Death in adults with Prader-Willi syndrome may be correlated with maternal uniparental disomy

A Smith, G Loughnan, K Steinbeck

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Prader-Willi syndrome (PWS) is a disorder comprising severe neonatal hypotonia, hypogonadism, gross obesity, short stature, small hands and feet, mental handicap, a characteristic facial appearance (almond shaped eyes, thin downturned upper lip, and a narrow bitemporal diameter), nasal, inarticulate speech, and a particular personality profile.\(^1,2\) Prader-Willi syndrome has a biphasic course. Initially there is severe neonatal hypotonia, difficulty in feeding, and failure to thrive, usually persisting for 12 months. This is followed by weight gain, and if unchecked obesity is well developed by 6 years of age.\(^3\) The gain in weight is primarily attributable to a hypothalamic defect resulting in an inconstant appetite and hyperphagia,\(^4,5\) but a lowered metabolic rate and lack of exercise owing to continuing hypotonia contribute.\(^6\) The patients have a food obsession with a rather specific food related behavioural phenotype, which includes foraging for food, stealing food, and eating inedibles.\(^1,3\)

The clinical diagnosis of PWS can now be confirmed by accurate genetic testing. Methylation testing makes a definitive diagnosis in about 99% of patients, but will not define the genetic mechanism. Further simple DNA studies of the chromosome 15 (q11-q13) region will do this. These include fluorescence in situ hybridisation (FISH) to check for deletion and DNA polymorphisms for maternal uniparental disomy (UPD).\(^7\) A patient with a positive methylation result who is non-deleted and non-disomic has an imprinting defect (ID).\(^7\) The commonest genetic mechanism is paternal deletion of the imprinted region (about 75% of patients), followed by UPD in 24% and about 1% have an ID for this region.\(^7\)

Adults with PWS are cared for in various ways throughout the community.\(^3,4,5,7\) Cohorts of adults with PWS seen at clinics in the past found that morbid obesity was usual.\(^1,4,5\) A recent study from the United Kingdom has confirmed a continuing high morbidity, despite better early diagnosis, knowledge, and management of PWS.\(^8\) This morbidity among adults is largely the result of complications associated with obesity, such as diabetes (mainly type 2), sleep apnoea, respiratory arrest, peripheral circulatory stagnation, slow healing of skin lesions, and osteoporosis,\(^1,6,10,11\) but the hypotonia, which continues into adult life, contributes (for example, scoliosis, kyphosis, lack of exercise). Psychological problems are a cause of major concern to families, reported in 5%–15% of adult patients, and range from obsessive skin picking to overt cyclical psychosis.\(^10,12-15\) Hypothalamic insufficiency contributes to hypogonadism, temperature instability, low activity levels, and low metabolic rate, further affecting morbidity.\(^1\) A mortality rate for PWS has not been established by prospective studies. A retrospective prevalence population study in the United Kingdom estimated a mean mortality rate of 3% a year across all ages and 7% a year in those over 30 years of age.\(^2\)

We present our findings in a cohort of adults with PWS consistently attending a multidisciplinary PWS clinic over the 10 year period 1991–2001. Our review was conducted to assess outcome data for adult patients and to look for possible future interventions which might improve clinical management.

**PATIENTS AND METHODS**

A multidisciplinary medical clinic for adults and adolescents with PWS at the Royal Prince Alfred Hospital, Sydney receives referrals from clinicians, carers, and parents throughout the State of New South Wales. The service, staffed by an endocrinologist, dietician, and physiotherapist, has remained constant for 10 years since its inception in 1991. A social worker joined the team in 2001. Consultation is available for sleep disorders, and dermatological, psychological, psychiatric, and genetic indications, if required. General practitioners and other specialists are often peripherally involved. The clinics are held bimonthly.

At the clinic, patients initially attended an individual consultation in which history and physical examination were obtained and other disorders, for example, diabetes and sleep apnoea, were ascertained. A blood specimen was taken for biochemistry, haematology, and genetic testing. Genetic testing starts with routine cytogenetics, followed by a DNA based test.\(^13,16\) Measurements of height and weight were recorded and body mass index (BMI) calculated.

**Key points**

- Prader-Willi syndrome (PWS) in adulthood is difficult to manage. We present our findings in 36 adults, seen at a multidisciplinary PWS clinic in a major Sydney teaching hospital over a 10 year period.
- There were 18 women and 18 men; mean age on admission was 26 (range 14–48) years. All patients had PWS established by DNA testing. On admission, the BMI of the patients with deletion was 41.2, the same as those with UPD (42.6). Morbidity was high; all had a history of sleep apnoea, 19% had diabetes, and 28% had episodes of psychiatric illness. There were 10 deaths (28%) during the time of the study, six women, four men, mean age at death 33.2 (range 20–49) years.
- In 60%, the cause of death was considered to be circulatory in origin, either strokes, coronary occlusion, or heart failure. There was no significant difference in obesity between those who died and those still alive, and there were no predictive variables for premature death. More than the expected numbers of patients who died had UPD.
- Our findings suggest that a thorough heart survey is required in the long term management of PWS.

**Abbreviations:** BMI, body mass index; FISH, fluorescence in situ hybridisation; ID, imprinting defect; PWS, Prader-Willi syndrome; UPD, uniparental disomy
All patients had standard clinical cardiovascular assessment for blood pressure and auscultation. Food intake, exercise output, and living conditions were assessed. Strict management guidelines included a restrictive diet (1000–1200 kcal/day) and regular daily exercise, to be recorded on a standard form. Very strong emphasis was placed on regular daily exercise.

At subsequent PWS clinics, each patient was reviewed individually, and then all attended a one hour group session. This has an educational component with discussion of appropriate food intake, exercise, body awareness, hygiene, and self care. Physical activity and socialisation within the group were encouraged. Those patients who have achieved weight loss were 18 female and 18 male patients. The mean age of patients on admission was 26 years (range 14–48 years).

The three longest standing patients have attended on 54, 53, and 49 occasions, whereas four have attended only once. There were 18 female and 18 male patients. The mean age of patients on admission was 26 years (range 14–48 years).

The height, weight, BMI on admission, and other variables are shown in tables 1 and 2. There were no significant sex differences in age, weight, or BMI. Female patients were shorter than male patients (p=0.002). One patient (F8) had been on an appetite suppressant at the time of admission. No patient had been on growth hormone at any time. No patient had an appetite suppressant at the time of admission. No patient had been on growth hormone at any time.

All patients had PWS established by a DNA test. The mechanism was undetermined in five, that is, methylation was positive, FISH was non-deleted, but further work up was not done. It is likely that these patients had UPD, but they have been excluded from correlations based on genetic mechanisms. Of the remaining 31 patients, the mechanism was paternal deletion in 22 (71%) (10 female and 12 male patients), UPD in eight (26%) (four women and four men)’ and an imprinting defect in one woman. On admission, the mean age of the patients with deletion was 23.6 years (range 15–44) and with UPD it was 26.75 years (range 18–34) (p=0.5).

On admission, the mean BMI for those with deletion was 36.5 m²/kg (range 29–52.2) and for those with UPD it was 43.8 m²/kg (range 35–56.5) (p=0.03). Most patients (21/36 (58%)) were in obesity class III (BMI ≥40) whereas 10 (28%) were in obesity class II (BMI 35–39.9), that is, 31/36 (86%) were significantly obese. One patient was in obesity class I (BMI 30–34.9) and four patients were pre-obese (BMI 25–29.9). Diabetes was present in seven patients (18%); 4/7 had deletion (57%) and 3/7 had UPD (43%) (p=0.5). Skin picking was common, manifest in 30/39 patients (15/19 female (79%) and 15/20 male patients (75%)). Lymphoedema was present in 14/36 (39%) (in 10/18 female (55.3%) and 4/18 male patients (22%)). All patients gave a history of sleep apnoea at some time; sleep apnoea was present in 4/4 tested in the sleep laboratory. Eleven patients (30.5%) were known smokers but it was not possible to obtain an accurate figure for the number of cigarettes smoked each day. At least one episode of psychiatric illness, necessitating consultation and treatment by a psychiatrist, occurred in 10 patients (28%). Of these, one had an imprinting defect, five were deleted, and four had UPD. One patient (F8) had osteoporosis and had hip replacement surgery at the age of 32. No patient was capable of independent living, but the level of care and supervision varied. Three patients lived in a dedicated PWS home, 15 patients lived in the family home with one or both parents (15/36 (42%)), and

### Table 1 Characteristics of patients still living

<table>
<thead>
<tr>
<th>ID</th>
<th>Age (oa)</th>
<th>Wt (oa)</th>
<th>BMI (oa)</th>
<th>Genetic mechanism</th>
<th>Diabetes</th>
<th>Psych illness</th>
<th>Smoking</th>
<th>Years of FU</th>
<th>Alive age</th>
<th>Last wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>14</td>
<td>66.7</td>
<td>28.9</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>19</td>
<td>105.4</td>
</tr>
<tr>
<td>F2</td>
<td>15</td>
<td>62.2</td>
<td>32.7</td>
<td>Del</td>
<td>y</td>
<td></td>
<td></td>
<td>9</td>
<td>24</td>
<td>114.7</td>
</tr>
<tr>
<td>F3</td>
<td>15</td>
<td>79.1</td>
<td>40.4</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>19</td>
<td>79.1</td>
</tr>
<tr>
<td>F4</td>
<td>23</td>
<td>62.2</td>
<td>33.6</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>y</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>F5</td>
<td>25</td>
<td>142</td>
<td>79.2</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>y</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>F6</td>
<td>26</td>
<td>79.5</td>
<td>38.3</td>
<td>Del</td>
<td>y</td>
<td></td>
<td></td>
<td>2.5</td>
<td>36</td>
<td>65.9</td>
</tr>
<tr>
<td>F7</td>
<td>27</td>
<td>66</td>
<td>34.2</td>
<td>UPD</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>34</td>
<td>74.7</td>
</tr>
<tr>
<td>F8</td>
<td>34</td>
<td>102</td>
<td>44.7</td>
<td>UPD</td>
<td>y y</td>
<td></td>
<td></td>
<td>10</td>
<td>44</td>
<td>98.1</td>
</tr>
<tr>
<td>F9</td>
<td>36</td>
<td>83.6</td>
<td>38.7</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>39</td>
<td>76</td>
</tr>
<tr>
<td>F10</td>
<td>38</td>
<td>68.3</td>
<td>37.5</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td>35</td>
<td>66.4</td>
</tr>
<tr>
<td>F11</td>
<td>39</td>
<td>74.3</td>
<td>35.3</td>
<td>ID</td>
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<td></td>
<td></td>
<td>5.5</td>
<td>44</td>
<td>72.1</td>
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<tr>
<td>F12</td>
<td>48</td>
<td>90.8</td>
<td>46.7</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>50</td>
<td>90.8</td>
</tr>
</tbody>
</table>

F, female; M, male; oa, on admission; wt, weight; psych, psychiatric; FU, follow up; age is in years; weight is in kg; del, deletion; ID, imprinting defect; UPD, maternal uniparental disomy; y, yes; * insulin dependent; under last wt, weight in bold is gain since admission, weight in italics is loss since admission.

Patient ID F11a is in Buiting et al. 7.
the remaining 18 patients (50%) lived in hostel accommodation or other supervised non-PWS group home. All the patients had periods of living at home interspersed with supervised care during this 10 year period and most patients living away from home visited family at weekends.

Clinical progress over the 10 years fluctuated for all patients, with periods of weight loss interspersed with periods of weight gain. One patient (F8) (table 1) with UPD showed a 30 kg weight fluctuation several times over a six year period, depending on living conditions, with the least weight recorded (72.3 kg) when living in a restricted environment. Patient F2, with a weight of 62.2 kg on admission at age 15 years, weighed 129 kg at the age of 20. Exercise charts showed that many patients were able to maintain a regular routine of, for example, walking, but strict supervision and encouragement were needed to achieve this.

Deaths
Ten patients have died, with a mean age at death of 33.2 years (range 20–49 years). In comparing those who died with those still alive (tables 1 and 2), there were no significant differences between the two groups for sex (six female patients, 33% died; four male patients, 22% died), the frequency of diabetes, weight gain or weight loss, exercise compliance, obesity class on admission, living conditions, smoking, or psychiatric illness. Among those extremely overweight on admission (BMI over 50) 4/26 are alive (15%) compared with 2/10 (20%) with UPD (which is most likely), then the trend is maintained, with 5/10 with UPD among those who died (50%) compared with 8/26 among those alive (31%) (p<0.05). Thus UPD seems to be an independent risk factor for death in the young adult age range in PWS.

There was a significant difference when comparing the genetic mechanisms between the two groups, 5/9 (56%) with deletion died compared with 17/22 with deletion still alive (77%); 4/9 (44 %) with UPD died compared with 4/22 (18%) with UPD still alive (p<0.05). The numbers in each cohort are small; if we assumed that those with unknown mechanisms had UPD (which is most likely), then the trend is maintained, with 5/10 with UPD among those who died (50%) compared with 8/26 among those alive (31%) (p<0.05). Thus UPD seems to be an independent risk factor for death in the young adult age range in PWS.

The cause of death is shown in table 2. Overall, the cause of death was cardiopulmonary disease in 6/10 patients, 7/10 patients died unexpectedly, and in five patients death was sudden. In only three patients was the illness before death prolonged, patients F14, F17, and M15. In patients F13 and M16, the cause of death was not precisely determined. Postmortem examinations were performed on two patients, M16 (non-contributory findings) and M17 (he had rectal bleeding, which may have resulted from skin picking; postmortem showed a singular rectal ulcer with rectal prolapse and confirmed cardiorespiratory disease).

**DISCUSSION**

The patients in our study form a unique source of information on the natural history of PWS established by DNA testing, managed optimally in an informed state of the art clinic over a 10 year period. Other sources of natural history data, from case reports, reviews of clinic patients, reviews of patients in institutions, or population studies, have shown a high morbidity among adults with PWS, but the care has varied considerably and mostly a genetic diagnosis was not made. We confirm here the continuing high morbidity, even with consistent supportive optimal management.

Although it is difficult to consider any death in a group of patients with a known pre-morbid disease as totally unexpected, death may still be considered as unpredictable at the time it occurred, and this applied to most patients with PWS followed up at our clinic. Gross obesity is known to have serious complications affecting the cardiovascular and respiratory systems, which was the cause of death in most of our patients. The age of onset of coronary artery disease in PWS is not known but there is a report of severe disease, detected by imaging, already present in a 26 year old patient. Our data also point to early onset coronary artery disease in PWS.

Two patients had achieved significant weight loss, all were doing some exercise, and there were no additional diseases unrelated to obesity comorbidity among these patients, which could have compromised health further. One patient (M17), with rectal bleeding, had lost significant weight, had psychiatric illness, and smoked. Severe respiratory problems seem to be a cause of sudden unexpected death in infants and young children with PWS. In view of our findings, it is our intention to alter clinical practice to include electrocardiography and echocardiography on all patients at entry to the clinic and at defined intervals thereafter.

Although the numbers are small, a factor among the deaths seen in our study has been the effect of genotype. The patients with UPD overall were not heavier than the deleted patients when first seen, and followed a similar path of fluctuating control over the time period, but nevertheless were more likely to die. The search for clinical differences between those with deletion and those with UPD has not yielded consistent findings (apart from hypopigmentation in deletion patients), but

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**Table 2 Characteristics of patients who died**

<table>
<thead>
<tr>
<th>ID</th>
<th>Age (oa)</th>
<th>Wt (oa)</th>
<th>BMl (oa)</th>
<th>Genetic mechanism</th>
<th>Diabetes</th>
<th>Psych illness</th>
<th>Smoking</th>
<th>Years of FU</th>
<th>Age at death</th>
<th>Last wt</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>F13</td>
<td>17</td>
<td>101</td>
<td>42.6</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>22</td>
<td>101</td>
<td>Not determined, sudden collapse, died in hospital</td>
</tr>
<tr>
<td>F14</td>
<td>26</td>
<td>129</td>
<td>52.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>27</td>
<td>141</td>
<td>Pneumonia, died at home</td>
</tr>
<tr>
<td>F15</td>
<td>30</td>
<td>86</td>
<td>42.7</td>
<td>UPD</td>
<td>y</td>
<td></td>
<td>y</td>
<td>1</td>
<td>32</td>
<td>82</td>
<td>Profound hypoglycaemia of sudden onset, died in nursing home</td>
</tr>
<tr>
<td>F16</td>
<td>32</td>
<td>122</td>
<td>51.5</td>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>39</td>
<td>133</td>
<td>Coronary occlusion, sudden, died at home</td>
</tr>
<tr>
<td>F17b</td>
<td>33</td>
<td>85</td>
<td>41.5</td>
<td>UPD</td>
<td>y*</td>
<td></td>
<td>y</td>
<td>8</td>
<td>42</td>
<td>73</td>
<td>Several small strokes over a month, died in nursing home after a massive stroke</td>
</tr>
<tr>
<td>F18</td>
<td>38</td>
<td>88</td>
<td>38.9</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>40</td>
<td>96</td>
<td>Pulmonary embolus, sudden death in group home</td>
</tr>
<tr>
<td>M15c</td>
<td>18</td>
<td>91</td>
<td>32.7</td>
<td>UPD</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>20</td>
<td>130</td>
<td>Cardiac and respiratory failure, deteriorating over 3 months, died at home</td>
</tr>
<tr>
<td>M16</td>
<td>19</td>
<td>81</td>
<td>34.1</td>
<td>Del</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>24</td>
<td>73</td>
<td>Not determined, sudden collapse with unconsciousness, died in hospital</td>
</tr>
<tr>
<td>M17</td>
<td>28</td>
<td>102</td>
<td>45.3</td>
<td>UPD</td>
<td>y</td>
<td></td>
<td>y</td>
<td>9</td>
<td>37</td>
<td>66</td>
<td>Postoperative (complicated rectal surgery)</td>
</tr>
</tbody>
</table>

For abbreviations see table 1. Patient ID; F17b is in Smith and Noel; M15c is in Lamb and Johnson.

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studies of psychotic disease in adults have also shown more UPD than expected. A hypothesis to explain these findings is that another gene(s) on chromosome 15 is maternally associated with morbidity and mortality in adults with PWS.

Complications associated with obesity, including cardiopulmonary disease, are considered to be the main risk factors. Other factors also contribute, such as hypotension, decreased pain sensation, sleep apnoea, diabetic complications, and obsessive behaviour. It has been shown that patients with PWS can lose weight in the short term on medication, but no studies of long term weight reduction have appeared. No other study has followed up a cohort of patients for a long period, as we have done, and to date it has not been shown that improved weight control lengths life in PWS. Long term weight reduction is a major goal of PWS management, but in our cohort consistent weight reduction was difficult to achieve. Strict supervision in the living environment seems to be of major benefit, accompanied by positive encouragement and awards.

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REFERENCES
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