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Diversity in the incidence and spectrum of organic acidemias, fatty acid oxidation disorders, and amino acid disorders in Asian countries: Selective screening vs. expanded newborn screening

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ABSTRACT

Background: Expanded newborn screening (ENBS) utilizing tandem mass spectrometry (MS/MS) for inborn metabolic diseases (IMDs), such as organic acidemias (OAs), fatty acid oxidation disorders, (FAODs), and amino acid disorders (AAs), is increasingly popular but has not yet been introduced in many Asian countries. This study aimed to determine the incidence rates of OAs, FAODs, and AAs in Asian countries and Germany using selective screening and ENBS records.

Materials and methods: Selective screening for IMDs using gas chromatography–mass spectrometry and MS/MS was performed among patients suspected to be afflicted in Asian countries (including Japan, Vietnam, China, and India) between 2000 and 2015, and the results from different countries were compared. Similarly, ENBS results from Japan, South Korea, Taiwan, and Germany were compared. Additionally, the results of selective screening and ENBS in Japan were compared.

Results: Among 39,270 patients who underwent selective screening, IMDs were detected in 1170. Methylmalonic acidemia was frequently identified in several countries, including Japan (81/377 diagnosed IMDs), China (94/216 IMDs), and India (72/293 IMDs). In Vietnam, however, β-ketothiolase deficiency was particularly frequent (33/250 IMDs). ENBS yielded differences in overall IMD rates by country: 1:8557 in Japan, 1:7030 in Taiwan, 1:13,205 in South Korea, and 1:2200 in Germany. Frequently discovered diseases included

Abbreviations: GC/MS, gas chromatography–mass spectrometry; MS/MS, tandem mass spectrometry; OA, organic acidemia; FAOD, fatty acid oxidation disorder; AA, amino acid disorder; UCD, urea cycle disorder; IMD, inherited metabolic disease; NBS, newborn screening; ENBS, expanded newborn screening; MMA, methylmalonic acidemia; PPA, propionic acidemia; MCD, multiple carboxylase deficiency; GA1, glutaric acidemia type I; MCCD, 3-methylcrotonyl-CoA carboxylase deficiency; MGA, 3-methylglutaconic aciduria; HMGL, 3-hydroxy-3-methylglutaryl-CoA lyase; 4-OH-BA, 4-hydroxybutyric acidemia; 2-OH-GA, 2-hydroxyglutaric acidemia; BKTD, β-ketothiolase deficiency; HMGS, 3-hydroxy-3-methylglutaryl-CoA synthetase; OXPA, 5-oxoprolinemia; GA2, glutaric acidemia type II; VLCAD, very long-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; SCAD, short-chain acyl-CoA dehydrogenase; PCD, primary carnitine deficiency; CPT1, carnitine palmitoyltransferase I; CPT2, carnitine palmitoyltransferase II; TFP, trifunctional protein; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; CACT, carnitine-acylcarnitine translocase; HAD, 3-hydoxyacyl-CoA dehydrogenase; PKU, phenylketonuria; MSUD, maple syrup urine disease; HCU, homocystinuria; CTLN1, citrullinemia type I; ASA, argininosuccinic aciduria

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propionic acidemia (PPA) and phenylketonuria (PKU) in Japan, 3-methylcrotonyl-CoA carboxylase deficiency (MCCD) and PKU in Taiwan, MCCD and citrullinemia type I in South Korea, and PKU and medium-chain acyl-CoA dehydrogenase deficiency in Germany. Furthermore, in Japan, selective screening and ENBS yielded respective PPA frequencies of 14.7% and 49.4% among all organic acidemias.
Conclusion: The incidence rates of IMDs vary by country. Moreover, the disease spectra of IMDs detected via selective screening differ from those detected via ENBS.

1. Introduction

In recent years, mass spectrometric techniques, including gas chromatography–mass spectrometry (GC/MS) and tandem mass spectrometry (MS/MS), have been used for the biochemical diagnosis of inherited metabolic diseases (IMDs) such as organic acidemias (OAs), fatty acid oxidation disorders (FAODs), and amino acid disorders (AAs). Newborn screening (NBS) for OAs, FAODs, and AAs utilizing MS/MS is becoming popular worldwide and is referred to as expanded NBS (ENBS) [1]. The prognoses of patients with diseases targeted by ENBS have markedly improved in countries that have implemented [2–4].

Japan introduced nationwide NBS in 1977 and implemented nationwide ENBS in 2014 following a pilot study performed between 1997 and 2012 [5]. The latter is also being implemented in other Asian countries, including Taiwan [6] and South Korea [7]. However, ENBS has yet to be introduced in several other Asian countries in which epidemiological data pertaining to IMDs remain limited [8,9]. Accordingly, Shimane University has provided biochemical IMD diagnostic services using GC/MS and MS/MS for symptomatic patients (defined as selective screening) from several Asian countries, including Vietnam, China, and India, for > 15 years.

To investigate variations in the incidence rates of IMDs by nation, we investigated the frequencies of OAs, FAODs, and AAs among Asian countries using our selective screening and ENBS records. Furthermore, we compared the detection rates using selective screening and ENBS in Japan with the aim of reevaluating the target diseases of ENBS.

2. Materials & methods

2.1. Selective screening

2.1.1. Subjects

Screening for IMDs was performed for symptomatic patients upon request by medical institutes in Japan and other Asian countries, including Vietnam, China, India, Indonesia, Thailand, Mongolia, South Korea, Malaysia, Taiwan, and Turkey. The screening was performed using GC/MS and MS/MS at the Department of Pediatrics, Shimane University Faculty of Medicine, Japan between 2000 and 2015. Samples from patients with clinical findings suspected to indicate IMDs, such as metabolic acidosis, ketosis, hyperammonemia, hypoglycemia, lethargy, hypotonia, myopathy-like symptoms, acute encephalopathy, and sudden infant death of unknown cause, were analyzed. If the request included the above symptoms, blood and/or urine samples with the patient's data (e.g., clinical course and administered medication) were sent to Shimane University. The frequencies of detected IMDs were retrospectively compared between countries. This study was approved by the Shimane University Institutional Committee on Ethics (registration No. 20170920-2).

2.1.2. GC/MS analysis

Urine samples were delivered at room temperature from Asian countries using dried urine filter paper [10], whereas frozen urine samples were sent from Japanese medical institutes to Shimane University. The urinary organic acid analysis was conducted as reported previously [10,11]. A 'GCMS QP-2010 Plus' instrument (Shimadzu, Kyoto, Japan) was used for the analysis.

2.1.3. MS/MS analysis

Dried blood filter papers were shipped from overseas at room temperature to Shimane University, as used for ENBS. Blood serum samples from some Japanese patients were analyzed. Only samples from India were analyzed at Fukui University, Japan. Blood acylcarnitines and amino acids were analyzed with MS/MS using in butyl-derivatized specimens [12] at both Shimane and Fukui Universities. An API-3000 or API-4000 instrument (Applied Biosystems, Foster City, CA, USA) or an LC/MS/MS-8040 instrument (Shimadzu, Kyoto, Japan) was used for MS/MS.

2.1.4. Diagnosis

Biochemical diagnoses were based on the results of GC/MS and/or MS/MS. Data of organic acid analysis were processed using a personal computer-based automated GC/MS data processing and diagnostic system [11]. Whereas the diagnoses of nearly all Japanese patients were finally confirmed based on enzyme activity measurements and/or gene mutations, the diagnoses of foreign patients were based on the results of biochemical analyses indicating obvious specific abnormal metabolites in accordance with clinical data (e.g., age, sex, clinical course, laboratory data, and medication use) by several expert physicians who were familiar with IMDs.

2.2. ENBS

To investigate the detection rate of IMDs using ENBS, we obtained nationwide ENBS data from the principal ENBS investigators in Japan, Taiwan, South Korea, and Germany (the latter is a representative European country).

The nationwide ENBS data for each country were acquired as follows. The screening data of approximately 3.36 million infants were screened between 1997 and 2015 in Japan; this population included 1.95 million infants screened during the pilot study period between 1997 and 2012 as described in a domestic journal [5] and available data of 1.41 million infants screened from 2013 to 2015. Nationwide ENBS data were not available at least in the period, because ENBS was conducted on a province-by-province basis. Although the annual birth number in Japan was about 1.0 million and the coverage rate was > 99.9%. In Taiwan, approximately 1.39 million babies (coverage rate was > 99.9%; government-funded) participated in ENBS during the period between 2001 and 2014, which included a pilot study conducted from 2001 to 2009 [6]. In South Korea, approximately 3.44 million babies (coverage rate was approximately 40 to 80%; paid screening) were screened between 2000 and 2015 as described in a Korean-language domestic report. In Germany, approximately 7.51 million babies (coverage rate was > 99.9%; government-funded) were screened between 2002 and 2015, as described in a domestic report [13].

In each country, ENBS was performed according to nationally standardized methods as follows. In Japan, the butyl-derivatization method was used during pilot study; subsequently, a non-derivatized method has been used since at least 2014. In other countries, the butyl-derivatization method was used during the study period, as previously described [4,6,7]. Dried blood spots were collected 4–5 days after birth in Japan, 48–72 h after birth in South Korea and Taiwan, and 36–72 h after birth in Germany.