10.7%) with organic acidurias. These included 16 cases of propionic aciduria, 15 cases of methyl

malonic aciduria, 13 cases of MSUD and 1 case of isovaleric aciduria. Out of the 13 MSUD patients diagnosed 7 were of classic form [16].

International Studies

Global surveys conservatively estimate the occurrence of inherited metabolic disorders in the range of three to four per thousand live born infants [39]. The World Health Organization (WHO) estimated amino acid disorders to account for approximately 10% of profoundly retarded children.

In one review of cases of IEM diagnosed in British Columbia (a predominantly Caucasian population) between 1969 and 1996, organic acidurias were found at 3.7 per 100,000 [14]. In another review of cases of IEM diagnosed in the West Midlands of the United Kingdom (where approximately 11 percent of the population is from black and ethnic minority groups) during 1999 to 2003 found that the incidence of organic acidemias was 12.6 per 100,000 [40].

A study by Satwani et al. [41] from Pakistan found 10 cases of organic acidemias in a total of 62 children screened. There were a total of 16 cases of IMD in this study which also include lactic acidosis and OTC deficiency.

Survival and quality of life for organic acidemias (OA) is improving due to early diagnosis with newborn screening and vigorous management as reported by Filiano et al. [42], Glass et al. [43] and Dionisi et al. [44].

In contrast, in countries without newborn screening, patients may not be diagnosed, are misdiagnosed or diagnosed late with permanent sequels, as the key factor determining diagnosis and subsequent prognosis is physician's acumen. Hans et al. [45] studied 3070 children suspected with IMD in China and diagnosed 212 cases with IMD including 92 amino acidurias and 107 organic acidurias.

Study conducted by Tan et al. [46] revealed the incidences of organic acidurias is 32.3%. Among the organic acidurias, 24.4% were glutaric aciduria, 19.6% propionic aciduria, 17.1% methylmalonic aciduria, 12.2% glutaric aciduria Type I and 2.4% were alkaptonuria. The overall detection of organic acidurias revealed by Daisuke Hori et al. [47] was 3.1% comprising mainly MMA and PA i.e., the predominance of MMA over PA was seen in Asian children [47]. MMA is the most common organic acidemias in many studies [47, 48].

A recent study by Moammar et al. (2010) [49] spanning 25 years between 1983 and 2008 in Saudi Arabia, organic acidurias was identified as the most common IMD. They identified 48 OAD cases out of a total of 248 cases of IMD (19%). Niu et al. [12] identified MSUD, MMA and GA-1 as the commonest OADs in Taiwan in a study spanning

2000–2009. Wajner et al. [50] identified 218 cases of OADs between 1994 and 2008 in Brazil.

Maple Syrup Urine Disease

Classic MSUD is the most common form of MSUD with symptoms developing in neonates aged 4–7 days, depending on feeding regimen. In cases of nonclassic MSUD, onset may be later. In the original family with MSUD reported by Menkes, four sibs died in the newborn period. MSUD with a neonatal onset of encephalopathy is now considered as the classic form, and represents the most severe and most common form of the disease. The levels of branched chain amino acids (BCAA), particularly leucine are greatly increased in the blood, cerebrospinal fluid (CSF) and urine. In all patients with the classic form of MSUD, there was more than 10 fold increase in leucine levels and significant elevation in valine and isoleucine. In classic MSUD 50% or more of the branched chain ketoacid (BCKA) are derived from leucine. A reduction in glutamate, glutamine and γ amino butyric acid (GABA) was noted in these patients. Free amino acids in the brain from a 25-day-old infant with untreated MSUD showed marked elevation of BCAA and significant reduction of glutamate, glutamine and GABA [51]. Mutations are known in BCKDHA, BCKDHB, DBT and DLD genes.

Propionic Acidurias

The first documented case of propionic aciduria was described in 1961 by Childs et al. They described a male infant with episodic metabolic ketoacidosis, protein intolerance, and very high levels of plasma glycine. Propionic acidurias are in reality a heterogeneous group of disorders and may result from massive propionate accumulation in blood, impaired propionate oxidation, defective carboxylase enzyme in fibroblasts or a combination of these factors. It can also be a feature of multiple carboxylase deficiency. The original patient described by Childs died at age 7, but a sister of the patient lived a relatively normal life till age 15. Propionic acidurias have also been identified in adults. Relapse is precipitated by dietary factors, especially branched chain amino acids, threonine and methionine, and infections. Butanone, a 4-carbon ketone which is a byproduct of isoleucine metabolism, has been reported uniquely in PA [51]. A large number of mutations in *pccA* and *pccB* genes have been described.

Methyl Malonic Acidurias

Methyl malonic aciduria as a separate entity was known from 1967 from the separate reports by Oberholzer et al. and Stokke et al. They described critically ill children with

Table 3 Rare organic acidurias [51]

Organic acidurias	Enzyme deficiency	Clinical features
Alkaptonuria	Homogentisic acid oxidase	Benign; ochronosis and arthritis late in life
Isolated 3 methyl crotonyl CoA carboxylase deficiency	3 methyl crotonyl CoA carboxylase	Acute metabolic acidosis, hypoglycemia, carnitine deficiency
3 methyl glutaconic acidurias	3 methyl glutaconyl CoA hydratase	Mild form—Mild acidosis, speech retardation; Second form—Dilated cardiomyopathy, neutropenia, growth retardation; Third form—Progressive neurologic deterioration, optic atrophy, hearing loss, movement disorders
HMG CoA lyase deficiency	HMG CoA lyase	Hypoglycemia, metabolic acidosis, no ketosis, hyperammonemia, vomiting, hypotonia, coma and death
Mevalonic aciduria	Mevalonate kinase	Dysmorphic features, anemia, hepatosplenomegaly, gastroenteropathy, failure to thrive, severe developmental delay
2 keto adipic aciduria	2 keto adipic dehydrogenase	Benign; no clinical effects
Glutathione synthetase deficiency	Glutathione synthetase	Severe metabolic acidosis, CNS dysfunction, massive urinary excretion of 5-oxoproline

profound metabolic acidosis and developmental retardation who accumulated large amounts of methylmalonate in blood and urine. Many reports of methylmalonic acidurias followed. As with PA, methylmalonic acidurias are heterogeneous groups of diseases and distinct genetic mutations in *mut*, *cbIA* and *cbIB* genes are known. Methylmalonic acidurias are also associated with homocystinuria due to defects in *cbIC*, *cbID* and *cbIF* genes [51] as well as nutritional deficiency of Vitamin B12.

Isovaleric Acidurias

Initial report of isovaleric acidurias was by Tanaka et al. in 1966. Isovaleric aciduria is the first OAD discovered by GC/MS analysis of metabolites. Two varieties are described, the acute neonatal type and the chronic intermittent type. One of the characteristic features of isovaleric aciduria is the presence of “sweaty foot” odour to urine due to elevated isovaleric acid. Normal development occurs with leucine restriction and administration of carnitine/glycine [51].

Glutaric Aciduria Type I

The condition was first described in 1975. Glutaric acid concentrations are elevated in all tissues, including liver, brain, kidney, eyes, muscles etc. Treatment by restriction of glutarigenic amino acids, lysine, tryptophan and hydroxyl lysine, and supplementation with L- carnitine and riboflavin has been successful. Laboratory features are present only during the acute phase of the disease [51].

Multiple Carboxylase Deficiency

The first case of multiple carboxylase deficiency was described by Gompertz et al. in 1971. There was a dramatic improvement

in symptoms by the administration of biotin. The disease could be due to two distinct diseases of biotin metabolism. The first group is due to holocarboxylase deficiency, where there are distinct clinical features including the characteristic skin rash and/or alopecia. The second larger group is due to biotinidase deficiency, but both groups respond dramatically to biotin therapy. Urinary metabolite identification is very important to prevent misdiagnosis as well as therapeutic purposes [51]. “Tomcat urine” smell is characteristic.

Other Organic Acidurias

There are a large number of rarer OAD entities; some of the important ones are summarized in Table 3. Most of them are very rare and in some cases, only a few cases have been reported.

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