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Brief communication (Original)

Clinical and laboratory findings and outcomes of classic organic acidurias in children from north-eastern Thailand: a 5-year retrospective study

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Background: Classic organic acidurias, including isovaleric aciduria (IVA), propionic aciduria (PA) and methylmalonic aciduria (MMA), are rare inherited metabolic disorders caused by deficiencies of enzymes in catabolic pathways.
Objective: To report clinical and laboratory findings and outcomes of classic organic acidurias in children north-eastern Thailand and their outcomes over the past 5 years.
Methods: During 2010–2014, twelve patients were identified as having classic organic acidurias confirmed by urine organic acids analysis.
Results: Classic organic acidurias were identified as follows; 5 patients with IVA, 4 patients with PA, and 3 patients with MMA. Ten patients had neonatal-onset and 9 cases were diagnosed during the neonatal period with clinical signs and symptoms of altered consciousness, poor feeding, respiratory distress, abnormal odor, and shock. Common laboratory findings included metabolic acidosis with an elevated anion gap, hyperammonemia, hypocalcemia, and cytopenia. Ammonia levels could be extremely high, especially in PA. Three patients with neonatal-onset of acidurias died during their first catabolic crisis, and one patient died later. One patient with MMA had exfoliative erythema after excessive dietary restriction. Four of 8 surviving patients had IVA and had better neurodevelopmental outcomes than those with PA and MMA.
Conclusion: Neonatal-onset classic organic acidurias are more common than late-onset cases and usually mimic neonatal sepsis. Laboratory findings that include hematologic abnormalities should raise suspicion. Close monitoring of biochemical parameters, growth and neurodevelopmental outcomes is necessary in a long-term follow-up.

Keywords: Isovaleric aciduria, methylmalonic aciduria, neutropenia, organic acidurias, propionic aciduria

Organic acidurias are a group of rare inherited metabolic disorders producing defects in metabolism of branched-chain amino acids followed by excretion of nonamino organic acids in urine. The defects are due to deficiencies of enzymes in catabolic pathways that result in accumulation of organic acids causing toxicity in various organ systems. The classic organic acidurias are propionic aciduria (PA), methylmalonic aciduria (MMA) and isovaleric aciduria (IVA) [1]. They can be diagnosed by urine organic acid analysis using gas chromatography-mass spectrometry (GC/MS). Clinical presentation may be during the neonatal period, or later. Neonatal-onset classic organic acidurias usually present as severe metabolic acidosis and encephalopathy shortly after birth. Typical signs and symptoms are respiratory distress, generalized hypotonia, feeding refusal, vomiting, lethargy, seizure, and coma. The metabolic derangements include metabolic acidosis with elevated anion gap, ketosis, and hyperammonemia. Moreover, hematological involvement including neutropenia, thrombocytopenia, anemia, or pancytopenia is also

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found. Thus, the clinical presentation usually mimics neonatal sepsis, often easily leading to misdiagnosis. Neonates without appropriate treatment usually die within a few days or develop severe encephalopathy. Some children have late-onset disorder, after the neonatal period. Clinical presentation of this group is highly variable, ranging from acute intermittent attacks to chronically progressive symptoms. An acute intermittent attack is usually triggered by catabolic stress such as infection, starvation or high protein intake, while chronic symptoms include failure to thrive, recurrent vomiting, global delayed development, and neurological deterioration [1]. Making a diagnosis of classic organic acidurias requires a high index of suspicion and well-equipped laboratories. An expanded newborn screening program using tandem mass spectrometry (MS/MS) for inborn errors of metabolism (IEM) is not available in most hospitals in Thailand. Therefore, knowledge of the clinical presentation of organic acidurias is important for pediatricians to make a diagnosis. A clinical genetics unit was established in Srinagarind Hospital in 2010. It is a referral center for inborn errors of metabolism in north-eastern Thailand. The authors report clinical presentation of classic organic acidurias in children from north-eastern Thai and their outcomes over the past 5 years.

Materials and methods

The Ethics Committee in Human Research, Khon Kaen University approved this retrospective descriptive study (approval No. HE581407). The population comprised patients at Srinagarind Hospital who were diagnosed as having organic aciduria between January 1st, 2010 and December 31st, 2014. Diagnosis was confirmed in 12 patients by urine organic acid analysis using GC/MS. The authors obtained basic information from their medical records including sex, gestational age, birth weight, and history of parental consanguinity and affected siblings. Clinical presentations including age of onset, clinical signs and symptoms, and physical examination are described. Laboratory findings documented include complete blood count, blood chemistry, ammonia level, lactate level, MS/MS analysis, and urine organic acid profiles. Long-term outcomes consisting of follow-up time, number of metabolic crises, complications, and neurodevelopmental outcomes are reported. Descriptive statistics were used in this study. Written informed consent for publication of the clinical photograph (**Figure 1**) was obtained from the legal guardian of this patient.

Results

There were 6 male and 6 female patients. The diagnoses were as follows: IVA in 5 patients (42%), PA in 4 patients (33%), and MMA in 3 patients (25%). The mean gestational age at birth was 37.4 weeks (ranging from 36 to 39 weeks) and birth weight was 2,852.8 grams (ranging from 2,480 to 3,288 grams). The mean maternal age was 29.5 years (ranging from 18 to 39 years). Four patients had a family history of neonatal or infant death in siblings. Only 2 patients had consanguineous parents. Ten patients had neonatal-onset (range, 2 to 13 days): mean and median ages of onset were 4.9 and 3.5 days after birth, respectively. The remaining 2 patients had late-onset of symptoms (2.6 and 9 months after birth) and their diagnoses were MMA or PA. In the neonatal-onset group, the mean and median ages at diagnosis were 20.5 and 14 days respectively (range, 3 to 89 days). All patients were referred from provincial hospitals. Definitive diagnoses were established by urine organic acid analysis using GC/MS in all patients. Initial MS/MS analysis of dried blood spots from 3 patients returned abnormal results: elevated levels of propionyl carnitine, C3, consistent with MMA and PA, in 2 cases, and elevated isovaleryl carnitine, C5, consistent with IVA in the third. Nine cases (75%) were diagnosed at the first episode of metabolic crisis. Three patients (25%) had previously experienced recurrent infection, such as pneumonia, meningitis or clinical sepsis, before the definitive diagnosis. In 2 cases, definitive diagnoses were reached at the fourth admission, and in one case at the seventh admission. Clinical data for all patients are shown in **Table 1** and clinical findings at the time of diagnosis are in **Table 2**. All patients had an elevated anion gap metabolic acidosis with serum bicarbonate ranging from 1.8 to 17.4 mEq/L (mean 10.7 mEq/L). Hyperammonemia was found in 7 patients with neonatal-onset ranging 209–1,617 μmol/L and mean of 742.3 μmol/L (normal range 21–95 μmol/L) and 2 patients with late-onset (103.1 and 194 μmol/L). Hypocalcemia was found in 6 patients with levels ranging between 6.1 and 7.8 mg/dL (mean 6.9 mg/dL). Hematological abnormalities were found in 10 patients (83%) including anemia, neutropenia, thrombocytopenia, and pancytopenia. Lactic acidosis was found in 5 patients (42%) and ketonuria in one. Laboratory findings at the time of diagnosis are also shown in **Table 2**.

Table 1. Clinical data of 12 patients with classical organic acidurias

No	Diagnosis	Sex	Parental consanguinity	Birth weight (grams)	Age of onset	Age at diagnosis	MS/MS	Age at last follow-up (months)	Metabolic crisis after diagnosis	Outcome
1	IVA	f	–	2640	4 d	8 d	NA	19 d	0	Death
2	IVA	f	–	2480	9 d	23 d	NA	2 y 8 mo	0	Normal
3	IVA	f	–	2960	13 d	19 d	NA	1 y 1 mo	0	Normal
4	IVA	m	–	2795	2 d	19 d	+	1 y 2 mo	0	Normal
5	IVA	m	–	3120	5 d	22 d	NA	4 y 2 mo	0	Normal
6	MMA	f	–	2780	2 d	2 mo 29 d	+	1 y	4	DD
7	MMA	m	–	2700	6 d	9 d	NA	11 d	0	Death
8	MMA	m	–	2530	9 mo	1 y 9 mo	NA	2 y 11 mo	1	DD
9	PA	f	+	3288	3 d	5 d	+	8 mo	4	DD
10	PA	f	–	3140	3 d	8 d	NA	3 mo	3	Death
11	PA	m	+	3000	2 d	3 d	NA	8 d	0	Death
12	PA	m	–	2800	2 mo 17 d	7 mo 2 d	NA	1 y 3 mo	3	DD

IVA, isovaleric aciduria; MMA, methylmalonic aciduria; PA, propionic aciduria; f, female; m, male; MS/MS, tandem mass spectrometry analysis; NA, data not available; d, day(s); mo, month(s); y, year(s); DD, delayed development

Table 2. Clinical and laboratory findings of classical organic acidurias

	Total n = 12	Neonatal onset (<1 month) n = 10	Late onset (>1 month) n = 2
Clinical findings			
Alteration of consciousness	10	10	–
Poor feeding	6	6	–
Respiratory distress	6	5	1
Abnormal odor	5	5	–
Shock	5	5	–
Hypotonia	4	4	–
Seizure	4	4	–
Family history	4	3	1
Hepatomegaly	3	2	1
Recurrent vomiting	2	2	–
Developmental delay	2	1*	1
Failure to thrive	2	–	2
Recurrent infection	2	–	2
Laboratory findings			
Metabolic acidosis with elevated anion gap (>16 mEq/L)	12	10	2
Hyperammonemia			
Neonate >150 µmol/L			
After neonatal period >100 µmol/L	9	7	2
Hypocalcemia (<8 mg/dL)	**6**	**6**	0
Lactic acidosis (>19 mg/dL)	5	4	1
Anemia (neonate; hemoglobin (Hb) <14.5 g/dL) (after 6 months; Hb <11 g/dL)	9	8**	1
Neutropenia (ANC <1000 cell/mm^3)	6	5**	1
Thrombocytopenia (platelet <100,000 cell/mm^3)	3	2**	1
Ketonuria	1	1	0

*Patient had neonatal onset, but was diagnosed beyond the neonatal period. **Two patients had pancytopenia

Table 3. Frequency of classic organic acidurias in high-risk patients among different populations

Country (study time)	Number of classic organic acidurias diagnosed	MMA n (%)	PA n (%)	IVA n (%)
Germany (18 years) [2]	83	34 (41)	33 (40)	16 (19)
China (5 years) [3]	77	58 (75)	13 (17)	6 (8)
France (20 years) [4]	66	31 (47)	21 (32)	14 (21)
Malaysia (6 years) [5]	62	41 (66)	8 (13)	13 (21)
Syria (5 years) [6]	60	40 (66)	16 (27)	4 (7)
Brazil (15 years) [7]	59	34 (58)	18 (31)	7 (12)
Japan (8 years) [8]	47	34 (72)	12 (26)	1 (2)
Egypt (5 years) [9]	42	23 (55)	11 (26)	8 (19)
Singapore (13 years) [10]	15	7 (47)	8 (53)	0
Lebanon (12 years) [11]	11	5 (46)	2 (18)	4 (36)
Thailand (3 years) [12]	8	3 (38)	2 (25)	3 (38)
North-eastern Thailand (5 years; present study)	12	3 (25)	4 (33)	5 (42)

IVA, isovaleric aciduria; MMA, methylmalonic aciduria; PA, propionic aciduria

Three neonatal patients died at the time of first admission and one patient with PA died after the third episode of catabolic crisis when she was 3 months old. The remaining 8 patients survived with regular follow-up at the genetics clinic. All surviving patients were treated by dietary restriction of precursor amino acids supplemented with specific vitamin cofactors and L-carnitine. Four patients with IVA experienced no catabolic crises after treatment. The remaining MMA and PA patients suffered from several episodes of catabolic crises provoked by infections. One patient with MMA had exfoliative erythema over her entire body and extremities, especially flexural areas (**Figure 1**) after excessive protein restriction. Her levels of the following amino acids were low; leucine, 19.71 μmol/L (normal range, 42.09–133.19 μmol/L); methionine, 9.19 μmol/L (normal range, 13.49–56.97 μmol/l); tyrosine, 17.23 μmol/L (normal range, 30.51–139.04 μmol/L); alanine, 145.62 μmol/L (normal range, 149.89–565.00 μmol/L). Her skin lesion was completely resolved within 2 weeks after correction of amino acid deficiencies. Four patients (33%), all with IVA, achieved normal developmental milestones.

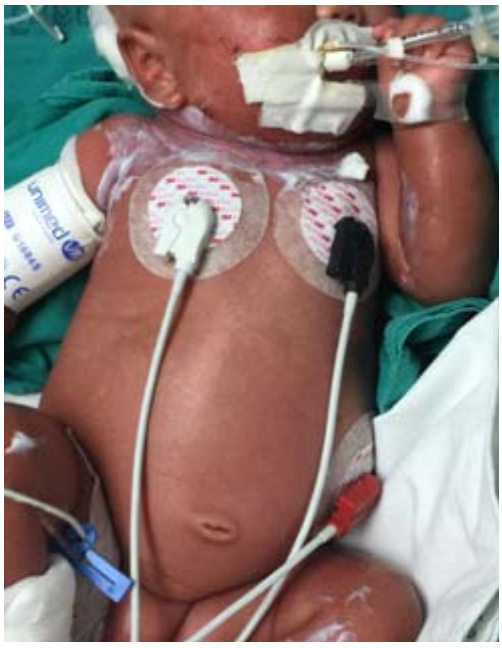

Figure 1. Exfoliative erythema on trunk and extremities, especially flexural areas, in a patient with methylmalonic aciduria who had excessive dietary restriction (published with written permission from the guardian).

Discussion

Twelve patients with organic acidurias were seen over a period of 5 years. MMA is the most common classic organic aciduria reported among different populations, followed by PA or IVA [2-12]. However, the present study found that IVA is the most common form in the north-eastern Thai population. The frequency of classic organic acidurias in high-risk patients in different populations is compared to the present study as shown in **Table 3**. Individuals with IVA usually have a characteristic abnormal odor, while those with other acidurias do not. Making a diagnosis of IVA is therefore less difficult than other types of classic organic acidurias. This may be one reason for the higher frequency of IVA in the present study. Another explanation could be a founder effect in the studied population. However, an estimation of the true prevalence of each type of organic acidurias requires study of a larger population.

Clinical presentation of neonatal-onset classic organic acidurias usually mimics clinical sepsis, making a correct diagnosis difficult. Thus, a high index of suspicion is necessary to diagnose classic organic acidurias. Moreover, classic organic acidurias are autosomal-recessive inherited metabolic disorders, so a family history of parental consanguinity and of affected siblings are important clues for diagnosing these diseases. Nevertheless, the proportion of patients with parental consanguinity in this study was lower than in previous studies. For example, from 57.1% to 88% of patients with organic acidurias [6, 9, 10] and 53.8% of patients with MMA [13] had consanguineous parents. By contrast, the proportion of patients with a family history of affected siblings in this study was higher than in a previous report (15.9%) [8]. Therefore, whether the patient has a suspected family history or not, organic acidurias should be considered in an individual who has clinical features of sepsis, but does not respond to antibiotic treatment.

Although neonatal-onset cases made up the majority, some were diagnosed after the neonatal period [1, 6, 8, 12, 14]. Previous reports from Thailand revealed that fewer than half of all cases could be diagnosed during the neonatal period [12, 13, 15, 16]. Late diagnosis certainly results in poorer neurodevelopmental outcomes in the long-term [14]. Therefore, this is important evidence to support the value of expanded newborn screening for organic acidurias using MS/MS. Such screening is highly sensitive and specific [17] and has been used for early detection of IEM in many countries [18]. However, it is not yet a national policy in Thailand because of its cost and limited information about the epidemiology of IEM [19].

An individual with classic organic aciduria during a critical catabolic crisis has many abnormal laboratory findings. Metabolic acidosis with elevated anion gap, ketosis, and hyperammonemia are common [6-8, 11, 20]. During such a crisis, hyperammonemia can reach extremely high levels, such as found in individuals with urea-cycle defects. It has been proposed that suppression of *N*-acetylglutamate synthetase in the urea cycle occurs because of excess of some organic acids, especially propionyl-coenzyme A (CoA), methylmalonyl-CoA, tiglyl-CoA, and isovaleryl-CoA [21]. In this study, the severity of hyperammonemia is quite different in each type. Ammonia levels in individuals with PA can reach over 1,000 μmol/L, while individuals with MMA and IVA have lower ammonia levels. Other metabolic derangements were liver dysfunction, hypoglycemia, hyperglycemia, hypocalcemia, and lactic acidosis [6, 7, 11].

Hematologic abnormalities are also found in classic organic acidurias including neutropenia, anemia, thrombocytopenia, or pancytopenia. Reversible inhibition of proliferation of bone marrow stem cells Because of excess organic acids plays an important role in hematopoietic dysfunction in infants with organic acidurias [22-24]. Although neutropenia can be found in all types of classic organic acidurias, IVA and PA are associated with more severe neutropenia than MMA [23]. In this study, hematologic abnormalities were found in all types of classic organic acidurias. Anemia was the most common hematologic presentation at the first metabolic crisis followed by neutropenia and thrombocytopenia. Pancytopenia was found in 2 patients in this study. Severity of cytopenia is known to be related to blood levels of organic acids and usually recovery occurs within 2 weeks of correction of acidosis [25]. Blood transfusion and supportive treatment are required. The relationship between neutropenia and morbidity/mortality in this study remains unclear. Of 6 patients who had isolated neutropenia or pancytopenia, 2 received granulocyte-colony stimulating factor (G-CSF) for treatment of neutropenia. Their absolute neutrophil count was increased in a week. Although there is no recommendation for the treatment of neutropenia-complicated organic acidurias by G-CSF at this moment, it may be useful in a patient who is suffering

from an acute catabolic crisis when neonatal infection cannot be excluded.

Long-term outcomes of classic organic acidurias depend on their severity, early diagnosis and treatment. Patients with neonatal-onset usually have more severe clinical presentation than those with late-onset that results in poorer clinical outcome [1, 8]. Moreover, mortality rate of patient with PA is higher than MMA and IVA [6, 8]. In this study, 3 of 12 patients died in the first neonatal catabolic crisis, and 1 patient died during the fourth episode of catabolic crisis when she was 3 months old. All the surviving patients were treated with dietary management and L-carnitine. Patients with IVA received glycine, and patients with MMA received methylcobalamin in addition. Four patients with IVA did not experience any catabolic crises after treatment. Those with MMA and PA suffered from several episodes of catabolic crisis. Infection was the most frequent condition increasing catabolism in this study. Other conditions such as fasting, high protein intake, injury or surgery can also provoke a catabolic crisis. Each catabolic crisis results in a worsening of psychomotor development; therefore, close monitoring of growth, nutritional and metabolic status is highly recommended to prevent decompensated catabolic crisis and psychomotor deterioration. Close monitoring of plasma amino acids is very necessary in long-term dietary management because the patients have higher risk of essential amino acid deficiency. In this study, one patient with MMA was deficient in several amino acids after excessive protein restriction. She had exfoliative erythema over her entire body, especially flexural areas. This clinical presentation can be found in individuals with deficiencies of essential amino acids, essential fatty acids, or zinc [26, 27].

From 8 surviving patients, 4 had normal developmental milestones. This was better than reported previously from Thailand because of early diagnosis [13, 15, 16]. In this study, neurological outcome of PA and MMA was more severe than IVA and not different to that previously reported [1, 14]. All patients with normal developmental milestone had IVA. There appear to be better clinical outcomes in IVA relative to other classic organic acidurias in the present study. All surviving patients with IVA were diagnosed during the neonatal period and treatment started early. The remaining surviving patients with PA and MMA were diagnosed and treated later, resulting in worse neurodevelopmental outcomes.

Conclusion

The present study reveals additional knowledge about clinical presentations and laboratory findings of organic acidurias in children from the north-eastern of Thailand. Neonatal-onset is more common and usually mimics neonatal sepsis. Newborn screening by MS/MS is very helpful for early diagnosis and treatment, consequently leading to improved clinical outcomes. Abnormal laboratory findings including hematological abnormalities should be considered. Close monitoring of biochemical parameters, growth and neurodevelopmental outcome is necessary in a long-term follow-up.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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