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Aberrant, autistic, and food-related behaviors in adults with Prader-Willi syndrome. The comparison between young adults and adults

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ABSTRACT

This study aims to explore the differences of age as well as genotype in regards to the severity of behavioral symptoms in Prader-Willi syndrome (PWS), with emphasis on the comparison between youngadults and adults.The Food Related Problem Questionnaire (FRPQ), the Aberrant Behavior Checklist Japanese Version (ABC-J), and the Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS) were administered to 46 PWS patients, including 33 young adults (ages 18–28) and 13 adults(ages 30–45). To examine the differences between young adults and adults, Mann-Whitney *U* tests were conducted. Statistically significant differences were found in ABC-J ($p = .027$) and PARS ($p = .046$), with higher scores in young adults than adults. Such differences between the two age groups were still true for the subgroups having a paternal chromosome 15q deletion (DEL) for ABC-J ($p = .050$) and part of PARS ("Problematic behavior"; $p = .007$). By contrast, there was no significant differences between young adults and adults regarding FRPQ ($p = .65$).These results suggest that aberrant behaviors decline from around the ages of thirty, in PWS patients in general and in DEL subgroups in particular, while food-related behaviors give no indication of diminishing in spite of developmental growth

1. Introduction

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder, characterized by neonatal hypotonia, hypogonadism, hyperphagia, progressive obesity, and mild to moderate mental retardation (Prader, Labhart, & Willi, 1956; Crino et al., 2003; Cassidy & Driscoll, 2009). As a contiguous gene syndrome, PWS is caused by a loss of expression of the paternally derived genes in the q11-13

Abbreviations: ABC-J, Aberrant behavior checklist Japanese version; ASD, autism spectrum disorders; BMI, body mass index; FRPQ, food-related problem questionnaire; IQ, intelligence quotient; mUPD, maternal uniparental disomy 15; DEL, paternal deletion of 15q11-13; PDDs, pervasive developmental disorders; PARS, pervasive developmental disorders autism society japan rating scale; PWS, prader-Willi syndrome

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region of chromosome 15. A paternal deletion (DEL) of 15q11-13 is found in 70% of patients, and maternal uniparental disomy 15 (mUPD; when both copies of chromosome 15 are maternally inherited) is found in 25% (Buiting et al., 1995; Cassidy & Driscoll, 2009; Nicholls, Knoll, Butler, Karam, & Lalande, 1989; Ledbetter et al., 1981). Its prevalence is estimated at about 1 in 25,000 births (Diene et al., 2010; Vogels et al., 2004; Whittington et al., 2001). The syndrome is often associated with minor dysmorphic features: short stature, small hands and feet, hypopigmentation, and characteristic facial features, such as a narrow forehead, almond-shaped eyes and a triangular mouth.

Compared with other types of intellectual disabilities, individuals with PWS tend to show a wide variety of maladaptive behaviors. Those include hyperphagia (Holland et al., 1993), temper tantrums (Tunnicliffe, Woodcock, Bull, Oliver, & Penhallow, 2014), obsessive-compulsive behaviors (Descheemaeker et al., 2002; Dykens, Leckman, & Cassidy, 1996), repetitive and ritualistic behaviors (Greaves et al., 2006), self-injurious behaviors (Arron, Oliver, Moss, Berg, & Burbidge, 2011; Klabunde et al., 2015), autistic behaviors (Descheemaeker et al., 2006; Dykens, Lee, & Roof, 2011), and hyperactive/impulsive behaviors (Wigren & Hansen, 2005). Behavioral characteristics of this syndrome have been relatively well studied, most of which examined phenotypical differences between DEL and mUPD. It has been reported that the mUPD subtype has a higher risk for autistic-like symptomatology (Dimitropoulos & Schultz, 2007; Milner et al., 2005; Veltman et al., 2004).

These findings mainly based on Caucasian patients were consistent with a recent study about Japanese PWS patients, suggesting ethnicity-free phenotypical differences between the two main genotypes in PWS (Ogata et al., 2014). Aside from autistic behavior and psychosis (Vogels, Matthijs, Legius, Devriendt, & Fryns, 2003), the mUPD subtype may have a lower risk for other maladaptive behaviors than the DEL subtype, in terms of skin-picking (Dykens, Cassidy, & King, 1999; Symons, Butler, Sanders, Feurer, & Thompson, 1999), food-related problems (Dykens, Maxwell, Pantino, Kossler, & Roof, 2007) and obsessive-compulsive behaviors (Dykens & Roof, 2008).

To date, however, there is a paucity of data in regards to the developmental trajectory of problem behaviors. The majority of studies so far conducted have dealt mainly with childhood, due perhaps to the fact that between the ages of 2 and 3 years they start to present hyperphagia and associated food-related behaviors. Little is known how these behaviors progress over the course of development after chronological adolescence.

According to researchers (Dimitropoulos & Schultz, 2007; Dkyens, 2004; Jauregi, Laurier, Copet, Tauber, & Thuilleaux, 2013; Sinnema, Boer et al., 2011; Sinnema, Einfeld et al., 2011), the relation between age and problem behaviors is a non-linear one, featured by gradual increase as children get older, young adults manifesting the highest degree of aggravation, and older adults with the decline of the behaviors. At the same time, a few behavioral problems are presumed to remain unchanged throughout patients' lives.

In addition to differences in behavioral profiles, it is likely that such a behavioral transition from childhood through adolescence to adulthood would have been influenced by phenotypical differences between the two main genotypes. Ogata et al. (2014) reported that there is a growing tendency of the autistic-like and impulsive behavioral problems, which are more severe in mUPD than in DEL that can manifest themselves later in adolescence. In adults with PWS much less is known about the effect of age and genotype on behavioral difficulties in adults with PWS.

This study aims to explore the effects of age as well as genotype have on the behavioral aspects of PWS, with special emphasis on the difference between young adults (ages 18–28) and adults (ages 30–45). The age of young adult is an important transitional epoch for two reasons. First, during this period young adults with PWS leave educational institutions and enroll in adult service systems which are more vocationally oriented. Second, for their medical care, pediatricians are, partly or entirely, replaced by physicians and psychiatrists. Such drastic changes of environmental factors are likely to have a negative impact on behavior and emotion of patients with PWS. This is because most of PWS patients are accompanied with intellectual disability, which can lead to low adaptability.

To highlight behavioral changes related to age, this study attempts to bring out the contrast between young adults and adults. Indeed, Dkyens (2004) showed in "older adults" maladaptive and compulsive symptoms diminished significantly. However, researchers have not yet rigorously examined adults with PWS regarding a wide variety of behavioral symptoms.

2. Methods

2.1. Participants

46 Japanese participants with PWS were 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. The participants consisted of 33 young adults (ages 18–28) and 13 adults (ages 30–45), including 23 young adults and 11 adults confirmed as having a DEL involving 15q11-13, and 10 young adults and 2 adults confirmed as having mUPD of chromosome 15 (Table 1).

2.2. The assessment of behavior

An extended battery of behavioral assessment was employed with regards to aberrant, autistic-like, and food-related behaviors, and intelligence. In all cases, the psychologist (H.O.) involved in collecting data was blind to the genetic status of each patient. For each participant, HO had 3–8 sessions in order to collect behavioral data. While behavioral instruments used in this study were originally constructed as self- administered or informant-based scale, some parts of questionnaire instructions are difficult to understand for informants, most of whom are nonspecialists with behavioral sciences. Considering this, all behavioral measures were

Table 1
Participants Characteristics.

	Total		DEL		mUPD		P-value		
	Young Adults	Adults	Young Adults	Adults	Young Adults	Adults	Total	DEL	mUPD
Number	33	13	23	11	10	2			
Male/Female	18/15	11/2	13/10	9/2	5/5	2/0			
Mean age	21.88	35.85	22.61	35.73	20.2	36.5			
Age range	18–28	30–45	18–28	30–45	18–23	36, 37			
BMI	33.06	33.21	32.6	34.09	34.11	28.39	0.821	0.797	–
BMI range	19.05–72.23	19.21–61.12	19.05–61.81	19.21–61.12	22.31–72.23	23.84, 32.93			
IQ mean (N)	48.62 (26)	46.3 (10)	49 (18)	46.44 (9)	47.75 (8)	45(1)	0.28	0.126	–
IQ range	40–62	42–54	42–62	42–54	40–62	45			

P-values from the Mann-Whitney test.

administered in direct interview of the parent of the PWS patients, soon followed by being checked for completeness and accuracy by HO. As a consequence, the quality of data obtained in this study was expected to be better than that conducted by means of mail-out survey of a questionnaire booklet.

2.3. Intellectual ability

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.) applied the tests in a similar condition, in a calm and comfortable atmosphere. When participants gave signs of fatigue or somnolence, the session were stopped for a break or adjourned until another day. The participants completed all the subtests in two or three sessions. Few participants showed a negative attitude towards the tests.

2.4. Aberrant behaviors

To assess the degree of problem behaviors in individuals with PWS, the Aberrant Behavior Checklist Japanese Version (ABC-J) (Aman, Singh, & Ono, 2006) was applied. It is a 58 item checklist which takes about 10–15 min to complete. There are five subscales: a) irritability and agitation, b) lethargy and social withdrawal, c) stereotypic behavior, d) hyperactivity and noncompliance, and e) inappropriate speech. It was found that the ABC identifies salient features of mental illness in individuals with intellectual disability (Shedlack, Hennen, Magee, & Cheron, 2005) including autism spectrum disorder (Brinkley et al., 2007) and is an effective tool in measuring treatment response (Schroeder, Rojahn, & Reese, 1997; Shedlack, Hennen, Magee, & Cheron, 2005).

2.5. Food-related behaviors

To assess the severity of food-related behaviors, the Food Related Problem Questionnaire (FRPQ) was administered. This is an informant-based questionnaire to assess eating behaviors in people with PWS, consisting of 16 items, with three subscales (preoccupation with food (P), impairment of satiety (S) and other food-related negative behaviors (N)). Examples of the questions are: “How often does the person compare the size or content of their meal with others?” (P); “After a normal sized meal, how often does the person say they still feel hungry?” (S); and “If given the opportunity, how often would the person ‘help themselves’ to food which they should not have?” (N). As Russell and Oliver (2003) presented, the FRPQ has sufficiently robust psychometric properties to appraise the food-related problems in individuals with PWS.

2.6. Autistic-like symptomatology

Autistic-like symptomatology was assessed using the Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS) (Adachi et al., 2006; Kamio et al., 2006). This scale is a behavior checklist developed as a screening questionnaire to determine pervasive developmental disorders (PDDs). When assessing adolescents and adults, 33 items for adolescents are applied for the evaluation of current autistic states. The PARS for adolescents is made up to five clinical subscores consisting of interpersonal skills (6 items), communication (7 items), obsession (6 items), problematic behaviors (11 items), and hypersensitivity (3 items).

2.7. Statistical analyses

By means of a numerical coding system, all date were guarded under strict confidentiality and anonymity. The date were analyzed by SPSS 20J for Windows. Mann-Whitney *U* tests were conducted to make two comparisons: one between young adults and adults and another between young adults with DEL and adults with DEL. For additional information with regards to the two genotype groups, the same nonparametric tests were applied to the two samples: total DEL patients (N = 34) and total mUPD patients

Table 2
ABC-J Total Scores and Subscores in the Groups and Comparison of the Two Age Groups.

	Total		DEL		mUPD		P-value		
	Young Adults (N = 33)	Adults (N = 13)	Young Adults (N = 23)	Adults (N = 11)	Young Adults (N = 10)	Adults (N = 2)	Total	DEL	mUPD
	Median (Q1; Q3)	Median (Q1; Q3)	Median (Q1; Q3)	Median (Q1; Q3)	Median (Q1; Q3)	Raw score UA1, UA2			
Total score	41 (21.5; 79.5)	21 (6; 36)	29 (18; 66)	12 (6; 27)	77 (40.5; 91:25)	122, 21	0.027*	0.05*	–
Subscore									
Irritability and agitation	13 (8; 26.5)	7 (2.5; 11.5)	11 (8; 25)	4 (2; 11)	21 (9.5; 29)	36, 9	0.038*	0.038*	–
Lethargy and social withdrawal	8 (2.5; 17.5)	2 (1.0; 13)	6 (1; 10)	1 (1; 10)	19 (11; 22.75)	29, 8	0.156	0.308	–
Stereotypic behavior	2 (0; 7)	1 (0; 1.5)	7 (3; 15)	0 (0; 1)	7 (1; 9)	11, 1	0.075	0.123	–
Hyperactivity and noncompliance	12 (3.5; 19)	2 (0; 7.5)	4 (1; 7)	2 (0; 7)	19 (8; 21)	34, 1	0.014*	0.038*	–
Inappropriates speech	5 (1.5; 7)	3 (1.5; 4.5)	14 (9; 20)	3 (1; 4)	6 (4; 7.5)	12, 2	0.177	0.243	–

Q1, 1 st quartile; Q3, 3rd quartile P-values from the Mann-Whitney test UA1, mUPD Adult 1; UA2, mUPD Adult 2.
* $P < 0.05$.

(N = 12).

3. Results

3.1. Participants characteristics

As Table 1 shows, no statistically significant differences were found in terms of the BMI and IQ between young adults and adults; also between young adults with DEL and adults with DEL. The mean BMI in young adults with mUPD was 34.11. In our sample there are only two adults with mUPD whose BMI were 23.84 and 32.93, respectively.

3.2. ABC-J total scores and subscores

Table 2 shows the results in regards to the total scores and subscores of ABC-J in the two age groups of PWS individuals. In order to examine the differences between young adults and adults in terms of the symptom's severity, Mann-Whitney *U* tests were conducted. Statistically significant differences were found in the total score of ABC-J (median = 41, 21; p = 0.027) and two of its subscores, such as "irritability and agitation" (median = 13, 7; p = 0.038), and "hyperactivity and noncompliance" (median = 12, 2; p = 0.014), with higher scores in young adults than adults, respectively. In terms of DEL subgroups, young adults scored higher in the total score of ABC-J (median = 29, 12; p = 0.05) and two of its subscores, such as "irritability and agitation" (median = 11, 4; p = 0.038), and "hyperactivity and noncompliance" (median = 4, 2; p = 0.038). Compared with young adults with mUPD, one adult with mUPD scored higher in the total score of ABC-J and all of the subscores, while the other adult with mUPD scored lower in the total score of ABC-J and all of the subscores.

3.3. FRPQ total scores and subscores

Table 3 presents the total scores and subscores of FRPQ in the two age groups of PWS patients. No statistically significant difference was found between the two groups in any of the FRPQ scores (median = 42, 45; p = 0.65). Examining DEL subgroups, no remarkable findings were observed between young adults and adults. For additional information, the two mUPD adults scored lower in the total score and most of the subscores of FRPQ than young adults with mUPD, although statistically this was indeterminable.

3.4. PARS total scores and subscores

As are shown in Table 4, young adults scored higher than adults in terms of the total score of PARS (median = 17, 12; p = 0.046) and two of its subscores, such as "obsession" (median = 2,1; p = 0.019) and "problematic behavior" (median = 6, 2; p = 0.003). Assessing DEL subgroups separately from mUPD subgroups, there was a statistically significant difference in the "problematic behavior" subscore of PARS (median = 4, 2; p = 0.007), with young adults higher than adults. Compared with young adults with

Table 3
FRPQ Total Scores and Subscores in the Groups and Comparison of the Two Age Groups.

	Total		DEL		mUPD		P-value		
	Young Adults (N = 33)	Adults (N = 13)	Young Adults (N = 23)	Adults (N = 11)	Young Adults (N = 10)	Adults (N = 2)	Total	DEL	mUPD
	Median	Median	Median	Median	Median	Raw score			
	(Q1; Q3)	(Q1; Q3)	(Q1; Q3)	(Q1; Q3)	(Q1; Q3)	UA1, UA2			
Total score	42 (27.5; 50)	45 (22.5; 48.5)	44 (28; 49)	45 (25; 49)	35.5 (19; 52)	9, 28	0.65	0.913	–
Subscore									
Preccupation with food	10 (6; 13)	11 (5.5; 13)	11 (7; 13)	12 (6; 13)	7.5 (2; 13.75)	5, 8	0.93	0.885	–
Impairment of satiety	19 (15; 21)	18 (12; 19.5)	19 (15; 21)	19 (15; 20)	18.5 (9.75; 23.25)	4, 12	0.216	0.468	–
Composite negative behavior	12 (6; 17.5)	14 (5; 16)	14 (9; 20)	16 (9; 16)	9 (3.5; 15.25)	0, 8	0.778	0.856	–

Q1, 1 st quartile; Q3, 3rd quartile P-values from the Mann-Whitney test UA1, mUPD Adult 1; UA2, mUPD Adult 2.

Table 4
PARS Total Scores and Subscores in the Groups and Comparison of the Two Age Groups

	Total		DEL		mUPD		P-value		
	Young Adults (N = 33)	Adults (N = 13)	Young Adults (N = 23)	Adults (N = 11)	Young Adults (N = 10)	Adults (N = 2)	Total	DEL	mUPD
	Median	Median	Median	Median	Median	Raw score			
	(Q1; Q3)	(Q1; Q3)	(Q1; Q3)	(Q1; Q3)	(Q1; Q3)	UA1, UA2			
Total score	17 (95; 24)	12 (8.5; 14.5)	14 (9; 20)	12 (8; 14)	21 (18.5; 27.5)	26, 13	0.046*	0.133	–
Subscore									
Interpersonal skills	3 (1; 4.5)	1 (0.5; 4)	2 (1; 4)	1 (0; 3)	4 (2; 7)	8, 2	0.174	0.214	–
Communication	5 (3.5; 6.5)	5 (3.5; 6)	4 (3; 6)	5 (3; 6)	5 (4; 7.25)	8, 4	0.684	0.856	–
Obsession	2 (1.5; 4.5)	1 (1; 2.5)	2 (1; 4)	1 (1; 2)	4 (2; 5)	2, 3	0.019*	0.06	–
Problematic behaviors	6 (2.5; 8)	2 (0.5; 3.5)	4 (2; 7)	2 (0; 2)	8 (5.75; 9)	7, 3	0.003**	0.007**	–
Hypersensitivity	1 (0; 2)	1 (1; 2)	1 (0; 1)	1 (1; 2)	1.5 (0; 2.25)	1, 1	0.458	0.308	–

Q1, 1 st quartile; Q3, 3rd quartile. *P*-values from the Mann-Whitney test UA1, mUPD Adult 1; UA2, mUPD Adult 2.
* $P < 0.05$.
** $P < 0.01$.

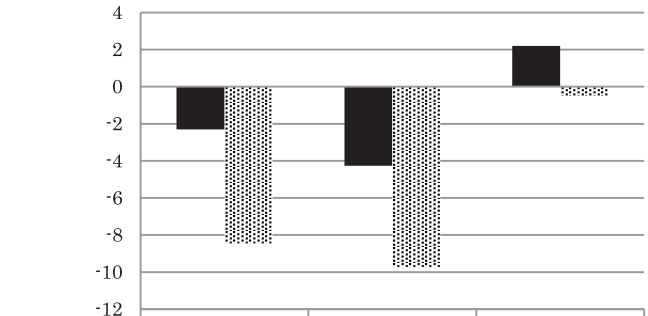
mUPD, one adult with mUPD scored higher in the total score of PARS and most of the subscores, while the other adult with mUPD scored lower in the total score and all of the subscores.

3.5. Difference between PARS total score and the cut-off value based on normative data

The PARS scores in both total young adults with PWS and total adults with PWS were below the cut-off point cited in Kamio et al. (2006) based on normative data collected from 95 adolescents. These results for young adults and adults are equally true for DEL subgroups. On the contrary, the PARS total score for young adults with mUPD was above the cut-off value. For adults with mUPD it was almost the same as the cut-off value (Fig. 1).

3.6. Differences between DEL and mUPD groups

It has been relatively well documented that the mUPD subtype has a higher risk for problematic behaviors including autistic-like symptomatology. As an added precaution, Mann-Whitney *U* tests were conducted to make comparisons between the two genetic subgroups in terms of ABC-J, FRPQ and PARS scores. As expected, higher scores were found in mUPD subgroup than in DEL subgroup



	Total	DEL	mUPD
Youg Adults	-2.3	-4.26	2.2
Adults	-8.46	-9.73	-0.5

Fig. 1. Difference Between PARS Total Score and the Cut-off Value Based on Normative Date (Adachi et al., 2006; Kamio et al., 2006).

in terms of ABC total score ($p = 0.004$) and four of its subscores, such as "irritability and agitation" ($p = 0.029$), "lethargy and social withdrawal" ($p = 0.000$), "stereotypic behavior" ($P = 0.002$), and "hyperactivity and noncompliance" ($p = 0.005$). Moreover, the subgroup of mUPD scored higher than the subgroup of DEL in terms of the total score of PARS ($p = 0.005$), and all of the three subscores, such as "interpersonal skills" ($p = 0.019$), "obsession" ($p = 0.026$), and "problematic behaviors" ($p = 0.008$). By contrast, no statistically significant difference was found between the two genotype groups in any of the FRPQ scores.

4. Discussion

Empirical research in regards to behavioral and psychological problems in patients with intellectual disability is of significant importance for three reasons. First, these problems prevent individuals with the disability from adapting their community, resulting in social isolation (Fotheringham, 1999). Second, these problems can damage the quality of life in their caregivers and parents, since living with family members with problem behaviors as well as intellectual disability is associated with a major increase in caregiving demands (Gray et al., 2011). Thirdly, the more levels of behavioral and emotional problems increase, the more the financial cost of caring for an individual with intellectual disability increase (Einfeld et al., 2010).

As for PWS, the clarification of the developmental change in maladaptive behavior is particularly beneficial for patients and caregivers. Some problem behaviors might tend to change, although other behaviors might not change over the course of the entire life span. Such information could highlight an urgent need for further management to minimize patients' psychosocial difficulties and parents' caregiving burden.

This study aimed to investigate the severity of problem behaviors, such as aberrant, autistic-like and food-related behaviors, and to illuminate the difference between young adults and adults. The results show that young adults were more severe than adults in terms of aberrant behaviors. Such differences between the two age groups were still true for DEL subgroups. By contrast, there was no significant difference between young adults and adults regarding food-related behaviors.

These results suggest that aberrant behaviors follow a developmental trajectory declining from around the age of thirty, while food-related behaviors follow another trajectory giving no indication of diminishing at this age. Final judgment should be reserved on this matter regarding the genetic minority, i.e. mUPD cases. This is because two adults with mUPD in this study showed irregular patterns of behaviors. One adult with mUPD presented more severe aberrant and autistic-like behaviors and milder food-related behaviors than young adults with mUPD. However, the other adult with mUPD showed lower severity in aberrant behaviors, food-related behaviors, and autistic-like behaviors.

Rice et al. (2015) demonstrated that individuals with PWS have temper tantrums and show physical aggression during adolescence. After the age of 19 temper tantrums and physical aggression begin to decline. According to them, in this regard, PWS is different from other genetic syndrome groups such as Down syndrome, Fragile X syndrome and Williams syndrome, for which physical aggression and tantrums decrease under 19 years of age. As for typically developing children, aberrant behaviors such as physical aggression (Cote, Vaillancourt, Leblanc, Nagin, & Tremblay, 2006) and temper tantrums (Wakschlag et al., 2012) begin to decline during early childhood. In the present study maladaptive behaviors in individuals with PWS certainly decline with age. Even so, such decline of behaviors in PWS is delayed, in comparison with typically developing population and even other types of genetic syndromes.

As for autistic-like behaviors common to autistic spectrum disorder (ASD), the results of this study offer an optimistic view about developmental changes in symptoms of PWS in general and of DEL in particular. Although the core symptoms of autism, such as interpersonal skills and communication do not decline, a certain degree of symptom abatement in non-core symptoms like problematic behaviors can be expected around the age of thirty in individuals with PWS, particularly in those with DEL. Apart from PWS, there is positive evidence that autism symptoms and maladaptive behaviors in ASD are improved in adolescents and adulthood (Seltzer et al., 2003; Smith, Maenner, & Seltzer, 2012; Woodman Smith, Greenberg, & Mailick, 2015). For example, conducting a longitudinal study in adolescents and adults with ASD, Smith et al. (2012) found that daily living skills improved for ASD individuals during adolescence and their early 20s, but plateaued during their late 20s. Likewise, there might be a decline of problematic

behaviors in PWS, which are prominent in DEL, that can become obvious later than maladaptive bahaviors in ASD.

At the same time, the difference across the two age groups in terms of problematic behaviors common to ASD should not be overgeneralized to apply to the entire group of PWS. We should take account of the possibility that the difference could simply be due to a higher number of participants with mUPD in the young adult group (n = 10) vs the adult group (n = 2). A probable conclusion is that as far as autistic-like problematic behaviors in DEL are concerned, there is a possibility of symptoms' declining around the age of 30.

As for DEL subgroups, the fact is not negligible that the only difference between young adults and adults was found in the subscore of "Problematic behaviors", non-core symptoms of ASD. This subscore includes following items: "Tics (such as blinking, head jerking, coprolalia, etc.)", "Tendency to freeze up in social situations", "Head banging, hand biting and other self-harming behaviors", and so on. Since they bear a resemblance to compulsivity and insistence on sameness, this supports the possibility that among the variety of autistic-like behaviors there are more compulsion-like, but not autism's core, symptoms and that after the age of 30 they show signs of weakening. This view is consistent with Dkyens's (2004) finding that maladaptive and compulsive symptoms were significantly milder in older adults than young adults with PWS.

With respect to mUPD, statistical tests cannot be conducted due to the limitation of numbers in the sample. In our sample, the two age groups of DEL did not show clinically relevant indices of ASD, according to normative data cited in Kamio et al. (2006). By contrast, the PARS total score for young adults with mUPD reached the level of clinical ASD and this is almost true for adults with mUPD (Fig. 1). Interestingly enough, two adults with mUPD showed opposite patterns of autistic-like behaviors: one with severe autistic-like behaviors than young adults with mUPD, whereas the other with less severe autistic-like behaviors. Considering these findings, in mUPD adults there might be some individuals who do not have the same mellowing of autistic-like behaviors as those with DEL as they aged. This possibility is consistent with the following findings. According to Dykens and Roof (2008), while in Type I (relatively large) DEL group age was consistently associated with lower problem behaviors, adaptive skills and externalizing symptoms, in mUPD and Type II (smaller) DEL groups age did not emerge as a significant correlate of behaviors. Examining 108 adults with PWS at the age of 25 or higher, Sinnema, Einfeld et al. (2011) found that problem behaviors in individuals with mUPD were more severe than those in DEL. Based on the study of 100 adults with PWS at the age between 18 and 53 years, Jauregi et al. (2013) showed that rates of disturbed behavior, such as self-absorbed behavior, communication disturbance, and social relating difficulties are higher in patients with mUPD than with DEL. These studies along with this study suggest that the improvement of problem behaviors in PWS from childhood to adulthood may not apply to the case of mUPD subtype. Indeed, a consistent pattern of increased autistic-like symptom impairments are observed in the DEL cases that are less observable in the mUPD cases (Ogata et al., 2014; Veltman et al., 2004).

Moreover, there is ample evidence that the presence of psychosis is more frequent in mUPD than DEL (Boer et al., 2002; Verhoeven, Tuinier, & Curfs, 2003). Perhaps, these regards could be a reason for the discrepancies between DEL and mUPD in terms of the pattern of developmental changes from around the ages of thirty.

In any aspects of food-related behaviors, this study found no statistically significant differences between young adults and adults. This result is consistent with Jauregi et al. (2013), who did not find any correlations between hyperphagia scores and age. These findings mostly agree with those of Dykens et al. (2007), who conducted factor analyses of the Hyperphagia Questionnaire based on data obtained from 153 PWS patients at the ages of 4–51. They produced three statistically robust factors: Hyperphagic behaviors, Drive, and Severity. They found that Hyperphagic behaviors increased with age and that Drive remained stable. At the same time, Severity factor which positively correlated with non-food behavior problems caused a dip in older adults. These findings suggest that the food-related behaviors, unless being exacerbated by non-food aberrant behaviors, would not be mitigated, contrary to the aberrant behaviors that decline in the course of development.

Considering the uniqueness of food-related behaviors in the modes of evolution, this problem should be considered as an independent expression of the behavioral phenotype in PWS. Unlike hyperphagia, other maladaptive behaviors such as "irritability and agitation", "hyperactive and noncompliance", "obsession", and "problematic behaviors" diminished in adults. These findings support the results of Pignatti et al. (2013) who, conducting statistical clustering, found excessive food intake belongs to the cluster different from the other cluster to which some obsessive-compulsive symptoms and aggressive actions belong.

It is evident that a number of methodological limitations consist in the current study. Since this is a single-institution study that aims at a rare genetic disorder, the size of the sample is relatively small, containing only two adults with mUPD. Future research will require multicenter studies based on a large number of PWS patients, including adults with mUPD. Another limitation is that this study is cross-sectional rather than longitudinal. Therefore, cross-sectional comparison between different age brackets cannot avoid the influence of inter-generational differences. For assessing behavioral development across time, longitudinal studies, which track the same cohort, would make observing changes more accurate than cross-sectional ones.

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Disclosure ststement

The authors have nothing to disclose.

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The manuscript has not been and will not be submitted to any other journal while it is under consideration by Research in Developmental Disabilities

Ethics

Ethical approval was obtained from the Research Ethics Committee of Dokkyo Medical University Koshigaya Hospital (No. 21107). Written informed consent was obtained from both the patients and their parents

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.

Conflict of interests

Kazutaka Shimoda has received research support from Shionogi & Co., Ltd., Eli Lilly Japan, K.K., Yoshitomi Pharmaceutical Industries, Ltd., Meiji Seika Pharma Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Co., and honoraria from Takeda Pharmaceutical Co., Ltd., Kracie Pharmaceutical, Ltd., Pfizer Inc., MSD K.K., Janssen Pharmaceutical K.K., Sumitomo Dainippon Pharma Co., Ltd., Eisai Co., Ltd., Meiji Seika Pharma Co., Otsuka Pharmaceutical Co., Ltd. All other authors declare no biomedical or financial interests or potential conflicts of interest directly relevant to the content of the present study.

Author's contributions

HO and HI managed this work and were equal contributors in writing the manuscript. HO conducted the assessments. MS, MG drafted the figure. NM, TA YO and TN collected the samples. TN is the leader of the PWS research project and KS is the coordinator at the department.

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References

Adachi, J., Yukihiro, R., Inoue, M., Uchiyama, T., Kamio, Y., & Kurita, H. (2006). Reliability and validity of the childhood part of the PARS (PDD-Autism society Japan rating scale). *Rinsyoseishinigaku, 35*, 1591–1599.

Aman, G. M., Singh, N. N., & Ono, Y. (2006). *Clinical evaluation of aberrant behavior checklist japanese version (ABC-J)*. [Tokyo : Jiho].

Arron, K., Oliver, C., Moss, J., Berg, K., & Burbidge, C. (2011). The prevalence and phenomenology of self-injurious and aggressive behaviour in genetic syndromes. *Journal of Intellectual Disability Research, 55*, 109–120.

Boer, H., Holland, A., Whittington, J., Butler, J., Webb, T., & Clarke, D. (2002). Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet, 359*, 135–136.

Brinkley, J., Nations, L., Abramson, R. K., Hall, A., Wright, H. H., Gabriels, R., et al. (2007). Factor analysis of the aberrant behavior checklist in individuals with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 37*, 1949–1959.

Buiting K., Saitoh S., Gross S., Dittrich B., Schwartz S., Nicholls RD. et al. 1995. Inherited microdeletions in the Angelman and Prader-Willi syndromes define an imprinting centre on human chromosome 15. Nat Genet9: 395–400.

Cassidy, S. B., & Driscoll, D. J. (2009). Prader-Willi syndrome. *European Journal of Human Genetics, 17*, 3–13.

Cote, S. M., Vaillancourt, T., LeBlanc, J. C., Nagin, D. S., & Tremblay, R. E. (2006). The development of physical aggression from toddlerhood to pre-adolescence: A nation wide longitudinal study of Canadian children. *Journal of Abnormal Child Psychology, 34*, 71–85.

Crino, A., Schiaffini, R., Ciampalini, P., Spera, S., Beccaria, L., Benzi, F., et al. (2003). Hypogonadism and pubetal development in Prader-Willi syndrome. *European Journal of Pediatrics, 162*, 327–333.

Descheemaeker, M. J., Vogels, A., Govers, V., Borghgraef, M., Willekens, D., Swillen, A., et al. (2002). Prader-Willi syndrome: New insights in the behabioural and psychiatric spectrum. *Journal of Intellectual Disability Research, 46*, 41–50.

Descheemaeker, M. J., Govers, V., Vermeuren, P., & Fryns, J. P. (2006). Pervasive developmental disorders in Prader-Willi syndrome: The Lenven experience in 59 subjects and controls. *American Journal of Medical Genetics A, 140A*, 1136–1142.

Diene, C., Mimoun, E., Feigerlova, E., Caula, S., Molinas, C., Grandjean, H., et al. (2010). Endocrine disorders in children with Prader-Willi syndrome − data from 142 children of the French database. *Hormone Research in Paediatrics, 74*, 121–128.

Dimitropoulos, A., & Schultz, R. T. (2007). Autistic-like symptomatology in Prader-Willi syndrome: A review of recent findings. *Current Psychiatry Reports, 9*, 159–164.

Dkyens, E. M. (2004). Maladaptive and compulsive behavior in Prader-Willi syndrome: New insights from older adults. *American Journal of Mental Retardation, 109*, 142–153.

Dykens, E. M., & Roof, E. (2008). Behavior in Prader-Willi syndrome: Relationship to genetic subtypes and age. *Journal of Child Psychology and Psychiatry, 49*, 1001–1008.

Dykens, E. M., Leckman, J. F., & Cassidy, S. B. (1996). Obsessions and compulsions in Prader-Willi syndrome. *Journal of Child Psychology and Psychiatry, 37*, 995–1002.

Dykens, E. M., Cassidy, S. B., & King, B. H. (1999). Maladaptive behavior differences in Prader-Willi syndrome due to paternal deletion versus maternal uniparental disomy. *American Journal of Mental Retardation, 104*, 67–77.

Dykens, E. M., Maxwell, M. A., Pantino, E., Kossler, R., & Roof, E. (2007). Assessment of hyperphagia in Prader-Willi syndrome. *Obesity (Silver Spring), 15*, 1816–1826.

Dykens, E. M., Lee, E., & Roof, E. (2011). Prader-Willi syndrome and autism spectrum disorders: An evolving story. *Journal of Neurodevelopmental Disorders, 3*, 225–237.

Einfeld, S. L., Ellis, L. A., Doran, C. M., Emerson, E., Horstead, S. K., Madden, R. H., et al. (2010). Behavioral problems increase costs of care of children with intellectual disabilities. *Journal of Mental Health Research in Intellectual Disabilities, 3*, 202–209.

Fotheringham, J. B. (1999). Living arrangement requirements for individuals with developmental disability and behavioral problems. *The Canadian Journal of Psychiatry, 44*, 589–591.
Gray, K. M., Piccinin, A. M., Hofer, S. M., Mackinnon, A., Bontempo, D. E., Einfeld, S. L., et al. (2011). The longitudinal relationship between behavior and emotional disturbance in young people with intellectual disability and maternal mental health. *Research in Developmental Disabilities, 32*, 1194–1204.
Greaves, N., Prince, E., Evans, D. W., & Charman, T. (2006). Repetitive and ritualistic behaviour in children with Prader-Willi syndrome and children with autism. *Journal of Intellectual Disability Research, 50*, 92–100.
Holland, A. J., Treasure, J., Coskeran, P., Dallow, J., Milton, N., & Hillhouse, E. (1993). Measurement of excessive appetite and metabolic changes in Prader-Willi syndrome. *International Journal of Obesity and Related Metabolic Disorders, 17*, 527–532.
Japanese WAIS-III Publication Committee. 2006. Nihonban WAIS-III chinou kensahou (Japanese Wechsler Adult Intelligemce Scale, 3rd ed). Tokyo : Nihon Bunka Kagakusya.
Japanese WISC-III Publication Committee. 1998 Nihonban WISC-III chinou kensahou (Japanese Wechslar Intelligence Scale for Children-3rd ed). Tokyo : Nihon Bunka Kagakusya.
Jauregi, J., Laurier, V., Copet, P., Tauber, M., & Thuilleaux, D. (2013). Behavioral profile of adults with Prader-Willi syndrome: Correlations with individual and environmental variables. *J Neurodev Disord, 5*, 18.
Kamio, Y., Yukihiro, R., Adachi, J., Ichikawa, Inoue, M., Uchiyama, T., et al. (2006). Reliability and validity of the pervasive developmental disorder(PDD)-Autism Society Japan Rating Scale(PARS): A behavior checklist for adolescents and adults with PDDs. *Seishinigaku, 48*, 495–505.
Klabunde, M., Saggar, M., Hustyi, K. M., Hammond, J. L., Reiss, A. L., & Hall, S. S. (2015). Neural correlates of self-injurious behavior in Prader-Willi syndrome. *Human Brain Mapping, 36*, 4135–4143.
Ledbetter, D. H., Riccardi, V. M., Airhart, S. D., Strobel, R. J., Keenan, B. S., & Crawford, J. D. (1981). Deletions of chromosome 15 as a cause of the Prader-Willi syndrome. *The New England Journal of Medicine, 304*, 325–329.
Milner, K. M., Craig, E. E., Thompson, R. J., Veltman, M. W., Thomas, N. S., Roberts, S., et al. (2005). Prader-Willi syndrome: Intellectual abilities and behavioural features by genetic subtype. *Journal of Child Psychology and Psychiatry, 46*, 1089–1096.
Nicholls, R., Knoll, J. H., Butler, M. G., Karam, S., & Lalande, M. (1989). Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. *Nature, 342*, 281–285.
Ogata, H., Ihara, H., Murakami, N., Gito, M., Kido, Y., & Nagai, T. (2014). Autism spectrum disorders and hyperactive/impulsive behaviors in Japanese patients with Prader-Willi syndrome: A comparison between maternal uniparental disomy and deletion cases. *American Journal of Medical Genetics A, 164A*, 2180–2186.
Pignatti, R., Mori, I., Bertella, L., Grugni, G., Giardino, D., & Molinari, E. (2013). Exploring patterns of unwanted behaviours in adults with Prader-Willi syndrome. *Journal of Applied Research in Intellectual Disabilities, 26*, 568–577.
Prader, A., Labhart, A., & Willi, H. (1956). Ein syndrom von adipositas, kleiwuchs, kryptorchidismus und ologophrenie nach mytoniertigem zustand im neugehorenalter. *Schweizerische Medizinische Wochenschrift, 86*, 1260–1261.
Rice, L. J., Gray, K. M., Howlin, P., Taffe, J., Tonge, B. J., & Einfeld, S. L. (2015). The developmental trajectory of disruptive behavior in Down syndrome, fragile X syndrome, Prader-Willi syndrome and Williams syndrome. *American Journal of Medical Genetics Part C, Seminars in Medical Genetics, 169C*, 182–187.
Russell, H., & Oliver, C. (2003). The assessment of food-related problems in individuals with Prader-Willi syndrome. *British Journal of Clinical Psychology, 42*, 379–392.
Schroeder, S. R., Rojahn, J., & Reese, R. M. (1997). Reliability and validity of instruments for assessing psychotropic medication effects on self-injurious behavior in mental retardation. *Journal of Autism and Developmental Disorders, 27*, 89–102.
Seltzer, M. M., Krauss, M. W., Shattuck, P. T., Orsmond, G., Swe, A., & Lord, C. (2003). The symptoms of autism spectrum disorders in adolescence and adulthood. *Journal of Autism and Developmental Disorders, 33*, 565–581.
Shedlack, K. J., Hennen, J., Magee, C., & Cheron, D. M. (2005). A comparison of the Aberrant Behavior Checklist and the GAF among adults with mental retardation and mental illness. *Psychiatric Services, 56*, 484–486.
Sinnema, M., Boer, H., Collin, P., Maaskant, M. A., van Roozendaal, K. E., Schrander-Stumpel, C. T., et al. (2011). Psychiatric illness in a cohort of adults with Prader-Willi syndrome. *Research in Developmental Disabilities, 32*, 1729–1735.
Sinnema, M., Einfeld, S. L., Schrander-Stumpel, C. T., Maaskant, M. A., Boer, H., & Curfs, L. M. (2011). Behavioral phenotype in adults with Prader-Willi syndrome. *Research in Developmental Disabilities, 32*, 604–612.
Smith, L. E., Maenner, M. J., & Seltzer, M. M. (2012). Developmental trajectories in adolescents and adults with autism: The case of daily living skills. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*, 622–631.
Symons, F. J., Butler, M. G., Sanders, M. D., Feurer, I. G., & Thompson, T. (1999). Self-injurious behavior and Prader-Willi syndrome: Behavioral forms and body locations. *American Journal of Mental Retardation, 104*, 260–269.
Tunnicliffe, P., Woodcock, K., Bull, L., Oliver, C., & Penhallow, J. (2014). Temper outbursts in Prader-Willi syndrome: Causes, behavioural and emotional sequence and responses by cares. *Journal of Intellectual Disability Research, 58*, 134–150.
Veltman, M. W., Thompson, R. J., Roberts, S. E., Thomas, N. S., Whittington, J., & Bolton, P. F. (2004). Prader-Willi syndrome–a study comparing deletion and uniparental disomy cases with reference to autism spectrum disorders. *European Child and Adolescent Psychiatry, 13*, 42–50.
Verhoeven, W. M., Tuinier, S., & Curfs, L. M. (2003). Prader-Willi syndrome: The psychopathological phenotype in uniparental disomy. *Journal of Medical Genetics, 40*, e112.
Vogels, A., Matthijs, G., Legius, E., Devriendt, K., & Fryns, J. P. (2003). Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. *Journal of Medical Genetics, 40*, 72–73.
Vogels, A., Van Den Ende, J., Keymolen, K., Mortier, G., Devriendt, K., Legius, E., et al. (2004). Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. *European Journal of Human Genetics, 12*, 238–240.
Wakschlag, L. S., Choi, S. W., Carter, A. S., Hullsiek, H., Burns, J., McCarthy, K., et al. (2012). Defining the developmental parameters of temper loss in early childhood: Implications for developmental psychopathology. *Journal of Child Psychology and Psychiatry, 53*, 1099–1108.
Wechsler, D. (1991). *Wechslar intelligence scale for children-3rd ed.* Sun Antonio, TX: The Psycholigical Corporation.
Wechsler, D. (1997). *Wechsler adult intelligence scale-3rd.* San Antonio, TX: The Psychological Corporation.
Whittington, J. E., Holland, A. J., Webb, T., Butler, J., Clarke, D., & Boer, H. (2001). Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. *Journal of Medical Genetics, 38*, 792–798.
Wigren, M., & Hansen, S. (2005). ADHD symptoms and insistence on sameness in Prader-Willi syndrome. *Journal of Intellectual Disability Research, 49*, 449–456.
Woodman, A. C., Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2015). Change in autism symptom and maladaptive behaviors in adolescence and adulthood: The role of positive family processes. *Journal of Autism and Developmental Disorders, 45*, 111–126.