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ORIGINAL RESEARCH

Impaired Health-Related Quality of Life in Children and Families Affected by Methylmalonic Acidemia

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Abstract An understanding of health related quality of life (HRQoL) in children and families affected by methylmalonic acidemia (MMA) is important in planning counseling and therapeutic intervention. Liver transplantation (LT) is used as a treatment for MMA; however, its risks and benefits continue to be investigated. The purpose of this study was twofold: (1) to measure HRQoL in children and families affected by MMA using the Pediatric Quality of Life Inventory (PedsQL™) parent version, and (2) to assess the impact of LT on HRQoL by comparing LT and non-LT patient scores and free responses. Parents/caregivers reported lower scores on the majority of the PedsQL™ scales as compared to samples of healthy children, children with solid organ transplants for indications other than MMA, and families affected by chronic conditions. Scores for children with MMA were lowest in school and social functioning and scores for families were lowest in worry and activity impairment. There were no significant differences in LT and non-LT patient scores on the PedsQL™ scales. Our results document the negative impact of MMA on HRQoL.

Keywords Methylmalonic acidemia · Health-related quality of life · Inborn error of metabolism · Liver transplantation

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Introduction

Isolated methylmalonic acidemia (MMA) is a rare organic acid disorder caused by a deficiency of methylmalonyl-CoA mutase (mut^0, mut^-) or a defect in adenosylcobalamin synthesis (cblA, cblB, cblD variant 2) (Oberholzer et al. 1967; Stokke et al. 1967, Suormala et al. 2004). The disease course of MMA mut^0 tends to be more severe than that of individuals with other subtypes of MMA (mut^-, *cblA*, *cblB*, *cblD*) (Baumgarter and Viardot 1995; Horster et al. 2007; Matsui et al. 1983). Children with MMA mut^0 typically present with hyperammonemia and metabolic ketoacidosis during the neonatal period and are at risk for neurologic damage, coma, and death. Secondary complications include developmental delay, movement disorders, renal failure, pancreatitis, failure to thrive, immune impairment, and optic atrophy (Baumgarter and Viardot 1995; Heidenreich et al. 1988; Horster and Hoffmann 2004; Horster et al. 2007; Leonard 1995; Molteni et al. 1991; Nicolaides et al. 1998; van der Meer et al. 1994; van't Hoff et al. 1999).

Although clinical outcomes of MMA mut^0 have been reported, knowledge of its psychosocial impact is limited. Measuring health-related quality of life (HRQoL) is a method to quantify the psychosocial impact of health conditions and treatments (Cella 1996; Seid et al. 1999; Spieth and Harris 1996; Varni et al. 2001; Weissberg-Benchell et al. 2010). HRQoL is the individual's perception of the ways in which health impacts functioning and is a more specific measure

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than overall quality of life (QoL), which may include factors unrelated to health (CDC 2000). HRQoL can be assessed using generic and disease-specific modules. Generic modules typically measure physical and psychosocial functioning and disease-specific modules measure factors related to the disease in question that may impact HRQoL, such as medication or treatment burden (Droter 1997; Holmbeck et al. 2003; Palermo et al. 2008; Schmidt et al. 2003). The Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales and supplemental modules have been developed to measure HRQoL in healthy children and children affected by various conditions. The PedsQL™ Generic Core Scales, Transplant Module, and Family Impact Module were used in this study and have demonstrated reliability and validity (Varni et al. 2001; Varni et al. 2004; Weissberg-Benchell et al. 2010).

Measuring HRQoL has the potential to elucidate the psychosocial impact of MMA *mut*^{0} on children and families. Currently, knowledge of QoL and HRQoL is largely limited to the extrapolation of results from studies of individuals and families affected by multiple different biochemical genetic disorders, including carbohydrate metabolism disorders, lysosomal storage diseases, amino acid metabolism disorders, urea cycle disorders, organic acidurias, and mitochondrial disorders (Eminoglu et al. 2013; Fabre et al. 2013; Hatzmann et al. 2009). In this population, psychosocial determinants, like emotional support and participation in leisure activities, better predict HRQoL than socio-demographic and medical factors (Fabre et al. 2013; Hatzmann et al. 2009). However, parents express difficulty participating in activities due to the possibility of metabolic decompensation (Fabre et al. 2013). The QoL of individuals with organic acid disorders also appears more impaired than that of individuals with disorders of carbohydrate and amino acid metabolism (total: n = 14, MMA: n = 5), hypothesized by the authors to be the result of delayed diagnosis and increased frequency of metabolic decompensation (Eminoglu et al. 2013).

In recent years, liver transplantation (LT) and combined liver-kidney transplantation (LKT) have been used as treatment options for patients with MMA *mut*^{0} with the goal of preventing hyperammonemia and metabolic ketoacidosis during illness or metabolic stress (Chakrapani et al. 2002; Kasahara et al. 2006; Leonard 1995; van't Hoff et al. 1998). After LT, patients have demonstrated increased energy, muscle strength, mobility, and protein tolerance; however, permanent neurologic damage, kidney disease, graft loss, and death as a result of acidosis and sepsis have also been described post-LT (Chakrapani et al. 2002; Horster et al. 2007; Kaplan et al. 2006; Kayler et al. 2002; McGuire et al. 2008; Morioka et al. 2005; Morioka et al. 2007; Nagarajan et al. 2005; Niemi et al. 2015; Nyhan et al. 2002; Perito et al. 2014; van't Hoff et al. 1999). Given the varied outcomes, LT is not considered curative and there is ongoing interest in determining its most appropriate role in the management of children with MMA (Burfield et al. 2012; Shneider et al. 2011). Improved QoL in seven of seven children with MMA after LT has been reported by Morioka et al. (2007). This study was limited by the use of parent report via non-validated measures and relatively small sample size (Morioka et al. 2007). As a result, it was not clear which domains of QoL were most impaired and which may have improved post-LT.

Further understanding of HRQoL in children and families affected by MMA *mut*^{0} is expected to guide counseling and intervention strategies for this population. Knowledge of how LT impacts HRQoL would improve understanding of the role of LT and other measures in the management of children with MMA *mut*^{0}. The goal of our study was twofold: (1) to measure HRQoL in children and families affected by MMA *mut*^{0} using the Pediatric Quality of Life Inventory (PedsQL™) parent version and free responses, and (2) to assess the impact of LT on HRQoL by comparing responses between LT and non-LT patients. We present the findings from 35 parent/caregiver responses regarding the HRQoL of their children with MMA *mut*^{0} with and without LT. Our data document the negative impact of MMA *mut*^{0} on HRQoL. In particular, school and social functioning are impaired in children and daily activities are impaired in families. On the PedsQL™ measure, daily activities include family activities and household tasks. While HRQoL scores did not significantly differ between LT and non-LT patients on standardized measures, several parents/caregivers reported improvements post-LT on free-response questions.

Methods

Participants and Procedures

Parents and caregivers of children with MMA were invited to participate in this study through the Organic Acidemia Association (OAA), an MMA Facebook group, the Stanford Children's Hospital biochemical genetics clinic, and members of the Metab-L mailing list managed by Dr. Christian Renner. If parents/caregivers expressed interest, they were directed to an online survey. To be eligible for the study, participants were required to be a parent/caregiver of a child between ages 2 and 18 years with a reported diagnosis of MMA *mut*^{0}. Diagnostic testing results were not available to confirm parent/caregiver reported subtypes. Participants were at least 18 years old and able to complete a survey in English or Japanese.

The survey was designed and administered through Qualtrics.com and was available from November 2013 to February 2014. Parent/caregivers completed the survey in an anonymous manner and completed surveys implied respondent consent. The study protocol was approved by the Institutional Review Board at Stanford University.

Instrumentation

Demographic and Clinical Information

Demographic and clinical survey questions were asked in dichotomous, multiple choice, and free response formats. Demographic information gathered included age and sex. Clinical information collected included: (1) information about diagnosis (whether child was diagnosed by newborn screening, age at diagnosis, MMA subtype), (2) information about metabolic crisis (peak ammonia level, age at peak level, hospital stays (number, length of longest stay), number of emergency room visits), (3) current interventions related to MMA (ammonia scavengers, carnitine, vitamin B12, protein restriction, medical foods/formulas, chronic hemodialysis, feeding by gastrostomy tube (G tube), fasting precautions), (4) developmental status (concerns about development, IQ, developmental age), and (5) transplant specific information (age at transplant, type of transplant, time since transplant, post-transplant complications).

HRQoL- Pediatric Quality of Life Inventory (PedsQL™)

The Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales, Transplant Module, and Family Impact Module were used to measure HRQoL (Online Resource 1). These modules have demonstrated reliability and validity (Varni et al. 2001; Varni et al. 2004; Weissberg-Benchell et al. 2010). Parents/caregivers completed one of four age-specific versions of the parent-proxy modules, which were used due to age and/or intellectual disability of the child. All questions required answers on a 5-point Likert scale ranging from 0 (never) to 4 (almost always).

The PedsQL™ Generic Core Scales measure physical, emotional, social, and social functioning of the child. The PedsQL™ Transplant Module measures the impact of medicines, transplant, social interactions, pain, hurt, worry, treatment anxiety, appearance, and communication on child functioning. To our knowledge there is not a disease specific module for inborn errors of metabolism or MMA specifically. The PedsQL™ Family Impact Module measures physical, emotional, social, and cognitive functioning of the family; it also measures worry and impairments in communication, daily activities, and family relationships.

HRQoL- Parent/Caregiver Free Responses

To gather information about the impact of MMA and LT that may not have been addressed by the PedsQL™ modules, free responses were collected. Parents/caregivers were asked to describe the impact of MMA on their child and family. Parents/caregivers of children post-LT were also asked to explain the impact of LT on their child's development and the functioning of their child and family.

Data Analysis

Analyses were conducted using SAS 9.4 (Copyright, SAS Institute Inc., Cary, NC, USA). HRQoL scores and other continuous variables were compared using t-tests and ANOVA, where applicable. When appropriate, continuous variables were converted to either categorical or dichotomous and compared using Chi-Square tests.

The PedsQL™ modules were scored according to the Scaling and Scoring of the PedsQL™ Manual. Each response was reverse coded and rescaled to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). A score of 100 represents the best HRQoL possible. Scores for the individual scales were computed as the sum of the items divided by the number of items answered in the scale. If more than 50 % of the items in the scale were missing, the scale score was not computed.

The total score from the PedsQL™ Generic Core Scales was calculated as the average of the scores measuring physical functioning and psychosocial health (calculated as the average of the scores measuring emotional, social, and school functioning). The total score from the PedsQL™ Transplant Module was calculated as the average of the questions that pertained to the LT and non-LT patients (calculated as the average of the scores measuring the impact of medicines, pain, hurt, worry, treatment anxiety, and communication). The total score from the PedsQL™ Family Impact Module was calculated as the average of the scale scores on the Family Impact Module. The parent HRQoL score was computed as the average of the scores measuring physical, emotional, social, and cognitive functioning. The family functioning score was calculated as the average of the scores measuring daily activities and family relationships. Mean scale and total scores on the PedsQL™ modules were compared using independent *t*-tests to assess differences in HRQoL between LT and non-LT patients. *P*-values corresponding to less than 0.003 were considered significant after the Bonferroni correction.

Parent/caregiver free responses were systematically analyzed by the first author. Using an open coding technique, text was assigned codes based on emergent concepts (Strauss and Corbin 1998). Codes were compared across responses and were sorted, revised, merged, and split. Through this process, recurring concepts and categories were identified and illustrative examples were chosen.

Comparison with Literature Control Populations

To assess the HRQoL of children with MMA mut^0, mean total and subscale scores from the PedsQL™ Generic Core Scales and Transplant Module were compared to mean scores of healthy children (Varni et al. 2001) and children post-

transplant (Alonso et al. 2010; Weissberg-Benchell et al. 2010). The published sample of healthy children included 1629 individuals with a mean age of 9.3 years (SD = 4.4) (Varni et al. 2001). The published sample of children post-transplant included 872 patients post-LT from a study by Alonso et al. (2010) and 338 patients post-solid organ transplant (liver (53.8 %), kidney (26.3 %), heart (9.6 %), small bowel (1.8 %), multiple organ (8.5 %)) from a study by Weissberg-Benchell et al. (2010). The mean ages of these samples were 8.2 (SD = 4.4) and 11.3 years (SD = 5.0), respectively (Alonso et al. 2010; Weissberg-Benchell et al. 2010).

To assess the HRQoL of families affected by MMA *mut*^{0}, mean total and subscale scores on the PedsQL™ Family Impact Module were compared to mean scores of families with children with complex chronic conditions, like severe cerebral palsy and birth defects. There were 23 families in this published sample; 12 families had a child with a chronic condition living in a care facility and 11 families had a child with a chronic condition living in the home (Varni et al. 2004).

Results

Demographic Characteristics

Demographic characteristics provided by parents/caregivers are presented in Table 1. A total of 35 responses from parents/caregivers of children (16 males, 19 females, mean age = 8.0 years (SD = 4.7)) with a reported diagnosis of MMA *mut*^{0} were received. 71.4 % of responses (25/35) were from English-speaking parents/caregivers and 28.6 % (10/35) were from Japanese-speaking parents/caregivers. 45.7 % of responses (16/35) were from parents/caregivers of children with LT (7 males, 9 females, mean age = 8.4 years (SD = 4.5)).

Clinical Information

Clinical information provided by parents/caregivers is presented in Table 2. Mean age at time of diagnosis was less than one year. The mean age at time of transplant was 3.3 years (SD = 4.0). Of the post-transplant sample, 62.5 % of respondents (10/16) reported that their child underwent only LT and 31.3 % (5/16) reported that their child underwent LKT. One parent/caregiver did not specify the type of transplant that his/her child received. 25.0 % of respondents (4/16) reported post-transplant complications.

The use of MMA-related interventions as reported by parents/caregivers is presented in Fig. 1. Parents/caregivers were asked to select the MMA related interventions that their child receives. Responses for children post-LT therefore only pertained to the period of time after transplant. The use of enteral feeding by gastrostomy tube (G-tube) was significantly higher in children post LT than in children without LT ($p = 0.05$). 75 % of post-LT respondents (12/16) reported that their child requires enteral feeding by G-tube, whereas only 42.1 % of non-LT respondents (8/19) reported G-tube feedings. The use of chronic hemodialysis was also significantly higher in children with LT than in children without LT ($p = 0.04$). 31.3 % of post-transplant respondents (5/16) reported that their child requires hemodialysis, whereas only 5.3 % of non-transplant respondents (1/19) reported the use of hemodialysis. Of the post-transplant respondents, 80 % (4/5) reported that their child underwent only LT and 20 % (1/5) reported that their child underwent LKT.

HRQoL of Children with MMA *mut*^{0}

Children with MMA *mut*^{0} had a lower mean score (mean = 64.5) on the PedsQL™ Generic Core Scales than healthy children (mean = 80.9) (Varni et al. 2001) and children

Table 1 Demographic characteristics

	Total ($n = 35$)	Transplant ($n = 16$)	No Transplant ($n = 19$)
Sex			
Males, n (%)	16 (45.7)	7 (43.8)	9 (47.4)
Females, n (%)	19 (54.3)	9 (56.3)	10 (52.6)
Age			
Current[a]	8.0 +/− 4.7	8.4 +/− 4.5	7.7 +/− 4.9
Language			
English-speaking, n (%)	25 (71.4)	10 (62.5)	15 (78.9)
Japanese-speaking, n (%)	10 (28.6)	6 (37.5)	4 (21.1)

[a] The mean age +/− standard deviation (in years) for each subgroup of patients is indicated

Table 2 Clinical information

	Total ($n = 35$)	Transplant ($n = 16$)	No Transplant ($n = 19$)
Age			
At time of diagnosis[a]	0.2 +/− 0.6	0.2 +/− 0.6	0.2 +/− 0.6
At time of transplant[a]	-	3.3 +/− 4.0	-
Type of transplant			
Liver, n (%)	-	10 (62.5)	-
Liver/Kidney, n (%)	-	5 (31.3)	-
Post-transplant complications, n (%)	-	4 (25)	-

[a] The mean age +/− standard deviation (in years) for each subgroup of patients is indicated

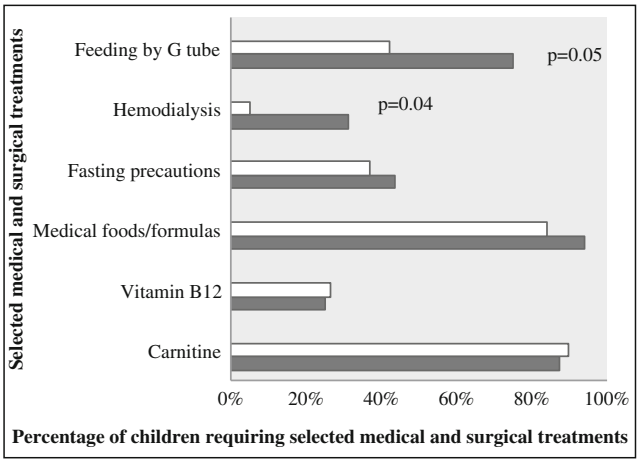

Figure legend:

☐ No transplant ■ Transplant

Fig. 1 Selected medical & surgical treatment use by children with methylmalonic acidemia (MMA) *mut*^{0}

post-LT for indications other than MMA (mean = 77.3) (Alonso et al. 2010). On the PedsQL™ Transplant Module, the social functioning, transplant and others, and communication scale scores were lower for children with MMA (social functioning = 59.8, transplant and others = 49.3, communication = 55.9) than children with solid organ transplants (social functioning = 76.5, transplant and others = 76.9, communication = 77.6) (Weissberg-Benchell et al., 2010). These scores are presented in full in Table 3.

In order to identify the most impaired domains of HRQoL in our cohort, the two lowest scores on the PedsQL™ Generic Core Scales and Transplant Module were noted. On the PedsQL™ Generic Core Scales, lowest scores were reported on the social (mean = 59.8) and school (mean = 59.9) functioning scales. On the PedsQL™ Transplant Module, lowest scores were on the transplant and others (mean = 49.3) and treatment anxiety (mean = 51.9) scales.

HRQoL of Families Affected by MMA *mut*^{0}

Families affected by MMA *mut*^{0} had a lower mean score (mean = 62.0) than families with children with chronic health conditions living in a long-term care facility (Varni et al. 2004) (mean = 81.0). The mean score of families affected by MMA *mut*^{0} was comparable to the mean score of families with children with chronic conditions living at home (Varni et al. 2004) (mean = 62.5). Compared to this cohort, families affected by MMA *mut*^{0} had slightly lower scores in cognitive functioning (65.7 compared to 74.1), worry (50.5 compared to 56.8), and impairment of daily activities (48.9 compared to 51.9), and a considerably lower score in family relationships (61.3 compared to 79.0). To determine the most impaired domains of family HRQoL in our cohort, the two lowest scores on the PedsQL™ Family Impact Module were identified. The lowest scores were reported on the daily activities (mean = 48.9) and worry (mean = 50.5) scales. These scores are presented in full in Table 3.

Free responses from parents/caregivers were analyzed to gather additional information about the psychosocial impact of MMA *mut*^{0} on the family. Twenty-three free responses were obtained and eight recurring concepts were identified. Recurring concepts included a better perspective on life, increased family member anxiety, stronger family bonds, social isolation, strains on family relationships, a general negative impact on the parents and child, and financial burden (Online Resources 3 and 4).

Impact of LT on Children and Families Affected by MMA *mut*^{0}

To measure the impact of LT on HRQoL, mean total and subscale scores from the PedsQL™ Generic Core Scales, Transplant Module, and Family Impact Module were compared between the LT and non-LT patients. No significant differences were observed (Online Resource 2).

Free responses from parents/caregivers were also analyzed and provide additional information about the psychosocial impact of LT on the child and family. When asked, "In your opinion, did the transplant positively or negatively affect your child's development", the majority (93 %) of parents/caregivers of children post-LT responded that the transplant had had a positive impact on their child's development (Online Resource 3). In addition, fourteen free responses were collected regarding the impact of the transplant on the child and family. Six recurring concepts were identified from these responses, including health-related improvement, increased family social involvement, decrease in parental anxiety, a more positive outlook, and intellectual and emotional improvements in the child (Online Resources 3 and 4).

Discussion

MMA *mut*^{0} is an organic acid disorder with risk for permanent neurologic damage and death during periods of metabolic stress, with significant disease burden including developmental delay, movement disorder, renal failure, pancreatitis, failure to thrive, immune impairment, and optic atrophy during intervening times of health (Heidenreich et al. 1988; Matsui et al. 1983; Nicolaides et al. 1998; Oberholzer et al. 1967; Stokke et al. 1967). The goals of this study were to investigate the HRQoL of children and families affected by MMA *mut*^{0} using PedsQL™ modules and free responses and to assess the impact of LT on HRQoL. This study was the first to query parents/caregivers regarding the impact of both MMA and LT on the HRQoL of their children and families using standard

Table 3 Pediatric Quality of Life Inventory™ (PedsQL™) mean scores across populations

	Present study	Varni et al. 2001	Alonso et al. 2010	Weissberg-Benchell et al. 2010	Varni et al. 2004- Parents of children with chronic condition in care facility	Varni et al. 2004-Parents of children with chronic condition in home
Number of participants	35	1629	873	338	12	11
Age[a]	8.0+/−4.7	9.3+/−4.4	8.2+/−4.4	11.3+/−5.0	–	–
Generic Core Scales						
Total score	64.5	80.9	77.3	74.9	–	–
Phys. health sum. Score	62.9	81.4	79.3	79.1	–	–
Psych. health sum. Score	65.1	80.6	75.7	72.7	–	–
Emotional functioning	72.7	78.0	73.3	74.1	–	–
Social functioning	59.8	85.4	79.0	76.5	–	–
School functioning	59.9	77.8	67.4	65.9	–	–
Transplant module						
Total score	59.6	–	–	79.4	–	–
Medicines I	87.2	–	–	84.8	–	–
Transplant and others	49.3	–	–	76.9	–	–
Pain and hurt	88.0	–	–	75.6	–	–
Worry	80.8	–	–	78.1	–	–
Treatment anxiety	51.9	–	–	71.6	–	–
Communication	55.9	–	–	77.6	–	–
Family Impact Module						
Total score	62.0	–	–	–	81.0	62.5
Parent HRQoL sum. Score	67.5	–	–	–	83.8	62.9
Physical functioning	65.9	–	–	–	83.0	53.0
Emotional functioning	70.5	–	–	–	78.3	64.5
Social functioning	71.4	–	–	–	85.4	61.9
Cognitive functioning	65.7	–	–	–	88.8	74.1
Communication	64.1	–	–	–	73.6	52.2
Worry	50.5	–	–	–	69.2	56.8
Family function. Sum. score	55.1	–	–	–	84.3	68.8
Daily activities	48.9	–	–	–	85.1	51.9
Family relationships	61.3	–	–	–	83.8	79.0

[a] The mean age +/− standard deviation (in years) for each subgroup of patients is indicated

measures and presents the largest sample of children with MMA post-LT published to date.

HRQoL of Children with MMA *mut*^{0}

Our results revealed that the HRQoL of children with MMA *mut*^{0} is substantially impaired compared to a sample of healthy children (Varni et al. 2001) and a group of children post-LT (Alonso et al. 2010). More specifically, school and social functioning are low in children with MMA *mut*^{0}. School performance has been noted previously (Eminoglu et al. 2013) to be poor in individuals with organic acid disorders, with 57 % scoring behind their age group on developmental screening tests, and is consistent with the natural history of MMA (Baumgarter and Viardot 1995; Horster et al. 2007). Very few respondents reported IQ scores for their children, preventing a comparison between IQ and school and social functioning HRQoL scores.

Results from our study also demonstrate that children with MMA *mut*^{0} specifically experience difficulties with social interactions, measured by the social functioning, transplant and others, and communication scales of the PedsQL™ Transplant Module. Children with MMA *mut*^{0} had lower mean scores on all of these scales as compared to a sample of children with solid organ transplants (Weissberg-Benchell et al. 2010). In a prior study measuring the QoL of individuals with biochemical disorders (Fabre et al. 2013), social interactions were similarly found to be an impaired domain of QoL. Parent/caregiver responses in our study revealed that children MMA *mut*^{0} experience particular difficulty in communicating with medical providers. Communicating with clinicians may therefore be especially difficult for children with MMA *mut*^{0}, potentially due to the substantial risk of neurologic damage in children with this condition (Baumgarter and Viardot 1995; Horster et al. 2007).

HRQoL of Families Affected by MMA *mut*^{0}

The HRQoL of families affected by MMA *mut*^{0} is impaired as compared to the HRQoL of families with children with

chronic health conditions living in a long-term care facility (Varni et al. 2004). The HRQoL of families affected by MMA *mut*^{0} is comparable to the HRQoL of families with children with chronic conditions living at home (Varni et al. 2004). This suggests that taking care of a child with a chronic condition, like a biochemical genetic disorder, at home is more detrimental to HRQoL than caring for a child in a long-term care facility.

Looking specifically at families with children affected by MMA *mut*^{0} and chronic conditions living at home, families affected by MMA *mut*^{0} had lower scores in cognitive functioning, worry, and impairment of daily activities, and a considerably lower score in family relationships (Varni et al. 2004). In our study, worry and impairment of daily activities had the greatest negative impacts on family HRQoL. In free responses, parents/caregivers expressed that worry and impairment of daily activities, like family social activities, were caused by the potential for metabolic decompensation that can lead to neurologic damage and death. As LT has been shown to reduce the risk of hyperammonemia and metabolic decompensation, this should be highlighted in discussions with parents considering LT.

Impact of LT on Children and Families Affected by MMA *mut*^{0}

There were no statistically significant differences in scores between children with and without LT on the standardized HRQoL modules, yet the majority of parents/caregivers reported positive impacts of LT in free responses. This positive perception of quality of life post-LT is congruent with results from other studies of children with MMA post-LT (Morioka et al. 2007, Niemi et al. 2015). In a recent study, improved energy and an increased ability to attend school were observed (Niemi et al. 2015). This discrepancy between scores on standardized HRQoL modules and parent reports may reflect greater disease severity in children post-LT as compared to children without LT. Children post-LT may have had more severe symptoms pre-transplant, leading to the decision for transplantation. The children with LT had a higher reported use of G-tube feeding and dialysis, suggesting that this group may have had more severe symptoms that necessitated these interventions. To control for these possible differences in disease severity, it would be helpful to administer standardized HRQoL modules before and after LT to the same patient/family in future studies.

Limitations

Our study was potentially limited by its sample size and recall and response biases. Additionally, when asked to report current interventions, some parents/caregivers may have been referring to interventions used in the past, like a history of hemodialysis, rather than current interventions.

We also acknowledge the inherent risk and potential adverse outcomes of LT, including death, and our sample only reflects the experiences of survivors of LT. In addition, the scales measuring HRQoL have not previously been utilized in the Japanese language and it is possible that in translation may not fully capture the life experience of individuals with MMA *mut*^{0}. We, however, observed no clear differences in response patterns between English and Japanese speaking respondents.

In free responses, many parents expressed positive changes to their child's development and health post-LT, but the scales measuring HRQoL only requested responses about one point in time. Furthermore, while parents described positive changes to their child's development, we did not have results of formal developmental assessments before and after LT on these patients.

Practice Implications

Our results substantiate and additionally delineate the negative impact of MMA *mut*^{0} on both patient and family HRQoL. These findings should help to increase awareness amongst clinicians of the domains of HRQoL most impacted by the condition, namely child school and social functioning and parental worry and social involvement. Counseling of families with newly diagnosed children should also be focused on these areas. For instance, clinicians could provide anticipatory guidance to parents and caregivers of the potential need for increased educational support for children with MMA. In addition, clinicians should recognize that children with MMA might have difficulty communicating and take special care to ensure that these children are involved during appointments, as their abilities allow.

Research Recommendations

As our results support the possibility that more severely affected children are more likely to undergo LT, in future studies it would be beneficial to administer standardized HRQoL modules before and after LT to the same patient/family to control for possible differences in disease severity. This would potentially be facilitated by a registry of patients with MMA *mut*^{0} undergoing LT. In addition, the HRQoL modules utilized in this study may not have fully captured the change in development and course of illness of children with MMA *mut*^{0}. Since MMA *mut*^{0} is a progressive condition, measuring trajectories may be more important in this condition than in more static conditions. This suggests that a new HRQoL survey should be created to specifically address this area.

Conclusions

Our results demonstrate a negative impact of MMA mut^0 on both patient and family HRQoL, adding to the literature on biochemical genetic disorders and HRQoL. In particular, school functioning and social interactions are impaired in children and daily activities, like family activities and household tasks, are impaired in families. There were no significant differences in LT and non-LT patient scores on the standardized HRQoL scales. Findings such as these from HRQoL studies should be combined with developmental and medical outcome measures when considering LT as a treatment for children with MMA mut^0.

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Compliance with Ethical Standards

Conflict of Interest Kimberly Splinter, Anna-Kaisa Niemi, Rachel Cox, Julia Platt, Monisha Shah, Gregory M. Enns, Mureo Kasahara, and Jonathan A. Bernstein declare that they have no conflict of interest.

Human Studies and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Animal Studies No animal studies were carried out by the authors for this article.

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