RESEARCH ARTICLE

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QOL in Caregivers of Japanese Patients With Prader–Willi Syndrome With Reference to Age and Genotype

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This study aimed to measure quality of life (QOL) of the primary family caregivers for patients with Prader–Willi syndrome (PWS). Comparisons were made between caregivers' QOL in regard to their dependents' genotype and age group. The participants with PWS consisted of 22 children (aged from 6 to 12 years) and 23 adolescents (aged from 13 to 19 years), including 6 children and 7 adolescents with maternal uniparental disomy (mUPD) and 16 children and 16 adolescents with deletion (DEL). The QOL of the primary family caregiver for each patient was assessed using the Japanese version of the WHOQOL-BREF. To examine the effect that age (children vs. adolescents) and genotype (DEL vs. mUPD) have on the QOL of caregivers, a two-way ANOVA was conducted, followed by the Bonferroni procedure to test the simple main effects. The two age groups and the two genotypes of PWS were used as independent variables and the total QOL of caregivers as a dependent variable. The two-way ANOVA ($F(1, 41) = 6.98$, $P < 0.05$), followed by the Bonferroni procedure, showed the following: the total QOL of caregivers of DEL adolescents showed little difference from that with DEL children, but the QOL of caregivers for mUPD adolescents was shown to be lower than that with mUPD children along with that of caregivers with DEL adolescents. There is hence a growing tendency for the deterioration in the QOL of caregivers to manifest itself later in the patients' adolescence, found mainly with mUPD patients.

Key words: quality of life; Prader–Willi syndrome; caregiver; uniparental disomy

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INTRODUCTION

Prader–Willi syndrome (PWS) is a neurodevelopmental disorder, associated with neonatal hypotonia, hypogonadism, hyperphagia, progressive obesity and mild to moderate mental retardation. The physical manifestation of PWS includes short stature, small hands and feet, hypopigmentation and craniofacial anomalies. This syndrome is a genetic disorder caused by a loss of expression of paternally derived genes on chromosome 15q11–13. The causes

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Ascertainments: This study started upon receiving approval from the ethics committee of the hospital which the authors were affiliated with. After obtaining informed consent, the neurocognitive and behavioral assessment of each participant was carried out.
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of this disruption include maternal uniparental disomy 15 (mUPD; when both copies of chromosome 15 are maternally inherited) and a paternal deletion (DEL) of 15q11–13. Based on epidemiological surveys, the birth incidence is estimated at around 1 in 25,000 [Whittington et al., 2001].

Living with intellectually disabled family members like PWS patients is associated with a major increase in caregiving demands in the family [Greenberg et al., 1993; Heller et al., 1997; Pinquart and Sorensen, 2006]. The adverse influence of providing care for affected members on the family caregivers has been discussed in the literature under various terms, such as caregiver stress [Nolan et al., 1990; Pearlin et al., 1990], caregiver burden [Zarit et al., 1980] and caregiver strain [Archbold et al., 1990]. Lifelong family caregivers for individuals with PWS may also experience a range of considerable stress. Yet, so far little attention has been paid to the primary caregivers of PWS patients.

Due to the paucity of research, we conducted this study into the adverse effect of caring for affected individuals with PWS. It had three key features. Firstly, we, for the first time, aimed to measure quality of life (QOL) of the primary family caregivers, who take primary responsibility for patients with PWS. Secondly, considering the impact of the two genotypes of PWS on the behavioral manifestations of this syndrome, we compared mUPD and DEL forms of PWS in regard to caregivers' QOL. Thirdly, this study took into account the behavioral differences between children and adolescents. Several studies have identified considerable behavioral changes across time in relation to physical development in PWS individuals. Adolescents with PWS are different from younger children with PWS in such respects as emotional lability, repetitive and ritualistic behaviors, stealing and hoarding [Cassidy, 1984; Clarke et al., 1996].

MATERIALS AND METHODS

This study started upon receiving approval from the ethics committee of the hospital with which the authors were affiliated. After obtaining informed consent, the neurocognitive and behavioral assessment of each participant and the assessment of the caregivers' QOL were carried out. The participants included were 45 Japanese individuals with PWS recruited from a single location. The Department of Pediatrics, Dokkyo Medical University Koshigaya Hospital was used for this purpose. All patients were diagnosed with PWS using fluorescence in situ hybridization or the methylation test. Alongside these patients, the primary family caregiver for each patient participated in this study. Here, "the primary family caregiver" refers to the family member who takes primary responsibility for the individual with PWS. In this study, each of them was the mother of a patient.

The caregivers' QOL was assessed using the Japanese version [Ishizaki et al., 2002] of the WHOQOL-BREF [Katschnig et al., 1997]. The WHOQOL-BREF is a shorter version of the original instrument WHOQOL developed collaboratively in a number of centers worldwide and has been widely field-tested. The WHOQOL-BREF, a generic measure of QOL, consists of 26 items, two general items and 24 others, across the following five domains: Physical, Psychological, Social, Environmental, and QOL impression (two items assessing overall QOL).

To measure intellectual ability, a Japanese version of the Wechsler Intelligence Scale [Wechsler, 1991, 1997; Japanese WISC-III Publication Committee, 1998; Japanese WAIS-III Publication Committee, 2006] was administered. The same clinical psychologist (H.O.), blind to the genetic status of each patient, applied the tests in similar conditions of a calm environment and a comfortable atmosphere.

By means of a numerical coding system, all data were guarded under strict confidentiality and anonymity. The data were analyzed with SPSS 20.0 J for Windows. The results are expressed as mean (SD and range). To examine the effect that age and genotype have on the QOL of caregivers, two-way ANOVA was conducted, using the two age groups (children vs. adolescents) and the two genotypes of PWS (DEL vs. mUPD) as independent variables and the total QOL and each of the five domains of caregivers as dependent variables.

RESULTS

As shown in Table I, the participants consisted of 22 children (aged from 6 to 12 years) and 23 adolescents (aged from 13 to 19 years). Six children and seven adolescents were confirmed as having mUPD of chromosome 15. Sixteen children and 16 adolescents were confirmed as having a DEL involving 15q11–13. The mean IQ in both groups of DEL and mUPD as well as both groups of children and adolescents in our sample was approximately 47. These scores are more than 50 points under the normative population score of 100, indicating a global impairment in intellectual abilities.

Table II shows the characteristics of family caregivers of the PWS participants. All primary family caregivers were mothers. The caregivers' ages for participants with mUPD were significantly older than for those with DEL ($P < 0.01$). This finding accords with previous reports, suggesting mUPD is associated with advanced maternal age [Robinson et al., 1991; Cassidy et al., 1992; Mascari et al., 1992; Sinnema et al., 2010]. Naturally, the mean age was younger and the length of caregiving was shorter in caregivers for children than in caregivers for adolescents ($P < 0.001$). Table III shows the results in regard to the QOL of caregivers for PWS individuals. In order to examine the effect that age and genotype have on the total QOL of caregivers, we conducted two-way ANOVA, using the two age groups and the two genotypes of PWS as independent variables and the total QOL of caregivers as a dependent variable. Then, we conducted two-way ANOVA, using each of the five domains (physical, psychological, social, environmental, and overall impression) of caregivers as a dependent variable.

Examining the total QOL as a dependent variable, we found a statistically significant interaction between age and genotype ($F(1, 41) = 6.98$, $P < 0.05$). Based on this, we performed a Bonferroni procedure to test the simple main effects. We found that the QOL of caregivers for mUPD adolescents is lower than that of caregivers for mUPD children ($F(1, 41) = 6.53$, $P < 0.05$) and that the QOL of caregivers for mUPD adolescents is lower than that with DEL adolescents ($F(1, 41) = 6.61$, $P < 0.05$) (Fig. 1).

In the physical domain there was a marginally significant interaction between age and genotype ($F(1, 41) = 4.05$, $P < 0.10$). A Bonferroni post-hoc test of the simple main effects revealed that

TABLE I. Patient Characteristics

		Genotype groups		Age groups		*P*-Value	
	Total	DEL	mUPD	Children	Adolescents	Genotype groups	Age groups
Number (patients)	45	32	13	22	23		
Male	29	21	8	14	15		
Female	16	11	5	8	8		
Mean age	12.42	12.31	12.69	8.95	15.74	0.77	0.000***
Age range	6–19	6–19	7–19	6–12	13–19		
IQ mean ± SD	47.07 ± 8.04	49.09 ± 8.43	42.08 ± 3.90	46.45 ± 8.91	47.65 ± 7.25	0.000***	0.62
IQ range	39–68	39–68	39–49	39–68	39–62		

***$P < 0.001$.

the QOL of caregivers for mUPD adolescents is significantly lower than that of caregivers for DEL adolescents ($F(1, 41) = 4.70$, $P < 0.05$). Within the psychological domain, we found a statistically significant interaction between age and genotype ($F(1, 41) = 4.46$, $P < 0.05$). We then performed a Bonferroni procedure to test the simple main effects. We found that the QOL of caregivers for mUPD adolescents is significantly lower than that of caregivers for mUPD children ($F(1, 41) = 7.43$, $P < 0.01$) (Fig. 1). In the social domain, two-way ANOVA revealed a statistically significant interaction between age and genotype ($F(1, 41) = 6.44$, $P < 0.05$). On finding this, we performed a Bonferroni procedure to test the simple main effects. We found that the QOL of caregivers for mUPD adolescents is significantly lower than that of caregivers for mUPD children ($F(1, 41) = 6.11$, $P < 0.05$) and that the QOL of caregivers for mUPD adolescents is significantly lower than that of caregivers for DEL adolescents ($F(1, 41) = 7.94$, $P < 0.01$; Fig. 1). In the environmental domain there was no statistical significance in the interaction between age and genotype ($F(1, 41) = 3.57$, n.s.) or in the simple main effects.

Turning to the QOL impression domain, we found a statistically significant interaction between age and genotype ($F(1, 41) = 6.99$, $P < 0.05$). A Bonferroni post-hoc test of the simple main effects showed that the QOL of caregivers for mUPD adolescents is significantly lower than that of caregivers for mUPD children ($F(1, 41) = 6.90$, $P < 0.05$) and that the QOL of caregivers for mUPD adolescents is significantly lower than that of caregivers for DEL adolescents ($F(1, 41) = 4.96$, $P < 0.05$) (Fig. 1).

DISCUSSION

To our knowledge, this study is the first attempt so far to conduct a profile of QOL of primary family caregivers for patients with PWS. It is worth mentioning that in our sample the primary family caregivers were without exception female parents, including single ones (3 out of 45, 6.7%). The family caregivers for mUPD patients were older than those for DEL patients and the caregivers for adolescent patients were older than those for child patients. The length of caregiving for PWS patients almost extended their entire life.

The two-way ANOVA to examine the interaction between age and genotype, followed by the Bonferroni procedure to test the simple main effects, showed the following: the QOL of caregivers of DEL adolescents shows little difference from that with DEL children, but the QOL of caregivers for mUPD adolescents is

TABLE II. Caregiver Characteristics

		Genotype groups		Age groups		*P*-Value	
	Total	DEL	mUPD	Children	Adolescents	Genotype groups	Age groups
Number (patients)	45	32	13	22	23		
Male	0	0	0	0	0		
Female	45	32	13	22	23		
Mean age	43.82	41.53	49.46	40	47.48	0.001**	0.000***
Age range	28–60	28–54	38–60	28–49	36–60		
Married	42	30	12	20	22		
Single	3	2	1	2	1		
Length of caregiving	12.42	12.31	12.69	8.95	15.74	0.771	0.000***
Length of range	6–19	6–19	7–19	6–12	13–19		

**$P < 0.05$.
***$P < 0.001$.

TABLE III. The QOL of Caregivers for PWS Individuals and the Results of Two-Way ANOVA Using the Two Age Groups and the Two Genotypes

	Total caregivers for PWS (n = 45)	Genotype groups		Age groups		ANOVA interaction (age and genotype)	
		Caregivers for DEL (n = 32)	Caregivers for mUPD (n = 13)	Caregivers for Children (n = 22)	Caregivers for adolescents (n = 23)	*F*	*P*
Total QOL	3.46 (0.44; 2.3–4.4)	3.50 (0.45; 2.3–4.4)	3.35 (0.44; 2.7–4.2)	3.50 (0.46; 2.3–4.2)	3.42 (0.43; 2.7–4.4)	6.98	0.013*
Physical	3.59 (0.55; 2.14–4.86)	3.64 (0.56; 2.14–4.43)	3.45 (0.54; 2.71–4.86)	3.60 (0.63; 2.14–4.86)	3.57 (0.48; 2.71–4.43)	4.05	0.051†
Psychological	3.34 (0.53; 2.17–4.17)	3.35 (0.52; 2.17–4.17)	3.31 (0.60; 2.33–4.17)	3.48 (0.52; 2.17–4.17)	3.21 (0.53; 2.33–4.17)	4.46	0.041*
Social	3.50 (0.60; 2–5)	3.58 (0.55; 2–5)	3.31 (0.69; 2–4)	3.56 (0.53; 2–4)	3.45 (0.66; 2–5)	6.44	0.015*
Environmental	3.43 (0.47; 2.6–4.9)	3.46 (0.51; 2.6–4.9)	3.33 (0.36; 2.8–4.1)	3.40 (0.45; 2.6–4.1)	3.45 (0.51; 2.6–4.9)	3.57	0.066 n.s.
QOL impression	3.40 (0.70; 2–5)	3.44 (0.72; 2–5)	3.31 (0.69; 3–5)	3.48 (0.68; 2–5)	3.33 (0.73; 3–5)	6.99	0.012*

Mean (SD; range); n.s., not significant.
†$P < 0.10$.
*$P < 0.05$.

lower than that with mUPD children as well as that with DEL adolescents. There is hence a growing tendency for the deterioration in the QOL of caregivers to manifest itself later in the patients' adolescence, found mainly with mUPD patients. Examining each of the five domains, this tendency is prominent in the psychological, social, and overall impression domains and marginal in the physical domain, but not significant in the environmental domain.

Which aspects of PWS impair the QOL of caregivers, particularly that for mUPD adolescents, remains unanswered. But, there are some possibilities that behavioral and psychological symptoms of this syndrome may contribute to the deterioration in the QOL of caregivers. In contrast to many other genetic disorders, the behavioral manifestations of PWS differ at various stages in the life cycle as was suggested by long-term studies [Cassidy and Ledbetter, 1989; Descheemaeker et al., 2002; Sinnema et al., 2011b]. The adolescence of PWS individuals features a gradually exacerbating process of behavioral and psychological problems and even psychosis. For example, there is ample evidence to show an increased risk for developing psychotic disorder in PWS patients, particularly in adolescent patients and those with mUPD genotypes [Soni et al., 2007; Sinnema et al., 2011a; Lionti et al., 2012]. Also, the behavior of some patients with PWS gradually comes to resemble that of an autism spectrum disorder (ASD) [Veltman et al., 2005]. In this respect, it has been suggested that the maternal duplications of 15q11–13 have an association with autistic spectrum disorders (ASD) [Bolton et al., 2001; Veltman et al., 2005; Dimitropoulos and Schultz, 2007; Hogart et al., 2010]. Furthermore, there is a growing tendency for autistic behavioral problems, which are more severe in mUPD than in DEL, to manifest themselves later in adolescence [Ihara et al., 2013]. There seems to be a need for further investigation in terms of the impact of the behavioral changes of PWS patients on the QOL of caregivers.

One of the limitations in this study lies in the fact that the relationship between the QOL of caregivers and their socioeconomic background such as education level and family income remained unexamined. With respect to primary family caregivers with profound intellectual and multiple disabilities, Chou et al. [2011] found that higher QOL in caregivers was associated with being employed, being healthier, having a higher level of education and having a higher family income. In terms of PWS, future studies are warranted to analyze the relationship between the QOL of caregivers and their socioeconomic characteristics.

It is evident that further methodological limitations exist in the current study. First, the size of sample is relatively small. This is owing mainly to the fact that this is a single-institution study aimed at a rare genetic disorder. Second, this study is cross-sectional rather than longitudinal. In fact, cross-sectional comparison between different age brackets cannot avoid inter-generational differences. For assessing the impact of behavior development of PWS patients on the QOL of their caregivers, longitudinal studies tracking the same cohort could make observing changes more accurate than cross-sectional ones. Third, whilst this is a study conducted in an Asian country, applicability of the result to other populations including Western societies remains unclear. An interesting finding, however, is the resemblance of the results to findings from Western countries in regard to genetic subtype differences. In this

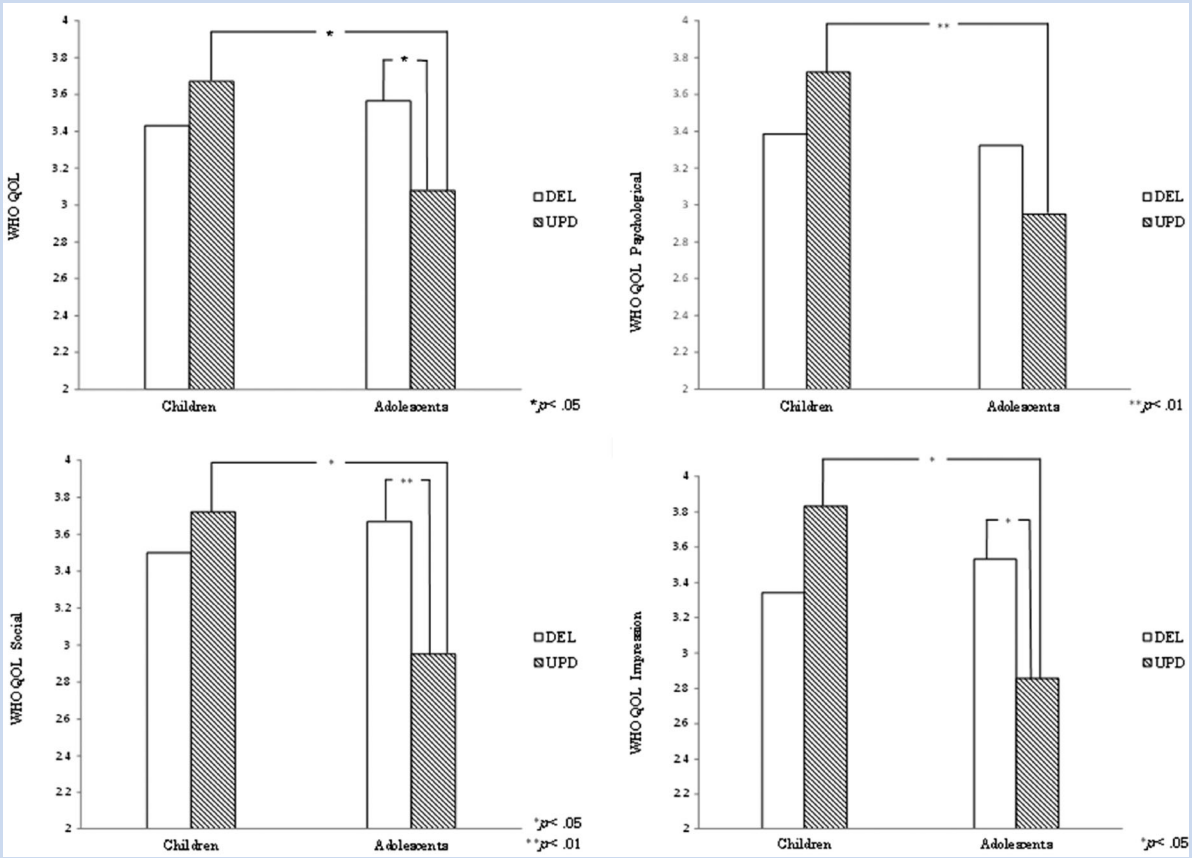

FIG. 1. The effect of age (children vs. adolescents) and genotype of PWS (DEL vs. UPD) on the total score and psychological, social, and impression domains of WHO-QOL of caregivers.

matter, further investigation is required [Sinnema et al., 2010, 2011b].

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