学 位 論 文 の 要 旨

氏名　　高橋　知男

学　位　論　文　名　Metabolic Survey of Hidden Inherited Metabolic Diseases in Children With Apparent Life-Threatening Event (ALTE) or Sudden Unexpected Death in Infancy (SUDI) by Analyses of Organic Acids and Acylcarnitines Using Mass Spectrometries

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著　　者　　名　Tomoo Takahashi, Yuki Hasegawa, Kenji Yamada, Ryosuke Bo, Hironori Kobayashi, Takeshi Taketani, Seiji Fukuda, Seiji Yamaguchi

論 文 内 容 の 要 旨

INTRODUCTION

Inherited metabolic disease (IMD) is caused by an inherited defect of metabolic enzyme, and many of such diseases result in impairments in multiple organs including central nervous system, liver, or skeletal muscles. Recently, new groups of IMD which may cause sudden infant death syndrome (SIDS)-like illness or apparent life-threatening event (ALTE), have been attracted attention. Especially, organic acidemias (OA-emias) or fatty acid oxidation defects (FAODs) are famous as causative diseases of SIDS or ALTE, with recent developments in diagnostic tools, including analyses of urinary organic acids (OAs) or blood acylcarnitines (ACs) using gas chromatography mass spectrometry (GC/MS) or tandem mass spectrometry (MS/MS),.

In this study, we surveyed hidden IMDs by analyses of urinary OAs and/or blood ACs in children presenting with sudden unexpected death in infancy (SUDI) or ALTE. Further, the clinical features including prodromal symptoms or routine laboratory findings in such cases were investigated.

MATERIALS AND METHODS

Subjects

Infants, who presented SUDI or ALTE, aged from neonates to 3 years or less, and were diagnosed with IMSs by analyses of OAs and/or ACs, were investigated. Samples of urine and/or blood were introduced to the Department of Pediatrics, Shimane University from all over Japan, during the period between January 2004 and December 2014. The criteria for our survey were as follows: (a) ages between 2 days and 3 years, (b) clinical diagnosis of SUDI (or SIDS) or ALTE, and (c) established diagnosis of OA-emia or FAOD.

Urinary organic acid analysis using GC/MS

Urine samples for analysis of OAs were pretreated as described previously. Briefly, to an aliquot of urine containing 0.2 mg of creatinine, 20 μg each of heptadecanoic acid and tetracosane (C24), and 40 μg of tropic acid were added as internal standards. Distilled water was added to yield 2.0 mL of the mixture, and solvent extraction, oximation, and trimethylsilyl derivatization were performed for GC/MS analysis.

Blood acylcarnitine analysis using MS/MS

ACs were analyzed by MS/MS after butyl derivatization. Serum sample aliquots of 10 μL were analyzed according to the method described previously. MS/MS analysis was carried out using an API 3000 (Lub Solution, Applied Biosystems, Foster City, CA, USA) or Shimadzu LC-MSMS 8040 (Kyoto, Japan).

This study was approved by the ethical committee of Shimane University (20150716-1)

RESULT AND DISCUSSION

We studied a total of 458 infants including 239 with SUDI and 219 with ALTE. IMDs, including OA-emia, urea cycle disorders or FAODs, were found in 25 (5.4%) of the total 458 infants, by analyses of OAs and/or ACs as well as gene analysis. Among the above 25 infants, 3 were SUDI cases, including 2 cases of carnitine palmitoyltransferase type II (CPT2) deficiency and 1 of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. The remaining 22 were ALTE. There is a possibility that cases introduced might have been biased in clinical setting, and samples after death might have rarely been introduced. Diseases found in 22 ALTE cases were as follows: 9 cases with urea

cycle disorders, followed by 8 with methylmalonic acidemia, 2 with 3-hydroxy-3-methylglutaryl-CoA synthase deficiency, and 1 case each with MCAD deficiency, trifunctional protein deficiency, and 3-methylglutaconic acidemia.

Prodromal symptoms seen in 14 of 15 neonates included poor feeding in 8; weight loss and hypotonia in 3 each; vomiting and lethargy in 2 each, and loss of Moro reflex in 2. One infant had a family history of acute encephalopathy of the sibling. In the neonatal cases, onset may be noted with the above non-specific symptoms. In 9 of 10 children between ages of 1 month and 3 years, common cold-like symptoms were often noted as prodromal symptoms. As acute symptoms in the 9 infants, intractable vomiting was seen in 4 cases; past history of episodic hypoglycemia in 3. Past history might give important clues for hidden IMDs.

Abnormalities in routine laboratory tests during the acute phase included as follows: metabolic acidosis was seen in 17 of 24 infants, positive ketone bodies in 5 of 15 children tested, liver dysfunction 20 of 25 cases tested, high blood creatine kinase levels in 16 of 22 cases tested, hyperammonemia in 21 of 23 cases tested, and hypoglycemia in 5 of 22 cases tested. The above findings may be useful to approach the diagnosis of IMDs.

In addition to the above described 25 infants, at least 12 infants were strongly suspected of IMDs, but lacked a definitive diagnosis because of less information/data. When we come across cases with SUDI or ALTE, hidden IMDs should be checked. We should keep collection of samples including urine, blood, or DNA in mind.

CONCLUTION

In this study, we found hidden IMDs in 25 (5.4%) of 458 cases of SUDI or ALTE that were introduced for MS/MS and/or GC/MS analysis to Shimane University. Twenty two (88%) of 25 cases were ALTE, and life-saving. Early detection of IMDs should be important in such cases. Furthermore, there are at least 12 infants whose definitive diagnosis could not be confirmed because of lack of enough information. When we come across the cases with ALTE or SUDI, collection of urine, blood, DNA, or specimen for cell culture for diagnosis of hidden IMDs should be kept in mind.