Difficulties in Daily Life and Associated Factors, and QoL of Children with Inherited Metabolic Disease and Their Parents in Japan: A Literature Review

Keiko Yamaguchi • Rie Wakimizu • Mitsuru Kubota

Received: 18 January 2016 / Revised: 18 March 2016 / Accepted: 09 May 2016 / Published online: 26 June 2016
© SSIEM and Springer-Verlag Berlin Heidelberg 2016

Abstract To assess the quality of life (QoL) of children in Japan with inborn errors of metabolism (IEM) as well as of their parents, we reviewed 23 previous studies published in Japanese and 1 published in English, focusing on the difficulties they encounter in daily life, the factors associated with these difficulties, and their QoL. We divided the difficulties and associated factors into three developmental stages. At the infant stage, individuals with IEM tend to be at high risk of hypercatabolism. Their parents suffered anxiety and distress because of the child's diet therapy and regarded the parents' support group as an essential presence, particularly given that IEM is a rare disease. At the school-age stage, as their sphere of social relationships expanded, children with IEM became nervous about being compared with healthy children of their own age because of their diet therapy. At the adolescence-to-adulthood stage, the children suffered medically, economically, and socially. Even in the absence of any IEM symptoms, the children's QoL was affected by the demands associated with the

metabolic disorder, such as diet and treatment. The psychological health of their caregivers was also poor. To improve the QoL of children with IEM and of their parents, future comprehensive quantitative and qualitative studies of their QoL and of their subjective support needs are required. Additionally, the specific factors related to the QoL of such individuals need to be explored in large population-based statistical studies.

Abbreviations

AA	Argininosuccinic aciduria
CD	Citrin deficiency
GA	Glutaric acidemia
HM	Hypermethioninemia
IA	Isovaleric acidemia
IEM	Inborn error of metabolism
MPS	Mucopolysaccharidosis
MSUD	Maple syrup urine disease
OA	Organic acidemia
PA	Propionic acidemia
PKU	Phenylketonuria

Communicated by: Georg Hoffmann

K. Yamaguchi (✉)

Department of Nursing Science Master's Program, Graduate School of Comprehensive Human Sciences, University of Tsukuba,
1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: yamaguchi.keiko.xa@alumni.tsukuba.ac.jp

R. Wakimizu

Faculty of Medicine, Division of Health Innovation and Nursing,
Department of Child Health Care Nursing, University of Tsukuba,
1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: riwaki@md.tsukuba.ac.jp

M. Kubota

Department of General Pediatrics and Interdisciplinary Medicine,
National Center for Child Health and Development, 2-10-1 Okura,
Setagaya-ku, Tokyo 157-8535, Japan
e-mail: kubota-nt@ncchd.go.jp

Introduction

According to the Japanese Ministry of Health Labour and Welfare (2013), the number of patients in Japan with inborn errors of metabolism (IEM) was about 19,000 in 2013. The Ministry has been supporting several studies on the diagnosis and treatment of IEM (The Japanese Ministry of Health Labour and Welfare 2015). As a result of the expansion of the newborn tandem mass screening test, studies not only on diagnosis and treatment but also on the

psychological and social aspects of the parents have been conducted (Sakoda et al. 2011; Abe 2012). At the same time, researchers have highlighted the importance of how patients with IEM and their families should be supported after diagnosis (Matsubara 2010).

Most patients with IEM have to follow a strict diet therapy throughout their life and to live with the permanent risk of metabolic crises (Zeltner et al. 2014). The diet therapy may affect many aspects of their daily life and quality of life (QoL), as well as of their family members'. In countries other than Japan, some studies have been conducted on the daily life and QoL of patients with IEM and of their parents (Lambert and Boneh 2004; Simon et al. 2008; Stockler et al. 2012; Cazzoria et al. 2014). As one of the factors associated with their QoL, children with IEM in Turkey with bad diet compliance reportedly had lower scores in two aspects of QoL assessment: school labeling and perception of disease (Eminoglu et al. 2013). However, only a few studies in Japan have been conducted and these focused mainly on the patients' and on their mothers' QoL (Kubo et al. 2008; Okano et al. 2013).

In this study, we sought to understand the problems encountered in the daily lives of Japanese children with IEM and of their parents by reviewing what has already been investigated in terms of their difficulties in daily life and the factors associated with those difficulties, and in terms of their QoL. And we considered future issues that need to be tackled to improve the QoL of these patients and their families.

Methods

Data Sources and Search Strategies

To identify eligible articles for this literature review, we conducted a search of the PubMed database and of the most popular database in the medical discipline in Japan – the Japan Medical Abstracts Society (version 5). The search was conducted using Japanese and English keywords such as “inborn error of metabolism,” the names of particular types of IEM, and “daily life” or “QoL.” At the initial search in March 2015, we retrieved 6,692 publications from the two databases. After reading the titles and abstracts, we excluded those articles focusing only on the diagnosis or the medical treatment or that were not about Japanese patients. After that, we conducted an additional search using quotations within quotations to ensure the comprehensiveness of the review. So as not to omit any reports on IEM studies in Japan, we included not only original articles but also feature articles and proceedings. Finally, we targeted 24 publications from 1987 to 2014. Only one of the articles was written in English, and the rest were written in Japanese.

Data Analysis

We intensively read the 24 articles and focused on the results related to difficulties faced by children with IEM and by their parents in daily life, the factors associated with those difficulties, and their QoL. We classified the results according to the child's developmental stages: infant stage, school-age stage, and adolescence-to-adulthood stage. And we summarized what has already been investigated in terms of their QoL. Finally, we considered future issues that need to be addressed to improve the QoL of these children and their parents.

Results

Table 1 shows the reviewed articles, and Fig. 1, the difficulties reported therein as experienced by children with IEM and their parents with regard to daily life, as well as the associated factors at each stage of the child's life. We have added the medical and clinical aspects of IEM to provide a more complete picture of their life. Other than those on MPS, most of the studies included only very small numbers of families, with many including only one family.

Difficulties in Daily Life and Associated Factors

Infant Stage

Newborn Mass Screening, Specialized Examinations, and Diagnosis In Japan, newborns who test positive for IEM on newborn tandem mass screening have to undergo several specialized examinations such as amino acid analysis, gas chromatography and mass spectroscopy (GC/MS), enzyme assay, and gene analysis. Doctors specializing in IEM then make a diagnosis (Endo et al. 2013).

Infants at High Risk of Hypercatabolism and Parents' Difficulty in Preventing the Child's Hypercatabolism Generally speaking, infants easily contract infections; thus, they are at high risk of hypercatabolism. In one case of maple syrup urine disease (MSUD), the child was admitted to hospital 30 times before the age of 10 years because of hypercatabolism caused by infections accompanied by diarrhea and fever (Fujiwara 2013). It is difficult to prevent infants with IEM from becoming sick in daily life. One mother of a child with *propionic acidemia* (PA) could not recognize the signs of severe acidosis in her child because she thought the child was just having another cold (Taketa et al. 1991). Families are also concerned about the risk of sickness for their child (Fujiwara 2013) because IEM causes, among others, hypercatabolism, psychomotor retardation, and intellectual disability (Yuhara et al. 1991).

Table 1 List of 24 eligible articles

Author (s)	Article type	Metabolic disease	N	Life stage ^a	Summary of articles focused on difficulties in daily life and associated factors, and QoL
Abe (2012)	Proceedings	PKU	1 ^b	1	Importance of cooperation with families in caring for children
Fujiwara (2013)	Feature article	PKU, MSUD	5 ^b	1, 2, 3	Difficulty in prevention of hypercatabolism caused by child's sickness, sharing their anxiety and distress related to raising children with IEM, and having people around them understand their child's diet therapy; importance of a parents' support group and genetic counseling to cope with anxiety and distress, worries about next pregnancy, and financial difficulties from adulthood related to diet therapy
Ishiyama et al. (1987)	Original article	PKU	4 ^b	1, 2	Difficulty of management of diet therapy with developmental stages; psychological burden of child's diagnosis and diet therapy
Kashiwagi (2011)	Proceedings	OA	N/A	1, 2, 3	Parents' anxiety and distress related to home-rearing of children with IEM; lack of information on disease and treatment; social discrimination such as refusal of permission to enter nursery school
Kashiwagi (2012)	Proceedings	IMD	N/A	1, 2, 3	Difficulty associated with sharing their anxiety and distress about raising a child with IEM; difficulties with diet therapy; financial difficulties from adulthood related to diet therapy
Kato and Kashiwagi (2010)	Original article	MMA, PA, GA, IA, AA,	19 ^c	N/A	Suffering from social discrimination when taking out insurance
Komatsu et al. (2011)	Original article	N/A	16 ^c	N/A	Suffering from social discrimination when taking out insurance
Kubo (2007)	Original article	MPS	4 ^b	1, 2	Positive impact of school as a chance to acquire the fundamental habit of daily life and to reduce mothers' stress and fatigue
Kubo (2010)	Original article	MPS	94(4) ^b	N/A	Lack of information on MPS; guilt feelings associated with the child's disease
Kubo and Tamura (2007)	Original article	MPS	11 ^b	1, 2	Lack of information on MPS or child's care; necessity of a parents' support group for gathering information about MPS
Kubo et al. (2008)	Original article	MPS	94(10) ^b	1	Delayed diagnosis caused by medical professionals' lack of knowledge of MPS
Kubo and Tazaki (2008a)	Original article	MPS	94 ^b	N/A	General Health Questionnaire 30: QoL of 28- to 70-year-old caregivers of children with MPS; the mean QoL score was higher than that for healthy parents, indicating poor psychological health; the associated factor of QoL was bathing assistance ($\beta = 0.363$, $r = 0.049$)
Kubo and Tazaki (2008b)	Original article	MPS	94 ^b	N/A	General Health Questionnaire 30: QoL of 28- to 71-year-old caregivers of children with MPS; the significant factors of QoL were bathing assistance ($r = 0.465$) and impossibility of communication with their children ($r = 0.38$)
Manba et al. (1997)	Original article	PKU, HM, MSUD, AA	11 ^b	1, 2	Most helpful role of parents' support group for families in the early phase after child's diagnosis; parents' support group as an inventory of their experience for families raising children for a long time; problems related to the child's expanding social life; suffering from social prejudice because of genetic disease
Matsumoto et al. (2014)	Proceedings	PKU	1 ^b	1	Fulfillment from raising a child; expectation of a child's development
Nakata et al. (1998)	Original article	PA	1 ^b	1	Difficulty of diet therapy because the child could not take enough milk
Nikaidou and Kosuga (2014)	Feature article	IEM	N/A	1	Psychological burden associated with the child's life and prognosis

(continued)

Table 1 (continued)

Author (s)	Article type	Metabolic disease	N	Life stage ^a	Summary of articles focused on difficulties in daily life and associated factors, and QoL
Okano (2011)	Feature article	PKU	N/A	1, 2, 3	Difficulty of management of the amount of milk and blood levels of phenylalanine; necessity of education about diet therapy from childhood; necessity of control during pregnancy of patients with PKU
Okano et al. (2013)	Original article	CD	52 ^b	1, 2, 3	PedsQL Multidimensional Fatigue Scale, PedsQL Generic Core Scale: QoL of children with CD aged 1–22 years based on self-reports and proxy reports by their guardians; the mean scores of both were lower than those for healthy children
Shigematsu et al. (2000)	Original article	PA	1 ^b	1	Difficulty of diet therapy because the child could not take enough milk; responsibility of the child's diet therapy concentrated on the mother; suffering from social discrimination from grandparents' generation
Taketa et al. (1991)	Feature article	PA	1 ^b	1	Difficulty in preventing child's sickness; importance of education at discharge from hospital for the first time
Ueno et al. (1990)	Feature article	IA	2 ^b	1	Struggles of coping with problems related to child's food restriction
Yoshino et al. (2010)	Feature article	PKU	N/A	3	Financial difficulty from adulthood associated with treatment
Yuhara et al. (1991)	Feature article	PKU	N/A	1, 2, 3	Realization and comparison with health children about diet; temptation to eat the restricted food; importance of special control of pregnancy

^a Child's life stage: 1. infant stage 2. school-age stage 3. adolescence-to-adulthood transitional stage

^b N: number of families

^c N: number of insurance companies

Fig. 1 Difficulties in daily life and associated factors, and medical involvement at each life stage of diagnosed children

Parents' Difficulty and Responsibility Concerning Their Child's Diagnosis and Diet Therapy Diet therapy is directly related to the daily life of children with IEM and their families (Okano 2011). A group interview study revealed that the mothers took about 2 months to face dealing with the diet therapy of their child; until then, they had been suffering from the psychological burden associated with the diagnosis and diet therapy of IEM (Ishiyama et al. 1987). On the other hand, one mother could face her child's diet therapy because her family cooperated in the care of her child (Abe 2012). One mother experienced a sense of fulfillment from taking care of her child with phenylketonuria (PKU) and looked forward to further developing their relationship (Matsumoto et al. 2014).

During the neonatal period, doctors instruct mothers of children with PKU to give them a certain amount of medical formula and as much breast milk as they want (Okano 2011). Starting with baby food, the children noticed the bad taste of medical formula and the good taste of baby food, and therefore, their mothers had difficulty in giving them the indicated quantity of medical formula (Fujiwara 2013). One mother, aware of the need to prevent ketoacidosis, experienced difficulty when her child with PA was not eating enough on a regular basis (Nakata et al. 1998; Shigematsu et al. 2000). For such mothers, deciding each day's combination of ingredients for the diet therapy was difficult (Ishiyama et al. 1987). They made every possible attempt so that their children could feel the same as their friends, for example, checking the school-lunch menu every day and adjusting the child's total protein intake (Ishiyama et al. 1987). Furthermore, mothers are often the ones who take responsibility for their child's diet therapy: one mother of a child with PA reported that she was dissatisfied with her husband's lack of understanding about the diet therapy (Shigematsu et al. 2000). Families carry the enormous burden of knowing that their child's life and prognosis is in their hands (Nikaidou and Kosuga 2014).

Essential Presence of the Parents' Support Group Because parents of children with IEM have few opportunities to meet parents in the same situation as themselves, they have difficulty in sharing their anxiety and distress (Kashiwagi 2012; Fujiwara 2013). Moreover, other than their primary doctor, they have no one with whom they can ask about the disease or talk about their distress (Kashiwagi 2012). Therefore, parents recognized their essential need for a parents' support group. To cope with their anxiety or distress, they participated in such a group or received counseling at hospital (Fujiwara 2013). They asked questions such as "What should we do when our child has symptoms?" For families at an early phase after their child's diagnosis, the parents' group was the most helpful place to hear about other families' actual experiences (Manba et al. 1997). And for those families raising a child

with IEM for some years, it was a good opportunity to look back on their experiences (Manba et al. 1997).

Another important reason for their participation in the parents' support group was to gather information about the disease and care. Mothers of children with IEM complained about the lack of information available (Kubo and Tamura 2007). They asked the following such questions at the parents' group or on an Internet search: "Why did our child get this disease?" and "What are the things we can do for our child?" (Kubo and Tamura 2007). As regards *mucopolysaccharidosis* (MPS), the medical professionals' lack of knowledge of MPS caused the diagnosis to be delayed until after the caregivers had noticed their child's abnormality (Kubo et al. 2008; Kubo 2010).

School-Age Stage

Children's Struggle and Parents' Difficulty with Diet Therapy as Children's Social Life Expands As children with IEM grow up and come into contact with more and more people, they tend to become nervous about being compared with healthy children of their own age; for example, this tension leads them to feel tempted to eat restricted food items (Yuhara et al. 1991). Children with isovaleric acidemia (IA) wanted to eat the same foods as their healthy siblings and friends; their family members also struggled with coping with these problems related to food restriction (Ueno et al. 1990). The representative of the PKU parents' support group reported that the main anxieties about diet therapy when their children were of school age were how to explain the diet therapy to the school staff and what to do about diet therapy when their child went on trips or sleepovers (Fujiwara 2013). In this way, as the children grow older, their families live with many new problems related to their social lives (Manba et al. 1997). On the other hand, studies on MPS revealed that most children with MPS attended school and that school life was good for them because it allowed them to settle into the normal routine of everyday life. Simultaneously, it was a good opportunity for their parents to feel less stress and fatigue (Kubo 2007).

Worries About the Next Pregnancy In the school-age stage, mothers of children with IEM were worried about their next pregnancy and about whether the next child would have the same disease, because IEM is a genetic disease (Fujiwara 2013).

Adolescence-to-Adulthood Stage

At this stage, new problems occur medically, economically, and socially (Yoshino et al. 2010; Kashiwagi 2011; Fujiwara 2013).

Strict Metabolic Control During Pregnancy IEM patients need strict metabolic control during pregnancy. For example, patients with PKU need to plan pregnancies well and to maintain their blood levels of phenylalanine within the safety threshold from about 3 months before the pregnancy (Yuhara et al. 1991; Okano 2011).

Financial Difficulty From adulthood, IEM patients in Japan cannot receive any aid for their diet therapy. So they experience financial difficulty because of their diet therapy, for example, having to buy therapeutic formula (Yoshino et al. 2010; Fujiwara 2013). Because the market is small, the pharmaceutical price of therapeutic formulas is high, and as it is now, companies selling therapeutic formulas carry those costs. In 1 case of MSUD, the over-20-year-old patient would have to pay about 680,000 yen (about US \$5,600) per year for therapeutic formula if the companies stopped carrying the cost. Mothers cautioned that the expensive cost of treatment could lead patients to stop their treatments (Fujiwara 2013).

Social Discrimination Children with IEM in Japan suffer from social prejudice as a result of having a genetic disease. Generally, Japanese people do not have correct knowledge about IEM because it is a very rare disease (Manba et al. 1997). That study revealed that patients with IEM experience social discrimination from people of their grandparents' generation. After a mother told the child's grandparents about the child's diagnosis, they forced her not to disclose it to their neighborhood (Shigematsu et al. 2000). The results of a questionnaire survey revealed that about 52% of patients with IEM were discriminated against when they tried to take out private health insurance (Komatsu et al. 2011). The researchers indicated that even patients with mild IEM tend to suffer from discrimination regarding the insurance contract (Kato and Kashiwagi 2010).

QoL

Only two studies have been published in Japan about the QoL of children with IEM or of their families: one is about children with citrin deficiency (CD), and the other, about children with MPS. According to the study about children and young adults (1–22 years) with CD, the mean scores of the PedsQL[®] fatigue and generic core at the self-report and proxy report by their parents were both lower than those for healthy children (Okano et al. 2013). Even if there were no CD symptoms, the children felt fatigue due to compensation for metabolic failure, and it affected their QoL.

Of all the IEM types, MPS has the most clearly progressive symptoms, for example, intelligence disorders, movement disorders, and hearing loss (Endo et al. 2013). One survey study of parents of children with MPS revealed that they had low scores on the General Health Questionnaire (GHQ30) Japanese version (Kubo et al. 2008). The

factors related significantly to the GHQ30 scores were burden of bathing assistance ($r = 0.465$) and impossibility of communication with one's children ($r = 0.38$) (Kubo et al. 2008). Multiple regression analysis also showed that the significant factor on the GHQ30 score was bathing assistance ($\beta = 0.363$, $p = 0.049$) (Kubo et al. 2008).

Discussion

Difficulties in Daily Life and Associated Factors

Infant Stage

Previous research has revealed that infants with IEM tend to be at high risk of hypercatabolism and that their parents are concerned about this high risk, particularly at the infant stage (Yuhara et al. 1991). As a preventive measure, at the first discharge from hospital after a child has been diagnosed with IEM, family members need to be educated about infection prevention and what swift action to take when the child falls sick. Referring to a study on the medical system for diabetic patients (Nagayama et al. 2011), and given the small number of IEM medical specialists in Japan, researchers suggested the importance of expanding education for primary-care physicians about provision of medical care for IEM patients, because they usually assume the immediate responsibility of caring for patients with IEM when they present with symptoms. Therefore, a system of cooperation between IEM specialists and primary-care physicians should be put in place for daily medical practice.

In the early phase after the child's discharge from hospital, mothers suffer from the psychological burden brought on by their child's diagnosis and the responsibility associated with diet therapy (Ishiyama et al. 1987). Specialists should support the families psychologically after understanding well the four aspects of IEM: that it is a rare, metabolic, chronic, and genetic disease (Sakoda et al. 2013). At the same time, the child's health condition depends on the care provided by the family at home. Therefore, medical professionals, especially nurses, have a role in supporting the family in feeling positive toward raising and caring for the child (Nakata et al. 1998).

The primary caregivers tend to assume the burden of care and responsibility of children with IEM. Because they have a role of management of the diet therapy and preparation of the family meals, and it is usually mothers. A case was reported, in which a mother complained about her husband's lack of understanding about diet therapy (Shigematsu et al. 2000). And mothers experience difficulty with their child's diet therapy (Ishiyama et al. 1987). Although it is a different disease, the

families of children with food allergies also have to follow the child's diet therapy, for example, eliminating eggs or nuts. It was reported that mothers of children with food allergies have anxiety about eating out, and this anxiety was affected by the diet therapy (Tatematsu and Ichie 2008), and mothers had lower QoL than did fathers (Warren et al. 2015). Researchers pointed out that the parental burden borne by mothers affected their parenting behavior (Ogata and Miyashita 2003). For IEM families, parenting behavior is related to the management of the child's diet therapy and affects the child's QoL. Therefore, not only the child's health status but also the mother's burden or stress should be assessed and investigated at regular clinic visits for total family care.

Mothers who have a child with chronic disease need to associate with mothers who have a similar experience (Ito et al. 2013). Parents' support groups fulfill a precious function of peer support for parents of children with rare diseases. It is a good place for parents to share their particular anxieties and distresses, their daily life, and their future (Manba et al. 1997).

School-Age Stage

As their social life expands, children with IEM struggle with being different from healthy children in terms of food restriction (Yuhara et al. 1991). Moreover, their parents face the difficulty of making the people around them understand the child's diet therapy (Fujiwara 2013). Casework is important for families with IEM children and should be conducted according to seven principles: individualization, acceptance, purposeful expression of feeling, controlled emotional involvement, nonjudgmental attitude, client self-determination, and confidentiality (Felix 1957; Kubota 2014). All medical professionals should offer their patients attentive hearing, empathy, and reciprocity in daily clinical practice, focusing on each patient and his or her family, as well as understanding the features of IEM and these principles well.

The child's expanding social life is also associated with positive aspects, both for the child and for the parents. Going to school is a chance to acquire the fundamental routine of daily life and for the parents' stress and fatigue to be reduced. A previous study pointed out the benefit of parents' realizing the positive aspects of their child's development, thus increasing the mother's sense of fulfillment and competency (Kuno et al. 2006). To realize these positive aspects, it was efficient not only to calculate the child's protein intake but also to use a motherhood diary (Ueno et al. 1990). It is also important for parents that medical professionals recognize their daily efforts in raising their child at home, especially with regard to diet therapy, and at the same time to encourage them to also take a real look at the positive aspects, such as their child's development.

Adolescence-to-Adulthood Stage

For good health control, patients need to be educated about diet therapy from childhood (Okano 2011). They also need strict metabolic control during pregnancy (Yuhara et al. 1991). According to a previous study, education in self-care should be provided by all of the medical team with consideration for the child's growth and development, intelligibility, and sense of values, and also with praise for the child's efforts (Yoshida 2011). Other researchers suggested that it is necessary to make a model of self-care behavior for IEM patients and their families (Shigematsu et al. 2000). Therefore, medical professionals should consider these when cooperating with families in educating children with IEM from a young age. As regards parents' worries about their next pregnancy, it is important for them to receive genetic counseling (Okano 2011).

At this transitional stage from adolescence to adulthood, parents of children with IEM also have financial difficulty because of the costs of child's diet therapy (Yoshino et al. 2010). Fortunately, from July 2015, some IEM diseases have been accepted in Japan as specified intractable diseases. Some patients can receive medical aid in adulthood too, for example, patients with MSUD, PA, or IA.

Children with IEM and their families face the possibility of being discriminated against by the grandparents or when they take out life insurance (Shigematsu et al. 2000; Komatsu et al. 2011). Because Japanese generally form homogenous communities, they lack a basic awareness of social, ethnic, and economic diversity (Moriya et al. 2012). In addition, as discussed at a Eubios Ethics Institute seminar in 1992, the main anxiety of families of patients with genetic disease in Japan is the "honor of the family"; on the other hand, in the USA, it is the "well-being of patients" (Kubo 2010). However, that was nearly a quarter of a century ago; in the meantime, this unhealthy aspect of Japanese culture in terms of genetic disease has definitely been improving but has not completely disappeared. These social problems must be resolved immediately because social support affects the satisfaction with life of mothers who have a child with a chronic disease (Ohgino and Nakamura 2010). Other researchers emphasized the importance of social support for parents with IEM children (Gramer et al. 2014). Therefore, they should be helped to gain the support of the people around them, such as through diffusion of correct knowledge of IEM and its treatment for schoolteachers and neighbors.

QoL

CD patients tire easily owing to compensation for metabolic failure (Mutoh et al. 2008), and the features of this disease have an impact on their QoL (Okano et al. 2013). Furthermore, the results of a large international study

conducted in seven European countries showed that PKU affected the QoL of both the children and their parents (Bosch et al. 2015). Among the factors that strongly affected their QoL were the emotional aspects and anxiety about phenylalanine blood levels (Bosch et al. 2015). Parents of children with MPS have many more cares to contend with as the medical condition progresses: assisting bathing, eating, changing clothes, and so forth (Kubo et al. 2008). Even if children with MPS receive medical treatment such as enzyme replacement therapy, there is no way to stop the progress of this disease. This feature distinguishes MPS from other IEM types. Moreover, as the parents themselves grow older, their own burden and health problems also increase, thus affecting their own QoL (Yoshimoto et al. 1990). Therefore, research is needed on the QoL of not only the patients but also of their family members.

Until now, the lack of a registry of IEM patients in Japan has made recruitment of research participants difficult and probably explains the small number of studies conducted on the QoL of Japanese IEM patients. In 2013, the Japan Registration System for Metabolic and Inherited Diseases was established by the National Center of Child Health and Development (<http://jasmin-mcбанк.com>). As the first step since its establishment, the factors associated with the QoL of a larger number of IEM patients must be explored, as well as each type of IEM. With these factors in mind, we should consider what types of intervention or education need to be provided for IEM patients and their families in Japan.

Acknowledgements This study was supported by a research scholarship from the Pfizer Health Research Foundation 2015–2016 (principal investigator: Rie Wakimizu). The study was partially supported by the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED). I would like to show my greatest appreciation to Flamina Miyamasu for her courteous English proofreading.

Take Home Message

Both children with IEM and their parents have various difficulties in daily life; therefore, their QoL and the factors associated with it should be studied to determine how the QoL can be improved.

The Third Page

The corresponding author confirms that this work has not been published or submitted elsewhere. This article does not deal with any studies with human or animal subjects performed by any of the authors. All coauthors have seen the final version of the article.

Compliance with Ethics Guidelines

Conflict of Interest

I, Keiko Yamaguchi, have no conflict of interest to declare.

Rie Wakimizu received a research scholarship from the Pfizer Health Research Foundation.

Mitsuru Kubota received a research grant from the Practical Research Project for Rare/Intractable Diseases from the Japan Agency for Medical Research and Development (AMED).

Details of the Contributions of Individual Authors

Keiko Yamaguchi planned this review article, drafted its concept and design, analyzed the contents of each eligible article, and had a central role in writing it.

Rie Wakimizu provided advice concerning the review's conception, design, and analysis, and also contributed to the revising of the draft as a professional researcher of child health nursing.

Mitsuru Kubota provided advice concerning the review's conception, design, and analysis, and also contributed to the revising of the draft as a clinical specialist of IEM.

References

- Abe S (2012) The experience of the mother who had a child diagnosed by newborn mass-screening [in Japanese]. *Jpn J Inherit Metab Dis* 28:183
- Bosch AM, Burlina A, Cunningham A et al (2015) Assessment of the impact of phenylketonuria and its treatment on quality of life of patients and parents from seven European countries. *Orphanet J Rare Dis* 10:80–94
- Cazzoria C, Cegolon L, Burlina AP et al (2014) Quality of life assessment in a cohort of patients with phenylketonuria. *BMC Public Health* 14:1243–1252
- Eminoglu TF, Soysai SA, Tumer L et al (2013) Quality of life in children treated with restrictive diet for inherited metabolic disease. *Pediatr Int* 55(4):428–433
- Endo F, Yamaguchi S, Ooura T et al (2013) The handbook of inherited metabolic disease. Nakayama Shoten [in Japanese]
- Felix PB (1957) The casework relationship. Loyola University Press.
- Ozaki A, Fukuda T, Harada K (2015) The Principles of a casework relationship: methodology of establishment of supportive relationship [in Japanese]. Seishin Shobo. New translation revised version. 20–21
- Fujiwara K (2013) Suggestion for understanding of amino acid metabolism of nursing from heredity support group [in Japanese]. *J Jpn Soc Genet Nurs* 11(2):23–28
- Gramer G, Haeghe G, Glahn ME et al (2014) Living with an inborn error of metabolism detected by newborn screening-Parents' perspectives on child development and impact on family life. *J Inherit Metab Dis* 37(2):189–195
- Ishiyama S, Suzuki E, Nishimura A et al (1987) Diet therapy of children with phenylketonuria : analysis of 4 good control cases

- and development of program of diet therapy [in Japanese]. *Jpn J Child Nurs* 10(12):1634–1640
- Ito Y, Sirazaki E, Yamazaki Y (2013) Feeling of mothers have child with chronic disease: interview to mothers rearing child at home [in Japanese]. *Collect Articles Jpn Nurs Soc Community Nurs* 43:99–102
- Kashiwagi A (2011) Mass-screening and support for patients: importance of follow-up [in Japanese]. *Hokkaido J Public Health* 25(1):26
- Kashiwagi A (2012) The current situation and future issue of expanding newborn mass-screening [in Japanese]. *J Jpn Soc Genet Nurs* 10(2):33–36
- Kato T, Kashiwagi A (2010) Rare diseases and reconstruction of neonatal screening: wishes of patients [in Japanese]. *J Child Health* 69(1):3–5
- Komatsu S, Shintaku H, Hirata Y et al (2011) The current situation of contract of insurance of target disease of newborn mass-screening [in Japanese]. *J Jpn Pediatr Soc* 115(10):1573–1579
- Kubo K (2007) A basic study on children with mucopolysaccharidoses (MPS) and their families: changes in school-age children and their relationships with doctors [in Japanese]. *Annu Bull Dept Nurs* 2:31–39
- Kubo K, Tamura T (2007) A basic study on children with mucopolysaccharidoses (MPS) and their families: change in MPS children in their infancy based on observations by their parents. *Bull Tokyo Gakugei Univ Sci Edu* 58:387–395 [in Japanese]
- Kubo K, Tazaki C (2008a) Mental condition of Caregivers of patients with mucopolysaccharidosis and factors related to their condition [in Japanese]. *J Child Health* 67(6):878–884
- Kubo K, Tazaki C (2008b) The mind state of health of the family of the mucopolysaccharidosis child and connection with the everyday life care [in Japanese]. *Annu Bull Dep Nurs Kyoritsu Women's Univ Jr Coll* 3:103–107
- Kubo K, Tasaki C, Oikawa Y (2008) Indication of physical features of infants with mucopolysaccharidosis [in Japanese]. *Jpn J Mater Health* 49(2):295–302
- Kubo K (2010) Investigation of social and psychological problems of the caregiver or family of children with mucopolysaccharidosis [in Japanese]. *J Child Health* 69(1):63–39
- Kubota M (2014) The problems on daily life of children with inherited metabolic disease [in Japanese]. *Child Health* 17(3):177–180
- Kuno N, Yamaguchi K, Morita C (2006) The sense of burden of mother with severely disabled children at home and the related factors [in Japanese]. *J Jpn Soc Nurs Res* 29(5):59–69
- Lambert C, Boneh A (2004) The impact of galactosaemia on quality of life: a pilot study. *J Inherit Metab Dis* 27(5):601–608
- Manba T, Hori H, Takizawa M et al (1997) Family group of children with amino acid metabolism [in Japanese]. *J Saitama Med Sch* 13(2):81–83
- Matsubara Y (2010) The support system for new mass-screening [in Japanese]. *Jpn J Inherit Metab Dis* 26(1):55–56
- Matsumoto Y, Tajima G, Matsumoto Y et al (2014) Analysis of the psychological process of mother who had a child with inherited metabolic disease diagnosed by newborn mass screening : a case of phenylketonuria [in Japanese]. *J Jpn Soc Mass Screen* 24:2:179
- Moriya H, Ishibashi H, Wada K, Inoue I, Mizoguchi M (2012) Recognition on human diversity with mothers of preschool children. *Jpn J Genet Nurs* 10(2):3–9
- Mutoh K, Kurokawa K, Kobayashi K et al (2008) 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* 31(2):343–347
- Nagayama K, Kakisawa K, Ookawa Y et al (2011) Twenty-seven patients with hypoglycemic coma requiring hospitalization during oral hypoglycemic treatment [in Japanese]. *J Jpn Diab Soc* 54(4):271–276
- Nakata M, Kurio R, Sugiura S (1998) The consideration on discharge education for children with propionic acidemia: focused on an education of tubal feeding [in Japanese]. *Neonatal Care* 11(10):883–887
- Nikaidou M, Kosuga M (2014) Is Tandem mass screening a genetic screening? [in Japanese]. *Jpn J Pediatr Med* 46(4):452–455
- Ogata K, Miyashita K (2003) Examination of the factors relevant to maternal parenting behavior [in Japanese]. *Bull Fac Edu Chiba Univ* 51:5–15
- Ohgino A, Nakamura Y (2010) Factors affecting stress responses and satisfaction with life among mothers of children with chronic illness [in Japanese]. *J Jpn Soc Child Health Nurs* 19(1):1–7
- Okano Y (2011) Phenylketonuria [in Japanese]. *Jpn J Pediatr Med* 43(9):1509–1511
- Okano Y, Kobayashi K, Ihara K et al (2013) Fatigue and quality of life in citrin deficiency during adaptation and compensation stage. *Mol Genet Metab* 109(1):9–13
- Sakoda M, Yotsumoto J, Yamamoto K et al (2011) A review of the psychological effects on parents who received positive/false-positive result in newborn screening [in Japanese]. *Jpn J Genet Couns* 32(4):157–167
- Sakoda M, Yamamoto K, Yamaguchi S et al (2013) The life story of the mother who has children with propionic acidemia [in Japanese]. *J Jpn Pediatr Soc* 117(2):293
- Shigematsu Y, Sasakawa Y, Iemori Y et al (2000) The first case with propionic acidemia found in newborn screening by tandem mass spectrometry in Japan: clinical management during infancy [in Japanese]. *J Fukui Med Univ* 1(2):275–282
- Simon E, Schwarz M, Roos J et al (2008) Evaluation of quality of life and description of the sociodemographic state in adolescent and young adult patients with phenylketonuria [in Japanese]. *Health Qual Life Outcomes* 26(6):25–31
- Stockler S, Moeslinger D, Herle M et al (2012) Cultural aspects in the management of inborn errors of metabolism [in Japanese]. *J Inherit Metab Dis* 35(6):1147–1152
- Taketa M, Fujiwara Y, Endou M et al (1991) Nursing for children with propionic acidemia need lifelong treatment-focusing on education to mother independently and continually [in Japanese]. *Jpn J Child Nurs* 14(11):1433–1437
- Tatematsu S, Ichie K (2008) The feature of lifestyle of children with food allergy and their families, coordination of lifestyle by mothers and mothers' knowledge of allergy. *Jpn J Child Nurs* 31(7):942–947
- The Ministry of Health Labour and Welfare Equal Employment, Children Families Bureau, Maternal and Child health Division (2013) The implementation status of screening of inherited metabolic diseases [in Japanese]. <http://www.jsms.gr.jp/contents04-01.html>
- The Ministry of Health Labour and Welfare (2015) Research Grant for Research on Measures for Intractable Diseases [in Japanese]. http://www.mhlw.go.jp/seisaku_nitsuite/bunya/hokabunya/ken-kyujigyou/hojokin-koubo-h26/gaiyo/13.html
- Ueno K, Tochibora Y, Kado C et al (1990) Nursing of children with isovaleric acidemia: looking back to discharge education [in Japanese]. *Jpn J Child Nurs* 13(9):1153–1160
- Warren CM, Gupta RS, Sohn MW et al (2015) Differences in empowerment and quality of life among parents of children with food allergy. *Ann Allergy Asthma Immunol* 114(2):117–125
- Yuhara H, Fujino Y, Sekiya T et al (1991) A metabolic disease (phenylketonuria) and breast feeding [in Japanese]. *Jpn J Perinat Care* 10(6):477–485
- Yoshimoto M, Nishiuchi S, Nishina K et al (1990) The study of function and role and position of home-nursing visit related to QoL of children with severe motor and intellectual disabilities

- and their families rearing at home: focused on the survey of their needs, for systemization of a network of care of children with disabilities [in Japanese]. *J Sever Motor Intellect Disabil.* 24 (1):53–62
- Yoshino M, Watanabe Y, Ohira T et al (2010) Phenylketonuria: toward a better carry-over care [in Japanese]. *Jpn J Clin Med* 68 (1):123–126
- Yoshida Y (2011) Education for improving self-care ability on pediatric nursing field: looking back to involvement with early adolescent suffered from bronchial asthma repeatedly [in Japanese]. *Kawasaki Hosp Res Bull* 13:5–8
- Zeltner NA, Huemer M, Baumgartner MR et al (2014) Quality of life, psychological adjustment, and adaptive functioning of patients with intoxication-type inborn errors of metabolism: a systematic review. *Orphanet J Rare Dis* 9(1):159–177