J Community Genet (2017) 8:9–15
DOI 10.1007/s12687-016-0281-5

ORIGINAL ARTICLE

Challenges in the management of patients with maple syrup urine disease diagnosed by newborn screening in a developing country

Leniza G. De Castro-Hamoy[1,2] · **Mary Anne D. Chiong**[1,2] · **Sylvia C. Estrada**[1,2] · **Cynthia P. Cordero**[2]

Received: 24 June 2016 / Accepted: 23 September 2016 / Published online: 6 October 2016

Abstract Maple syrup urine disease (MSUD) is a rare inborn error of metabolism resulting from a deficiency in the branched-chain alpha-ketoacid dehydrogenase complex. MSUD has been reported to be the most common inborn error of metabolism in the Philippines. We described all patients with maple syrup urine disease patients diagnosed through newborn screening during its first 2 years of implementation and the challenges encountered during their medical management. There were 24 patients diagnosed with maple syrup urine disease for the 2-year period. All patients needed hospital admission. The most common complication during hospital admission was infection, needing intravenous antibiotics which were given to 21 of the patients. Out of the 24 diagnosed, 16 patients are alive, while eight have died. Several neurologic and non-neurologic complications have been observed during the follow-up of the patients. The common challenges of MSUD management in a low-resource setting identified in this study were late diagnosis, lack of access to metabolic specialists and medical supplies, nosocomial septicemia, and protein deficiency. Aside from early properly timed collection, improvement in other logistical concerns will also help in earlier diagnosis. Mechanisms of transfer of critically ill patients must be improved. Hospitals in difficult-to-reach areas must be equipped to handle critical metabolic cases when transfers are not possible. Newborn screening has been proven to improve outcome in patients with MSUD but the success of the program in preventing disability is also dependent on improvements in other aspects of healthcare.

Keywords Newborn screening · Maple syrup urine disease

✉ Leniza G. De Castro-Hamoy
ldhamoy@post.upm.edu.ph

[1] Department of Pediatrics, Section of Clinical Genetics, University of the Philippines—Philippine General Hospital, Manila, Philippines

[2] Institute of Human Genetics—National Institutes of Health, University of the Philippines Manila, Manila Pedro Gil Street, Malate, 1000, P.O. Box 297, Manila, Philippines

Introduction

Maple syrup urine disease (MSUD) is a rare inborn error of metabolism resulting from a deficiency in the branched-chain alpha-ketoacid dehydrogenase complex. This enzyme deficiency causes the accumulation of the branched chain amino acids leucine, isoleucine, and valine (Chuang & Shih, 2001).

Patients with MSUD appear normal at birth but may present with burnt sugar or maple syrup odor of the cerumen and urine within the 12th hour of life. Symptoms that may develop in the first week of life include vomiting, lethargy, poor suck, and irritability. Patients may develop seizures, and the progressive encephalopathy may lead to coma and death if left untreated (Chuang & Shih, 2001). The golden period for the initiation of treatment before irreversible neurologic damage occurs is between 7 and 10 days (Strauss, 2006).

Worldwide, the estimated incidence of MSUD is 1:185,000 live births (Chuang & Shih, 2001; Nellis, et al., 2003). However, MSUD has been reported to be the most common inborn error of metabolism in the country. Based on the latest data from the Newborn Screening Reference Center in the Philippines, 20 neonates out of 1,104,823 screened have been confirmed to have the disorder translating to a cumulative incidence of 1:55,241 (NSRC, 2014). This may be a result of a founder mutation reported in the Filipino population wherein a novel deletion creating a new terminal exon of the dihydrolipoyl transacylase gene was found in 8

out of 13 families, with 5 of them being homozygous for the mutation (Silao et al. 2004).

Being the most common IEM, maple syrup urine disease (MSUD) was added to the newborn screening panel in the last quarter of 2012 (Tayag, 2012). Capistrano-Estrada reported that the number of confirmed MSUD cases (15) was almost twice as high as the number of phenylketonuria/hyperphenylalaninemia (9) confirmed cases as noted in the course of second-tier testing for confirmation of elevated phenylalanine by thin layer chromatography. This confirmed that MSUD existed at a significantly higher prevalence in the Philippine newborn population, hence its inclusion in the newborn screening panel was proposed and subsequently implemented (Capistrano-Estrada & Jomento, 2009). Lee et al. (2008) described the two groups of Filipino MSUD patients diagnosed clinically prior to newborn screening, the first group involving 26 patients diagnosed from 1992 to 1998 and the second one composed of 21 patients diagnosed from 1999 to 2004. Both groups had late diagnosis overall, and majority underwent peritoneal dialysis and acquired septicemia as a complication. The mortality rates were 27 and 21 %, respectively. Developmental outcome in both series showed neurologic and developmental delays. Thus, this study clearly reemphasized that MSUD should be a part of a newborn screening. From 1992, there have been more than 120 cases diagnosed in our hospital (Metabolic Registry, Institute of Human Genetics, National Institutes of Health, UP Manila).

MSUD was included in the newborn screening with the goal to diagnose patients early and prevent the neurologic and other medical complications. However, the outcomes of patients with maple syrup urine disease not only depend on early diagnosis and treatment alone but also on subsequent metabolic control and associated comorbidities such as infections, seizures, and nutritional imbalance. Metabolic stability is achieved by reversing the catabolic state by providing adequate calories, fluids, and branched-chain amino acid-free protein (parenteral or in conjunction with enteral feeds). Some patients may need dialysis for removal of branched chain amino acids and toxic metabolites. Supplementation of isoleucine and valine is also important to help lower elevated plasma leucine. Management also includes close monitoring of plasma amino acids (Fraziera et al. 2014).

Due to financial and logistical issues in the country, the ideal management outlined above is not possible for the patients. Majority of medical care needs incur significant out of pocket costs. Isoleucine and valine supplements were not readily available in the Philippines due to health product import regulations. The cost of the products once imported is also not affordable for the patients. Plasma amino acid analysis for monitoring of branched chain amino acid levels is possible, but the cost for the test is not affordable for most patients. Peritoneal dialysis is available but is limited to the major tertiary referral centers. Hemofiltration for neonatal patients is currently not an option anywhere in the country due to lack of equipment, facilities, and expertise.

This study describes all patients with maple syrup urine disease patients diagnosed through newborn screening during its first 2 years of implementation and the challenges encountered during their medical management.

Methodology

This study involved the review of the medical records of all patients diagnosed with MSUD by newborn screening in the Philippines from its initiation in July 2012 to June 2014 and subsequently referred to either the Clinical Genetics Section of the Department of Pediatrics, Philippine General Hospital for patients in Luzon or to the geneticists in the Visayas and Mindanao regions. The Clinical Genetics section of the UP-PGH is the only institution in the country where metabolic geneticists with expertise in handling patients with inborn errors of metabolism were trained or are presently affiliated with.

Newborn screening was performed on dried blood spot samples to check for leucine levels using Alisei Kit (enzymatic/colorimetric testing) performed in any of the five newborn screening centers in the country. During the period of this study, the recommended screening was between 48 and 72 h of life. This recommendation has been subsequently adjusted to 24 h of life from July 2014. A "recall" mechanism is triggered by a positive result (leucine level >300 umol/L). Follow-up nurses are assigned to call the family, newborn screening facility, or patient's doctor for an urgent repeat test. If the level is above 700 umol/L, an immediate referral to a metabolic specialist is made.

The following data were obtained: sex, place (province or city) of birth, age at newborn screening, age at onset of symptoms, age at diagnosis, family history of MSUD, initial clinical manifestations, initial diagnosis, dried blood spot leucine levels on diagnosis, management, complications, and outcome (alive or dead, as well as presence or absence and degree of neurodevelopmental morbidity). The presence or absence of seizures was based on EEG findings.

Statistical analysis

Descriptive statistics such as mean, proportion, and percentages were used to describe the general data and socio-demographic profile of the subjects. The records of the cases were independently reviewed by three metabolic physicians, and challenges in the management were identified. Disagreements were discussed until consensus was obtained.

Ethical considerations

Records were anonymized during data compilation and analysis in order to uphold privacy and confidentiality of the patients. The primary investigator assigned a code for each patient, and the key to the code was password-protected.

The study was approved by the UP Manila Research Ethics Board of the Philippine General Hospital.

Results

General disease characteristics

There were 24 patients diagnosed with maple syrup urine disease by newborn screening for the 2-year period of July 2012–June 2014. There were 12 females and 12 males. The mean age at newborn screening is 4 days. The earliest that the screening was done at day 1 and the latest at 11 days. The mean age at referral was 9.5 days, while mean age at onset of symptoms was 6.8 days (Table 1).

Five of the patients had a positive family history; the siblings of these patients who were either diagnosed or presented with similar symptoms had died. All patients were born to non-consanguineous couples, except for one wherein consanguinity could neither be confirmed nor denied. All were of Filipino descent except for two patients who each had a parent with an American and an African descent.

All patients needed hospital admission. Patients in Luzon (20 out of the 24 patients) were admitted at the Philippine General Hospital, while patients from Visayas (4 patients) were admitted in local hospitals. There was no positive screen for MSUD in Mindanao during this time period. Upon admission, majority of the patients (16) already had the initial diagnosis of MSUD from newborn screening, while 8 of the patients were initially diagnosed with sepsis. The most common initial sign or symptom was fair or poor suck, which was seen in 58 % of the patients, followed by increased sleeping time, jerky movement, and poor activity. While sweet-smelling urine was seen in three patients, other symptoms which included irritability, lethargy, incessant crying, and high-pitched cry were non-specific and were easily interpreted as signs and symptoms of infection (Table 2).

Disease complications and outcomes

The most common complication during hospital admission was either community-acquired or nosocomial infection needing intravenous antibiotic therapy (Table 3). Majority of patients also needed either non-invasive or invasive ventilatory support during the initial hospital admission. Around 30 % of patients had to undergo peritoneal dialysis.

At the time of writing, 16 patients are alive, while 8 have died. The most common cause of death was septic shock. The probable cause of death recorded for each of the patients is seen in Table 4.

Several neurologic and non-neurologic complications have been observed during the follow-up of the patients. The most notable complications were neurologic, particularly seizures and developmental delay. However, a couple of nutritional complications, particularly anemia (hemoglobin level less than 100 g/L) and protein deficiency (leucine less than 100 umol/L) were noted as well (Table 5).

Based on the data obtained from this review, risk factors were tabulated against the outcomes and several observations could be made (Table 6). Patients with poor metabolic control, late diagnosis, and had nosocomial infections tend to have poor outcomes (either moderate/severe developmental delay or death) while those who maintain good control were diagnosed early and did not need antibiotics tend to have no or mild developmental delays.

Identified challenges in the diagnosis and management of patients

Late diagnosis

Despite the recommendation to have the newborn screening done on the first 24–48 h of life, 10 patients had newborn screening done beyond this period. On review of the cases, the reasons encountered for delayed screening were newborn screening not being requested at the onset and facilities having only specific days set for newborn screening collection.

Table 1 Characteristics of the 24 maple syrup urine disease cases, 2012–2014

Characteristic	*N*	Mean (SD)	Range
Age at NBS, days[a]	24	4.0 (3)	1–11
Age at referral, days	24	9.5 (3.2)	5–17
Time from NBS to referral, days	24	5.4 (3)	2–14
Age at onset of first symptom, days	24	6.8 (2.5)	2–13
Initial leucine level, mmol/L	24	1067.0 (529)	312–2330
Length of hospital stay, first admission, days	24	17.0 (11.1)	3–47

[a] Day of birth counted as day 0

Table 2 Initial presenting signs and symptoms of the 24 patients

Sign/symptom	*n*	%
Fair/poor suck	14	58
Increased sleeping time	9	37
Jerky movement/seizures	4	17
Poor activity	4	17
Sweet smelling urine	3	12
Irritability	2	8
Lethargy	2	8
Incessant crying	1	4
High-pitched cry	1	4

Two of the patients were already being treated for neonatal sepsis before newborn screening was eventually performed. At this time, they were already 10 and 11 days old. The results revealed markedly elevated leucine levels.

The time from initial newborn screening to referral to metabolic specialist was an average of 5.4 days (s.d. 3, range 2–14). On review of records, it was found that the problems encountered leading to such delays included delayed sending and transit from the newborn screening facility to the newborn screening center and specimens arriving at the newborn screening center on a weekend or holiday. In four patients, initial leucine levels fell in the "slightly elevated" range only and did not yet warrant a metabolic referral based on the existing protocol. However, repeat samples which were run for these four patients had "significantly elevated" levels, with the results being released beyond the first week of life. The four patients were already symptomatic on referral.

Majority of referrals (16/24 or 67 %) for the screen-positive cases were received beyond the golden period of 7 days. Furthermore, in 75 % (6/8) of mortalities in this subset, newborn screening diagnosis was established beyond the first week of life.

In this study, it was noted that patients who were diagnosed late (beyond 7 days) also have a higher percentage of delays and death, while patients who had no need for ventilator support were less prone to have poor outcomes (Table 6).

Table 3 Complications during hospital admission

Complications	*N*	%
Community-acquired or nosocomial infection needing IV antibiotics	21	88
Ventilatory support	15	62
Nosocomial infection	15	62
Peritoneal dialysis	7	30

Table 4 Causes of death

Cause of death	*N*
Septic shock	3
Disseminated intravascular coagulation	1
Respiratory failure	1
Multiple organ dysfunction syndrome	1
Pulmonary edema	1

Lack of access to metabolic specialists and medical supplies

Another common concern upon diagnosis was the inadequacy of the primary medical facility to attend to the needs of the patients, as well as the difficulty in transferring them to a well-equipped center. Specific problems identified in this area were financial constraints and distance and geographical concerns.

One patient was born in an island province around 200 km away from our institution, accessible only by small planes or sea travel. As the hospitals in the area were incapable of managing a critical metabolic patient, he was subsequently referred and had to be transferred to our institution by boat. He was discharged well after 17 days of admission. Another patient was also born in a remote island province, 400 km away from our institution. She presented with seizures and was initially being managed at a local hospital for neonatal sepsis. Upon release of the newborn screening result on the tenth day of life, patient's immediate transfer to a specialty hospital was not logistically possible. Ideal management could not be given due to lack of access to medications and equipment. She demised due to septic shock.

Table 5 Morbidities noted

Morbidity	*N*	%
Neurologic		
Developmental delay		
None	3	12
Mild	6	25
Moderate	4	17
Severe	3	12
Died prior to evaluation	8	33
Seizures[a]		
No seizures	8	33
With seizures	12	50
Died without formal evaluation for seizures	4	17
Nuritional		
Anemia	9	37
Protein deficiency	4	17

[a] Based on EEG findings

Table 6 Risk factors and outcomes

Risk factors	No/mild developmental delay	Moderate/severe developmental delay	Died	Total
Poor metabolic control (mean levels >600)	2 (14 %)	5 (36 %)	7 (50 %)	14
Good metabolic control (mean levels ≤600)	7 (70 %)	2 (20 %)	1 (10 %)	10
Late diagnosis (>7 days)	5 (31 %)	5 (31 %)	6 (38 %)	16
Prompt diagnosis (7 days or less)	4 (50 %)	2 (25 %)	2 (25 %)	8
Peritoneal dialysis	1 (14 %)	3 (43 %)	3 (43 %)	7
No peritoneal dialysis	8 (47 %)	4 (23 %)	5 (30 %)	17
Ventilatory support	2 (13 %)	7 (47 %)	6 (40 %)	15
No ventilatory support	7 (78 %)	0	2 (22 %)	9
IV antibiotics	6 (29 %)	7 (33 %)	8 (38 %)	21
No antibiotics	3 (100 %)	0	0	3
Nosocomial infection	3 (20 %)	6 (40 %)	6 (40 %)	15
No nosocomial infections	6 (67 %)	1 (11 %)	2 (22 %)	9
Anemia	4 (44 %)	3 (33 %)	2 (22 %)	9
No anemia	5 (33 %)	4 (27 %)	6 (40 %)	15
Protein deficiency	2 (50 %)	0	2 (50 %)	4
No protein deficiency	7 (35 %)	7 (35 %)	6 (30 %)	20

Nosocomial septicemia in a tertiary hospital

Majority of the patients incurred nosocomial infections during their initial treatment, which complicated the management of their metabolic crisis and prolonged their hospital stay. One patient had recurrent bacterial infections from different pathogens and even fungal sepsis, necessitating treatment with four different broad-spectrum antibiotics and an antifungal before she was eventually discharged after more than a month of hospital stay.

Protein deficiency and anemia

Four patients in this subset presented with protein deficiency as a consequence of protein-restricted dietary management.

In one case, the patient had to be re-admitted to the hospital because of acrodermatitis enteropathica with secondary infection leading to sepsis. The mother had given her more branched-chain amino acid-free formula and less protein-containing formula than was recommended. After being given nutritional supplements (particularly zinc) and increased protein intake, the patient improved and was discharged. However, the patient was re-admitted for the same symptoms of skin flaking with crusting and weeping lesions and immediately succumbed to septic shock. Two other patients were found to have acrodermatitis enteropathica on their follow-up consultations, and protein deficiency was documented by dried blood spot leucine levels as low as 21 and 18.13 umol/L, respectively. Both patients were managed by gradually increasing the amount of natural protein in the diet, oral antibiotics and zinc supplements, and application of emollients and topic antifungals.

In this study, nine patients developed anemia in the course of their treatment, despite the branched chain amino acid-free milk containing adequate iron to meet the daily recommended intake (BCAD 1. 2014).

Discussion

In the 24 patients presented above, several challenges and difficulties were noted that led to late diagnosis and inadequate management. Late diagnosis has already been reported as a problem in the management of MSUD in the Philippines even prior to newborn screening. Prior to the advent of newborn screening, this was due to clinicians having a low index of suspicion because of non-specificity of symptoms and lack of awareness about the disease (Lee, et al., 2008). With newborn screening now, geographic factors and physical distance or difficulty in transportation and delivery of newborn screening cards may contribute to the delays in diagnosis and consequently management in the country.

The problem of late diagnosis has been seen in other Asian countries as well. In Thailand, Pangkanon et al (2008) reported a median age of diagnosis of 55 days, with the delay being caused by many factors including screening for MSUD's not being an integral part of the newborn screening in Thailand, lack of awareness concerning inborn error in metabolism, and difficulty in diagnosis due to lack of available laboratory testing in up-country hospitals. In Malaysia, delayed diagnosis was also noted to be common in MSUD patients, which was attributed to lack of awareness among physicians and lack of diagnostic facilities (Yunus, Kamaludin, Mamat, Choy, & Ngu, 2012).

The importance of early diagnosis for MSUD cannot be over emphasized, as this allows earlier treatment of symptoms and prevention of complications. The age at diagnosis and the subsequent course are the most important determinants. Treatment initiated before 7 to 10 days of age gives the best results, and only a few patients treated after 14 days of age achieve normal intellect, while those diagnosed at a younger age usually present with a milder neonatal course (Chuang & Shih, 2001). Simon et al (2006) reported a favorable effect of early diagnosis by newborn screening on the prevention of neonatal encephalopathic crisis and faster detoxification of classical MSUD patients in Germany and Austria. In their study comparing neonates screened by newborn screening (who were diagnosed at 7 ± 1.3 days) compared to those who were diagnosed clinically (diagnosed at 12.1 ± 1.7 days), the mean day of life when the plasma leucine concentration fell below 1000 μ1.7/L was 9.5 ± 4.0 days for the screened patients, whereas in the 10 clinically diagnosed patients, this occurred significantly later (14.9 ± 3.0 days, $p = 0.010$). In the same study, they also concluded that NBS alone is not sufficient to ameliorate the neonatal course of the disease because the advantage of early screening may be lost with inefficient clinical management. Thus, prompt referral to a specialty institution that can provide proper management for patients with MSUD is essential.

Nosocomial sepsis is a general problem in our tertiary institution affecting 9 % of patients mainly due to the overcrowding of the wards, and lack of hospital supplies, manpower, and equipment (Philippine General Hospital Section of Infectious Disease and Tropical Medicine Nosocomial Infection Annual Report 2013). Being the only institution in the country with metabolic specialists and geneticists, most diagnosed patients are being referred to us. In the cases we have presented, the nosocomial rate was almost seven times higher. Much has been said in literature about the need to monitor for and promptly treat hospital-acquired infections due to the risk of catabolic crisis. Generally, patients who are admitted in metabolic crisis who require ventilation, central venous catheters, and invasive procedures such as peritoneal dialysis are also at a higher risk for hospital-acquired bacterial or fungal infections (Strauss, 2006; Rajendran, et al., 2016).

Iatrogenic essential amino acid deficiency with several manifestations including acrodermatitis have been reported by Puzenat et al (2004).Zinc, selenium, and omega-3 fatty acid deficiencies were also noted to be common among patients with classic MSUD (Strauss & Morton, 2003). Strauss et al. (2010) reported a 3-year-old MSUD patient with acrodermatitis enteropathica secondary to zinc deficiency and identified asymptomatic zinc deficiency among their other patients as well. It is recommended to provide milk formula enriched with vitamins, micronutrients, and essential fatty acids to prevent the malnutrition. Regular follow-up and monitoring of compliance to the diet is essential in order to prevent complications. In our experience, we have found that it is also critical to explain to the parents the complications of providing less regular milk than what is prescribed. Because of financial incapacity, some families tend to give more of the free special formula and less of the regular formula. Lack of education may also cause poor understanding of the disease and the subsequent complications of incorrect treatment regimen and poor dietary compliance. One of the most significant contributory factors to this problem is that isoleucine and valine supplements were neither accessible nor affordable during this time period.

A study in Turkey described anemia in 46 children with different inborn errors of metabolism. In those patients, 4 had MSUD with ages ranging from 2 to 3 months. Out of the 4 patients, they diagnosed 3 to have anemia of chronic disease (based on decreased plasma iron concentrations, decreased total iron binding capacity, decreased transferrin saturation, and normal or increased concentration of ferritin) and 1 with iron deficiency anemia (based on hemoglobin concentrations below 10 g/dl, transferrin saturation level below 12 %, and ferritin below 12 ng/ml). The accumulation of toxic metabolites and the generation of free radicals were identified as a possible mechanism for their observation (Tavil, et al., 2006).

Finally, it was also observed that patients with poor metabolic control tend to have a higher risk of developmental delay and death. Many factors such as lack of education and unavailability of protein-free options may affect dietary compliance. Subsequent control of leucine levels after the initial crisis is crucial to the attainment of good neurologic outcomes. Chronic mild to moderate elevations of the BCAA/BCKA have been associated with dysmyelinating changes in brain by imaging studies thus demonstrating the importance of good metabolic control (Chuang and Shih 2001).

Conclusion and recommendation

We have presented the profile of the 24 patients diagnosed with maple syrup urine disease by newborn screening during the first 2 years of implementation. The common challenges of MSUD diagnosis and management in a developing country were identified—late diagnosis, lack of access to metabolic specialists and medical supplies, nosocomial septicemia, and nutritional complications particularly protein deficiency and anemia.

Newborn screening alone is not enough to guarantee a favorable outcome in patients with MSUD. Screening recommendations such as the ideal day of life when the screening should be done and other guidelines need to be emphasized and implemented up to the grassroots level. Aside from early properly timed collection, improvement in other logistical concerns such as an efficient system of sending and delivery of samples will also help in earlier diagnosis.

Education and training of health professionals have to be done in order to reinforce the importance of newborn screening and to raise the index of suspicion for a metabolic problem. Mechanisms of transfer of critically ill patients, albeit challenging in our setting due to geographical concerns, must be improved. Hospitals in difficult-to-reach areas must be equipped to handle critical metabolic cases when transfers are not possible.

Follow-up mechanisms likewise have to be strengthened. Policy-makers need to be involved in the planning because the national health care system needs to address the logistics and accessibility of medical personnel, nutritional treatment options, and other medical supplies such as intravenous lipids and broad-spectrum antibiotics. The Rare Disease Act, which was signed in March 2016, specifies for the formulation of a comprehensive and sustainable health system for orphan or rare disorders (Republic Act No. 10747. 2016). Together with other supporting legislation, this will help assure the access to and sustainability of special milk and supplements needed by patients with rare inborn errors of metabolism such as MSUD.

Newborn screening has been proven to improve outcome in patients diagnosed to have MSUD, but the success of the newborn screening program in preventing disability is also dependent on improvements in other aspects of healthcare.

A cohort or case–control study is recommended in order to determine the statistical significance of the findings we have observed in our study. A larger sample size will also strengthen the statistical power and allow us to draw stronger conclusions.

Compliance of ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. For this type of study, formal consent is not required. The study was approved by the UP Manila Research Ethics Board of the Philippine General Hospital.

Conflict of interest The authors declare that they have no conflict of interest.

References

BCAD 1. (2014) Retrieved from Mead Johnson nutrition., https://www.meadjohnson.com/pediatrics/us-en/product-information/products/metabolics/bcad-1

Capistrano-Estrada S, Jomento CM (2009) Detection of maple syrup urine disease on newborn screening second tier testing for phenylketonuria. Acta Medica Philippina 43(2):26–28

Chuang D, Shih V (2001) Maple syrup urine disease (branched chain ketoaciduria). In: Scriver C, Beaudet AL, Sly W, Valle D (eds) The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, pp 1971–2006

Fraziera DM, Allgeierb C, Homerc C, Marriageb B, Ogatad B, Rohre F, Singhh R (2014) Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab 112(3):210–217. doi:10.1016/j.ymgme.2014.05.006

Lee J, Chiong MA, Estrada SC, Cutiongco-Dela Paz EM, Silao CL, Padilla CD (2008) Maple syrup urine disease (MSUD)—clinical profile of 47 Filipino patients. J Inherit Metab Dis 31(Suppl 2): S281–S285. doi:10.1007/s10545-008-0859-0

Nellis M, Kasinski A, Carlson M, Allen R, Schaefer AM, Schwartz EM, Danner DJ (2003) Relationship of causative genetic mutations in maple syrup urine disease with their clinical expression. Mol Genet Metab 80(1-2):189–195

NSRC (2014) Prevalence of disorders among Filipino newborns (1996-2013)., Retrieved from Newborn Screening Reference Center, http://www.newbornscreening.ph/images/stories/ResourcesPrevalence/prevalence-2013.pdf

Pangkanon S, Charoensiriwatana W, Sangtawesin V (2008) Maple syrup urine disease in Thai infants. J Med Assoc Thai 91(Suppl 3):S41–S44

Puzenat E, Durbise E, Fromentin C, Humbert P, Aubin F (2004) Iatrogenic acrodermatitis enteropathica-like syndrome in leucinosis. Ann Dermatol Venereol 131(8-9):801–804

Rajendran R, Sherry L, Deshpande A, Johnson EM, Hanson MF, Williams C, Munro CA, Jones BL, Ramage G (2016) A prospective surveillance study of candidaemia: epidemiology, risk factors, antifungal treatment and outcome in hospitalized patients. Front Microbiol 7:915. doi:10.3389/fmicb.2016.00915

Republic Act No. 10747. (2016) Retrieved from GovPH official gazette., http://www.gov.ph/2016/03/03/republic-act-no-10747/

Silao C, Padilla CD, Matsuo M (2004) A novel deletion creating a new terminal exon of the dihydrolipoyl trans-acylase gene is a founder mutation of Filipino Maple syrup urine disease. Mol Genet Metab 81(2):100–104

Simon ERF, Baumkötter J, Konstantopoulou V, Ratschmann R, Wendel U (2006) Maple syrup urine disease: favourable effect of early diagnosis by newborn screening on the neonatal course of the disease. J Inherit Metab Dis 29(4):532–537

Strauss KA (2006) Maple syrup urine disease., Retrieved from U.S from National Library of Medicine: http://www.ncbi.nlm.nih.gov/books/NBK1319/

Strauss K, Morton D (2003) Branched-chain ketoacyl dehydrogenase deficiency: maple syrup disease. Curr Treat Options Neurol 5(4): 329–341

Strauss K, Wardley B, Robinson D, Hendrickson C, Rider N, Puffenberger E, Morton D (2010) Classical maple syrup urine disease and brain development: principles of management and formula design. Mol Genet Metab 99:333–345. doi:10.1016/j.ymgme.2009.12.007

Tavil B, Sivri HSK, Coskun T et al (2006) Haematological findings in children with inborn errors of metabolism. J Inherit Metab Dis 29: 607. doi:10.1007/s10545-006-0379-8

Tayag E (2012) Inclusion of MSUD in the newborn screening panel of disorders., Retrieved from Newborn Screening Reference Center, http://www.newbornscreening.ph/images/stories/ResourcesDOHPolicies/doh-2012-0154.pdf

Yunus Z, Kamaludin DA, Mamat M, Choy YS, Ngu L (2012) Clinical and Biochemical Profiles of Maple Syrup Urine Disease in Malaysian Children. JIMD Rep., pp 99–107. doi:10.1007/8904_2011_105