34. Miyakoshi T, Takahashi T, Kato M, Watanabe M, Ito C. Abnormal citrulline metabolism of Inose-type hepatocerebral disease. Shinkeikagaku. 1968;7:88–91.
35. Mutoh K, Kurokawa K, Kobayashi K, Saheki T. Treatment of a citrin-deficient patient at the early stage of adult-onset type II citrullinaemia with arginine and sodium pyruvate. J Inherit Metab Dis. 2008;31 Suppl 2:S343–7. [PubMed: 18958581]
36. Nagasaka H, Okano Y, Tsukahara H, Shigematsu Y, Momoi T, Yorifuji J, Miida T, Ohura T, Kobayashi K, Saheki T, Hirano K, Takayanagi M, Yorifuji T. Sustaining hypercitrullinemia, hypercholesterolemia and augmented oxidative stress in Japanese children with aspartate/glutamate carrier isoform 2-citrin-deficiency even during the silent period. Mol Genet Metab. 2009;97(1):21–26. [PubMed: 19232506]
37. Ohura T, Abukawa D, Aikawa J, Nakagawa M, Ishizawa S, Tazawa Y, Narisawa K, Iinuma K. Disturbances of amino acid metabolism in infants with idiopathic neonatal hepatitis. J Jpn Pediatr Soc. 1997;101:1522–5.
38. Ohura T, Kobayashi K, Abukawa D, Tazawa Y, Aikawa J, Sakamoto O, Saheki T, Iinuma K. A novel inborn error of metabolism detected by elevated methionine and/or galactose in newborn screening: neonatal intrahepatic cholestasis caused by citrin deficiency. Eur J Pediatr. 2003;162:317–22. [PubMed: 12692712]
39. Ohura T, Kobayashi K, Tazawa Y, Abkawa D, Sakamoto O, Tsuchiya S, Saheki T. Clinical pictures of 75 patients with neonatal intrahepatic cholestasis caused by citrin deficiency. J Inherit Metab Dis. 2007;30:139–44. [PubMed: 17323144]
40. Palmieri L, Pardo B, Lasorsa FM, del Arco A, Kobayashi K, Iijima M, Runswick MJ, Walker JE, Saheki T, Satrustegui J, Palmieri F. Citrin and aralar1 are Ca(2+)-stimulated aspartate/glutamate transporters in mitochondria. EMBO J. 2001;20:5060–9. [PubMed: 11566871]
41. Saheki T, Iijima M, Li MX, Kobayashi K, Horiuchi M, Ushikai M, Okumura F, Meng XJ, Inoue I, Tajima A, Moriyama M, Eto K, Kadowaki T, Sinasac DS, Tsui L-C, Tsuji M, Okano A, Kobayashi T. Citrin/mitochondrial glycerol-3-phosphate dehydrogenase double-knockout mice recapitulate features of human citrin deficiency. J Biol Chem. 2007;282:25041–52. [PubMed: 17591776]
42. Saheki T, Inoue K, Tushima A, Mutoh K, Kobayashi K. Citrin deficiency and current treatment concepts. Mol Genet Metab. 2010;100:S59–64. [PubMed: 20233664]
43. Saheki T, Kobayashi K. Mitochondrial aspartate glutamate carrier (citrin) deficiency as the cause of adult-onset type II citrullinemia (CTLN2) and idiopathic neonatal hepatitis (NICCD). J Hum Genet. 2002;47:333–41. [PubMed: 12111366]
44. Saheki T, Kobayashi K. Physiological role of citrin, a liver-type mitochondrial aspartate-glutamate carrier, and pathophysiology of citrin deficiency. Recent Res Devel Life Sci. 2005;3:59–73.
45. Saheki T, Kobayashi K, Iijima M, Horiuchi M, Begum L, Jalil MA, Li MX, Lu YB, Ushikai M, Tabata A, Moriyama M, Hsiao KJ, Yang Y. Adult-onset type II citrullinemia and idiopathic neonatal hepatitis caused by citrin deficiency: involvement of the aspartate glutamate carrier for urea synthesis and maintenance of the urea cycle. Mol Genet Metab. 2004;81 Suppl 1:S20–6. [PubMed: 15050970]
46. Saheki T, Kobayashi K, Iijima M, Li MX, Horiuchi M, Tabata A, Lu YB, Ushikai M, Terashi M, Moriyama M. Pathophysiology of citrin deficiency. In: Haussinger D, Kircheis G, Schliess F, eds. *Hepatic Encephalopathy and Nitrogen Metabolism*. Dordrecht, Netherlands: Springer; 2006:320-8.
47. Saheki T, Kobayashi K, Terashi M, Ohura T, Yanagawa Y, Okano Y, Hattori T, Fujimoto H, Mutoh K, Kizaki Z, Inui A. Reduced carbohydrate intake in citrin-deficient subjects. J Inherit Metab Dis. 2008;31:386–94. [PubMed: 18415701]
48. Saheki T, Nakano K, Kobayashi K, Imamura Y, Itakura Y, Sase M, Hagihara S, Matuo S. Analysis of the enzyme abnormality in eight cases of neonatal and infantile citrullinaemia in Japan. J Inherit Metab Dis. 1985;8:155–6. [PubMed: 3939592]
49. Saheki T, Ueda A, Hosoya M, Kusumi K, Takada S, Tsuda M, Katsunuma T. Qualitative and quantitative abnormalities of argininosuccinate synthetase in citrullinemia. Clin Chim Acta. 1981;109:325–35. [PubMed: 6784969]
50. Shigematsu Y, Hirano S, Hata I, Tanaka Y, Sudo M, Sakura N, Tajima T, Yamaguchi S. Newborn mass screening and selective screening using electrospray tandem mass spectrometry in Japan. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;776:39–48. [PubMed: 12127323]
51. Shiohama N, Sugita Y, Imamura N, Sato T, Mizuno Y. Type II citrullinemia triggered by acetaminophen. No To Shinkei. 1993;45:865–70. [PubMed: 8217412]
52. Sinasac DS, Crackower MA, Lee JR, Kobayashi K, Saheki T, Scherer SW, Tsui LC. Genomic structure of the adult-onset type II citrullinemia gene, SLC25A13, and cloning and expression of its mouse homologue. Genomics. 1999;62:289–92. [PubMed: 10610724]
53. Soeda J, Yazaki M, Nakata T, Miwa S, Ikeda S, Hosoda W, Iijima M, Kobayashi K, Saheki T, Kojiro M, Miyagawa S. Primary liver carcinoma exhibiting dual hepatocellular-biliary epithelial differentiations associated with citrin deficiency: a case report. J Clin Gastroenterol. 2008;42:855–60. [PubMed: 18385606]
54. Song YZ, Deng M, Chen FP, Wen F, Guo L, Cao SL, Gong J, Xu H, Jiang GY, Zhong L, Kobayashi K, Saheki T, Wang ZN. Genotypic and phenotypic features of citrin deficiency: Five-year experience in a Chinese pediatric center. Int J Mol Med. 2011;28:33–40. [PubMed: 21424115]
55. Song YZ, Guo L, Yang YL, Han LS, Kobayashi K, Saheki T. Failure to thrive and dyslipidemia caused by citrin deficiency: a novel clinical phenotype. Zhongguo Dang Dai Er Ke Za Zhi. 2009a;11:328–32. [PubMed: 19470249]
56. Song YZ, Hao H, Ushikai M, Liu GS, Xiao X, Saheki T, Kobayashi K, Wang ZN. A difficult and complicated case study: neonatal intrahepatic cholestasis caused by citrin deficiency. Zhongguo Dang Dai Er Ke Za Zhi. 2006;8:125–8. [PubMed: 16613706]
57. Song YZ, Li BX, Chen FP, Liu SR, Sheng JS, Ushikai M, Zhang CH, Zhang T, Wang ZN, Kobayashi K, Saheki T, Zheng XY. Neonatal intrahepatic cholestasis caused by citrin deficiency: clinical and laboratory investigation of 13 subjects in

mainland of China. Dig Liver Dis. 2009b;41:683–9. [PubMed: 19185551]
58. Song YZ, Sheng JS, Ushikai M, Hwu WL, Zhang CH, Kobayashi K. Identification and diagnosis of three novel mutations in SLC25A13 gene of neonatal intrahepatic cholestasis caused by citrin deficiency]. Zhonghua Er Ke Za Zhi. 2008;46:411–5. [PubMed: 19099775]
59. Song YZ, Wen F, Chen FP, Kobayashi K, Saheki T. Neonatal intrahepatic cholestasis caused by citrin deficiency: efficacy of therapeutic formulas and update of clinical outcomes. Jpn J Inherit Metab Dis. 2010;26:57–69.
60. Tabata A, Sheng J-S, Ushikai M, Song Y-Z, Gao H-Z, Lu Y-B, Okumura F, Iijima M, Mutoh K, Kishida S, Saheki T, Kobayashi K. Identification of 13 novel mutations including a retrotransposal insertion in SLC25A13 gene and frequency of 30 mutations found in patients with citrin deficiency. J Hum Genet. 2008;53:534–45. [PubMed: 18392553]
61. Takagi H, Hagiwara S, Hashizume H, Kanda D, Sato K, Sohara N, Kakizaki S, Takahashi H, Mori M, Kaneko H, Ohwada S, Ushikai M, Kobayashi K, Saheki T. Adult onset type II citrullinemia as a cause of non-alcoholic steatohepatitis. J Hepatol. 2006;44:236–9. [PubMed: 16278034]
62. Takahashi H, Kagawa T, Kobayashi K, Hirabayashi H, Yui M, Begum L, Mine T, Takagi S, Saheki T, Shinohara Y. A case of adult-onset type II citrullinemia - deterioration of clinical course after infusion of hyperosmotic and high sugar solutions. Med Sci Monit. 2006;12:CS13–5. [PubMed: 16449956]
63. Takaya J, Kobayashi K, Ohashi A, Ushikai M, Tabata A, Fujimoto S, Yamato F, Saheki T, Kobayashi Y. Variant clinical courses of 2 patients with neonatal intrahepatic cholestasis who have a novel mutation of SLC25A13. Metabolism. 2005;54:1615–9. [PubMed: 16311094]
64. Tamakawa S, Nakamura H, Katano T, Yoshizawa M, Ohtake K, Kubota T. Hyperalimentation therapy produces a comatose state in a patient with citrullinemia. J Jpn Soc Intensive Care Med. 1994;1:37–41.
65. Tamamori A, Fujimoto A, Okano Y, Kobayashi K, Saheki T, Tagami Y, Takei H, Shigematsu Y, Hata I, Ozaki H, Tokuhara D, Nishimura Y, Yorifuji T, Igarashi N, Ohura T, Shimizu T, Inui K, Sakai N, Abukawa D, Miyakawa T, Matsumori M, Ban K, Kaneko H, Yamano T. Effects of citrin deficiency in the perinatal period: feasibility of newborn mass screening for citrin deficiency. Pediatr Res. 2004;56:608–14. [PubMed: 15295082]
66. Tamamori A, Okano Y, Ozaki H, Fujimoto A, Kajiwara M, Fukuda K, Kobayashi K, Saheki T, Tagami Y, Yamano T. Neonatal intrahepatic cholestasis caused by citrin deficiency: severe hepatic dysfunction in an infant requiring liver transplantation. Eur J Pediatr. 2002;161:609–13. [PubMed: 12424587]
67. Tanaka T, Nagao M, Tsutsumi H. Application of mutation analysis for the previously uncertain cases of adult-onset type II citrullinemia (CTLN2) and their clinical profiles. Tohoku J Exp Med. 2002;198:89–97. [PubMed: 12512993]
68. Tazawa Y, Abukawa D, Sakamoto O, Nagata I, Murakami J, Iizuka T, Okamoto M, Kimura A, Kurosawa T, Iinuma K, Kobayashi K, Saheki T, Ohura T. A possible mechanism of neonatal intrahepatic cholestasis caused by citrin deficiency. Hepatol Res. 2005;31:168–71. [PubMed: 15777702]
69. Tokuhara D, Iijima M, Tamamori A, Ohura T, Takaya J, Maisawa S, Kobayashi K, Saheki T, Yamano T, Okano Y. Novel diagnostic approach to citrin deficiency: Analysis of citrin protein in lymphocytes. Mol Genet Metab. 2007;90:30–6. [PubMed: 17092749]
70. Tomomasa T, Kobayashi K, Kaneko H, Shimura H, Fukusato T, Tabata M, Inoue Y, Ohwada S, Kasahara M, Morishita Y, Kimura M, Saheki T, Morikawa A. Possible clinical and histologic manifestations of adult-onset type II citrullinemia in early infancy. J Pediatr. 2001;138:741–3. [PubMed: 11343053]
71. Tsai C-W, Yang C-C, Chen H-L, Hwu W-L, Wu M-Z, Liu K-L, Wu M-S. Homozygous SLC25A13 mutation in a Taiwanese patient with adult-onset citrullinemia complicated with steatosis and hepatocellular carcinoma. J Formos Med Assoc. 2006;105:852–6. [PubMed: 17000460]
72. Tsuboi Y, Fujino Y, Kobayashi K, Saheki T, Yamada T. High serum pancreatic secretory trypsin inhibitor before onset of type II citrullinemia. Neurology. 2001;57:933. [PubMed: 11552040]
73. Wen PQ, Wang GB, Chen ZL, Cui D, Yuan Q, Song P, Chen SL, Liao JX, Li CR. SLC25A13 gene analysis in neonates with intrahepatic cholestasis caused by citrin deficiency. Zhongguo Dang Dai Er Ke Za Zhi. 2011;13:303–8. [PubMed: 21507300]
74. Wong LJ, Dimmock D, Geraghty MT, Quan R, Lichter-Konecki U, Wang J, Brundage EK, Scaglia F, Chinault AC. Utility of oligonucleotide array-based comparative genomic hybridization for detection of target gene deletions. Clin Chem. 2008;54(7):1141–8. [PubMed: 18487280]
75. Xing YZ, Qiu WJ, Ye J, Han LS, Xu SS, Zhang HW, Gao XL, Wang Y, Gu XF. Studies on the clinical manifestation and SLC25A13 gene mutation of Chinese patients with neonatal intrahepatic cholestasis caused by citrin deficiency. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2010;27:180–5. [PubMed: 20376801]
76. Yamaguchi N, Kobayashi K, Yasuda T, Nishi I, Iijima M, Nakagawa M, Osame M, Kondo I, Saheki T. Screening of SLC25A13 mutations in early and late onset patients with citrin deficiency and in the Japanese population: Identification of two novel mutations and establishment of multiple DNA diagnosis methods for nine mutations. Hum Mutat. 2002;19:122–30. [PubMed: 11793471]
77. Yasuda T, Yamaguchi N, Kobayashi K, Nishi I, Horinouchi H, Jalil MA, Li MX, Ushikai M, Iijima M, Kondo I, Saheki T. Identification of two novel mutations in the SLC25A13 gene and detection of seven mutations in 102 patients with adult-onset type II citrullinemia. Hum Genet. 2000;107:537–45. [PubMed: 11153906]
78. Yazaki M, Hashikura Y, Takei Y, Ikegami T, Miyagawa S, Yamamoto K, Tokuda T, Kobayashi K, Saheki T, Ikeda S. Feasibility of auxiliary partial orthotopic liver transplantation from living donors for patients with adult-onset type II citrullinemia. Liver Transpl. 2004;10:550–4. [PubMed: 15048800]
79. Yazaki M, Ikeda S, Kobayashi K, Saheki T. Therapeutic approaches for patients with adult-onset type II citrullinemia (CTLN2): effectiveness of treatment with low-carbohydrate diet and sodium pyruvate. Rinsho Shinkeigaku. 2010;50:844–7.

[PubMed: 21921468]
80. Yazaki M, Takei Y, Kobayashi K, Saheki T, Ikeda S. Risk of worsened encephalopathy after intravenous glycerol therapy in patients with adult-onset type II citrullinemia (CTLN2). Intern Med. 2005;44:188–95. [PubMed: 15805705]
81. Yeh JN, Jeng YM, Chen HL, Ni YH, Hwu WL, Chang MH. Hepatic steatosis and neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) in Taiwanese infants. J Pediatr. 2006;148:642–6. [PubMed: 16737877]
82. Zhao XJ, Tang XM, Zha QB, Shi SS, Song YZ, Xiao XM. Prenatal diagnosis of citrin deficiency in a Chinese family with a fatal proband. Tohoku J Exp Med. 2011;225:273–6. [PubMed: 22095253]

Suggested Reading

1. Chew HB, Ngu LH, Zabedah MY, Keng WT, Balasubramaniam S, Hanifah MJ, Kobayashi K. Neonatal intrahepatic cholestasis associated with citrin deficiency (NICCD): a case series of 11 Malaysian patients. J Inherit Metab Dis. 2010 [PubMed: 21161389]
2. Guo L, Li BX, Deng M, Wen F, Jiang JH, Tan YQ, Song YZ, Liu ZH, Zhang CH, Kobayashi K, Wang ZN (2011) Etiological analysis of neurodevelopmental disabilities: single-center eight-year clinical experience in south China. J Biomed Biotechnol 2011.pii: 318616.
3. Kobayashi K, Ushikai M, Song YZ, Gao HZ, Sheng JS, Tabata A, Okumura F, Ikeda S, Saheki T. Overview of citrin deficiency: SLC25A13 mutations and the frequency. J Appl Clin Pediatr. 2008;23:1553–7.
4. Ngu HL, Zabedah MY, Kobayashi K. Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) in three Malay children. Malays J Pathol. 2010;32:53–7. [PubMed: 20614727]
5. Saheki T, Inoue K, Ono H, Tushima A, Katsura N, Yokogawa M, Yoshidumi Y, Kuhara T, Ohse M, Eto K, Kadowaki T, Sinasac DS, Kobayashi K. Metabolomic analysis reveals hepatic metabolite perturbations in citrin/mitochondrial glycerol-3-phosphate dehydrogenase double-knockout mice, a model of human citrin deficiency. Mol Genet Metab. 2011;104:492–500. [PubMed: 21908222]
6. Sawada S, Kinjo T, Makishi S, Tomita M, Arasaki A, Iseki K, Watanabe H, Kobayashi K, Sunakawa H, Iwamasa T, Mori N. Downregulation of citrin, a mitochondrial AGC, is associated with apoptosis of hepatocytes. Biochem Biophys Res Commun. 2007;364:937–44. [PubMed: 18273444]
7. Shigeta T, Kasahara M, Kimura T, Fukuda A, Sasaki K, Arai K, Nakagawa A, Nakagawa S, Kobayashi K, Soneda S, Kitagawa H. Liver transplantation for an infant with neonatal intrahepatic cholestasis caused by citrin deficiency using heterozygote living donor. Pediatr Transplant. 2010;14:E86–8. [PubMed: 19413723]

Chapter Notes

Author Notes

The first author of this review, Keiko Kobayashi, PhD, died of colon cancer on December 21, 2010. The scientific community has lost a great scientist, teacher, and friend.

Keiko Kobayashi is recognized internationally as a pioneer in citrin deficiency research. An investigator with the research group of Professor Takeyori Saheki (Department of Molecular Metabolism and Biochemical Genetics, Kagoshima University, Japan), in 1999 she cloned the gene in which mutation is causative (*SLC25A13*) and designated the term citrin. Kobayashi also played essential roles in the discovery and designation of NICCD and FTTDCD, two early onset forms of citrin deficiency. As an outstanding molecular geneticist, she identified over 50 mutations in *SLC25A13* and diagnosed over 500 citrin-deficient patients worldwide (Japan, Korea, China, Vietnam, Malaysia, Israel, Palestine, Australia, Czech, France, Britain, and the US). She also worked tirelessly to educate the medical community about citrin deficiency, thus improving the care and prognosis of affected patients worldwide. Less than a month before her death, Dr. Kobayashi delivered a lecture on citrin deficiency to the 9th Asia-Pacific Conference on Human Genetics.

Keiko Kobayashi, the “mother of citrin deficiency,” will be remembered and sorely missed by her friends, students, colleagues, and the citrin-deficient patients whom she diagnosed.

Acknowledgments

This research was supported in part by Grants-in-Aid for Scientific Research (Nos. 16390100, 19390096 and 19591230) and for Asia-Africa Scientific Platform Program (AASPP) from the Japan Society for the Promotion of Science (JSPS), by a Grant for Child Health and Development (17-2) from the Ministry of Health, Labour and Welfare in Japan, by a Grant for Research for Promoting Technological Seeds from the Japan Science and Technology Agency and by Project 81070279 supported by the National Natural Science Foundation (NSFC) of China.

Revision History

- 5 January 2012 (me) Comprehensive update posted live
- 1 July 2008 (me) Comprehensive update posted live
- 28 December 2006 (kk) Revision: sequence analysis for *SLC25A13* clinically available

16 September 2005 (me) Review posted to live Web site

- 5 November 2004 (kk) Original submission

Figures

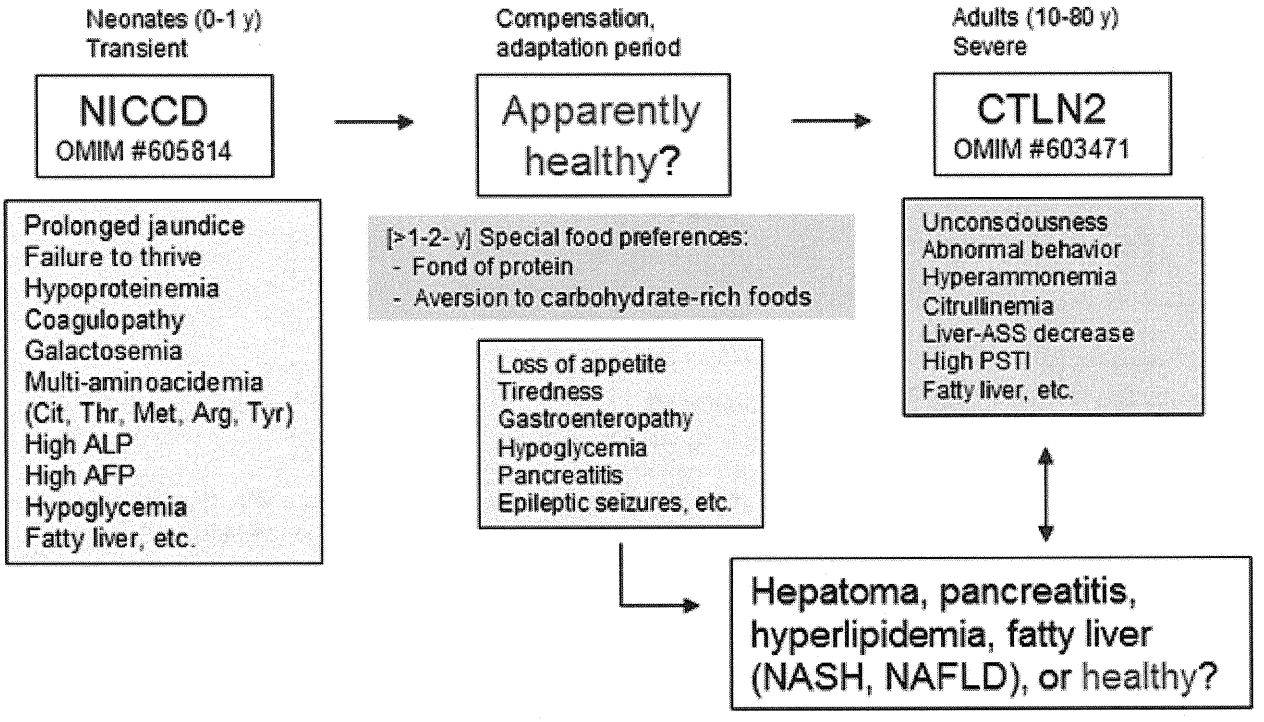

Figure 1. Citrin deficiency
NICCD = neonatal intrahepatic cholestasis caused by citrin deficiency
CTLN2 = adult-onset type II citrullinemia
Cit = citrulline
Thr = threonine
Met = methionine
Arg = arginine
Tyr = tyrosine
ALP = alkaline phosphatase
AFP = α-fetoprotein
ASS = argininosuccinate synthetase
PSTI = pancreatic secretory trypsin inhibitor
NASH = non-alcoholic steathepatitis
NAFLD = non-alcoholic fatty liver disease

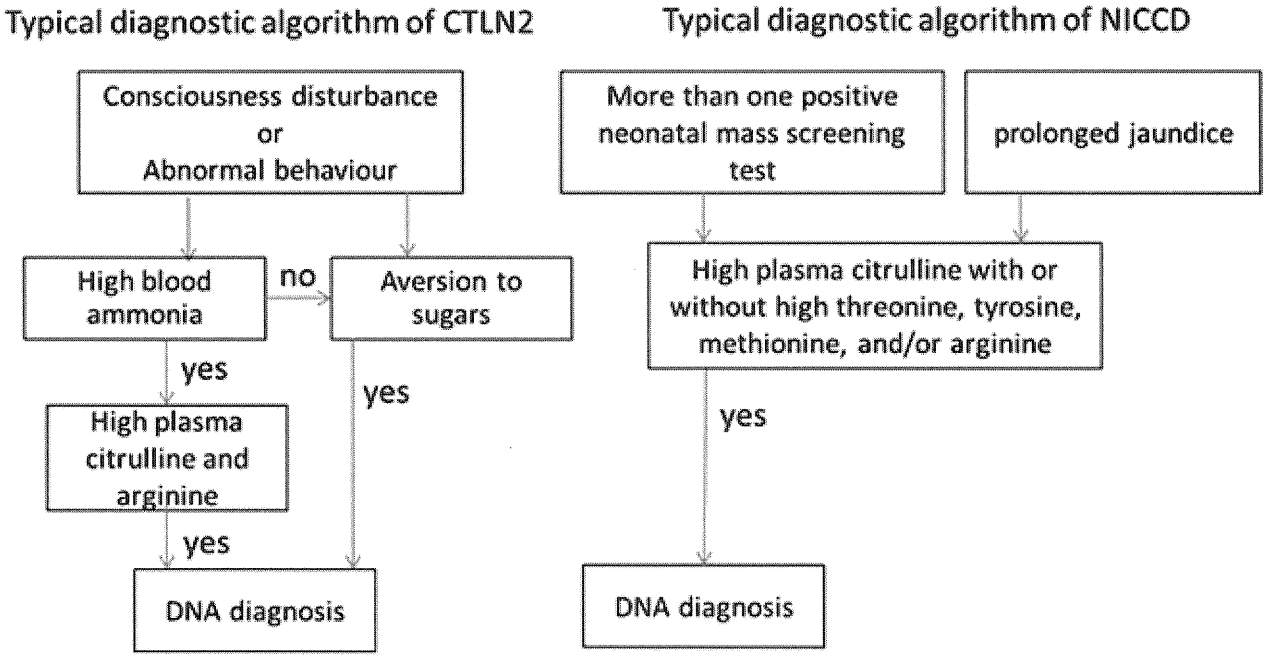

Fig. 2. Diagnostic algorithm of citrin deficiency. Note that food preferences (e.g., aversion to sugars) are important in the diagnosis of citrin deficiency, not only in typical CTLN2 but also in cases of growth retardation, hypoglycemia, pancreatitis, hypertriglyceridemia, etc. in both children and adults.

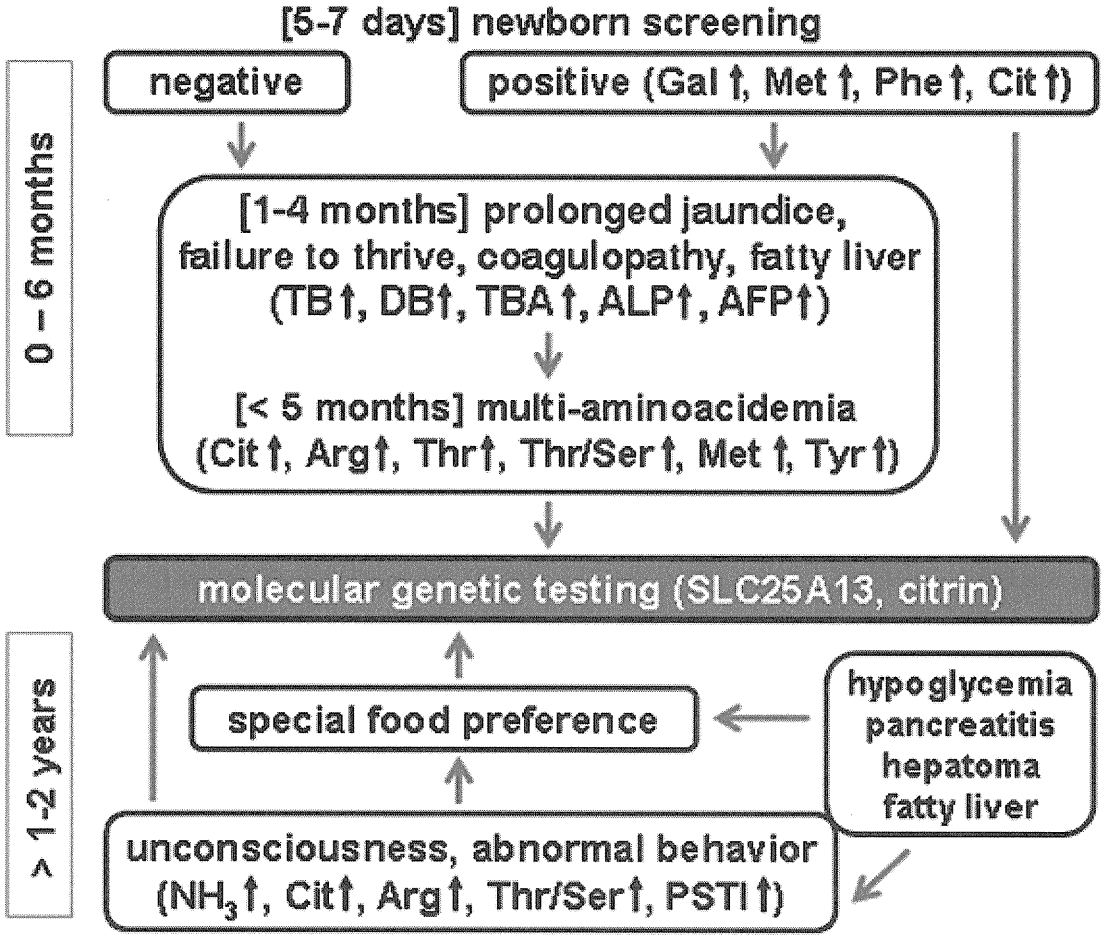

Figure 3. \Flow chart for diagnosis of citrin deficiency

Qual Life Res (2011) 20:1091–1102
DOI 10.1007/s11136-010-9834-y

Reliability and validity of the PedsQL™ Multidimensional Fatigue Scale in Japan

Kyoko Kobayashi · Yoshiyuki Okano · Naohiro Hohashi

Accepted: 18 December 2010 / Published online: 12 January 2011

Abstract
Purpose To examine the reliability and validity of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale and to investigate the agreement between child self-reported fatigue and parent proxy-reported fatigue.
Methods The Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale was administered to 652 preschoolers and schoolchildren aged 5–12 and their parents, and to 91 parents of preschool children aged 1–4.
Results Internal consistency reliability was 0.62–0.87 for children and 0.81–0.93 for parents. Known-group validity was examined between a group of healthy samples ($n = 530$) and chronic condition sample ($n = 102$); the chronically ill group reported a significantly higher perceived fatigue problem. Correlations between child self- and parent proxy reports ranged from poor to fair. In subgroups identified by cluster analysis based on child self-reported scores, the greatest agreement between child and parent reports was seen in the good HRQOL group, while the least occurred in the poor HRQOL group. The parents overestimated their child's fatigue more when the child's HRQOL was low.
Conclusion The Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale demonstrated good reliability and validity and could be useful in evaluating Japanese children in school and health care settings.

Keywords Health-related quality of life · Fatigue · Children · Parents · Agreement · PedsQL™

K. Kobayashi (✉)
Department of Family Nursing, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
e-mail: kyoko-ko@umin.ac.jp

Y. Okano
Department of Pediatrics, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
e-mail: okano@med.osaka-cu.ac.jp

N. Hohashi
Division of Family Health Care Nursing, Kobe University Graduate School of Health Sciences, 7-10-2, Tomogaoka, Suma-ku, Kobe, Hyogo 654-0142, Japan
e-mail: naohiro@hohashi.org

Background

In the last decade, the utility of pediatric health-related quality of life (HRQOL) measurement was closely examined, and HRQOL is now recognized as an essential point of reference in clinical trials, health care settings, and school health care. Numerous HRQOL measurements have been developed for children and adolescents [1–4], and the Pediatric Quality of Life Inventory (PedsQL™), developed in the United States, has demonstrated satisfactory psychometric properties in both diseased and healthy children [5–10]. The PedsQL™ includes well-established methods of child self-reporting and parent proxy reporting, which have been utilized in clinical trials in Japan and other countries worldwide [11–16].

Fatigue is a health problem that significantly impacts HRQOL and it is a frequent and ubiquitous complaint among patients with chronic disease [17]. Fatigue is also a frequent complaint in the general school population, and an association between fatigue and school absenteeism has been reported [18, 19]. A previous Japanese study reported that preschool children and elementary school children

suffer from fatigue more frequently than adolescents do [20]. Fatigue is a subjective and multidimensional phenomenon that is defined by how the affected individual describes it [21, 22]. Therefore, a child's fatigue may be more completely evaluated when self-reporting is included. Japanese measurements that have been developed, including a subjective fatigue scale for young adults [23], a child fatigue symptoms scale [24], and a questionnaire of subjective symptoms of fatigue for schoolchildren [25], make it possible for children to express their subjective fatigue. However, those measurements are limited by the child's age and are difficult to adapt to longitudinal evaluation. The PedsQL™ Multidimensional Fatigue Scale was designed as a generic symptom-specific instrument to measure fatigue in pediatric patients aged 2–18 years from the perspective of the children, adolescents, and their parents [7, 8, 26]. As the PedsQL™ Multidimensional Fatigue Scale would be a useful tool for measuring the fatigue of Japanese children, the primary aim of this study was to develop and test a Japanese-language version of this scale.

Although the primary source of information regarding HRQOL or fatigue is children themselves, obtaining child self-reporting poses a challenge because of cognitive developmental limitations. In addition, when children have insufficient cognitive or communication abilities, are too young, experience severe symptom distress, or find an interview to be too physically or emotionally burdensome, the use of parent proxy reports may be an effective means of obtaining information about the children. However, several studies on HRQOL and fatigue have reported imperfect agreement between child self-reports and parent proxy reports [27, 28]. Lower agreement has been found for internalized problems (e.g., pain, emotional problems) than for external problems (e.g., physical movement) [28]. In previous studies, correlations (r, ICC) between the scores of self-reports and proxy reports were measured by using total scores or domains of the measurement. These studies shed light on the degree of agreement on specific domains of HRQOL or fatigue (e.g., a high degree of agreement in external functioning was seen). Thereafter, questions were raised about how the child's age, health status, and HRQOL level affected the extent of agreement between child self-reports and parent proxy reports. Although previous studies have compared the self-reports and proxy reports of adult patients and their significant others by the levels of the patients' health status [29, 30], few have compared those of children and parents.

Consequently, the objective of this study was to examine the reliability and validity of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale for children aged 2–12 years as well as to investigate the agreement between child self-reported fatigue and parent proxy-reported fatigue.

Method

Participants

The participants were children aged 5–12 years ($n = 652$) and their parents ($n = 652$). Parents with children aged 1–4 years also participated in the survey ($n = 91$). Thus, 652 child self-reports and 743 parent proxy reports were obtained. Of the participants, 63 (9.7%) of the children and 154 (20.7%) of the parents were recruited from a preschool, and 589 (90.3%) of the children and 589 (79.3%) of the parents were recruited from an elementary school. The preschool and elementary school were located in Osaka, the second largest city of Japan, which had a population of 8,840,372 in 2009 and a gross prefecture product of 38,808,582 yen in 2006. All the children aged 5–12 years ($n = 652$) filled out the questionnaire sheet, and 20 parents did not complete the questionnaire. The average age of the 743 children (652 children with self-reporting and 91 children with only proxy reporting) studied was 8.74 years (SD = 2.41); there were 373 boys (50.2%) and 370 girls (49.8%). Of those who completed proxy reports, 704 were mothers (97.4%), 18 were fathers (2.5%), 1 was a grandmother (0.1%), and 20 were missing data. Of the 743 children, 125 (19.7%) had a chronic condition (e.g., asthma, atopic dermatology). The children with chronic conditions were those whose parents reported the presence of a chronic health condition that required control by regular medication and/or visiting an outpatient clinic.

Measures

The PedsQL™ Multidimensional Fatigue Scale (Japanese-language version)

The PedsQL™ Multidimensional Fatigue Scale was designed on the basis of the concept that disease-specific symptoms are causal indicators of generic HRQOL [31]. The measurements were developed in the United States by Dr. J. W. Varni [5] on the basis of a modular approach model measuring HRQOL in healthy children and adolescents aged 2–18 years and in those with acute and chronic health conditions [7, 8]. The PedsQL™ Multidimensional Fatigue Scale consists of 18 items that are divided into three subscales: (1) general fatigue (six items, e.g., "I feel tired"), (2) sleep/rest fatigue (six items, e.g., "I spend a lot of time in bed"), and (3) cognitive fatigue (six items, e.g., "It is hard for me to keep my attention on things"). The PedsQL™ Multidimensional Fatigue Scale comprises parallel child self-report and parent proxy report formats. Child self-reports exist for children aged 5–7, 8–12, and 13–18 years. Parent proxy reports exist for children aged 2–4 (toddler), 5–7 (young children), 8–12 (children), and

13–18 (adolescent) years, and they are used to assess the parent's perception of their child's fatigue. In this study, formats for children aged 2–4, 5–7, and 8–12 years were used. The instructions for the format for children aged 8–12 asked how much of a problem each item had during the past month. For the self-report format for children aged 5–7, the recall time was shortened to a few weeks. For both of these older age groups, a 5-point Likert scale (0: never a problem; 1: almost never a problem; 2: sometimes a problem; 3: often a problem; 4: almost always a problem) was used. For the self-report format for the younger children (aged 5–7), the response choice was simplified to a 3-point scale (0: not at all a problem; 2: sometimes a problem; 4: a major problem). The scores are calculated by using a linearly transformed reversed score range from 0 to 100 (0: 100, 1: 75, 2: 50, 3: 25, 4: 0). Higher scores indicate less fatigue. Scale scores are calculated as the sum of items divided by the number of items answered; however, when more than 50% of the items on the scale are missing, the scale score is not calculated.

The Japanese-language version was developed in three phases according to the suggested guidelines [6]: (1) forward translation (English–Japanese translation), (2) back translation (Japanese–English translation), and (3) pretesting with 21 children (5–18 years old) and 27 parents. Dr. J. W. Varni reviewed the reports of the results of each phase, and his approval was obtained before proceeding to the next phase or to the final Japanese-language version, which was used in this validation study.

The PedsQL™ 4.0 Generic Core Scales (Japanese-language version)

The Japanese-language version of the PedsQL™ 4.0 Generic Core Scales was used to assess the child's general HRQOL. The original PedsQL™ 4.0 Generic Core Scales were developed according to the definition of health given by the World Health Organization [32], and they consist of 23 items belonging to four subscales: (1) physical functioning (eight items, e. g., "It is hard for me to walk more than one block"), (2) emotional functioning (five items, e.g., "I feel afraid or scared"), (3) social functioning (five items, e.g., "I have trouble getting along with other kids"), and (4) school functioning (five items, e.g., "It is hard to pay attention in class").

The Japanese-language version of the PedsQL™ Generic Core Scales was developed by Kobayashi and Kamibeppu [16]. The Cronbach's alpha coefficients for healthy children were 0.64 for the self-reports of young children, 0.85 for the self-reports of older children and adolescents, 0.90 for the parent proxy reports for toddlers and young children, and 0.92 for the parent proxy reports for older children and adolescents [16]. A 5-point Likert scale was used with the children aged 8 and older, and a 3-point Likert scale was used with those aged between 5 and 7 years. In this study, the formats used for children aged 2–4, 5–7, and 8–12 were the same as those used for the PedsQL™ Multidimensional Fatigue Scale. Four scores can be calculated: the total score, subscale score (referring to each subscale), physical health summary score (referring to the score of the physical functioning subscale), and psychosocial health summary score (referring to the emotional functioning, social functioning, and school functioning subscales). Higher scores represent a better HRQOL.

Procedure

Children aged 8–12 years and all parents completed the measures without assistance, whereas children aged 5–7 years received assistance to complete the measures in preschool or elementary school. For children aged 2–4 years, only a proxy report was completed by the parents. All the participants received a written document that explained our procedure for the protection of their privacy and the voluntary nature of their participation. After the questionnaire and explanatory document were distributed to the parents and children, written parental informed consent and child assent were obtained. This study was approved by the Institutional Review Boards of Kobe University Graduate School of Health Sciences.

Statistical analysis

Reliability and validity

The feasibility of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale was determined by the percentage of missing values for each item [33]. Internal consistency reliability was determined by Cronbach's coefficient alpha [34].

Construct validity was examined by using the known-group method [35]. This method compares scale scores across groups known to differ in the health construct being investigated. In the given survey, the samples were divided into two groups that differed in known health condition—a healthy group ($n = 530$) and a chronic condition group of participants who needed medicine or hospital visits for treatment of their condition ($n = 102$). Independent sample t tests were used to compare the two groups. To determine the magnitude of the anticipated differences between the healthy and chronic condition groups, the effect sizes were computed by taking the difference between the healthy sample mean and the chronic sample mean, divided by the healthy sample standard deviation. The effect sizes were

designated as small (0.20), medium (0.50), and large (0.80) [36].

Construct validity was further examined by computing the intercorrelations between the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale and the Japanese-language version of the PedsQL™ Generic Core Scales. Computing the intercorrelations provides additional information on the construct validity of an instrument [37]. We hypothesized that more severe fatigue, as indicated by scores on the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale, would be associated with lower scores on the Japanese-language version of the PedsQL™ Generic Core Scales, on the basis of the concept of disease-specific symptoms as causal factors of generic HRQOL [31]. According to Cohen [36], Pearson's correlations effect sizes were considered as small (0.10–0.29), moderate (0.30–0.49), and large (≥0.50).

The factor structure of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale was extracted using confirmatory factor analysis (CFA) to assess the original three-subscale model: general fatigue, sleep/rest fatigue, and cognitive fatigue. As indices of goodness of fit, the chi-squared test, root mean squared error of approximation (RMSEA), comparative fit index (CFI), goodness of fit index (GFI), and adjusted goodness of fit index (AGFI) were used. Fit indices and reasonable values of these indices were considered as RMSEA less than 0.1 [38] and CFI, GFI, and AGFI less than 0.9 [39, 40]. Factor structure was further examined by using exploratory factor analysis (EFA). Principal components analysis with varimax rotation of the 18 items of the Japanese-language version of PedsQL™ Multidimensional Fatigue Scale was performed.

Agreement

Agreement between a child's self-report score and a parent proxy report score was examined by calculating the Pearson's correlation coefficient and intraclass correlation coefficients (ICCs). It was hypothesized that the correlations between child self-report scores and parent proxy report scores would show poor to fair correlation because fatigue is thought to be an internalized problem. In addition to correlation, the mean of the absolute differences between self-reports and proxy reports for total score and for all subscales of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale was calculated as a further indicator of the level of agreement between child and parent responses. Further, to evaluate the presence of a systematic tendency of parents to rate their children as having a better or poorer level of fatigue status than did the children themselves, the means of directional difference were calculated (proxy-reported score minus self-reported score). The mean of directional difference indicates the direction of the differences between parent proxy-reported scores and child self-reported scores [29, 41]. The mean values of directional differences were standardized (*d*) by relating a given score to its standard deviation to determine the statistical magnitude of any observed systematic bias. The size of the bias of a standardized difference (*d*) was labeled as small when it was 0.2, medium when it was 0.5, and large when it was 0.8.

To investigate how dependent the extent of agreement between child self-report and parent proxy report was on child health status, age, and HRQOL level, we calculated the ICC, the mean of the absolute difference, and the mean of the directional difference for three kinds of child–parent dyad groups. The first was determined by the child's age; the second by the parent-reported presence of the child's chronic health condition (healthy sample and chronic condition sample); and the third by the child's reported HRQOL level. With regard to the analysis of agreement levels by the child's HRQOL level, the child–parent dyads were divided into subgroups determined by cluster analysis by using the child's self-reported scores of all three subscales of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale (general fatigue, sleep/rest fatigue, and cognitive fatigue) and all four subscales of the Japanese-language version of the PedsQL™ Generic Core Scales (physical functioning, emotional functioning, social functioning, and school functioning). To determine the content of the subgroups, Ward's method was used. The ICC, the mean of the absolute difference between child self-reports and parent proxy reports, and the mean of directional differences of total score and subscales were calculated by identified subgroup. Paired *t* tests between the children's self-reports and the parents' proxy reports of total scores and subscales were also conducted. An analysis of variance (ANOVA) was performed to clarify the statistically significant differences of the mean of absolute difference, directional differences, and mean scores of parent proxy report across subgroups.

All the statistical analyses were conducted by using SPSS 14.0 and Amos 5.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Feasibility

For the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale, the percentage of data missing from child self-reports and parent proxy reports was calculated to assess the feasibility. The percentages were 0.008 and 0.169%, respectively.

Table 1 Scale descriptives and internal consistency reliability (Cronbach's alpha) for the PedsQL™ Multidimensional Fatigue Scale child self-reports and parent proxy reports

Scale	Total sample Mean (SD)	Healthy sample Mean (SD)	Chronic sample Mean (SD)	Difference	Effect size (ES)	Internal consistency reliability α			
						Total sample	Age 2–4	Age 5–7	Age 8–12
Child self-report	$n = 652$	$n = 530$	$n = 102$			$n = 652$		$n = 95$	$n = 557$
Total fatigue	76.7 (16.3)	77.6 (16.0)	72.3 (17.7)	5.3[b]	0.33	0.87	–	0.77	0.89
General fatigue	80.6 (19.0)	81.7 (18.3)	74.9 (22.1)	6.8[b]	0.37	0.81	–	0.61	0.84
Sleep/rest fatigue	71.9 (18.7)	72.8 (18.6)	67.6 (19.4)	5.2[a]	0.28	0.62	–	0.47	0.65
Cognitive fatigue	77.9 (20.2)	78.5 (20.4)	74.5 (19.4)	4.0	0.20	0.82	–	0.68	0.84
Parent proxy report	$n = 743$	$n = 594$	$n = 125$			$n = 743$	$n = 91$	$n = 95$	$n = 557$
Total fatigue	84.7 (13.9)	85.6 (13.6)	80.2 (14.4)	5.4[b]	0.40	0.93	0.93	0.91	0.94
General fatigue	84.0 (15.8)	84.9 (15.6)	79.4 (16.3)	5.5[b]	0.35	0.88	0.89	0.83	0.88
Sleep/rest fatigue	85.2 (15.4)	86.2 (14.8)	79.9 (17.2)	6.3[b]	0.43	0.81	0.73	0.80	0.82
Cognitive fatigue	85.1 (16.4)	85.8 (16.1)	81.3 (17.4)	4.5[b]	0.28	0.92	0.94	0.91	0.92

Twenty child self-reports and 24 parent proxy reports of chronic condition group were missing data

α Cronbach's coefficient alpha

ES effect size. Effect sizes are designated as small (0.20), medium (0.50), and large (0.80)

[a] The scores of children with a chronic condition were significantly lower than the scores of healthy children at $P < 0.05$ based on an independent sample student *t* test

[b] The scores of children with a chronic condition were significantly lower than the scores of healthy children at $P < 0.01$ based on an independent sample student *t* test

Internal consistency reliability

Internal consistency reliability alpha coefficients for the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale are shown in Table 1. The alpha coefficients of the sleep/rest fatigue scale of the total sample fell below the reliability standard of 0.70, which is required to compare groups [42]; however, the rest of the scales exceeded the satisfaction criterion. The alpha coefficients of younger children (aged 5–7 years) were lower than those of older children (aged 8–12 years).

Construct validity

Table 1 shows the mean scores and standard deviations of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale scores for child self-reports and parent proxy reports for the total sample, as well as for the healthy and chronic condition samples that were extracted out of the total sample. The scores of child self-reports and parent proxy reports of children with chronic conditions indicated that these children had statistically significant worse fatigue than the healthy children; the effect sizes were in the medium range (0.20–0.37 for child self-report and 0.28–0.43 for parent proxy report). Table 2 shows the intercorrelations between the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale and the Japanese-language version of the PedsQL™ Generic Core Scales. Scores of the PedsQL™ Multidimensional Fatigue scale and the PedsQL™ Generic Core Scales were significantly correlated, which indicated that worse fatigue correlated with worse generic HRQOL. The effect sizes (*r*) of Pearson's correlations were in the medium to large effect size range (for child self-report, *r* was 0.39–0.75; for parent proxy report, *r* was 0.35–0.73).

The results of the CFA for the 3-subscale model for both child self-report and parent proxy report are shown in Table 3. The GFI for child self-report was greater than 0.90; however, the CFI and AGFI for both child self-report and parent proxy report were slightly less than 0.9. Goodness of fits for the child self-report were better than the parent proxy report, which did not meet the pre-established criterion for RMSEA. Factor analysis with varimax rotation (EFA) extracted three factors for both child self-report and parent proxy report: Factor 1 (cognitive fatigue), Factor 2 (general fatigue), and Factor 3 (sleep/rest fatigue). The eigenvalues cutoff of 1.0, total variances explained were 39.6 and 58.1% variance for self-report and proxy report, respectively (Table 4). Four items of child self-report were loaded highest on a factor other than the a priori hypothesized factor structure. At the more detailed level, Items 8, 9, and 11 ("It is hard for me to sleep through the night," "I feel tired when I wake up in the morning," and "I take a lot of naps") split into general fatigue (Factor 2). Similarly, Item 5 ("I have trouble finishing things") loaded highest on cognitive fatigue (Factor

Table 2 Intercorrelations among the PedsQL™ Multidimensional Fatigue Scale and the PedsQL™ Generic Core Scales for child self-reports and parent proxy reports

Scale	Child self-report				Parent proxy report			
	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue	Total fatigue	General fatigue	Sleep/rest fatigue	Cognitive fatigue
Total score	0.75	0.69	0.59	0.62	0.72	0.66	0.61	0.61
Physical	0.62	0.59	0.49	0.50	0.45	0.42	0.43	0.35
Psychosocial	0.71	0.66	0.56	0.59	0.73	0.68	0.60	0.65
Emotional	0.62	0.54	0.52	0.49	0.60	0.56	0.52	0.49
Social	0.56	0.54	0.39	0.48	0.63	0.58	0.49	0.59
School	0.55	0.50	0.43	0.46	0.65	0.66	0.61	0.61

Pearson's correlations, effect sizes are designated as small (0.10), moderate (0.30), and large (0.50)

* $P < 0.01$ for all figures

Physical physical functioning, *psychosocial* psychosocial health summary score, *emotional* emotional functioning, *social* social functioning, *school* school functioning

Table 3 Results of confirmatory factor analysis for the 3-factor model

Model	χ^2	*df*	χ^2/df	RMSEA	CFI	GFI	AGFI
Child self-report	575.8*	132	4.36	0.072	0.88	0.90	0.87
Parent proxy report	1,148.4*	132	8.12	0.102	0.88	0.83	0.78

* $P < 0.001$

1). Regarding parent proxy reports, three items were split into a factor other than the a priori scale; Items 5 and 6 ("I have trouble finishing things" and "I have trouble starting things") were loaded on cognitive fatigue (Factor 1); and Item 9 ("I feel tired when I wake up in the morning") was loaded on general fatigue (Factor 2).

Agreement

There was no significant difference between the scores of male children and those of female children. Figure 1 shows how the age of the child affected directional differences between child self-report scores and parent proxy report scores on the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale. Children who were 10 years old demonstrated the smallest biases for total scores and all subscales. For most child age groups, parents overestimated their children's fatigue. The mean of the directional differences was significant across age groups.

Table 5 shows the agreement level by child health status. The ICCs of the chronic condition sample were slightly higher than those of the healthy sample; however, the mean differences of the means of the absolute difference and directional difference did not differ significantly between the healthy sample and chronic condition sample.

To identify subgroups by the children's HRQOL levels, the scores of 650 child self-reports for all subscales of the PedsQL™ Multidimensional Fatigue Scale and the PedsQL™ Generic Core Scales were entered into the cluster analysis. A three-cluster solution was obtained, where one subgroup ($n = 317$, 48.8%) included those with high scores on all subscales (good HRQOL group); a second subgroup ($n = 229$, 35.2%) included samples with intermediate level scores on all subscales (intermediate HRQOL group); and a third subgroup ($n = 104$, 16.0%) had low scores on all subscales (poor HRQOL group). Significant differences were seen in the average age of children found in the three subgroups: children in the intermediate HRQOL group were younger than children in the good HRQOL group (Tukey post hoc test, $P = 0.02$). The frequency among the subgroups of the number of children who had a chronic condition was significantly different (chi-square test, $P = 0.04$). Table 6 shows the means of the scores of the PedsQL™ Generic Core Scales by the subgroups identified by cluster analysis. Table 7 shows the means, standard deviations, correlation r and ICC, absolute difference, and directional difference (standardized difference d) of the child self-reported and parent proxy-reported total scores on the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale. The total scores of child self-reports and parent proxy reports and all the subscale scores of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale were significantly different among subgroups. The good HRQOL group had the highest total scores, subscale scores, and correlation r's and ICCs, and the poor HRQOL group had the lowest. The absolute and directional differences among the three subgroups were significantly different, with the largest differences seen in the poor HRQOL group, and the smallest differences, in the good

Table 4 Factor loadings for the Japanese version of PedsQL™ Multidimensional Fatigue Scale

Scale/item	Factor 1		Factor 2		Factor 3	
General fatigue						
1. I feel tired	.230	.196	**.549**	**.682**	.437	.338
2. I feel physically weak (not strong)	.313	.320	**.497**	**.634**	.148	.265
3. I feel too tired to do things that I like to do	.177	.215	**.717**	**.732**	.140	.314
4. I feel too tired to spend time with my friends	.074	.283	**.706**	**.642**	.136	.266
5. I have trouble finishing things	**.594**	**.553**	.490	.484	−.066	.213
6. I have trouble starting things	.465	**.540**	**.478**	.495	−.045	.235
Sleep/rest fatigue						
7. I sleep a lot	.066	.119	.030	.405	**.286**	**.514**
8. It is hard for me to sleep through the night	.109	.223	**.292**	.219	.263	**.337**
9. I feel tired when I wake up in the morning	.211	.172	**.497**	**.554**	.435	.470
10. I rest a lot	.370	.301	.280	.464	**.372**	**.584**
11. I take a lot of naps	.111	.169	**.307**	.207	.097	**.570**
12. I spend a lot of time in bed	.242	.260	.255	.240	**.398**	**.630**
Cognitive fatigue						
13. It is hard for me to keep my attention on things	**.541**	**.649**	.295	.317	.085	.192
14. It is hard to for me to remember what people tell me	**.622**	**.837**	.259	.233	.181	.141
15. It is hard for me to remember what I just heard	**.549**	**.775**	.123	.167	.255	.261
16. It is hard for me to think quickly	**.673**	**.752**	.129	.268	.159	.170
17. I have trouble remembering what I was just thinking	**.540**	**.773**	.119	.148	.294	.292
18. I have trouble remembering more than one thing at a time	**.588**	**.815**	.086	.135	.303	.176

Total variance explained was 39.6% for child self-report and 58.1% for parent proxy report

Highest factor loadings for each item are shown in bold

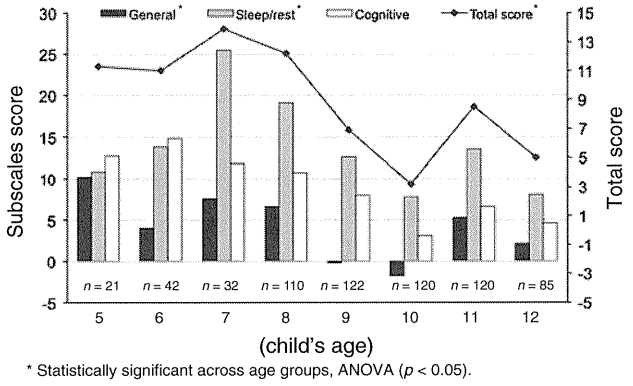

Fig. 1 Directional differences between child self-reports and parent proxy reports of scores on the PedsQL™ Multidimensional Fatigue Scale, by age of child. *Statistically significant across age groups, ANOVA ($P < 0.05$)

HRQOL group. Similarly, accounting for the direction, the good HRQOL group showed the smallest bias, and parents of this subgroup gave slightly lower ratings on the PedsQL™ Multidimensional Fatigue Scale than the children did, which means that parents estimated their children's fatigue worse than the children themselves. In contrast, the poor HRQOL group showed the largest bias, and the ratings of parents in that subgroup were higher than those of their children, by approximately 1 point of the PedsQL™ Multidimensional Fatigue Scale (where 1 point scores 25). The parents of children in the poor HRQOL group estimated their children's fatigue as less severe when compared to the severity of fatigue reported by their children.

Discussion

Reliability and validity

The results of this study supported the reliability and validity of the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale with specified report formats for toddlers (2–4 years old), young children (5–7 years old), and older children (8–12 years old). The lack of missing responses for items on the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale indicated the simplicity of each item on the scale, and children of all ages and their parents were willing and able to provide good quality data regarding the child's fatigue.

The internal consistency reliability of the total sample for both child self-reported and parent proxy-reported

Table 5 Agreement between child self-reports and parent proxy reports by children's health status

	n	PedsQL™ Fatigue Score		Difference	Correlation		Absolute child–parent difference[e]	Directional difference[f] (systematic bias)	
		Child	Parent	*t* score[b]	*r*[c]	ICC[d]	Mean (SD)	Mean (SD)	*d*[g]
Healthy sample									
PedsQL™ fatigue	530	77.6[a]	85.6[a]	−9.5**	0.17	0.29	16.1 (13.3)	8.0 (19.3)	0.41
General fatigue	525	81.7[a]	84.9[a]	−3.1**	0.20	0.32	16.0 (15.0)	3.0 (21.7)	0.14
Sleep/rest fatigue	526	72.8[a]	86.2[a]	−14.1**	0.19	0.31	19.9 (15.9)	13.4 (21.7)	0.62
Cognitive fatigue	526	78.5	85.8[a]	−7.3**	0.12	0.20	19.1 (17.0)	7.7 (24.4)	0.32
Chronic condition sample									
PedsQL™ fatigue	102	72.3[a]	80.2[a]	−3.6**	0.37	0.53	14.6 (13.3)	7.2 (18.4)	0.39
General fatigue	101	74.9[a]	79.4[a]	−1.2	0.24	0.38	18.2 (16.3)	3.0 (24.3)	0.12
Sleep/rest fatigue	101	67.6[a]	79.9[a]	−5.3**	0.32	0.49	18.6 (16.0)	11.5 (21.8)	0.53
Cognitive fatigue	101	74.5	81.3[a]	−3.1**	0.37	0.53	15.9 (14.9)	7.1 (20.7)	0.34

[a] Statistically significant between healthy sample and chronic condition sample, independent student *t* test at ($P < 0.05$)

[b] Paired student *t* test between child and parent scores, statistically significant difference between child and parent mean scores (** $P < 0.01$)

[c] Pearson's correlation

[d] Intraclass correlation coefficient

[e] Absolute difference between child and parent scores (indicator of agreement)

[f] Difference between child and parent scores (indicator of bias)

[g] Standardized difference d = mean direction of difference/standard deviation of direction of difference ($d = 0.2$ small, 0.5 medium, and 0.8 large bias)

Table 6 The characteristics of subgroups identified by the cluster analysis

PedsQL™ Generic Core	*n*	Score [mean(SD)]		Chronic condition[a]
		Child[b]	Parent[c]	Chronic/healthy (%)
All samples	650	80.3 (13.0)	87.5 (12.0)	102/530 (19.2)
Physical health summary score	650	86.1 (13.7)	88.7 (19.1)	
Psychosocial health summary score	650	78.4 (14.3)	87.2 (11.7)	
Good HRQOL group	317	89.9 (5.5)	89.4 (10.9)	41/270 (15.2)
Physical health summary score	317	93.8 (6.5)	89.8 (18.9)	
Psychosocial health summary score	317	88.7 (6.6)	89.3 (10.2)	
Intermediate HRQOL group	229	76.2 (7.2)	87.5 (12.7)	37/183 (20.2)
Physical health summary score	229	83.3 (12.9)	88.9 (19.3)	
Psychosocial health summary score	229	73.9 (8.4)	87.0 (12.5)	
Poor HRQOL group	104	59.7 (10.1)	82.0 (12.1)	24/77 (29.9)
Physical health summary score	104	68.8 (13.3)	84.7 (19.1)	
Psychosocial health summary score	104	56.7 (12.2)	81.1 (12.4)	

[a] Statistically significant across 3 subgroups, chi-square test ($P = 0.04$)

[b] Statistically significant across 3 subgroups, ANOVA ($P < 0.01$)

[c] Statistically significant across 3 subgroups for total score and psychosocial health summary score, ANOVA ($P < 0.01$)

scores achieved the recommended minimal Cronbach's alpha coefficient standard (0.70) for total score and for all the subscales except the self-reported score of the sleep/rest fatigue subscale, where the alpha coefficient was 0.62 and therefore fell short of the standard. It should be noted that in previous studies of the PedsQL™ Multidimensional Fatigue Scale, the sleep/rest fatigue subscale exhibited the lowest alpha value of the three subscales [43, 44]. Furthermore, the participants in this study were younger than those previously studied, and the low alpha value may be

Table 7 Agreement between child self-reports and parent proxy reports by subgroups based on cluster analysis

	n	PedsQL™		Difference	Child–parent correlation		Absolute difference[d]	Directional difference[e] (systematic bias)	
		Fatigue score		*t* score[a]	*r*[b]	ICC[c]	Mean (SD)[g]	Mean (SD)[g]	*d*[f]
		Child	Parent						
All samples	650	76.7	84.7	−10.4**	0.22	0.32	15.9 (13.3)	7.9 (19.1)	0.41
General fatigue	630	80.6	83.6	−3.4**	0.22	0.36	16.4 (15.2)	3.0 (22.2)	0.14
Sleep/rest fatigue	631	71.8	84.9	−15.2**	0.23	0.36	19.7 (15.9)	13.1 (21.7)	0.60
Cognitive fatigue	631	77.9	85.6	−8.1**	0.16	0.28	18.6 (16.7)	7.6 (23.8)	0.31
Good HRQOL group	317	89.3	86.7	3.4**	0.18	0.25	10.4 (9.4)	−2.7 (13.7)	−0.20
General fatigue	310	93.1	85.8	7.8**	0.12	0.18	12.6 (12.6)	−7.2 (16.3)	−0.44
Sleep/rest fatigue	311	83.6	87.0	−3.4**	0.16	0.27	13.7 (11.5)	3.4 (17.6)	0.19
Cognitive fatigue	311	91.5	87.4	4.3**	0.18	0.27	11.9 (12.4)	−4.1 (16.7)	−0.25
Intermediate HRQOL group	229	71.4	84.7	−12.7**	0.07	0.11	17.4 (11.1)	13.4 (15.7)	0.85
General fatigue	219	76.5	83.4	−5.3**	0.12	0.22	16.0 (12.5)	6.9 (19.1)	0.36
Sleep/rest fatigue	219	65.7	85.4	−14.8**	0.15	0.26	23.0 (15.6)	19.7 (19.6)	1.01
Cognitive fatigue	219	71.6	85.2	−9.2**	0.06	0.10	21.4 (14.5)	13.6 (22.0)	0.62
Poor HRQOL group	104	49.8	78.2	−15.7**	0.01	0.01	29.5 (17.0)	28.7 (18.3)	1.57
General fatigue	100	50.7	76.7	−10.8**	0.09	0.17	29.2 (20.1)	26.0 (24.2)	1.07
Sleep/rest fatigue	100	48.4	77.4	−12.7**	0.05	0.09	31.1 (19.9)	29.0 (22.9)	1.27
Cognitive fatigue	100	49.4	80.5	−12.7**	0.01	0.02	33.4 (21.1)	31.0 (24.5)	1.27

[a] Paired student *t* test between child and parent scores, statistically significant difference between child and parent mean scores (** $P < 0.01$)

[b] Pearson's correlation

[c] Intraclass correlation coefficient

[d] Absolute difference between child and parent scores (indicator of agreement)

[e] Difference between child and parent scores (indicator of bias)

[f] Standardized difference d = mean direction of difference/standard deviation of direction of difference ($d = 0.2$ small, 0.5 medium, and 0.8 large bias)

[g] Statistically significant difference across 3 subgroups for total score and all subscales, poor > intermediate > good based on ANOVA with Tukey's post hoc test

related to the child's age. Similarly, lower alphas for the formats of the self-reports and proxy reports for younger children may be influenced by the smaller sample size of younger children [45] as well as the child's age.

The Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale generally performed as hypothesized when the known-group method was used to compare fatigue in healthy children with that in children with chronic conditions. As a group, the children with chronic conditions manifested significantly more fatigue than the healthy children. The Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale demonstrated good construct validity and usefulness in a school population. It was also sensitive enough to detect differences in children even if the children's health levels are good enough to attend school or preschool. At the more detailed level, the cognitive fatigue subscale demonstrated the smallest effect sizes of the three fatigue subscales for both child and parent reports, which corresponded with the results of previous studies that used the PedsQL™ Multidimensional Fatigue Scale in cases involving rheumatology, type 1 diabetes, fibromyalgia, and bowel disease [7, 26, 43, 46]. However, in cases involving brain tumors, the cognitive fatigue effect sizes for both child self-reports and parent proxy reports were larger than the effect sizes for sleep/rest fatigue [47], and the effect sizes were larger than those in this study or in other previous studies. Perhaps cognitive fatigue is not easily influenced by disease, but brain tumors do influence children's cognitive fatigue.

The intercorrelations between the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale and the Japanese-language version of the PedsQL™ Generic Core Scales were consistent with the concept of disease-specific symptoms as causal indicators of HRQOL [31], and this result emphasizes the importance of recognizing the effect of fatigue on children's HRQOL.

The results of the factor structure analyses were generally consistent with the a priori hypothesized factor structure of the original PedsQL™ Multidimensional Fatigue Scale. First, we conducted CFA to examine the goodness of fit of

the original a priori factor structure, and the results indicated some exceptions. Then, EFA was conducted to examine the initial construct validity of the PedsQL™ Multidimensional Fatigue Scale for children aged 2–12 years in Japan. The result of EFA confirmed the exceptions with regard to four items for child self-report and three items for parent proxy report, respectively; otherwise, the factors that emerged were consistent with the a priori hypothesized factor structure. Regarding the child self-report, Item 8 ("It is hard for me to sleep through the night") and Item 9 ("I feel tired when I wake up in the morning") of sleep/rest fatigue were loaded on general fatigue. The same results were reported with a university student population [44]. Previous surveys of preschool children and schoolchildren reported that approximately 50% of preschool children and 80% of schoolchildren answered that sleepiness was a symptom of fatigue in Japan [48, 49]; therefore, it is possible that children of these ages think of sleepiness as general fatigue. Furthermore, Item 5 ("I have trouble finishing things") and Item 6 ("I have trouble starting things") were loaded on cognitive fatigue. Perhaps doing things is more related to cognitive fatigue than general fatigue in Japan.

Agreement

The findings of this study demonstrated poor to fair correlations between reports by children and their parents. The results supported our hypothesis, and they were similar to those reported by Varni et al. [26, 50] in previous studies that focused on children with type 1 diabetes and their parents as well as obese children and their parents.

We examined agreement across age groups, and the results showed that the older the child, the smaller the bias. Cremeens et al. [28] reported that age affects the correlation between child and parent ratings, with a higher agreement for older children with respect to psychosocial aspects of health compared to a higher agreement for younger children concerning physical health. Our study supported this finding and added further implications for the child–parent agreement by examining the bias between child and parent ratings.

Differences in the mean of absolute difference and directional difference between the healthy sample and chronic condition sample were not significant. This finding indicates the possibility that the child's health status does not affect the child–parent agreement level. However, Yeh et al. [51], who investigated the agreement between children with cancer and their parents, reported greater agreement of ICC for off-treatment children than for on-treatment children and they stated that the severity of cancer was a significant predictor of the level of disagreement. On the other hand, the majority of the chronic condition children in this study had asthma or atopic dermatitis that were adequately controlled by regular hospital visits and/or medication, and these children were not expected to manifest severe fatigue symptom such as those presented by children with cancer, rheumatology, heart disease, or other severe chronic illnesses. It is possible that the difference in illness severity among the participants caused these contrary findings (children with cancer versus children with a chronic condition that can be treated at home). Further investigation with participants varying in severity of illnesses will be of significance in this regard. However, the Japanese-language version of PedsQL™ Multidimensional Fatigue Scale showed significant differences between the scores of healthy children and those with a chronic condition. These results supported that the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale is adequately sensitive to small differences in child's fatigue.

Accounting for agreement between children and parents by the subgroups that were identified by cluster analysis based on the children's self-reported scores (in other words, the children's perceived HRQOL), the number of children who had chronic conditions was significantly different among the three identified subgroups, which supports the reliability of child self-reports. Integrating the results of the indicators we used in this study (r, ICC, absolute difference, directional difference) indicated that a maximum level of agreement was seen in the good HRQOL group, and a minimum level was seen in the poor HRQOL group. The parents estimated their child's fatigue as less severe when compared to the severity reported by their children, when the child's HRQOL was worse. On the other hand, the parents of children with high HRQOL rated them as having more fatigue. The average absolute difference between the child and parent scores in the poor HRQOL group was approximately 1 point. This suggests that in cases of high and low HRQOL, parents sometimes provide different information on fatigue than their children do themselves. Taken together, the findings suggest that the information on fatigue provided by the parent proxy report is not equivalent to that of the child self-report. However, this should not be interpreted as evidence of the inaccuracy of parent proxy-reported fatigue because child self-reports and parent proxy reports demonstrated acceptable reliability in this study. Thus, it will be helpful to understand the existence of differences and to identify the patterns of differences on the basis of the child's health status, child's age, parent's health status, and the child/parent relationship. This study showed that when a child is aged 5–12 years and is healthy enough to attend school, agreement between child and parent reports is high for children perceived to be in the good HRQOL group and low for those in the poor HRQOL group. Further, parents perceived

their children's fatigue as less severe when compared to the severity reported by their children, when the children had poor HRQOL scores. Our findings suggest that the child's age and HRQOL level could affect child–parent disagreement and that the child's health status would not affect disagreement as much as the age and HRQOL level.

The present study has several potential limitations. First, we did not examine the validity and agreement of the format for children aged 13–18 years. The PedsQL™ original version is formatted for children aged 13–18 years; therefore, validating the format for children aged 13–18 years will increase the value and usefulness of the Japanese version of the PedsQL™ Multidimensional Fatigue Scale. Based on the foregoing, additional documentation in this age range is needed, and we will address this issue in an ongoing study of fatigue of in adolescents. Second, we compared scores between healthy children and chronic condition children. However, these two groups were determined using parent reports of the presence of a chronic health condition that needed to be controlled by regular medication and/or visiting an outpatient clinic. In addition, the influence of illness severity was not considered, which could limit the generalizability of the findings. Illness severity may influence the HRQOL rating provided by children and parents and it could possibly explain the differences between the scores of children with chronic condition who belonged to the good HRQOL group or poor HRQOL group.

Acknowledgments We greatly appreciate the children and parents who participated in this study and the teachers who supported our research. We also appreciate Dr. James W. Varni, who gave us permission to develop the Japanese-language version of the PedsQL™ Multidimensional Fatigue Scale and provided great support during the process of development. This study was supported in part by grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan; grants from the Ministry of Health, Labor and Welfare of Japan; and funds from Suyama Research Foundation.

References

1. Langgraf, J. M., & Abetz, L. N. (1997). Functional status and well-being of children representing three cultural groups: Initial self-reports using the CHQ-CF87. *Psychology & Health, 12*, 839–865.
2. Feeny, D., Furlong, W., & Barr, R. D. (1998). Multiattribute approach to the assessment of health-related quality of life: Health Utilities Index. *Medical and Pediatric Oncology, 1*(Supplement), 54–59.
3. Vogels, T., Verrips, G. H., Verloove-Vanhorick, S. P., Fekkes, M., Kamphuis, R. P., Koopman, H. M., et al. (1998). Measuring health-related quality of life in children: The development of the TACQOL parent form. *Quality of Life Research, 7*, 457–465.
4. Ravens-Sieberer, U., & Bullinger, M. (1998). Assessing health-related quality of life in chronically ill children with the German KINDL: First psychometric and content analytic results. *Quality of Life Research, 7*, 399–407.
5. Varni, J. W., Seid, M., & Rode, C. A. (1999). The PedsQL™: Measurement model for the pediatric quality of life inventory. *Medical Care, 37*, 126–139.
6. Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ version 4.0 generic core scales in healthy and patient populations. *Medical Care, 39*, 800–812.
7. Varni, J. W., Burwinkle, T. M., & Szer, I. S. (2004). The PedsQL™ Multidimensional Fatigue Scale in pediatric rheumatology: Reliability and validity. *The Journal of Rheumatology, 31*, 2494–2500.
8. Varni, J. W., Burwinkle, T. M., Katz, E. R., Meeske, K., & Dickinson, P. (2002). The PedsQL™ in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer, 94*, 2090–2106.
9. Varni, J. W., Burwinkle, T. M., Jacobs, J. R., Gottschalk, M., Kaufman, F., & Jones, K. L. (2003). The PedsQL™ in type 1 and type 2 diabetes: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Type 1 Diabetes Module. *Diabetes Care, 26*, 631–637.
10. Varni, J. W., Burwinkle, T. M., & Seid, M. (2006). The PedsQL™ 4.0 as a school population health measure: Feasibility, reliability, and validity. *Quality of Life Research, 15*, 203–215.
11. Seid, M., Varni, J. W., Gidwani, P., Gelhard, L. R., & Slymen, D. J. (2010). Problem-solving skills training for vulnerable families of children with persistent asthma: Report of a randomized trial on health-related quality of life outcomes. *Journal of Pediatric Psychology*. http://jpepsy.oxfordjournals.org/cgi/reprint/jsp133v1?maxtoshow=&hits=10&RESULTFORMAT=&searchid=1&FIRSTINDEX=0&resourcetype=HWCIT. Accessed 10 May 2010.
12. Clarke, S. A., Skinner, R., Guest, J., Darbyshire, P., Cooper, J., Shah, F., et al. (2010). Health-related quality of life and financial impact of caring for a child with Thalassaemia Major in the UK. *Child: Care, Health and Development, 36*, 118–122.
13. Tahirović, E., Begić, H., Nurkić, M., Tahirović, H., & Varni, J. W. (2010). Does the severity of congenital heart defects affect disease-specific health-related quality of life in children in Bosnia and Herzegovina? *European Journal of Pediatrics, 169*, 349–353.
14. Varni, J. W., Limbers, C. A., Newman, D. A., & Seid, M. (2008). Longitudinal factorial invariance of the PedsQL™ 4.0 Generic Core Scales child self-report version: One year prospective evidence from the California State Children's Health Insurance Program (SCHIP). *Quality of Life Research, 17*, 1153–1162.
15. Eiser, C., Vance, Y. H., Horne, B., Glaser, A., & Galvin, H. (2003). The value of the PedsQL™ in assessing quality of life in survivors of childhood cancer. *Child: Care, Health and Development, 29*, 95–102.
16. Kobayashi, K., & Kamibeppu, K. (2010). Measuring quality of life in Japanese children: Development of the Japanese version of PedsQL™. *Pediatrics International, 52*, 80–88.
17. Swain, M. G. (2000). Fatigue in chronic disease. *Clinical Science, 99*, 1–8.
18. Bakker, R. J., van de Putte, E. M., Kuis, W., & Sinnema, G. (2009). Risk factors for persistent fatigue with significant school absence in children and adolescents. *Pediatrics, 124*, 89–95.
19. Sankey, A., Hill, C. M., Brown, J., Quinn, L., & Fletcher, A. (2006). A follow-up study of chronic fatigue syndrome in children and adolescents: Symptom persistence and school absenteeism. *Clinical Child Psychology and Psychiatry, 11*, 126–138.
20. Saito, K. (2000). Fatigue and stress in children. *The Journal of Child Health, 59*, 131–138. (in Japanese).
21. Gibson, F., Mulhall, A. B., Richardson, A., Edwards, J. L., Ream, E., & Sepion, B. J. (2005). A phenomenologic study of fatigue in adolescents receiving treatment for cancer. *Oncology Nursing Forum, 32*, 651–660.

22. Edwards, J. L., Gibson, F., Richardson, A., Sepion, B., & Ream, E. (2003). Fatigue in adolescents with and following a cancer diagnosis: Developing an evidence base for practice. *European Journal of Cancer, 39*, 2671–2680.
23. Kobayashi, H., Demura, S., Goshi, F., Sato, S., & Noda, M. (2000). Construction of a subjective fatigue scale for adolescent students. *Japanese Journal of Public Health, 47*, 638–646. (in Japanese).
24. Mitsuoka, S., Horii, S., Ohmura, N., Kasagara, M., Suzuki, M., & Oyama, M. (2003). The relationships between child fatigue and symptoms and children's lifestyles using a Child Fatigue Symptoms Scale. *The Journal of Child Health, 62*, 81–87.
25. Maehashi, A., & Ogata, M. (1993). Constructing a questionnaire to clarify the subjective symptoms of fatigue for elementary schoolchildren. Part 1: An assessment of the questions. *Kawasaki Medical Welfare Journal, 3*, 75–86. (in Japanese).
26. Varni, J. W., Limbers, C. A., Bryant, W. P., & Wilson, D. P. (2008). The PedsQL™ Multidimensional Fatigue Scale in type 1 diabetes: Feasibility, reliability, and validity. *Pediatric Diabetes, 10*, 321–328.
27. Drotar, D. (Ed.). (1998). *Measuring health-related quality of life in children and adolescents: Implications for research and practice*. Hillsdale, NJ: Lawrence Erlbaum Associates.
28. Cremeens, J., Eiser, C., & Blades, M. (2006). Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life Inventory™ 4.0 (PedsQL™) generic core scales. *Health and Quality of Life Outcomes, 4*, 58–65.
29. Sneeuw, K. C. A., Aaronson, N. K., Sprangers, A. G., Detmar, S. B., Wever, L. D. V., & Schornagel, J. H. (1998). Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. *Journal of Clinical Epidemiology, 51*, 617–631.
30. Williams, L. S., Bakas, T., Brizendine, E., Plue, L., Tu, W., Hendrie, H., et al. (2006). How valid are family proxy assessment of stroke patients' health-related quality of life? *Stroke, 37*, 2081–2085.
31. Fayers, P. M., & Machin, D. (2000). *Quality of life: Assessment, analysis, and interpretation*. New York, NY: Wiley.
32. World Health Organization. (1948). *Constitution of the World Health Organization basic documents*. Geneva: World Health Organization.
33. McHorney, C. A., Ware, J. E., Jr., Lu, J. F., & Sherbourne, C. D. (1994). The MOS 36-item Short-form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care, 32*, 40–66.
34. Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika, 16*, 297–334.
35. McHorney, C. A., Ware, J. E., & Raczek, A. E. (1993). The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care, 31*, 247–263.
36. Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.
37. Pedhazur, E. J., & Schemelkin, L. P. (1991). *Measurement, design, and analysis: An integrated approach*. Hillsdale, NJ: Lawrence Erlbaum Associates.
38. Browne, M. W., & Cudeck, R. (1993). Alternative ways of assessing model fit. In K. Bollen & J. S. Long (Eds.), *Testing structural equation models* (pp. 147–162). Newbury Park, CA: Sage Publications.
39. Bentler, P. M. (1995). Comparative fit indexed in structural models. *Psychological Bulletin, 107*, 238–246.
40. Bentler, P. M., & Bonett, D. G. (1980). Significance tests and goodness of fit in the analysis of covariance structures. *Psychological Bulletin, 88*, 588–606.
41. Sneeuw, K. C. A., Aaronson, N. K., Osoba, D., Muller, M., Hsu, M., Yung, W. K. A., et al. (1997). The use of significant others as proxy rates of the quality of life of patients with brain cancer. *Medical Care, 35*, 490–506.
42. Nunnally, J. C., & Bernstein, I. H. (1994). *Psychometric theory* (3rd ed.). New York, NY: McGraw-Hill.
43. Varni, J. W., Burwinkle, T. M., Limbers, C. A., & Szer, I. S. (2007). The PedsQL™ as a patient-reported outcome in children and adolescents with fibromyalgia: An analysis of OMERACT domains. *Health and Quality of Life Outcomes, 5*, 9–20.
44. Varni, J. W., & Limbers, C. A. (2008). The PedsQL™ Multidimensional Fatigue Scale in young adults: Feasibility, reliability and validity in a university student population. *Quality of Life Research, 17*, 105–114.
45. DeVellis, R. E. (2003). *Scale development: Theory and applications* (2nd ed.). Thousand Oaks, CA: Sage Publications.
46. Marcus, S. B., Strople, J. A., Neighbors, K., Weissberg-Benchell, J., Nelson, S. P., Limbers, C., et al. (2009). Fatigue and health-related quality of life in pediatric inflammatory bowel disease. *Clinical Gastroenterology and Hepatology, 7*, 554–561.
47. Palmer, S. N., Meeske, K. A., Katz, E. R., Burwinkle, T. M., & Varni, J. W. (2007). The PedsQL™ Brain Tumor Module: Initial reliability and validity. *Pediatric Blood & Cancer, 49*, 287–293.
48. Shibaki, M., Taniyama, N., Fujii, A., Nasaki, M., & Sasajima, Y. (2010). A study on symptoms of fatigue in preschool children (first report)—the relationship between fundamental lifestyle and eating habits. *Journal of Hokkaido University of Education, 60*, 83–96. (in Japanese).
49. Nakamura, K., Ueya, K., Miyamaru, G., Maebashi, A., Kawazoe, K., Yamada, N., et al. (1997). A study on lifestyle, physical activities, and subjective symptoms in schoolchildren. *Proceedings of the Congress of the Japanese society of Physical Education, 48*, 391. (in Japanese).
50. Varni, J. W., Limbers, C. A., Bryant, W. P., & Wilson, D. P. (2010). The PedsQL™ Multidimensional Fatigue Scale in pediatric obesity: Feasibility, reliability and validity. *International Journal of Pediatric Obesity, 5*, 34–42.
51. Yeh, C., Chang, C., & Chang, P. (2005). Evaluating quality of life in children with cancer using children's self-reports and parent-proxy reports. *Nursing Research, 54*, 354–362.

Molecular Genetics and Metabolism 100 (2010) S59–S64

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Citrin deficiency and current treatment concepts

Takeyori Saheki [a,*], Kanako Inoue [a], Anmi Tushima [a], Kozo Mutoh [b], Keiko Kobayashi [c]

[a] Institute for Health Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan
[b] Department of Pediatrics, Shimada Municipal Hospital, Shimada 427-8502, Japan
[c] Department of Molecular Metabolism and Biochemical Genetics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima 890-8544, Japan

ARTICLE INFO

Article history:
Received 4 January 2010
Accepted 22 February 2010
Available online 24 February 2010

Keywords:
Adult-onset type II citrullinemia (CTLN2)
Carbohydrate toxicity
Citrin deficiency
Hyperammonemia
Mitochondrial aspartate–glutamate carrier
Neonatal intrahepatic cholestasis (NICCD)
SLC25A13
Sodium pyruvate

ABSTRACT

In this paper, we describe the historical aspects of citrin and citrin deficiency, characteristic food preference and food aversion of citrin-deficient subjects, and carbohydrate toxicity in relation to ureogenesis and issues of the conventional treatment procedures for hyperammonemia in citrin deficiency, leading to current treatment concepts for citrin deficiency. We also emphasize the importance of a citrin deficiency mouse model in elucidating the pathophysiology and developing novel therapeutics based on the pathophysiology, such as sodium pyruvate.

Historical aspect citrin and citrin deficiency

Human citrin deficiency is a newly-established disease entity [1,2] that encompasses both adult-onset type II citrullinemia (CTLN2) and neonatal intrahepatic cholestasis (NICCD), and results from mutations in the *SLC25A13* gene that encodes citrin [3]. It was first described in Japan and East Asia, but is now a panethnic disease [4]. Citrin and the closely-related protein aralar (encoded by *SLC25A12*) [5] are isoforms of the mitochondrial aspartate (Asp)–glutamate (Glu) carrier (AGC) in the inner mitochondrial membrane and are responsible for the exchange of matrix Asp for cytosolic Glu and a H^+ ion, which is an electrogenic process [6]. Citrin is predominantly found in liver, kidney, heart and small intestine, while aralar is found in brain, skeletal muscle, kidney and heart [3,7,8]: citrin can be thought of as the liver-type, while aralar as the brain- and muscle-type, AGC. The function of the AGC is to participate in gluconeogenesis from lactate and transporting cytosolic NADH-reducing equivalents into mitochondria as part of the malate Asp shuttle, in addition to providing Asp from mitochondria to the cytosol for the synthesis of proteins, nucleotides and urea (Fig. 1).

Citrullinemia is caused by a deficiency of the urea cycle enzyme, argininosuccinate synthetase (ASS), which catalyzes the ligation of citrulline (Cit) and Asp to form argininosuccinate at the expense of ATP utilization. Saheki et al. [9] classified citrullinemia into classical or type one citrullinemia (CTLN1) caused by mutations in the *ASS* gene [10,11] and CTLN2 caused by mutations in *SLC25A13* [3]. CTLN2 is characterized by a liver-specific decrease in ASS protein [12] without any detectable abnormalities in the *ASS* gene or hepatic *ASS* mRNA levels [13,14]. The hepatic loss of ASS protein in CTLN2 patients is secondary to citrin deficiency [15], although its cause still remains to be clarified. Patients with CTLN2 suffer from recurring neuropsychiatric symptoms associated with hyperammonemia, including disorientation, delirium, seizures, and coma that can lead to death from brain edema [1,2,12].

Identification of mutations in *SLC25A13* of CTLN2 patients led to the discovery that patients with a type of neonatal hepatitis were also caused by the same mutations [16–18]. Since the neonatal symptoms were markedly different from those of adult CTLN2 patients, we named the neonatal presentation NICCD (neonatal intrahepatic cholestasis caused by citrin deficiency) [1,19]. Patients with NICCD show multiple metabolic abnormalities, including aminoacidemias (Cit, threonine, methionine, tyrosine, and arginine) accompanied by an increased threonine/serine ratio, galactosemia, hypoproteinemia, cholestasis, and fatty liver [2]. Human citrin deficiency therefore results in NICCD during the first few months of life, with symptoms usually self-resolving by the first year in most cases [20]. Following an apparently healthy period that can last from one to several decades, some patients with human citrin deficiency go on to develop severe CTLN2 [1,17,21].

* Corresponding author. Address: Institute for Health Sciences, Tokushima Bunri University, 180 Yamashiro-cho, Tokushima 770-8514, Japan. Fax: +81 88 622 2503.
E-mail address: takesah@tokushima.bunri-u.ac.jp (T. Saheki).

1096-7192/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.ymgme.2010.02.014

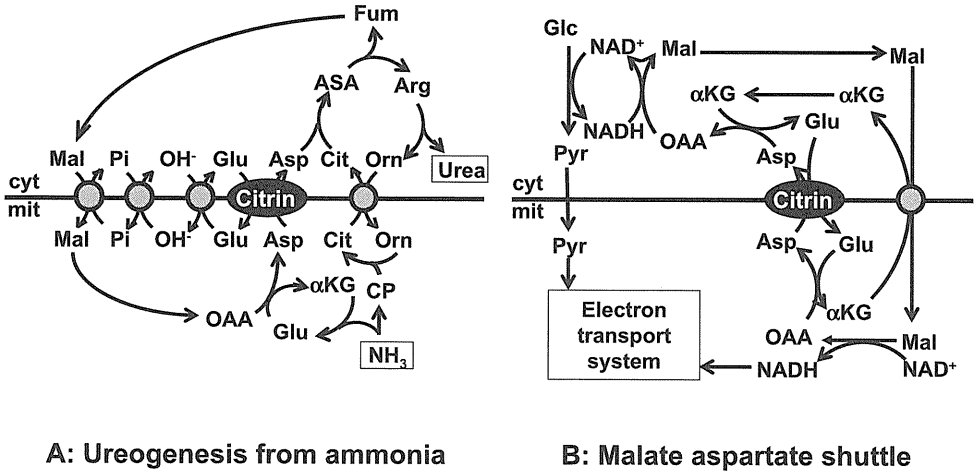

Fig. 1. Functions of citrin (liver-type AGC). (A) The role of citrin in ureogenesis from ammonia [35], and (B) the role of citrin in malate aspartate shuttle. Abbreviations are, Arg, arginine; ASA, argininosuccinate; Asp, aspartate; αKG, α-ketoglutarate; Cit, citrulline; CP, carbamoyl phosphate; cyt, cytosol; Fum, fumarate; Glc, glucose; Glu, glutamate; Mal, malate; mit, mitochondria; OAA, oxaloacetate; Orn, ornithine; Pyr, pyruvate.

Now, we propose a potentially different course of citrin deficiency (Fig. 2), because a number of Japanese subjects with citrin deficiency suffer from various kinds of disorders during the so-called "Apparently Healthy Period" [2,22–27]. There have been a few patients with NICCD that have required liver transplantation due to severe, prolonged symptoms [2,28,29], and patients presenting with CTLN2 typically continued to worsen unless also treated by liver transplantation [1,2,21,30,31]. The reason for the deterioration will be discussed later.

Characteristic food preference/food aversion of citrin-deficient subjects

It has been long known that CTLN2 patients have peculiar preference for protein- and fat-rich food, such as peanuts and soy beans. Recently, we noticed that aversion to carbohydrate-rich food, such as cooked rice and sweet things, was the other side of their food preference. Saheki et al. [32] performed nutritional assessment of 18 Japanese citrin-deficient subjects in the age ranged from 1 to 33 years old, who have been diagnosed as carrying mutation(s) in both alleles: some had suffered from NICCD, some are siblings or a father of NICCD patients, and one was at the early stage of CTLN2. The results (Fig. 3) clearly showed a marked decrease in carbohydrate intake in viewpoint of a smaller proportion of carbohydrates contributing to the total energy distribution (protein/fat/carbohydrate: PFC ratio), a reduced net intake relative to age- and sex-matched controls and a shift towards a lower centile distribution for carbohydrate intake. This unique food preference of citrin-deficient subjects is markedly different from the well-known aversion to protein among the patients with the other late-onset urea cycle enzymopathy or lysinuric protein intolerance. This unique food taste suggests some correlation of the tendency to the pathogenesis and pathophysiology of citrin deficiency.

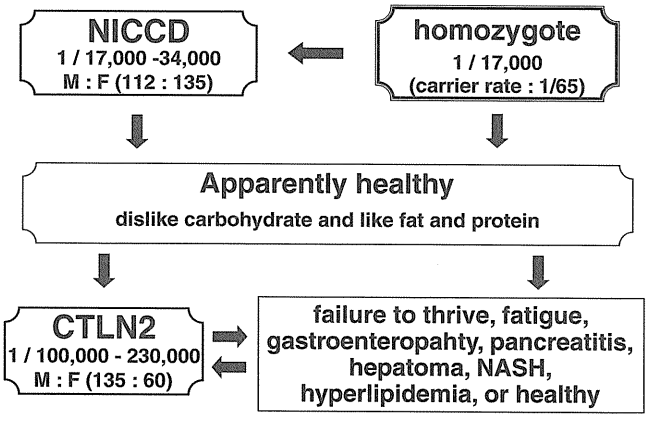

Fig. 2. Prognosis or life cycle of Japanese citrin-deficient subjects. M:F means numbers of male and female patients diagnosed. Incidence and prevalence were shown in the figure.

Carbohydrate toxicity in citrin deficiency

Tamakawa et al. [33] reported an interesting and important case with CTLN2. A 52-year-old woman fell into coma associated with hyperglycemia and hyperammonemia after receiving an infusion first composed of high dose of glucose (120 g/700 ml) and amino acids because of intractable pain and no appetite after operation for breast cancer. After recovering well, she received again a high-dose glucose infusion without amino acids. Again, she fell into coma with hyperammonemia.

Many CTLN2 patients died in a few weeks or months after infusion of glyceol composed of 10% glycerol and 5% fructose for the treatment of brain edema caused by hyperammonemia. Yazaki et al. [34] summarized reports in which the CTLN2 patients were treated with glyceol (8 cases), glyceol plus mannitol (4 cases), or mannitol (2 cases) for brain edema. All except one treated with glyceol alone or glyceol plus mannitol worsened after the treatment. Two CTLN2 patients treated with mannitol alone survived.

Concerning carbohydrate toxicity, we present a girl (P557S2) who was found to be a compound heterozygote carrying two different mutations in *SLC25A13* at 10 years old [26,32], together with her elder sister (P557) who suffered from CTLN2 and was treated with liver transplantation. Since at 13 years old, P557S2 complained of skinniness, fatigue and abdominal disorders, we examined her in connection with food intake (Figs. 3 and 4) [26,32]. As shown in Fig. 4, when she took hospital meals with high-carbohydrate energy ratios, she showed significant increases in plasma ammonia and Cit, and became drowsy. Therefore, we allowed her to take her favorite meals with fat- and protein-rich, and carbohydrate-low meals, resulting in only a slight increase in plasma ammonia with no increase in Cit. In this examination, we noticed a linear relation between plasma glucose and ammonia concentra-

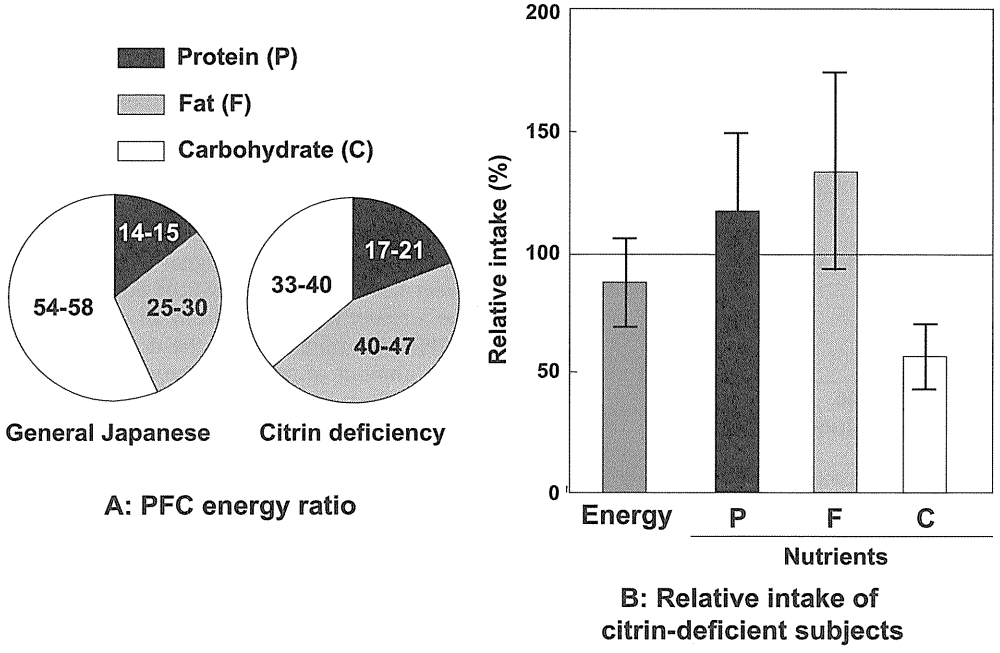

Fig. 3. Nutritional assessment of 18 citrin deficiency subjects revealed their characteristic dietary intakes. (A) Energy ratio of protein, fat and carbohydrate (PFC) of control general Japanese (left) and of citrin deficiency subjects (right), and (B) intake of energy and nutrients relative to age- and sex-matched controls [32].

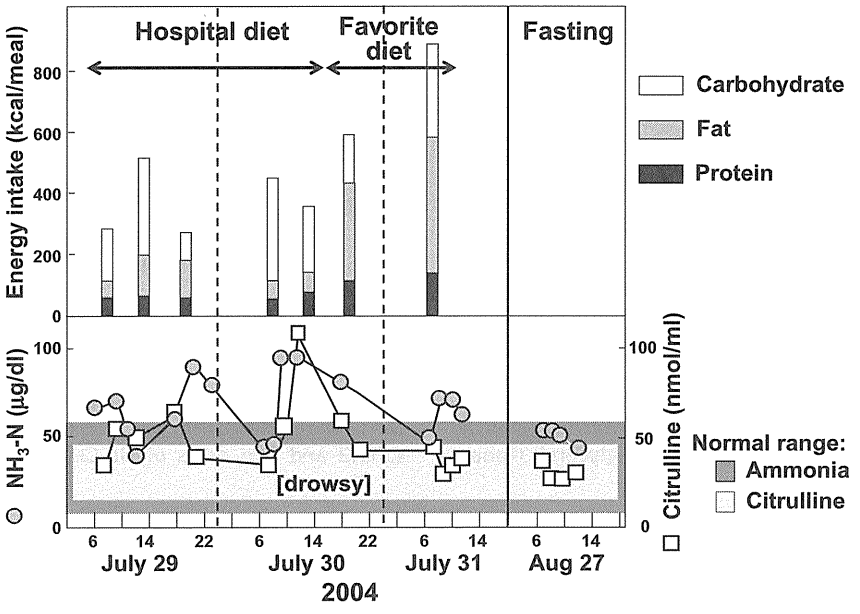

Fig. 4. Laboratory examination of 13-year-old girl (P557S2) at the early stage of CTLN2: relation between diets and plasma ammonia and citrulline. The upper panel depicts energy intake of each meal together with protein (black): fat (grey): carbohydrate (white) energy ratio. Arrows in the figure indicate duration of the hospital or her favorite meals taken. The lower panel, plasma ammonia (circle) and citrulline (square) concentrations with their control ranges (heavy and light grey, respectively).

tions after she took various kinds of breakfast (Fig. 5). All these results suggest carbohydrate toxicity in CTLN2. This can be explainable by metabolic disturbances in citrin deficiency as follows.

Ureogenesis in citrin-deficient state and its relation to carbohydrate toxicity

As described by Williamson in 1976 [35], ureogenesis under control states, liver-type AGC, citrin, plays a role in ureogenesis from ammonia as a nitrogen source (Fig. 1A). Under citrin deficiency without AGC (Fig. 6), Glu formed from ammonia, instead of Asp, goes out of mitochondria, converted to Asp by the action of cytosolic aspartate aminotransferase, and formed Asp is used for ASS reaction, indicating that urea may be synthesized in citrin deficiency. But in this metabolic pathway, oxaloacetate as an amino donor should be formed from fumarate via malate in the cytosolic compartment, which generates NADH. If the generated NADH is oxidized, urea can be synthesized under citrin deficiency. Under enhanced carbohydrate metabolism, liver plays a role in glucogenesis and fat synthesis. During the carbohydrate metabolism from glucose, fructose, glycerol and so on, NADH is formed and should be oxidized to continue aerobic glycolysis. The resultant NADH