Outcome of Organic Acidurias in China

Yanling Yang,[1 MD, PhD], Zhang Yao,[1 PhD], Jinqing Song,[1 Ms], Yuki Hasegawa,[2 MD], Masahiko Kimura,[2 MD], Seiji Yamaguchi,[2 MD], Yuwu Jiang,[1 MD], Jiong Qin,[1 MD], Xiru Wu,[1 MD]

Abstract

From June 1998 to May 2007, 9566 urine samples were collected from patients with psychomotor deficits, seizures, vomiting and unconsciousness in Peking University First Hospital. Their urine organic acids profiles were analysed using gas chromatography - mass spectrometry (GCMS), GCMS solution and Inborn Errors of Metabolism Screening System software. In all patients, blood acylcarnitines were analysed using tandem mass spectrometry. One hundred and sixty-eight patients (1.76%) with organic acidurias were detected. Among them, 116 (116/168, 69.0%) had methylmalonic aciduria, 63 (54.3%) of these 116 patients had methylmalonic aciduria combined with homocysteinemia. Sixteen (9.5%) of those patients detected with organic acidurias had propionic aciduria, and 15 (8.9%) had multiple carboxylase deficiency. Seven (4.2%) had glutaric aciduria type 1. After dietary treatment, medicine and rehabilitation, clinical improvements were observed in more than half of the patients. Twenty-eight of the 168 patients (16.7%) recovered and led a normal life. The method of urine organic acid analysis by gas chromatography - mass spectrometry and blood acylcarnitines analysis by tandem mass spectrometry have been established and applied successfully in China, namely Beijing, Shanghai, Wuhan and Guangzhou. The prognoses of Chinese patients with organic acidurias have also improved significantly.

Ann Acad Med Singapore 2008;37(Suppl 3):120-2

Key words: Gas chromatography - mass spectrometry, Tandem mass spectrometry

Introduction

China has a huge population, of whom more than 0.3 billion are children under 14 years. According to the cumulative incidence of organic acidurias, more than 2000 out of 20 million newborn babies would be affected by organic acidurias annually. China is a developing country and is quite different from western countries, especially in terms of socio-economic systems. Chinese doctors face a great challenge in performing a nationwide study on organic acidurias.

Research on organic acidurias started in 1996 with great support by Japanese experts. In the past 11 years, the techniques of urine organic acids analysis by gas chromatography - mass spectrometry (GCMS) and blood acylcarnitines analysis by tandem mass spectrometry have been introduced in some university hospitals in Beijing, Shanghai, Wuhan and Guangzhou for high-risk screening.[1-3] Collaborative networks played a critical role in the development of the programme. Now, in China, 7 labs are providing services for high-risk screening, diagnosis, treatment and genetic counselling for organic acidurias. By implementing high-risk screening, more and more patients with various organic acidurias were detected.

Subjects and Methods

In Peking University First Hospital, from June 1998 to May 2007, 9566 urine samples were collected from patients with psychomotor deficits, seizures, vomiting, unconsciousness and multiple organs dysfunction of unknown causes. The urine organic acids profiles were analysed using Shimadzu GCMS (Shimadzu QP2010, Kyoto, Japan) and Screening System software.[4,5] Amino acids and acylcarnitines in dried blood samples were quantitatively analysed by tandem mass spectrometry.[2] Plasma or serum total homocysteine concentration were measured by a fluorescence polarisation immunoassay described by Abbott Laboratories.[6]

[1] Department of Pediatrics, Peking University First Hospital, China
[2] Department of Pediatrics, Shimane University School of Medicine, Japan
Address for Correspondence: Dr Yanling Yang, Peking University First Hospital, No. 1, Xi-an-men Road, Xicheng District, Beijing 100034.
Email: yanlingy@vip.sina.com

Results

Prevalence

As shown in the Table 1, 182 patients (1.9%) with typical organic acidurias were detected. Among 182 patients with organic acidurias, methylmalonic aciduria was the most common disease[3] (116/168, 69.0%). Propionic aciduria was the second most common (9.5%). Fifteen patients (8.9%) had multiple carboxylase deficiency.[7]

Glutaric aciduria type 1, maple syrup urine disease, oxoprolinemia, ketothiolase deficiency, isovaleric aciduria, methylcrotonyl CoA carboxylase deficiency, alcaptonuria were detected in the rest of the patients.

Treatment and Outcome

After diagnosis, 132 (72.5%) patients were treated by diet, medicine and rehabilitation. Clinical improvement was observed in 96 (52.7%) patients. Unfortunately, 37 (20.3%) patients died. Thirteen (7.1%) patients did not have follow up.

(i) Methylmalonic aciduria

Methylmalonic aciduria is the most common detectable organic aciduria in China. Till May 2007, 116 patients with methylmalonic aciduria were detected. Fifty-three cases (45.7%) were isolated methylmalonic aciduria. They were treated by L-carnitine, cobalamin and special formula. Sixty-three cases (54.3%) were combined methylmalonic aciduria and homocysteinemia.[3] They were treated by cobalamin, folate, L-carnitine and betatine supplementations.

Out of 53 patients with isolated methylmalonic aciduria, 29 had onset during the neonatal period, and 14 died. Sixteen patients had the onset between 1 and 12 months, and 4 died. Eight of them had onset after the age of 1 year, and 1 died. Three of them had normal development later on in life.

Table 1. One Hundred Eighty-two Cases with Organic Acidurias Detected from 9566 High-risk Patients

Diseases	No.	%
Methylmalonic aciduria	116	63.7
Propionic aciduria	16	8.8
Multiple carboxylase deficiency	15	8.2
Glutaric aciduria type 2	11	6.0
Glutaric aciduria type 1	7	3.8
Maple syrup urine disease	5	2.7
Oxoprolinemia	3	1.6
Ketothiolase deficiency	3	1.6
Isovaleric aciduria	3	1.6
Methylcrotonyl CoA carboxylase deficiency	2	1.1
Alcaptonuria	1	0.5

The outcomes of 63 patients with combined methylmalonic aciduria and homocysteinemia were relatively better.[3] Nineteen patients had onset during the neonatal period, 5 of them died, 1 had normal development. Among the 26 patients who had onset after the age of 1 year, only 1 patient died. Twelve other patients had normal development.

Generally, the outcomes of the patients with combined methylmalonic aciduria and homocysteinemia with onset after the neonatal period are much better than those with isolated methylmalonic aciduria. The outcomes of patients who had onset at school age or later were more favourable. Among the 17 cases, 9 of them recovered completely, while 8 improved with a mild residual handicap.[3]

(ii) Multiple carboxylase deficiency

Among our patients with organic acidurias, the outcomes of patients with multiple carboxylase deficiency are the best. In my hospital, 15 patients aged between 1 month and 14 years were detected using urinary organic acids analysis. Biotinidase deficiency was detected in 9 of them. Thirteen patients were treated successfully by biotin supplement.[7] Two patients died before the treatment.

Propionic Aciduria

Generally, the outcomes of our patients with propionic aciduria were unfavourable. In our study, 13 out of 16 patients had onset in the neonatal period. Among the 9 patients who died, 4 were diagnosed by postmortem. One of the 7 patients who is still alive is 10 years old, with psychomotor retardation and epilepsy.

Glutaric Aciduria Type 2

Seven cases with lipid storage myopathy due to late-onset glutaric aciduria type 2 were studied.[8] These previously healthy patients began to develop progressive fatigue, muscular weakness and pain between the age of 8 years to 22 years. All patients had mild hepatomegaly, significant elevation of serum creatine kinase, creatine kinase-MB, lactate dehydrogenase, hydroxybutyrate dehydrogenase and carnitine deficiency. Muscle biopsy revealed lipid storage myopathy. All patients responded to high dose riboflavin (100-500 mg/d). Rapid clinical and biochemical improvement were observed. After 1 to 3 months of therapy, all of them could go back to school or work.

Conclusion

Organic acidurias are relatively common metabolic diseases in China,[1-3] but the precise incidence is not known yet. Affected patients manifest a wide variety of clinical,

biochemical and neurological symptoms involving multiple independent organ systems.[9-11] Diagnosis of organic acidurias especially in the patients with late onset symptoms were often not carried out until the manifestation of symptoms.[9-11]

Organic aciduria research is considered a novelty in China compared to many developed countries. Population distribution and diseases profile of organic acidurias are usually very complicated, thus making it difficult to effectively conduct screening of organic acidurias. Therefore, it is important to develop a nation-wide collaboration system.

Domestic and international cooperation have enabled many patients to be detected. Although the network system is in its infancy stage, it has contributed much to provide information, training of paediatricians and healthcare professionals.

Acknowledgements

This work was supported by a grant from the National Science Key Project of the Ministry of Science and Technology, China (No. 2006BAI05A07).

We are grateful for the technical support and collaboration of Prof. Yosuke Shigematsu at the Department of Health Science, Department of Pediatrics, Faculty of Medical Sciences, University of Fukui, and Dr. Tagami Yasuko at the Sapporo Health Association, Japan; Prof. Xuefan Gu at the Department of Pediatric Endocrinology, Xinhua Hospital, Shanghai Jiaotong University; Prof Luo Xiaoping at the Department of Pediatrics, Tongji Hospital; Prof. Kwang-Jen Hsiao, Taipei Veterans General Hospital and other Chinese colleagues for their kind collaboration.

REFERENCES

1. Hori D, Hasegawa Y, Kimura M, Yang Y, Verma IC, Yamaguchi S. Clinical onset and prognosis of Asian children with organic acidemias, as detected by analysis of urinary organic acids using gas chromatography mass spectrometry, instead of mass screening. Brain Dev 2005;27:39-45
2. Han LS, Gao XL, Ye J, Qiu WJ, Gu XF. Application of tandem mass spectrometry in diagnosis of organic acidemias [Chinese]. Zhonghua Er Ke Za Zhi 2005;43:325-30.
3. Yang Y, Sun F, Song J, Hasegawa Y, Yamaguchi S, Zhang Y, et al. Clinical and biochemical studies on Chinese patients with methylmalonic aciduria. J Child Neurol 2006;21:1020-4.
4. Fu XW, Iga M, Kimura M, Yamaguchi S. Simplified screening for organic acidemia using gas chromatography mass spectrometry and dried filter paper: a study on neonatal mass screening. Early Hum Dev 2000;58:41-55.
5. Kimura M, Yamamoto T, Yamaguchi S. Automated metabolic profiling and interpretation of gas chromatography mass spectrometry data for organic acidemia screening: a personal computer-based system. Tohoku J Exp Med 1999;188:317-34.
6. Ueland PM, Refsum H, Stabler SP, Malinow MR, Andersson A, Allen RH. Total homocysteine in plasma or serum: methods and clinical applications. Clin Chem 1993;39:1764-79.
7. Yang Y, Li C, Qi Z, Xiao J, Zhang Y, Yamaguchi S, et al. Spinal cord demyelination associated with biotinidase deficiency in 3 Chinese patients. J Child Neurol 2007;22:156-60.
8. Chang XZ, Zhou JY, Yuan Y, Wu Y, Li YX, Zhang W, et al. Diagnostic value of muscle, sural nerve and skin biopsies in childhood neuromuscular disorders [Chinese]. Zhonghua Er Ke Za Zhi. 2006;44:909-12.
9. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Basis of Inherited Disease. 8th ed. New York: McGraw-Hill, 2001.
10. Rosenblatt DS, Aspler AL, Shevell MI, Pletcher BA, Fenton WA, Seashore MR. Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). J Inherit Metab Dis 1997;20:528-38.
11. Rezvani I, Rosenblatt DS, Aranda JV, Bennett M, Baltimore RS, Chen YT, et al. In: Behrman RE, Kliegman RM, Jenson HB, editors Nelson Textbook of Pediatrics. 16th ed. US: Harcourt Publishers Limited, 2000.