Risk for Ingestion of Toxic Substances in Children With Prader–Willi Syndrome

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Individuals with Prader–Willi syndrome (PWS) have several common findings that may predispose to ingestion of potentially dangerous items. This study examined whether individuals with PWS have an increased prevalence of toxic ingestions. A survey regarding history of ingestions in PWS individuals and sibling controls was designed, piloted, and distributed on-line. The subjects were individuals with PWS (N = 129). The subjects’ non-PWS siblings served as controls (N = 134). Participants who completed the anonymous online survey were either the parents or the primary caretaker of individuals with PWS. Responses were submitted by 141 participants, providing information about 130 PWS subjects (M/F: 66:64) and 134 sibling controls. Subjects and controls ranged in age from 2 to 18 years at the time of the survey. Eleven participants did not answer the questions regarding ingestions. History of toxic ingestion was more prevalent in PWS subjects (20% vs. 2% of controls). Several features of PWS, including history of searching for food and eating unusual objects, along with decreased cognitive ability, appeared to associate with increased prevalence of toxic ingestion in PWS individuals. PWS children appear to have an 12-fold increased risk of ingesting toxins compared to the general population. Geneticists should include this information in counseling and in recommendations to primary care providers. Also, poison control centers need to be aware of this association and of the physiological and behavioral aspects of PWS that may complicate the diagnosis and management of a toxic ingestion.

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Key words: Prader–Willi syndrome; poisoning; toxic ingestion

INTRODUCTION

Prader–Willi syndrome (PWS) is a complex genetic disorder with a fascinating and well-documented pattern of clinical findings [Cassidy and McCandless, 2004] including abnormal food satiation and a willingness to eat what are generally considered to be inedible items. At least one study has confirmed the generally recognized clinical observation that individuals with PWS do not discriminate against eating contaminated food or unorthodox food combinations [Dykens, 2000]. That study suggested that the ability to reject contaminated or unusual food combinations is overpowered by a drive to reach a feeling of satiation.

The prevalence of accidental poisoning in people with PWS is unknown. The combination of hyperphagia, poor discrimination of edible versus non-edible items and intellectual disabilities suggests that PWS individuals may have an increased risk of ingesting toxic substances or poisons. This is supported by a case report of a woman fitting the clinical criteria for PWS who mistook table salt for sugar and ingested a fatal amount (3–4 tablespoons) with her breakfast jam [Johnston and Robertson, 1977]. While the association of PWS and potentially toxic ingestions seems intuitive, this is the first study to document the increased prevalence of potentially toxic ingestions in people with PWS as compared with non-PWS sibling controls, and the associated clinical and behavioral predictors of increased risk.

METHODS

This study was reviewed and approved by the Institutional Review Board (IRB) at The University of North Carolina at Greensboro. It was also reviewed by the Scientific Advisory Board of the Prader–Willi Syndrome Association (PWSA-USA) who provided helpful suggestions and approved posting a link to the survey on the PWSA-USA website (www.pwsausa.org).

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Participants, Subjects, and Controls

Participants were defined as individuals who completed the anonymous online survey. Subjects were defined as the individuals with PWS that were reported on in the survey. To ensure that reasonable data were available for each subject, participants were asked to only submit data for subjects who were \( \geq 4 \) years of age at the time of the survey. Controls were the non-PWS siblings or children living within the same household as the subject.

Study Design

The survey was designed to assess the prevalence of potentially toxic ingestions in children with PWS and the associated clinical and behavioral characteristics. After piloting with several families from the PWS clinic at the University of North Carolina—Chapel Hill and review by members of the Scientific Advisory Board of the PWSA-USA the final version was posted on the Internet (www.surveymonkey.com) for 3 months. Potential subjects were notified through several PWS clinics and via the newsletter and website of the PWSA-USA. For each subject and control, the survey gathered parent reported demographic information, developmental level, and previous history of ingestion; additional information gathered for subjects included cause of PWS, presence of endocrine anomalies, unusual behaviors (for PWS), and history of food related behaviors. No identifying information was collected. Eligible subjects had a reported diagnosis of PWS and were \( \geq 4 \)-year old at the time the survey was completed; controls were siblings or children within the same household as an individual with PWS. The initial page described the study and incorporated informed consent information, which was assumed by the participant’s submission of the completed survey. Participants were instructed to fill out the survey only once.

Statistical Analysis

Data were analyzed using SAS™ software (version 6, SAS Institute Inc., Cary, NC, 1996) for frequency procedures, Chi-squared test of association, Fisher’s exact test and relative risk analysis to assess any relationship between instances of poisoning and specific phenotypic features in subjects with PWS.

RESULTS

A total of 141 surveys were submitted, of which 11 contained no response to questions about ingestion. Of the 130 remaining responses, 102 (78%) were from mothers of individuals with PWS, 7 (5%) were from fathers, and the rest from a variety of other adult relations to the subject. Participants (the adults filling out the survey) were primarily from the United States. Roughly half of the households had annual incomes greater than $50,000 (USD). A total of 134 non-PWS sibling controls from 80 families were reported in this study, suggesting that 50 of the 130 PWS individuals were the only child in the family. Family size ranged from 1 to 9 children including the child with PWS, with 92% having three or less children. The cause of PWS was reported for 102 (78%) subjects; 75% had deletion of chromosome 15q11, 22% had uniparental disomy, and 3% had an imprinting defect. These proportions reflect the overall PWS population.

One or more instances of potentially toxic ingestion were reported in 25 of 130 individuals with PWS (19%). Seven individuals (5% of the total, but 28% of those having any ingestion) had more than one episode (range 2–5), for a total of 42 episodes. Nine ingestions involved two or more potentially toxic substances. Individuals with PWS ranged in age from 2 to 24 years old at the time of the ingestion. The types of substances ingested were reported by 24 participants and are listed in Table I. Fourteen of 18 (78%) reported episodes occurred at home, 3 occurred at a grandparent’s house (17%), 1 occurred at a neighbor’s house (6%), and 1 occurred at the school playground (6%). The majority of respondents reported calling the local poison control center, the pediatrician, or the local emergency room when the ingestion was discovered. No deaths or permanent injury were reported as a result of these ingestions, but the survey was not designed to collect detailed medical information as it relied on parent recall.

Three episodes (2%) of ingestions were reported in controls \( \chi^2 = 19.33, P < 0.0001, \) all in families with more than two children (3, 3, and 9 including the child with PWS). All three non-PWS siblings with ingestions were under the age of 4 years (mean age 3 years) at the time of the ingestion. One family reported a toxic ingestion in both the PWS subject and in a sibling. Of note, in this family the non-PWS sibling with an ingestion had mild intellectual disability. The remaining two controls were reported to have normal development, and their PWS sibling was not reported to have had a potentially toxic ingestion.

Ingesting a potential toxin was associated with food-related behaviors, reduced cognitive ability, a history of eating unusual items, and a history of “extreme behaviors.” Food-related behaviors offered as choices included: “preoccupation with food,” “storing up or acquiring food,” “looking or searching for food,” “stealing (food and/or money to buy food),” “ritualism,” “none,” or “other (please specify).” The concept of “extreme behaviors” was added in response to input from the family support group that helped to pilot and advertise the survey. For the purpose of this study the term was defined as a behavior that is not typically

<table>
<thead>
<tr>
<th>Toxic substance</th>
<th>Number of reports</th>
<th>% Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over-the-counter medicine</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Prescription medicine</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Vitamins</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Spoiled food</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Plant or wild mushroom</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Personal care product</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Cosmetic</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Alcohol</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Cleaning product</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>“Other” not specified</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

*Some ingestions involved multiple substances, so the total is greater that the 42 reported instances of ingestion.*
characteristic of PWS, or is much more severe than typically seen in PWS, primarily severe temper tantrums, violent behaviors and episodes of “rage.” There were no significant differences in gender, height, weight, cause of PWS, or endocrine problems noted between the subjects who did or did not ingest a toxic substance.

Information regarding history of food-related behaviors was reported for 129 subjects. All subjects reported to have a potentially toxic ingestion had at least one food-related behavior; there were no instances of poisoning among the 10 subjects reported to have no food-related behaviors. Ingestion was associated with a history of “looking or searching for food” ($\chi^2 = 5.7, P < 0.018$); subjects with a history of searching for food were 2.5 times more likely to have an ingestion than those without such history (Mantel–Haenszel relative risk = 2.5). The incidence of potentially toxic ingestion in subjects with a history of eating unusual objects was 44% (18/41) compared with 8% (7/89) in subjects without a history of eating unusual objects ($\chi^2 = 23.5, P = 0.0001$), suggesting a 5.6-fold greater risk of ingestions for PWS individuals with history of eating non-food items (Mantel–Haenszel relative risk = 5.6). No statistically significant relationship with ingestion was found for preoccupation with food, storing or “acquiring” food, stealing, ritualism, or ‘other’ behaviors.

Cognitive function was reported for 123 subjects (Fig. 1). None of the subjects reported as having no intellectual disability (N = 7) had a reported ingestion, whereas, all of the subjects reported as having “severe” intellectual disability (N = 3) had one or more potentially toxic ingestion. A linear trend was found between reported cognitive level and prevalence of ingestion (Mantel–Haenszel $\chi^2 = 11.7, P < 0.001$).

Thirty subjects were reported to exhibit “extreme behaviors,” such as severe temper tantrums, and outbursts of rage and violence. The incidence of ingestions in subjects with a history of extreme behaviors was 33.3% (10/30) compared with 15.3% (15/98) in subjects without a history of extreme behaviors ($\chi^2 = 4.7, P < 0.03$). Relative risk analysis showed that subjects with a history of extreme behaviors had a 2.2-fold greater risk of having a potentially toxic ingestion than subjects without a history of extreme behaviors (Mantel–Haenszel relative risk = 2.18).

DISCUSSION

This study provides a description of potentially toxic ingestions in a cohort of PWS patients and their non-PWS siblings obtained through an on-line survey, suggesting that there may be an increased risk of potentially toxic ingestions in individuals with PWS. The apparently increased risk is associated with a history of food-seeking behavior or eating non-food items, severe or unusual behavior problems, and with lower cognition. While this can be a serious problem for families dealing with PWS, like some other aspects of the disorder, it may be particularly amenable to preventive interventions.

Among 130 PWS subjects in the study there were 42 incidents of potentially toxic ingestion reported in 25 individuals. Review of the free text comments suggests, not surprisingly, that many of the ingestions in the PWS group occurred when the children were younger, although the wide age range (2–24 years) likely reflects the degree of cognitive impairment in this population. The ability to cognitively process that certain substances are poisonous or harmful appears to influence the prevalence of potentially toxic ingestion based on the observation that reduced cognitive level was related to a higher risk of ingestion. The relationship between cognitive function and ingestion may be independent of PWS, but this study was not designed to assess that possibility.

In children with PWS, history of “food-seeking behaviors” or “eating unusual objects” were, respectively, associated with a 2.5- and 5.6-fold greater risk of potentially toxic ingestion. Subjects with a history of “extreme behaviors,” meaning behaviors outside the range typically seen in PWS, were 2.2 times more likely to have an ingestion than those subjects with no history of extreme behaviors. This survey was not able to distinguish between PWS related “extreme” behaviors or a behavior disturbance from other causes, and it is therefore unclear if the “extreme behaviors” reported by study participants were independent of PWS or part of the behavioral phenotype. These data suggest that the presence of certain food-related behaviors and lower cognitive function correlate with risk and may predict that some individuals with PWS are at greater risk of potentially toxic ingestions than others. While this may be true, it would not be appropriate to assume the converse, namely that the absence of these findings suggests that a particular individual is not at increased risk. This study was not designed to answer that question.

Interestingly, while most of the ingestions were reported to be intentional, none were reported to be for the purpose of self-injury. The survey was not designed to measure the annual incidence of toxic ingestions, but these data show the prevalence of potentially toxic ingestion in this cohort to be ~20% in the children with PWS, compared to ~2% in the control group. Expressed differently, there were 42 ingestions per 443 person-years reported in this study, or ~95 ingestions per 1,000 person-years in the subjects with PWS. The American Association of Poison Control Centers reports an average of 8.1 exposures per 1,000 in the general population.
annually, a number that has been relatively stable over the past decade [Bronstein et al., 2008]. This suggests that PWS individuals may have an approximately 12-fold increased risk for toxic ingestion relative to the general population. It is interesting to note that the prevalence reported here is also higher than expected for control siblings, one of whom had developmental disability. The low absolute number of individuals affected restricts ascribing any significance to this finding.

Colorful and sweet-scented products were often reported as the toxic substance ingested, which is not surprising in that many of the food products that are “off-limits” to the child with PWS have similar qualities. In 38% of the potentially toxic ingestions in this study the substance was a medication, a pattern that reflects the general population exposure data for children [Bronstein et al., 2008]. Prescription and over-the-counter medications are particularly worrisome in the PWS population because affected individuals may not be put off by unpleasant taste, which may be partially mediated by abnormalities of saliva production. Further, many of the typical clinical findings in children with PWS may add to the difficulty in assessment and management of toxic ingestion, including the fact that they do not respond to pain or discomfort as other children do, they have low muscle tone, they often have reduced ability to vomit, and they may have gastric dilation and wall thinning with risk of rupture or necrosis if overfilled or if a large bore orogastric tube is placed for lavage.

Limitations of the study include those typical of all patient surveys, including, but not limited to, incomplete answers, reliance on self-reporting, potential for lack of knowledge of, or insight into, the medical history and, self-selection of individuals having experienced an ingestion. The last may be less likely as the majority of respondents did not report a potentially toxic ingestion. Accessibility may limit this study because the survey was only available on-line. While this could have limited participants who do not have regular access to the internet, Chi-squared analysis showed no statistically significant relationship between socio-economic level and poisoning ($P = .44$), suggesting that families with limited internet access because of socio-economic circumstances would not be more likely to have had a poisoning episode. The survey used was designed and piloted for this study, and has not been validated using a second cohort or by comparison to a standardly accepted tool. Finally, identifying information was not collected so it is possible that a subject was reported on more than once. Review of the individual responses did not identify any with overlapping responses, suggesting that all responses were unique.

CONCLUSIONS AND RECOMMENDATIONS

The health-care providers caring for PWS patients after potentially toxic ingestions, primary care providers, and emergency room staff are unlikely to be familiar with the disorder. Prevention is the best strategy for dealing with toxic ingestions, therefore, important contributions to the routine follow-up care of children with PWS are for the medical geneticist to inform the primary care provider about this risk and to help families to identify risks in the home and to create environmental protections. We recommend that the discussion include standard prevention practices, stressing the importance of maintaining a minimal supply of medicines and other poisonous products in the home; locking medicines, cleaning supplies, and other possible toxins in special cabinets; use of child-proof containers for medicines and cleaning supplies; and possibly using “Mr. Yuk” stickers to overcome the challenges brought about by lower cognitive skills. While the utility of these various methods in preventing potentially toxic ingestions has been debated [Kendrick et al., 2008], they may at least serve to alert the parent to the issue and give them a starting point for intervention. Sweet smelling cleaners or other toxic liquids (e.g., anti-freeze) and colorful, “candy-like” medications are of particular concern for individuals with PWS, and special attention to keeping these out of the house should be considered.

Specific information about common clinical manifestations of PWS should be noted, as discussed above. The high tolerance to pain [Priano et al., 2009] and intestinal discomfort, as well as the clinically observed high threshold for vomiting, in PWS individuals must be taken into account by the center or provider during the evaluation of the PWS patient suspected of having had a toxic ingestion. Specifically, the lack of discomfort should not be taken as a reassuring sign that there has not been a clinically significant ingestion. Emetics should not be used in individuals with PWS. Finally, the specialist should consider giving the family written information detailing the pertinent issues in management addressed above. This could take the form of an emergency letter, or a fact sheet, that could be shared with emergency room and poison center staff, when needed.

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REFERENCES


