Official Journal of the European Paediatric Neurology Society

Original article

Evolution of maple syrup urine disease in patients diagnosed by newborn screening versus late diagnosis

M.L. Couce [a,*], F. Ramos [b], M.A. Bueno [c], J. Díaz [d], S. Meavilla [e], M.D. Bóveda [a], A. Fernández-Marmiesse [a], A. García-Cazorla [b]

[a] Metabolic Unit, Servei of Neonatology, Department of Pediatrics, Hospital Clínico Universitario de Santiago, IDIS, CIBERER, ISCIII, Santiago de Compostela, Spain
[b] Department of Neurology, Neurometabolic Unit, Hospital Sant Joan de Déu, and CIBERER, ISCIII, Barcelona, Spain
[c] Metabolic and Dismorphology Unit, Department of Pediatrics, Hospital Universitario Virgen del Rocío, Sevilla, Spain
[d] Gastroenterolgy, Nutrition and Metabolic Unit, Hospital Central de Asturias, Spain
[e] Department of Gastroenterology and Nutrition, Metabolic Unit, Hospital Sant Joan de Déu, Barcelona, Spain

ARTICLE INFO

Article history:
Received 28 February 2015
Received in revised form
14 June 2015
Accepted 2 July 2015

Keywords:
MSUD
Outcome
Leucine
Newborn screening
Mood disorders
Encephalopathy

ABSTRACT

Maple syrup urine disease (MSUD) is a rare metabolic disorder for which the newborn screening (NBS) is possible but it has not been yet implemented for most Spanish regions. In the present study, we assess the clinical features and outcome of 14 MSUD Spanish patients with similar treatment protocol diagnosed either by NBS or by clinical symptoms. Eight patients were detected by NBS, four classic and four moderate MSUD. The average age at detection was 4.6 days, the mean plasmatic concentration of leucine at diagnosis was 1807 μM; the average number of days with leucine >1000 μM was 0.7 (0–4) and the mean number of total hospitalizations was 1.6 (0–5). Mean follow-up time was 70 months. They had good evolution: all remain asymptomatic, but 2 patients have attention deficit and hyperactivity disorder. Six patients with late diagnosis of classic MSUD were followed during 41 months. All presented with acute encephalopathy during the first month of life, mean leucine levels of 2355 μM, mean number of days with leucine >1000 μM of 6.6 (1–13) and mean number of total hospitalizations of 5.3 (4–7). Only two patients have a psychomotor development index in the lower limit (80 and 83). For all patients a good genotype–phenotype correlation was found and four novel mutations were identified: p.A311H, p.T84S, p.T397L, pL398P.

Our study support that NBS improves prognosis of MSUD patients. But early diagnosis and an aggressive treatment together with a close monitoring of leucine levels improve neurological evolution in MSUD patients, even for those not detected by NBS.

* *Corresponding author*. Metabolic Unit, Servei of Neonatology, Department of Pediatrics, Hospital Clínico Universitario de Santiago, IDIS, CIBERER, ISCIII, A Choupana s/n, 15706 Santiago de Compostela, Spain. Tel.: +34 981950162.
E-mail address: maria.luz.couce.pico@sergas.es (M.L. Couce).

http://dx.doi.org/10.1016/j.ejpn.2015.07.009

1. Introduction

Maple syrup urine disease (MSUD, OMIM 248600) is a rare metabolic disorder of autosomal recessive inheritance caused by deficiency in the activity of the branched-chain α-ketoacid dehydrogenase complex (BCKD, E.C.1.2.4.4.), which catalyzes the oxidative decarboxylation of the branched-chain keto acids in the second step from catabolic pathway of the branched chain amino acids (BCAAs) (leucine, isoleucine and valine). BCKD is a multi-enzyme complex comprised of three catalytic components: E1, a decarboxylase composed of E1α and E1β subunits which requires thiamine pyrophosphate as a coenzyme; E2, a homo-24-meric-transacylase; and E3, a dihydrolipoamide dehydrogenase.[1]

A deficiency of E1 or E2 component can cause MSUD whereas a deficiency of the E3 component produces a specific syndrome (dihydrolipoamide dehydrogenase deficiency) with congenital lactic acidosis.[2] Traditionally, the metabolic phenotype of MSUD on the basis of residual BCKD enzyme activity is termed classic (<3%) or intermediate (3–30%). Rarely, affected individuals have partial BCKD that only manifests intermittently or responds to dietary thiamine therapy. In the classical MSUD (75% of cases), clinical onset usually occurring within the first weeks after birth, including a maple syrup odor, acute metabolic decompensation with feeding problems and drowsiness, followed by progressive coma with involuntary movements, seizures and respiratory failure. The diagnosis is usually established by measuring plasma BCAA levels including alloisoleucine, which is pathognomonic for the disorder, and their corresponding BCKAs in urine. Treatment consists of dietary leucine restriction, BCAA-free medical foods, judicious supplementation with isoleucine and valine, and frequent clinical and biochemical monitoring, attending for a possible metabolic decompensation.[3,4] Phenylbutyrate therapy for maple syrup urine disease may be a valuable treatment during the acute phase.[5] The main goal is to maintain leucine levels below 200 μmol/L within the first 6 years,[38] and there after keep up those levels below 300 μmol/L. Orthotropic liver transplantation can be an effective therapy for classic MSUD.[6,7] Leucine and 2-ketoisocaproic acid appear to be the most neurotoxic metabolites.[8–10] The occurrence of oxidative stress in MSUD, probably secondary to the high production of free radicals and low total oxidant status during treatment, also contributes to the neurological sequelae present in most patients.[11–13]

An estimated prevalence of 1 in 185,000 newborns has been found.[1] However, in certain communities there is an overexpression of this entity, such as the Mennonite[14,15] and Galician (North-West of Spain) populations where the reported incidence was 1 in 52,541 newborns.[16] To date, over 160 disease-causing mutations have been detected among the three different genes encoding for the BCKD components, *BCKDHA* (E1α subunit), *BCKDHB* (E1β subunit) and *DBT* (E2 subunit) (Human Gene Mutation Database, http://www.hgmd.cf.ac.uk).[17–19]

Expanded newborn screening by tandem mass spectrometry detects MSUD by measuring the whole blood combined leucine–isoleucine concentration and its ratio to other amino acids (AA) such as alanine and phenylalanine. The clinical evolution of patients detected by NBS seems to be favorable in most cases,[20–22] but not always[23] and long-term evolution is still doubtful. We present the genotype, phenotype and the follow up data of the children with MSUD diagnosed in four regions of Spain in the last twelve years, either by NBS or by clinical symptoms.

2. Methods

2.1. Study population

The present study population comprised MSUD patients diagnosed in four of the Spanish regional (Galicia, Asturias, Cataluña and western Andalusia) NBS programs or by clinical symptoms. The period of study was from January of 2001 to December of 2013.

At diagnosis, the following parameters were evaluated: age, familiar consanguinity, deceased siblings with similar symptoms, results of dried blood spots obtained in newborn screening and/or plasma concentrations of BCAAs and alloisoleucineto detection, presence or absence of clinical symptoms, plasma AA concentrations in the beginning of the treatment with maximum peak for leucine, the need of dialysis measures, the days with leucine concentration above 1000 μM. Diagnosis was confirmed by BCKD activity and/or mutation analysis of the *BCKDHA/BCKDHB/DBT* genes.

Treatment was held according to the Spanish MSUD Guidelines,[24] during follow-up patients received not only a dietary leucine restriction, according to age and tolerance, but also valine and isoleucine supplementation. Thiamine (100–300 mg per day) and supplement of vitamins A and E was also administered. Micronutrient profile was analyzed annually providing specific mineral and/or vitamin supplement if deficiencies were detected. The main goal was to maintain leucine concentrations below 300 μmol/L and, in children under 6 years old, keep this level in 200 μmol/L, with isoleucine and valine levels between 200 and 400 μmol/L, controlling the normal range concentrations of glutamine, alanine, tryptophan, tyrosine, methionine and the ratios Leu/Tyr and Leu/Ala. During an acute intercurrent illness the treatment protocol was carefully managed with cessation or reduction of protein intake to 50% for 24–48 h, depending on the severity of the illness, whilst providing a high energy intake with an extra 20% of caloric requirements through carbohydrates, lipids and double dose of carnitine, valine and isoleucine. In case of vomiting or clinical deterioration, an urgent hospital admission for intravenous glucose infusion without branched-chain amino acids was recommended. Clinical course was subsequently monitored. Follow-up included measurement of AAs in blood spot/plasma, with individual yearly median values of leucine and maximum leucine concentrations, IQ testing and gross motor function measurements. Possible associations between leucine levels, maximum concentration of leucine and type of diagnosis, clinical findings, neuroimaging and IQ outcome were assessed. Informed consent was obtained from the parents of all patients. The study was approved by the Ethics Committee of each Hospital.