Obsessive-Compulsive Symptoms in Prader-Willi and "Prader-Willi–Like" Patients

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ABSTRACT

Objective: To compare obsessive-compulsive (OC) symptoms in patients with Prader-Willi syndrome (PWS) and symptoms in a group of patients presenting with "Prader-Willi–like" features but without the genetic abnormalities associated with PWS. **Method:** 16 patients aged 4 through 20 years were evaluated in a clinic specializing in the assessment and management of behavioral and food-related problems in PWS. Eight patients were found to have key features of the syndrome but did not have a PWS genotype. These PWS-like subjects were matched to 8 clinic patients with a confirmed deletion of the PWS critical region of the paternally derived chromosome 15. All subjects were evaluated for obesity, IQ, food-related problems, maladaptive behaviors, and non–food-related OC symptoms. **Results:** There were no differences between the 2 groups with respect to measures of obesity, IQ, food-related difficulties, or overall maladaptive behaviors. The PWS group showed significantly greater numbers of OC symptoms and greater symptom severity. **Conclusions:** Patients with PWS have elevated numbers of OC symptoms and significant symptom-related impairment which are not explained by developmental delay, food-related difficulties, or obesity. OC symptoms are part of a behavioral phenotype that accompanies deletions on the proximal long arm of chromosome 15 in PWS. *J. Am. Acad. Child Adolesc. Psychiatry,* 1999, 38(3):329–334.

Key Words: Prader-Willi syndrome, obsessive-compulsive disorder, mental retardation, behavioral phenotypes.

Prader-Willi syndrome (PWS) is characterized by multiple congenital anomalies and results from abnormalities involving the proximal long arm of chromosome 15 (Holm et al., 1993). The most commonly recognized manifestations of PWS include infantile hypotonia and failure to thrive, hypogonadism, short stature, mild to moderate mental retardation, and the childhood onset of hyperphagia, which regularly leads to severe food-related difficulties including food foraging and life-threatening obesity (Prader et al., 1956). However, those with PWS also suffer from behavioral and emotional difficulties not related to food, including temper tantrums, dramatic mood lability, stubbornness, skin picking and obsessive and compulsive symptomatology (Dykens and Cassidy, 1995; Dykens et al., 1992, 1996; Whitman and Accardo, 1987). Moreover, the degree of resulting psychiatric impairment is often very severe. While children and adolescents with PWS have, on average, mild levels of cognitive delay (Curfs et al., 1991; Dykens et al., 1992), their behavioral and psychiatric dysfunction typically results in highly restrictive levels of care and is often the source of enormous distress for patients and their families (Hodapp et al., 1997).

Recent studies have underscored the degree to which children, adolescents, and adults with PWS suffer from non–food-related obsessive-compulsive (OC) symptoms (Dykens and Cassidy, 1996; Dykens et al., 1996; Stein et al., 1994). Dykens and colleagues found that PWS subjects have an average of 3 different obsessions and compulsions as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS) (Dykens et al., 1996).

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Moreover, when PWS patients are compared with non–mentally retarded adults with obsessive-compulsive disorder (OCD), the 2 groups are quite similar, demonstrating equal levels of symptom-related distress and functional impairment (Dykens et al., 1996). These findings are particularly striking when contrasted with the relatively low prevalence of OCD in patients with retardation of mixed etiology (Menolascino et al., 1986; Vitiello et al., 1989).

In addition, Dykens and Kasari identified a distinct set of signs and symptoms which reliably distinguished PWS children from children with Down syndrome or with nonspecific mental retardation. These included obsessions, compulsions, and skin picking (Dykens and Kasari, 1997). Other studies have supported high rates of repetitive behaviors, perseverative speech, and skin picking in subjects with PWS (Clarke et al., 1996; Schepis et al., 1994; Stein et al., 1994).

However, questions remain about the strength of the association between OC symptoms and the PWS genotype. For instance, OC symptoms could conceivably arise as a psychological consequence of hyperphagia and may not be indicative of PWS per se, but rather a secondary characteristic of persons with significant food preoccupations. Along similar lines, the combination of excessive appetite and mild to moderate cognitive delay could lead to repetitive behaviors such as repeated questioning or the need for reassurance which might mistakenly be characterized as non–food-related OC symptoms, especially when studies rely on parental or caregiver report. Finally, researchers have tended to recruit subjects through PWS advocacy groups (Clarke et al., 1996; Dykens and Kasari, 1997; Dykens et al., 1996; Stein et al., 1994) and therefore have difficulty controlling for the impact of reporting bias. It could be that parents and guardians of PWS subjects are inadvertently reconciling their reports of OC symptoms with widespread ideas about how persons with the syndrome generally behave.

To clarify the association of OC symptoms with the Prader-Willi genotype, we have compared subjects with PWS with a particularly powerful control group who presented to a clinic specializing in the assessment and treatment of behavioral problems in PWS. All subjects included in the study presented with key features of PWS including obesity, food preoccupations, maladaptive behaviors, and mild to moderate mental retardation or learning difficulties. However, patients in our comparison group were found not to have a genetic lesion associated with PWS. This "PWS-like" group was matched with a group of patients with a confirmed diagnosis of PWS because of a deletion on the paternally derived chromosome 15. We hypothesized that the 2 groups would show similar levels of behavioral problems but that the PWS group would show higher rates of OC symptoms and symptom-related distress.

METHOD

Subjects

The study included 16 subjects, 4–20 years of age (mean 12.3 years). Eight subjects had PWS associated with a deletion of the PWS critical region of the paternally inherited chromosome 15, and 8 did not have a PWS genotype. All study participants presented for evaluation to a clinic specializing in the assessment and treatment of behavioral and food-related problems in PWS.

During the first 12 months the clinic was in operation, a total of 8 children, adolescents, and young adults presented with behavioral complaints, difficulties with food, and mild to moderate mental retardation but either failed to meet diagnostic criteria for PWS (Holm et al., 1993) or had previously had genetic testing that did not identify a PWS genotype (Anonymous, 1996). Patients who presented to our clinic without a confirmed diagnosis of PWS were offered molecular genetic testing using methylation-sensitive restriction enzymes to rule out abnormalities on chromosome 15 at the locus q11-q13 (Anonymous, 1996; Driscoll et al., 1992). These tests were performed in the laboratory of Dr. Wayne Grody at UCLA. The methylation-sensitive restriction enzyme technique allows identification of the most common types of genetic problems that lead to PWS including deletions on the paternally transmitted chromosome and maternal uniparental disomy (inheriting 2 copies of the maternal chromosome and no paternal chromosome). All patients categorized as PWS-like in this study underwent this testing and were negative for a PWS genotype.

A total of 60 patients presented to the clinic over the same period who met clinical diagnostic criteria for PWS and/or had confirmatory genetic testing (Anonymous, 1996). From this group, the first 8 patients who presented chronologically to the clinic with confirmed deletions of chromosome 15 (either by cytogenetic analysis or fluorescence in situ hybridization) and who matched the PWS-like group by age and gender were identified as the PWS group.

At the time of initial evaluation, 6 patients had a diagnosis of impulse control disorder not otherwise specified (NOS) (3 from the PWS group and 3 from the PWS-like group). One patient in the PWS-like group had a diagnosis of OCD and eating disorder NOS, and one patient from the PWS group had a diagnosis of anxiety disorder NOS. All patients with borderline intellectual functioning or mental retardation had the appropriate diagnoses on Axis II. One patient from each group had a history of seizures. One patient was taking medication for obsessions and compulsions at the time of presentation. This subject was in the PWS-like group and was being treated with a selective serotonin reuptake inhibitor.

Measures and Procedures

Parents and caregivers of patients who arranged for evaluation in our clinic were mailed a previsit packet which they were asked to complete prior to initial presentation. This packet included the following:

Demographic Questionnaire. A demographic questionnaire requested information regarding the patient's age, sex, IQ, height, weight, living and work arrangements, and genetic testing status.

Yale-Brown Obsessive Compulsive Scale. Parents and caregivers of all patients presenting to the clinic filled out an informant version of the YBOCS (Goodman et al., 1989a,b), which has been shown to have good reliability and validity (see Skeketee et al., 1996; and Taylor, 1995). The version used in this study consists of a 56-item checklist of OC symptoms which is drawn from the adult version of the YBOCS, though it covers all symptom areas contained in the child version's checklist. Each item is rated as being present ever or in the previous week. Three additional items assess symptom severity. Informants are asked to rate, on a 5-point scale, the extent to which obsession and compulsions (1) are time-consuming; (2) are distressful; and (3) cause social or occupational impairment (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = extreme). For the informant version of the checklist, YBOCS items are reworded to reflect informant rather than self-ratings.

Child Behavior Checklist. The Child Behavior Checklist (CBCL) (Achenbach, 1991) is a widely used instrument consisting of 112 behaviors that are rated on a scale from 0 to 2 (0 = not present; 1 = somewhat or sometimes true; 2 = very true or often true). The CBCL includes 8 "narrow-band" and 2 broad-factor *T* scores which denote overall internalizing and externalizing behaviors. CBCL *T* scores greater than 70 are considered to be in the range of clinical significance. The CBCL is both a reliable and valid measure of psychopathology in children and adolescents and has been used successfully in previous studies of persons with mental retardation.

During the initial evaluation in clinic, these measures were reviewed with a clinician (M.W.S., E.M.D., B.H.K.). All the patients in the study had a completed set of instruments. Symptom endorsements on the YBOCS which pertained to food were discarded. For example, the checklist item "ritualized eating behaviors" was not included in the tally of symptoms. On presentation to the clinic, all patients had vital signs measured and recorded, including heart rate, blood pressure, height, weight, and head circumference. Body mass index (BMI) was calculated by the formula weight (kg)/height $(m)^2$ (Smalley et al., 1990). Patients and caregivers were clinically interviewed by one of the authors (M.W.S., E.M.D., B.H.K.), and, in cases in which recent cognitive testing was not available, an IQ evaluation was performed by a clinician experienced in cognitive assessment of patients with mental retardation syndromes (E.M.D.).

RESULTS

Subject Characteristics

The PWS and PWS-like groups of patients were matched for age and gender and then assessed for significant differences in IQ, height, weight, BMI, and total CBCL scores. One-way analyses of variance (ANOVAs) revealed no significant differences between groups. However, BMI approached statistical significance, with the PWS-like group tending to be more obese than the PWS group. Table 1 shows the means, standard deviations, and *F* values for all comparisons. Given the trend toward significance in a measure of obesity, an additional analysis was undertaken to assess for any correlation between BMI, YBOCS scores, or total CBCL score. None of these were significant.

TABLE 1
Subject Characteristics

	PWS		"PWS-Like"			
	Mean	SD	Mean	SD	*F*	*p*
Age	12.4	4.9	12.2	5.9	0.0076	.93
IQ	57	15.4	70.6	23	1.75	.20
Weight	126.4	50.4	165	102.9	0.909	.36
BMI	25.9	8.9	36.4	11.6	4.18	.06
Total CBCL	66.7	17.1	68.9	23	0.049	.82

Note: Subjects with and without Prader-Willi syndrome (PWS) were matched for age and sex and then compared with respect to the variables listed in the table. BMI = body mass index calculated as weight in kilograms divided by height in meters squared; CBCL = Child Behavior Checklist (see text).

YBOCS

Both the number and severity of OC symptoms were compared across groups using a Mann-Whitney *U* test. A nonparametric statistical analysis was chosen because of the small numbers in each group and the uncertain distribution of the data. The Prader-Willi group showed significantly more OC symptoms than the PWS-like controls. Figure 1A shows the distribution of scores for YBOCS symptom number and the means and standard deviations for each group. Relative to controls, subjects with PWS also had significantly higher ratings of symptom severity (Fig. 1B).

CBCL

To clarify these findings, we conducted follow-up one-way ANOVAs with 4 selected items from the CBCL: obsessions, overeating, compulsions, and skin picking. In all 16 subjects, endorsements on the CBCL item regarding obsessions were related to food. Consistent with our hypotheses, the 2 groups had similarly high levels of food obsessions and overeating. However, the PWS group demonstrated significantly more compulsions and skin picking than controls. Table 2 summarizes the means, standard deviations, and *F* values for the PWS and PWS-like groups.

DISCUSSION

Patients with PWS had significantly higher numbers of non–food-related OC symptoms as well as significantly increased levels of symptom-related severity com-

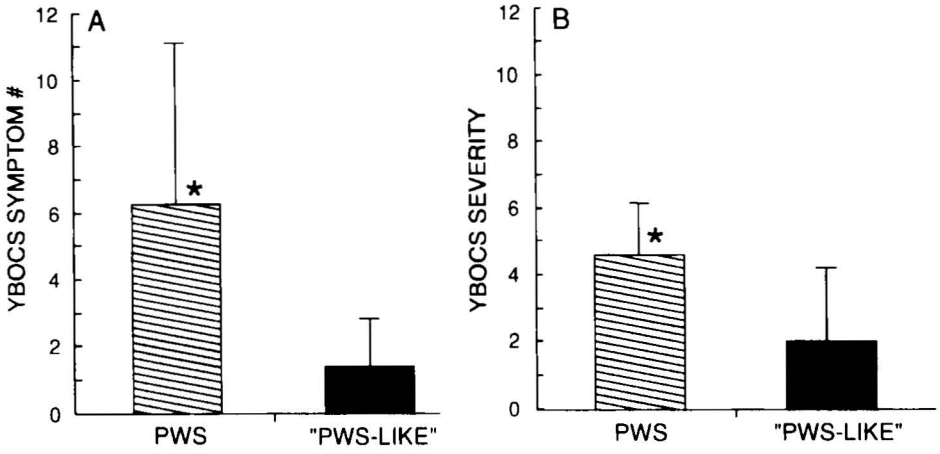

Fig 1 A: Total number of Yale-Brown Obsessive Compulsive Scale (YBOCS) symptoms in subjects with and without Prader-Willi syndrome (PWS). For the PWS group: mean = 6.25; SD = 4.86. For the PWS-like subjects: mean = 1.37; SD = 1.41. *p = .015. B: YBOCS symptom severity scores for patients with and without PWS. For the PWS group: mean = 4.5; SD = 1.77. For the PWS-like subjects: mean = 1.87; SD = 2.29. *p = .038. Three severity-related questions are totaled to calculate the severity index. The maximum possible score is 12.

pared with controls. Our findings are particularly robust in that we compared subjects with PWS with a group of age- and gender-matched developmentally delayed, obese, food-preoccupied subjects. Importantly, PWS and PWS-like groups were similar with respect to IQ, levels of food-related difficulties, and overall levels of psychopathology based on CBCL scores. While the PWS-like group tended toward higher mean weights than the PWS group, neither weight nor BMI was related to OC symptoms, symptom severity, or maladaptive behaviors in either group.

Our findings are consistent with recent studies demonstrating high rates of OC symptoms in people with PWS (Dykens et al., 1996; Stein et al., 1994) and delineating a distinctive behavioral phenotype for Prader-Willi subjects. In particular, OC symptoms clearly distinguish persons with PWS versus those with mental retardation of mixed etiologies or other genetic causes, such as Down syndrome and Smith-Magenis syndrome (Dykens and Kasari, 1997; Smith et al., 1998). The present study expands on the current literature by allowing us to control for some of the key phenotypic features of PWS while assessing the relationship between OC symptoms and genotype.

TABLE 2
One-Way Analysis of Variance of Four Items From the CBCL Comparing PWS and "PWS-Like" Groups

	PWS		"PWS-Like"			
	Mean	SD	Mean	SD	F	p
CBCL item 55 Overeating	1.5	0.76	1.9	0.35	1.61	.224
CBCL item 9 Obsessions (regarding food)	1.6	0.52	1.9	0.35	1.27	.272
CBCL item 66 Compulsions	1.4	0.75	0.5	0.76	5.44	.035
CBCL item 58 Skin picking	1.9	0.35	0.5	0.76	21.71	.0004

Note: CBCL = Child Behavior Checklist; PWS = Prader-Willi syndrome.

In light of these data, the heightened levels of OC symptoms in PWS cannot be accounted for simply as a result of patients having food preoccupations, obesity, and/or developmental delay. The 2 groups were equally food-obsessed, had similar cognitive abilities, and had similar degrees of obesity. It is possible that eating difficulties are experienced differently by PWS patients than by other developmentally delayed, obese adolescents and children and therefore result in particularly severe psychological outcomes. However, all the available indices measured suggest that the 2 groups of patients in this study not only were equally subject to food-related problems but also were equally prone to psychopathology in general, though not the development of OC symptoms in particular.

Reporting biases are unlikely to have influenced these findings. If parents and caregivers of PWS patients were mistaking food preoccupations with other non–food-related OC symptoms, one would presume that the par-

ents and caregivers of the PWS-like subjects would demonstrate a similar propensity. Also, given the composition of the control group, the bias toward reporting symptoms consistent with PWS would likely influence both sets of subjects. This is particularly the case as the PWS-like group generally sought evaluation because a clinical diagnosis of PWS had been suggested. In practice, it was usual for parents and caregivers of subjects in this group to be familiar with the clinical picture of PWS and to present with a stated hope of obtaining a diagnosis.

The emerging identification of a behavioral phenotype in PWS raises the intriguing question of how the underlying genetic lesion(s) might lead to these complex neuropsychiatric symptoms. In the case of PWS, no distinct brain area has been identified as grossly pathological by neuroimaging techniques, though there is but a single controlled study in the current literature (Miller et al., 1996). The syndrome is thought, however, to involve significant hypothalamic dysfunction. This hypothesis is supported by the common occurrence of growth hormone abnormalities, temperature and sleep abnormalities, and delayed sexual maturation in PWS (Bray, 1992; Seyler et al., 1979; Swaab, 1997). In addition, a recent neuropathological study in PWS found a decrease in oxytocin (OXT) secreting neurons in the hypothalamic paraventricular nucleus of postmortem PWS brains compared with matched control brains (Swaab et al., 1995). OXT abnormalities have been linked to OC symptoms more broadly through research which has demonstrated abnormally high levels of this neuropeptide in the CSF of a subgroup of patients with OCD (Leckman et al., 1994; Swedo et al., 1992). In addition, we have identified OXT elevations in the CSF of 5 patients with PWS (Martin et al., 1998) compared with controls. It is difficult to reconcile the apparently conflicting findings that OC symptoms and PWS appear in some cases to be associated with increased CSF OXT while there also seems to be a significant decrease in OXT neurons in at least one important CNS nucleus in Prader-Willi subjects. It is possible, however, that the techniques used to identify OXT neurons in Swaab's study were not able to distinguish between a paucity of OXT-secreting cells and a normal population of cells that had been relatively depleted of OXT. Regardless, what is clear at present is that multiple lines of investigation point to the hypothalamus as the prime brain region for additional research into the relationship between the genetic underpinnings of PWS and its many behavioral consequences.

Several methodological shortcomings limit the strength of our findings. This study relied on a relatively small number of patients, limited by the rarity of our natural control group. Larger numbers would have allowed for an analysis of OC symptom profiles both within and between groups as well as for some assessment of genotype–phenotype relationships in PWS patients. Furthermore, the study was naturalistic in that it included patients who presented for clinical evaluation. As a result, patients with other psychiatric and medical diagnoses and those taking medications were not excluded. Of note, only a single patient was being treated with an antiobsessional medication at the time these symptoms were assessed. This subject was in the PWS-like group. However, excluding this patient in a repeated analysis of the data had no impact on the statistical significance of any of the results.

While the 2 groups appear to very similar along a number of important criteria, there may have been some undetected differences between them, apart from the differences in genetic status, which would account for the significant findings with respect to OC symptoms. Moreover, while the molecular genetic techniques used to distinguish the 2 groups are able to identify more than 95% of patients with the PWS genotype, it is possible that some patients in our PWS-like group could have had an undetected PWS genotype. However, given the direction of the differences found between the 2 groups, inclusion of PWS patients in our PWS-like group would have served to minimize the differences between groups, making our findings even less likely to represent a type I error. It should be noted that our PWS group consisted only of patients whose syndrome was caused by a deletion of chromosome 15. While at present there do not appear to be important phenotypic differences between patients with varying types of lesions associated with PWS (Cassidy et al., 1997; Mitchell et al., 1996), further investigations are needed to clarify this issue as it pertains to behavioral and psychiatric sequelae. Under the circumstances, we considered it prudent to rely on a homogeneous group with respect to genetic causation.

Despite these limitations, our data extend findings from several groups regarding the presence of OC symptoms in PWS patients and the central role of such symptoms in the PWS behavioral phenotype. The ongoing clarification of this phenotype may provide relevant information to psychiatrists and other physicians who treat persons with PWS. Moreover, the continuing inves-

tigation into the relationships between genetic abnormalities and behavioral phenotypes promises to shed new light on the complex interplay of genes, brain, and behavior in the etiology of psychiatric illnesses.

Clinical Implications

The elucidation of particular psychiatric symptom clusters in persons with PWS will help clinicians anticipate and recognize key behavioral difficulties that afflict these patients and will highlight for clinicians the importance of assessing and treating all the varied aspects of this syndrome. A better understanding of the PWS behavioral phenotype should also provide families and patients with a sounder basis for their expectations about the course and natural history of the disorder. Finally, the clarification of the relationship between OC symptoms and PWS may serve as an impetus for much-needed clinical investigations of antiobsessional treatments, pharmacological and otherwise, aimed at helping those with PWS.

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