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Behavioral phenotype in adults with Prader–Willi syndrome

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ABSTRACT

Prader–Willi syndrome (PWS) is characterized by temper tantrums, impulsivity, mood fluctuations, difficulty with change in routine, skinpicking, stubbornness and aggression. Many studies on behavior in PWS are limited by sample size, age range, a lack of genetically confirmed diagnosis of PWS and inconsistent assessment of behavior. The aim of this study was to explore systematically the relation between behavioral problems and age groups, genetic subtypes and BMI categories in an adult PWS population. Participants were contacted via the Dutch Prader–Willi Parent Association and through physicians specialized in persons with ID. Behaviors were studied using the Developmental Behavior Checklist for Adults (DBC-A). The forms were completed by the main caregivers of 98 adults with a genetically confirmed diagnosis of PWS.

Differences between age groups were statistically significant (ANOVA, $p = 0.03$). DBC-A total scores were higher in the consecutive age groups, with the most behavioral problems in the oldest age groups. Differences between genetic subtypes were also statistically significant (ANOVA, $p < 0.01$). Persons with mUPD had higher total scores on the DBC-A than persons with a deletion. Those with a Type I deletion showed higher total DBC-A scores than persons with a Type II deletion. There were no statistically significant differences in DBC-A total scores between the different BMI categories. Individuals with a BMI < 25 had higher scores on the self-absorbed subscale compared to persons with a BMI between 25 and 30. Unlike previous descriptions of the behavioral phenotype in adults with PWS, we did not find a reduction in behavioral problems in older adults. Therefore, special attention should be paid to behavioral problems as part of general management of adults with PWS. Longitudinal studies are warranted to gain more insight into the natural history and course of behavioral problems in adults and older people with PWS over the long term and possible risk and preventive factors.

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1. Introduction

Prader–Willi syndrome (PWS) is characterized by neonatal hypotonia with feeding problems, global developmental delay, small hands and feet, hypogonadism, small stature and facial features (Cassidy, 1997; Holm et al., 1993). Later on, childhood onset hyperphagia results – without dietary restrictions – in marked obesity and secondary medical complications (Goldstone, Holland, Hauffa, Hokken-Koelega, & Tauber, 2008). The majority of persons with PWS (70%) have a paternal deletion of 15q11–q13 (Ledbetter et al., 1981), and approximately 25% have a maternal UPD (Nicholls, Knoll, Butler, Karam, & Lalande, 1989). The remaining cases (5%) have imprinting center defects or translocations (Buiting et al., 1995).

Individuals with a paternal deletion can be further divided according to deletion size (Bittel & Butler, 2005). Both subtypes share a breakpoint at BP3, but differences are present at breakpoints at BP1 and BP2. Deletions between BP3 and BP1 are classified as Type I deletions. Deletions between BP3 and BP2 are classified as Type II deletions (Christian et al., 1995). The larger Type I deletions are seen in approximately 40% of the persons with PWS due to a deletion (Bittel & Butler, 2005).

Besides the physical and eating problems, PWS is characterized by behavior including temper tantrums, impulsivity, mood fluctuations, difficulty with changes in routine, skinpicking, stubbornness and aggression (Beardsmore, Dorman, Cooper, & Webb, 1998; Clarke et al., 2002; Curfs, Verhulst, & Fryns, 1991; Dykens, 2004; Dykens, Leckman, & Cassidy, 1996; Einfeld, Smith, Durvasula, Florio, & Tonge, 1999). Not only developmental life stage, but also genetic status and weight issues may influence behavioral characteristics (Ho & Dimitropoulos, 2010).

The majority of behavioral studies in PWS have focused on childhood and adolescence. Hyperphagia and food-seeking behavior usually start between 2 and 6 years of age, along with temper tantrums and self-injurious behavior (Dimitropoulos, Feurer, Butler, & Thompson, 2001). During childhood under-activity, excessive sleeping, obsessiveness, argumentativeness, compulsive behavior and talking too much are more frequent relative to persons with Down syndrome or ID in general (Dykens & Kasari, 1997). Sadness and low self-worth are also seen during childhood development (Dykens & Cassidy, 1995). An increase in behavioral problems such as overeating, skinpicking, stubbornness, hoarding and temper tantrums are described during adolescence and young adulthood (Clarke, Boer, Chung, Sturmey, & Webb, 1996; Dykens, Hodapp, Walsh, & Nash, 1992; Einfeld et al., 1999; Whitman & Accardo, 1987).

Greenswag (1987) found the following behaviors to be relatively frequent in adults with PWS compared to youngsters: slow moving, good natured, belligerent (related and non-related to food), irritable, impulsive, lazy, antisocial with peers and family, moody and physically aggressive. However, research on behavior of older adults, above the age of 30, with PWS is scarce. In a study regarding adults with PWS (Clarke et al., 1996) only 5 out 30 adults were in their thirties. Dykens et al. (1992) also included only 6 (out of 21) participants in their thirties. In these studies the older adults were described as much less destructive and impulsive than participants in younger age groups, and had higher rates of underactivity, fatigue and withdrawal. In a larger study (Dykens, 2004) maladaptive and compulsive behaviors in 45 older adults with PWS (30–50 years) were compared to children, adolescents and young adults. It was concluded that young adults were at the highest risk for behavioral problems, and that maladaptive and compulsive behaviors were considerably less in older adults.

Differences in behavioral profiles have also been suggested for the different genotypes. Persons with mUPD have been found to have less skinpicking and maladaptive behavior (Dykens, Cassidy, & King, 1999; Symons, Koppekin, & Wehby, 1999), but to have heightened vulnerability for psychiatric disorders, such as atypical psychosis and affective disorders in young adulthood (Beardsmore et al., 1998; Boer et al., 2002; Vogels, Matthijs, Legius, Devriendt, & Fryns, 2003). Reports on behavioral differences between those with Type I and Type II deletions have been contradictory (Butler, Bittel, Kibiryeva, Talebizadeh, & Thompson, 2004; Hartley, Maclean, Butler, Zarcone, & Thompson, 2005; Milner et al., 2005; Varela, Kok, Setian, Kim, & Koiffmann, 2005; Zarcone et al., 2007). Research showed (Butler et al., 2004) that individuals with Type I deletions generally have more behavioral and psychological problems than individuals with Type II deletion or mUPD. Milner et al. (2005) and Varela et al. (2005) found that differences between the deletion types were minimal, although persons with Type I deletion performed worse on all measures of ability (Milner et al., 2005). Hartley et al. (2005) reported higher physical depression scores in persons with Type I deletions than in persons with Type II deletions. In another study (Zarcone et al., 2007) more washing/cleaning compulsions were found in those with Type I deletions and more rereading/rewriting compulsions in those with Type II deletions. In a recent study (Dykens & Roof, 2008), no statistically significant differences between deletion subtypes were found, but within subtype analyses showed a relationship between age and behavior. Although age did not emerge as a significant correlate of behavior in the Type II and mUPD group, in the Type I group older age was associated with lower problem behaviors, adaptive skills and externalizing symptoms (Dykens & Roof, 2008).

A negative correlation between worsening behavioral problems and increasing BMI has been suggested in the literature. Dykens and Cassidy (1995) reported that adolescents and adults with lower BMIs had significantly more maladaptive behaviors, specifically confused thinking, delusions, hallucinations, anxiety, fear, sadness and dependency relative to persons with higher BMIs. Most of these features represented internal affective states and problems in thinking as opposed to overt behavior. Other authors (Whitman & Accardo, 1987) found a non-significant trend of more psychiatric concerns among subjects with more weight control. Another study (Greenswag, 1987) showed that adults with a higher BMI were viewed as more lazy, slow-moving and anti-social with their families relative to PWS subjects with a lower BMI. Increased irritability, agitation, hyperactivity and non-compliance were found to be associated with increased BMI (Clarke et al., 1996).

Many of these studies on behavior in PWS are limited by sample size, age range, and lack of genetically confirmed diagnosis of PWS (e.g. Clarke et al., 1996; Dykens & Cassidy, 1995; Greenswag, 1987; Hartley et al., 2005). Moreover, not all studies used standardized methods for assessing behavior. The aim of this study was to explore systematically the relation between behavioral problems and age groups, genetic subtypes and BMI categories in an adult PWS population through a standardized method for measuring behavior.

2. Methods

2.1. Study population

Participants were contacted via the Dutch Prader–Willi Parent Association and through physicians specializing in persons with ID. The current study on behavior was part of a larger study in The Netherlands on "Ageing in PWS". The individuals with PWS and their main caregivers (family and/or professional caregivers) were visited at home. They were interviewed using a semi-structured interview that included questions about physical and mental health problems, and behavior experienced over the participant's lifetime. The caregivers were asked to complete the Developmental Behavior Checklist for Adults (DBC-A) before the interview. Current height and weight were measured. Medical files were retrieved from treating physicians. The level of intellectual disability was reported by the main caregivers.

2.2. Participants

In total 149 nominees with a (possible) diagnosis of PWS were identified. At time of contacting the participants, two nominees had died and two parents informed us that genetic testing had revealed that the candidates did not have PWS. Hence, 145 possible participants were left. Of these, 108 agreed to participate in the study. Detailed genetic test results were available in 68 patients, and in 40 patients the diagnosis and genetic subtype were confirmed during the study. The genetic diagnosis of PWS was confirmed in 102 out of 108 participants. The caregivers of 98 participants completed the DBC-A (response rate: 96%). Four age groups were formed: <25 years, 25–34 years, 35–44 years, 45+ years.

2.3. Genetic diagnosis

During the interviews, parents were asked whether genetic tests on PWS including genetic subtype were undertaken previously. Written confirmation on genetic diagnoses was retrieved from genetic centers, with the permission of the legal representatives. Genetic testing was undertaken in participants who did not have a confirmed genetic diagnosis ($n = 40$). Cytogenetic analysis and molecular analysis using the SALSA MLPA kit P245 (MRC Holland, Amsterdam) were performed to establish whether deletions were present. A diagnosis of PWS was confirmed by DNA methylation studies on the SNURF/SNRPN loci. mUPD was confirmed with microsatellite analysis at various loci on chromosome 15, when blood of parents was available. All 98 participants were genetically confirmed as having PWS: 54 (55%) had paternal deletion, 42 (43%) had mUPD and two (2%) participants had an imprinting defect. Within the deletion subtype, 23 persons had a Type I deletion, 22 persons had a Type II deletion and six persons had an atypical deletion (larger than Type I or smaller than Type II deletions). In three persons, a deletion had been confirmed in the past, but there was no blood available to distinguish between a Type I and Type II deletion for this study.

2.4. BMI

The weight status was determined by the body mass index, BMI (weight in kilograms/[height in meters]^2). Height and weight of the participants were measured by the first author. Three different BMI categories were formed: BMI < 25, BMI 25–30, BMI 30+. Mean body mass index (BMI = kg/m^2) was 32.5 ($SD = 7.9$, range = 16.8–51.9).

2.5. Developmental Behavior Checklist for Adults (DBC-A)

The DBC-A (Einfeld, Tonge, & Mohr, 2002) was used to assess behavioral problems. The 107-item questionnaire was completed by the participants' main caregiver (family and/or professional caregivers). It measures psychopathology at three levels: severity of overall behavior and emotional disturbance (total behavior problem score; TBPS); disturbance in six particular dimensions of psychopathology (six subscale scores derived from factor analysis); and level of disturbance of particular individual behaviors (107 items or symptoms). The questionnaire employs a 3-point rating scale (0 = not true; 1 = somewhat or sometimes true; 3 = very true or often true). The DBC-A consists of the following subscales (with examples of relevant items):

1. *Disruptive*: tantrums, irritable, impatient, whines, jealous;
2. *Self absorbed*: pica, hums, bites, hits, screams, chews, bangs head;
3. *Communication disturbance*: talks fast, thoughts, stands, not capable, hallucinations;
4. *Anxiety/antisocial*: lights fires, panics, nightmares, inappropriate sexual activity, hides things, steals;

5. *Social relating*: loner, shy, arranges objects, distressed over small changes in routine, resists being cuddled, aloof;
6. *Depressive*: withdrawn, lost enjoyment, lost self-care, depressed.

The caregiver-completed DBC-A has satisfactory psychometric properties (Mohr, Tonge, & Einfeld, 2005). The intraclass correlations for test–retest and inter-rater reliability ranged from 0.72 to 0.85. Concurrent validity with the Aberrant Behavior Checklist (ABC) (Aman, Singh, Stewart, & Field, 1985) and the Psychiatric Assessment Schedule for Adults with Developmental Disabilities Checklist (PAS-ADD) (Moss et al., 1998) was satisfactory. Normative data were collected in a large representative population in South Australia of adults with ID. The population covered the age span of late adolescence (16 years) through the transition to adult life then through to the elderly.

2.6. Statistical analyses

Differences between age groups, genetic subtypes, and weight status on the TBPS, DBC-A subscales and DBC-A items were analyzed. The following statistical tests were used: ANOVA to compare means of three or more groups, independent sample *t*-tests to compare means of two independent groups, Chi-square to compare frequencies of nominal data, and Kendall's tau to compare frequencies of ordinal data. SPSS (version 16.0) was used to analyze the data. A *p*-value of 0.05 or less was taken as significance level for all statistical tests.

3. Results

3.1. Study population

The DBC-A was completed for 98 participants and consequently this report is based on these 98 individuals. Forty-eight (49%) participants were male. The mean age of the participants was 36.4 years (*SD* 12.4, range 18–66 years). Seventy-eight (78%) participants lived in an institutional residential or community residential facility, while 19 (19%) participants lived at home with their parents or family; one (1%) participant lived almost independently. The level of ID was mild (48%, $n = 47$) or moderate (29%, $n = 28$) in most participants. Eight (8%, $n = 8$) participants had severe ID. The other participants were functioning on a borderline ID level (10%, $n = 10$) or did not have ID (5%, $n = 5$). Five persons had a current prescription of growth hormone.

3.2. DBC-A total scores in PWS compared to persons with intellectual disabilities (ID) in general

The mean item score (MIS) on the DBC-A in our sample (0.48) was high compared with the MIS of people with ID in general (0.27) as retrieved from the DBC-A norms. The MIS score in our sample was on the 79 percentile.

3.3. DBC-A total scores and DBC-A subscales

3.3.1. Relation with age

Table 1 shows the mean total and mean subscale scores on DBC-A according to age groups. DBC-A total scores were higher in the consecutive age groups, with the highest scores in the oldest age groups. Differences between age groups were statistically significant (ANOVA, $p = 0.03$). Further analyses showed that the differences between the age group <25 and 45+ mostly counted for this statistical significance (*t*-test, $p = 0.04$). Additional analyses of the subscales showed that only differences between the age groups on subscale 2 (self-absorbed) were statistically significant (ANOVA, $p < 0.01$). Differences between individuals <25 years as compared to persons from age group 35–44 years and ≥45 years counted most for these differences (*t*-test, $p \leq 0.03$).

3.3.2. Relation with genetic subtypes

Table 2 shows the mean total and mean subscale scores on DBC-A according to genetic subtypes: the differences between genetic subtypes were statistically significant (ANOVA, $p < 0.01$). Further analyses showed that the differences between persons with Type II deletions and mUPD accounted for most of this statistical significance (*t*-test, $p < 0.01$). Additional analyses of the subscales showed that differences between the genetic subtypes on subscale 1 (disruptive), subscale 2

Table 1
Mean total and mean subscale scores on DBC-A according to age groups.

Age groups	*N*	Mean total*	Mean subscale 1	Mean subscale 2*	Mean subscale 3	Mean subscale 4	Mean subscale 5	Mean subscale 6
<25	20	38.5	8.9	7.0	4.6	2.0	4.4	3.2
25–34	27	50.5	11.0	9.9	6.1	2.7	4.8	5.0
35–44	26	56.6	12.9	12.8	6.0	3.6	4.6	5.0
45+	25	57.1	13.8	12.4	6.1	3.3	4.4	5.4
Total	98	51.3	11.8	10.7	5.8	2.9	4.6	4.7

* Statistically significant (ANOVA, $p \leq 0.05$).

Table 2
Mean total and mean subscale scores on DBC-A according to genetic subtypes.

Genetic subtype	*N*	Mean total*	Mean subscale 1*	Mean subscale 2*	Mean subscale 3	Mean subscale 4	Mean subscale 5*	Mean subscale 6*
Type I del	23	45.3	9.5	7.4	5.6	2.2	5.4	4.6
Type II del	22	39.6	9.0	8.5	4.7	2.4	4.3	3.0
mUPD	42	58.0	13.4	13.2	6.1	3.5	4.1	5.4
Total	87[a]	50.0	11.3	10.5	5.6	2.9	4.5	4.6

* Statistically significant (ANOVA, $p \leq 0.05$).
[a] 11 persons were excluded from this part of the study: 6 with an atypical deletion, 3 with a missing blood sample, 2 with an imprinting defect.

(self-absorbed), subscale 5 (social relating) and subscale 6 (depressive) were statistically significant (ANOVA, $p < 0.05$). Differences between persons with a Type I deletion and persons with a mUPD accounted for most of this statistical significance on subscale 2 (self absorbed) and subscale 5 (social relating) (*t*-test, $p < 0.05$). Differences between persons with a Type II deletion and persons with a mUPD accounted for most of this statistical significance on subscale 1 (disruptive) and subscale 6 (depressive) (*t*-test, $p < 0.05$).

3.3.3. Relation with BMI categories

Table 3 shows the mean total and mean subscale scores on DBC-A according to BMI categories. There were no statistically significant differences in DBC-A total scores between the different BMI categories. However, additional analyses of the subscales showed statistically significant differences on subscale 2 (self-absorbed), mainly due to differences between individuals with a BMI < 25 and persons with a BMI between 25 and 30 (*t*-test, $p = 0.04$).

3.3.4. Relation with other factors

Gender and level of intellectual disabilities were not significantly related to mean total and mean subscale scores on the DBC-A.

3.4. DBC-A item analysis

Table 4 shows the DBC-A items in relation to age groups, genetic subtypes and BMI categories.

3.4.1. Relation with age

Persons < 25 years scored highest on biting others (item #8) (χ^2, $p = 0.05$). Persons in the age group 25–34 showed highest scores on the items hiding things (#35), rapid mood changes (#54) and stubbornness (#85) (χ^2, $p \leq 0.04$). Increase in appetite (#40) was most prominent in age group 35–44 years and over 45 years (χ^2, $p = 0.04$). People above the age of 45 were most inactive (#55) (χ^2, $p = 0.03$). The following items were related to age and most prominent in the oldest age group: gorges food (#28), laughs for no obvious reason (#46), panics (#63) and soils outside the toilet (#80) (χ^2 and Kendall's tau, $p \leq 0.05$).

3.4.2. Relation with genetic subtypes

Persons with mUPD scored significantly higher than persons with a Type I and Type II deletion on the following DBC-A items: unhappy (item #1), abusive (#4), poor attention span (#10), facial twitches (#25), flicks (taps and twirls objects repeatedly) (#26), impatient (#38), overactive (#58), screams a lot (#76), soils outside the toilet (#80), whispers (#81), strips of clothes (#87), tells lies (#94) and wanders aimlessly (#105) (χ^2, $p \leq 0.05$). Persons with Type I deletions scored the highest on repeating the same word/phrase (#73).

3.4.3. Relation with BMI categories

Persons with BMI < 25 scored significantly higher than persons with higher BMI on the following DBC-A items: bangs the head (#6), becomes over-excited (#7), bites (#8), hits oneself (#36), repeated movements (e.g. of hands, head of body) (#70) and screams a lot (#76) (χ^2, $p \leq 0.05$). Overactiveness (restless, unable to sit still) (#58) is negatively related to BMI, with the highest scores in the BMI category < 25 (χ^2 and Kendall's tau, $p \leq 0.05$). Hiding things (#35) is positively related to BMI, with the highest scores in the BMI category ≥30 (χ^2 and Kendall's tau, $p \leq 0.05$). Attention seeking (#61) was most prominent in the BMI category ≥30 (χ^2 and Kendall's tau, $p = 0.01$).

Table 3
Mean total and mean subscale scores on DBC-A according to BMI categories.

BMI	*N*	Mean total	Mean subscale 1	Mean subscale 2*	Mean subscale 3	Mean subscale 4	Mean subscale 5	Mean subscale 6
<25	17	54.3	12.1	14.4	5.8	2.9	4.0	3.9
25–30	25	48.2	10.9	9.4	6.0	2.7	4.6	3.8
30+	56	51.8	12.1	10.2	5.6	3.1	4.7	5.4
Total	98	51.3	11.8	10.7	5.8	2.9	4.6	4.7

* Statistically significant (ANOVA, $p \leq 0.05$).

Table 4
DBC-A items in relation to age groups, genetic subtypes, and BMI categories.

DBC-A item (subscale)		Age groups	Genetic subtypes	BMI categories
		χ^2, p-value[a]	χ^2, p-value[a]	χ^2, p-value
1	Unhappy (1,6)	n.s.	0.02[3]	n.s.
2	Eye contact	n.s.	n.s.	n.s.
3	Aloof (5)	n.s.	n.s.	n.s.
4	Abusive (1)	n.s.	0.02[3]	n.s.
5	Routine (5)	n.s.	n.s.	n.s.
6	Bangs head (2)	n.s.	n.s.	0.02[1]
7	Excited (1,2)	n.s.	n.s.	0.03[1]
8	Bites (2)	0.05[1]	n.s.	<0.01[1]
9	Bizarre speech	n.s.	n.s.	n.s.
10	Attention	n.s.	0.03[3]	n.s.
11	Mouths (2)	n.s.	n.s.	n.s.
12	Cries (1)	n.s.	n.s.	n.s.
13	Sounds	n.s.	n.s.	n.s.
14	Pronouns (3)	n.s.	n.s.	n.s.
15	Runs away	n.s.	n.s.	n.s.
16	Delusions	n.s.	n.s.	n.s.
17	Alone	n.s.	n.s.	n.s.
18	Affection	n.s.	n.s.	n.s.
19	Feelings (2)	n.s.	n.s.	n.s.
20	Distracted (3)	n.s.	n.s.	n.s.
21	Easily led (3)	n.s.	n.s.	n.s.
22	Non food (2)	n.s.	n.s.	n.s.
23	Familiar	n.s.	n.s.	n.s.
24	Fears	n.s.	n.s.	n.s.
25	Twitches (2)	n.s.	0.01[3]	n.s.
26	Flicks (2)	n.s.	<0.01[3]	n.s.
27	Food fads	n.s.	n.s.	n.s.
28	Gorges (2)	<0.01[4*]	n.s.	n.s.
29	Obsessed	n.s.	n.s.	n.s.
30	Grinds (2)	n.s.	n.s.	n.s.
31	Confused (6)	n.s.	n.s.	n.s.
32	Withdrawn (6)	n.s.	n.s.	n.s.
33	Nightmares (4)	n.s.	n.s.	n.s.
34	Tantrums (1)	n.s.	n.s.	n.s.
35	Hides (4)	0.04[2]	n.s.	0.04[3*]
36	Hits self (2)	n.s.	n.s.	0.05[1]
37	Hums (2)	n.s.	n.s.	n.s.
38	Impatient (1)	n.s.	0.01[3]	n.s.
39	Sexual (4)	n.s.	n.s.	n.s.
40	Increase of appetite	0.04[3]	n.s.	n.s.
41	Impulsive	n.s.	n.s.	n.s.
42	Irritable (1)	n.s.	n.s.	n.s.
43	Jealous (1)	n.s.	n.s.	n.s.
44	Kicks (2)	n.s.	n.s.	n.s.
45	Esteem	n.s.	n.s.	n.s.
46	Laughs (2)	0.05[4*]	n.s.	n.s.
47	Fires (4)	n.s.	n.s.	n.s.
48	Strings (2)	n.s.	n.s.	n.s.
49	Loss of appetite (6)	n.s.	n.s.	n.s.
50	Loss of enjoyment (6)	n.s.	n.s.	n.s.
51	Loss of self-care (6)	n.s.	n.s.	n.s.
52	Gloomy (4)	n.s.	n.s.	n.s.
53	In public (4)	n.s.	n.s.	n.s.
54	Mood (6)	0.02[2]	n.s.	n.s.
55	Underactive (6)	0.03[4]	n.s.	n.s.
56	Noisy (2)	n.s.	n.s.	n.s.
57	Communicating (6)	n.s.	n.s.	n.s.
58	Overactive (2,3)	n.s.	<0.01[3]	0.05[1*]
59	Overaffectionate (3)	n.s.	n.s.	n.s.
60	Vomits	n.s.	n.s.	n.s.
61	Attention seeking (1)	n.s.	n.s.	0.01[3]
62	Mechanical	n.s.	n.s.	n.s.
63	Panics (4)	<0.01[4*]	n.s.	n.s.
64	Danger (4)	n.s.	n.s.	n.s.
65	Her own (5)	n.s.	n.s.	n.s.
66	Preoccupied	n.s.	n.s.	n.s.
67	Problems with cigarettes	n.s.	n.s.	n.s.
68	Problems with drugs	n.s.	n.s.	n.s.

Table 4 (*Continued*)

DBC-A item (subscale)		Age groups	Genetic subtypes	BMI categories
		χ^2, p-value[a]	χ^2, p-value[a]	χ^2, p-value
69	Refuses to go (1)	n.s.	n.s.	n.s.
70	Movements (2)	n.s.	n.s.	0.04[1]
71	Cuddled (5)	n.s.	n.s.	n.s.
72	Echo (3)	n.s.	n.s.	n.s.
73	Repeats	n.s.	0.04[1]	n.s.
74	Smells (2)	n.s.	n.s.	n.s.
75	Scratches (2)	n.s.	n.s.	n.s.
76	Screams (2)	n.s.	<0.01[3]	0.05[1]
77	Sleeps little	n.s.	n.s.	n.s.
78	Stares (2)	n.s.	n.s.	n.s.
79	Sleeps much (6)	n.s.	n.s.	n.s.
80	Soils (2)	<0.01[4*]	0.03[3]	n.s.
81	Whispers	n.s.	0.03[3]	n.s.
82	Spits (2)	n.s.	n.s.	n.s.
83	Lights (2)	n.s.	n.s.	n.s.
84	Steals (4)	n.s.	n.s.	n.s.
85	Stubborn (1)	0.03[2]	n.s.	n.s.
86	Shy (5)	n.s.	n.s.	n.s.
87	Clothes (2)	n.s.	0.05[3]	n.s.
88	Not capable (3)	n.s.	n.s.	n.s.
89	Stands (3)	n.s.	n.s.	n.s.
90	Hallucinates (3)	n.s.	n.s.	n.s.
91	Kill self	n.s.	n.s.	n.s.
92	Talks fast (3)	n.s.	n.s.	n.s.
93	Talks to self (3)	n.s.	n.s.	n.s.
94	Lies (2,3)	n.s.	0.02[3]	n.s.
95	Thoughts (3)	n.s.	n.s.	n.s.
96	Tense (1)	n.s.	n.s.	n.s.
97	Throws (1)	n.s.	n.s.	n.s.
98	Manipulates (1)	n.s.	n.s.	n.s.
99	Pain	n.s.	n.s.	n.s.
100	Elated	n.s.	n.s.	n.s.
101	Posture	n.s.	n.s.	n.s.
102	Changes (1,5)	n.s.	n.s.	n.s.
103	Urinates (2)	n.s.	n.s.	n.s.
104	Bossy (1)	n.s.	n.s.	n.s.
105	Wanders	n.s.	0.05[3]	n.s.
106	Whines (1)	n.s.	n.s.	n.s.

[a] Highest scores in the group: age groups: 1. <25 years, 2. 25–34 years, 3. 35–44 years, 4. 45+ years; Genetic subtypes: 1. Type I deletion, 2. Type II deletion, 3. mUPD; BMI categories: 1. <25, 2. 25–30, 3. 30+.

[*] Also statistical significance on Kendall's tau ($p \leq 0.05$).

3.5. Relationship to genetic subtype and age

Two-tailed independent *t*-tests were performed to test whether the differences between younger (<40 years) and older (≥40 years) adults within the genetic subtypes were statistically significant. Results showed that scores on both the total DBC-A and the subscales did not differ significantly.

4. Discussion

In this study, we assessed problem behavior in a large group of genetically confirmed adults with PWS, with a valid and reliable questionnaire on behavioral problems (DBC-A). Our results show that adults with PWS have higher rates of maladaptive behaviors compared to people with ID due to other etiologies (non-specified ID, Down syndrome or fragile X syndrome). This is in line with other studies (Clarke et al., 1996; Dykens & Kasari, 1997; Einfeld et al., 1999).

Previous studies have noted a sequence of distinct behavioral "epochs" in PWS (Butler, Lee, & Whitman, 2006; Whitman & Accardo, 1987). For a broader view of how maladaptive behavior might change over the entire lifespan, the information of older adults with PWS has to be linked to the behavioral characteristics in childhood and young adulthood. Most studies described an increase in behavioral problems during adolescence and young adulthood (Clarke et al., 1996; Whitman & Accardo, 1987). We found biting, hiding things, rapid mood changes and stubbornness to be more frequent under the age of 35. Young adulthood may be a period of psychosocial adjustments and consequently heightened behavioral problems, compared to childhood and adolescence. Graduation from school and starting to work, out of home placement (in a residential facility) and the awareness of their differences in abilities and dependency compared with siblings, may contribute to an increase in maladaptive behavior. First psychiatric episodes in persons with PWS are also frequently associated with young adulthood (Boer et al., 2002).

Unlike previous descriptions of the behavioral phenotype in adults with PWS, we did not find reductions in behavioral problems in older adults. To the contrary, we found that behavioral problems were more prevalent in older adults. This behavior included underactivity, gorging food, laughing for no obvious reason, panicking and soiling outside the toilet. These behaviors may be refractory to behavioral and dietary interventions. Behavioral problems in older age may also be a result of increasing physical morbidity, functional decline or behavioral problems of other residents in the house.

We found most behavioral problems in adults with the mUPD subtype. In contrast, other studies reported that persons with a mUPD have less skinpicking and maladaptive behavior than persons with a deletion (Dykens et al., 1999; Symons et al., 1999), but heightened vulnerabilities in young adulthood for psychiatric disorders, such as atypical psychosis and affective disorders (Beardsmore et al., 1998; Boer et al., 2002; Vogels et al., 2003).

Psychiatric symptoms are frequent in adults with PWS and are associated with psychosis and affective disorders (Soni et al., 2007, 2008; Verhoeven, Tuinier, & Curfs, 2003; Vogels et al., 2004). Persons with mUPD are at increased risk to develop a first episode of psychopathology in young adulthood (Boer et al., 2002). Results from our study on psychopathology in this same cohort (Sinnema et al., submitted for publication) revealed nine out of 53 persons with a 15q11–q13 deletion and 28 out of 44 persons with mUPD with a current or previous psychiatric illness. It is likely that there is an overlap between behavioral symptoms and psychiatric disorders, attributing to higher problem behavior scores in persons with mUPD. Many adults with PWS need psychiatric support, including psychotropic medication and sometimes hospitalization, during several periods of their lives. It is important for professionals to be aware of any increases in behavioral problems, as these may be early indicators of underlying medical or psychiatric disorders.

Individuals with a BMI < 25 had higher scores on the self-absorbed scale (e.g. biting, screaming, and banging of the head) compared to persons with a BMI between 25 and 30. Both psychological and physiological mechanisms may be implicated in these BMI findings. Very strict dietary control to achieve a healthy weight status may cause more frustration and internal stress in persons with PWS, resulting in an increase of behavioral problems. Our results are in line with the literature (Dykens & Cassidy, 1995; Whitman & Accardo, 1987). It was suggested (Dykens, 2004) that achieving adequate weight control is inherently stressful for most individuals with PWS and that they are often in a state of denial. Weight loss does not seem to be a cure for all aspects of the disorder. A lower BMI may influence the physiological and hormonal status which contributes to specific behavior. This may be an argument to balance the need for weight loss and the increased risk of behavioral problems.

Our results on the relation between problem behavior and age and genetic subtype, differed from results from other studies (Butler et al., 2004; Dykens, 2004; Dykens et al., 1999; Dykens & Roof, 2008). This may be explained by the use of different behavioral measurements and a possible different focus of interest (e.g. obsessive-compulsive behavior or depressive symptomatology). Moreover, the study population in this study differed from other study groups (Butler et al., 2004; Clarke et al., 1996; Dykens, 2004; Dykens et al., 1999; Dykens & Roof, 2008). Our study population is characterized by a predominance of older persons with PWS. We also found a different distribution of genetic subtypes (Sinnema et al., 2010). Genetic testing showed 55% with a paternal deletion, 43% with a mUPD and 2% with a defect of the imprinting center. The observed distribution in our study differed significantly from the classic distribution in the literature (70% deletion, 30% mUPD) (Sinnema et al., 2010). This difference was mainly due to a higher proportion of mUPD in the advanced age groups. The mUPD subtype is associated with higher prevalence of psychiatric and, presumably, co-occurring behavioral problems. These unique characteristics of our study population probably contribute to different findings on behavioral problems.

Behavioral issues often impact on individuals with PWS and their families and caregivers more than any other aspect of the disorder (van den Borne et al., 1999). Compared to reported stress levels in families of children with mixed etiologies of ID, parents of children with PWS showed higher levels of parent and family problems, and comparable levels of pessimism. Families experienced greater levels of stress when the child showed more behavior problems overall (Hodapp, Dykens, & Masino, 1997). Therefore, parents and professional caregivers should be supported in dealing with behavioral problems, not only in childhood, but also during the entire lifespan.

General management of adults with PWS should include attention for behavioral problems. Persons in the older age groups as well as persons with PWS due to mUPD and individuals with low BMI may be at increased risk of certain behavioral problems. Further research is needed in older adults and should among other things focus on the relationship between behavioral problems and psychiatric episodes. Longitudinal studies are warranted to gain more insight into the natural history and course of behavioral problems in adults and older people with PWS over the long term and possible risk and preventive factors.

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