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Screening of newborns and high-risk group of children for inborn metabolic disorders using tandem mass spectrometry in South Korea: a three-year report

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Abbreviations: PA, propionyl-CoA carboxylase deficiency; MMA, methylmalonyl-CoA mutase deficiency; GA 1, glutaryl-CoA dehydrogenase deficiency; GA 2, multiple-CoA dehydrogenase deficiency; MCC, multiple-CoA carboxylase deficiency; HMG, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; HCS, holocarboxylase synthase deficiency; DCA, medium-chain dicarboxylic aciduria; CPT, carnitine palmitoyl transferase; CACT, carnitine/acylcarnitine translocase; SCAD, short-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; VLCAD, very-long-chain acyl-CoA dehydrogenase; M-TFP, mitochondrial trifunctional protein (long-chain enoyl-CoA hydratase, long-chain 3-hydroxyacyl-CoA dehydrogenase, and long-chain 3-ketoacyl-CoA thiolase); LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; LCKAT, long-chain-3-ketoacyl-CoA thiolase; C4, C5, C6, C8, C10:1, C12, C14, C14:1, butyryl-, glutaryl-, hexanoyl-, octanoyl-, decenoyl-, dodecanoyl-, tetradecanoyl-, and tetradecenoyl-carnitine, respectively.

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Abstract

Background: Mass screening using tandem mass spectrometry(MS/MS) was initiated to determine if the incidence of metabolic disorder is sufficiently high to meet the criteria for newborn screening, and whether or not early medical intervention might be beneficial to the patients.
Methods: Newborns and children in a high-risk group were screened using MS/MS from April 2001 to March 2004. Blood spots of newborns were collected between 48 and 72 h after birth. The dried blood spots was extracted with 150 μl of methanol, and analyzed by MS/MS.
Results: From April 2001 to March 2004, 79,179 newborns were screened for organic, amino and fatty acid metabolism disorders, which account for ≈5.4% of annual births in South Korea. Twenty-eight newborns were diagnosed with one of the metabolic disorders and the collective estimated prevalence amounted to 1 in 2800 with a sensitivity of 97.67%, a specificity of 99.28%, a recall rate of 0.05%, and a positive predictive value of 6.38%. 6795 infants/children at high risk were screened and 20 were confirmed to have metabolic disorders.
Conclusion: The collective total prevalence of 1:2800 in newborns indicates an underestimation of the incidence of metabolic disorders prior to implementing MS/MS screening in South Korea.

Keywords: Newborn screening; Inborn metabolic disorders; Tandem mass spectrometry; Prevalence; South Korea

1. Introduction

The recent development of electrospray tandem mass spectrometry (MS/MS) has made it feasible to use a single test to screen a newborn for multiple rare disorders, which have previously been undetectable [1–7]. MS/MS now allows the screening of newborns for more than 20 biochemical genetic disorders [8–12]. MS/MS amino acid and acylcarnitine analyses of newborns are rapidly gaining worldwide support as the preferred method for high-throughput newborn mass screening, especially in cases in which a shorter analytical time is highly desirable, and early diagnosis is crucial to the life quality of the newborn, if affected [13]. More than 10 million newborns worldwide are screened per year [14], and formal evidence of the cost benefit and clinical effectiveness of expanding newborn screening by MS/MS is still being gathered [15–19]. The main aim of this approach is early diagnosis and medical intervention for treatable metabolic disorders, in order to minimize morbidity and mortality as early as possible, particularly in the newborn period.

The number of disorders to be included in expanded MS/MS newborn screening protocols will depend on the ethnic background, customs, social characteristics, research environment, and economic status of the country under consideration. For example, the incidence of PKU in Asians (~1:50,000 in Korea; ~1:110,000 in Japan) is much lower than in Caucasians (~1:10,000). Another example would be medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, which is the most frequent genetic metabolic disorder in Caucasian children with the A985G common mutation. In contrast to Caucasians, MCAD, although occasionally observed, is extremely rare in Korea and Japan, and is not associated with a common mutation [20,21].

In South Korea, a pioneering newborn screening program was initiated in Kyungki Province in 1985 [22]. A practically nationwide newborn screening program for 2 mandated disorders − congenital hypothyroidism and phenylketoneuria (PKU) − was conducted in 1997 [22], long after such a system was instituted in the US, where it was begun in 1963 [23]. In 2000, the use of the bacterial inhibition assay (Guthrie test) was prohibited due to its low sensitivity and, instead, the enzyme immunoassay was recommended and advocated by the Quality Control Committee of Neonatal Screening in Korea.

The effectiveness and risks of expanded newborn screening for biochemical genetic disorders require thorough evaluation before it can be generally accepted as a nationally mandated program. The lack of epidemiological data regarding frequency is one reason for hesitation in the expansion of population-