Prader Willi Syndrome

Background

Prader Willi Syndrome (PWS) is a complex medical condition. Newborns with PWS are typically severely hypotonic and feed poorly. Their development is delayed and they have hypogonadism, typical facial features and excessive sleepiness. Behavioural difficulties, especially relating to food, and obesity related problems, develop in childhood and have a large impact on the family. PWS is a genetic disorder and an abnormality of chromosome 15 is seen in virtually all patients. DNA testing is now commonly used to identify this abnormality and confirm the clinical diagnosis of PWS.

Objectives

- To ascertain the incidence of PWS and the mean age of diagnosis
- To estimate how often DNA testing is used in making the diagnosis and the methods used
- To establish whether different PWS phenotypes are associated with different genetic abnormalities

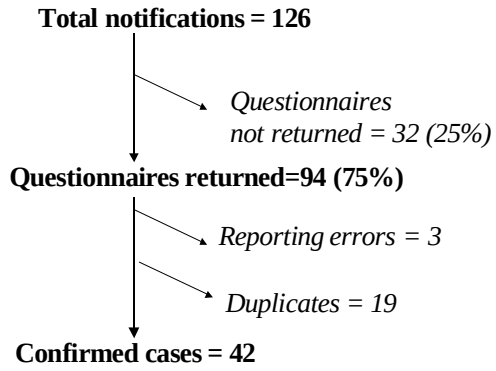
Case definition

Any child less than 15 years seen in the last month with newly diagnosed Prader-Willi Syndrome. Diagnosis may be made either clinically or following genetic investigation (karyotype, FISH test or methylation test).

Results and discussion

Between January 1998 and December 2000, the APSU received 126 notifications of PWS. From these notifications, 94 (75%) questionnaires were returned. Forty-two children were confirmed with newly diagnosed PWS. Nineteen cases were duplicate reports and 33 were errors (Figure 7). The majority of errors were children diagnosed outside the study period (prevalent cases). Based on 42 confirmed cases, the reported incidence of PWS for the study period was estimated as 0.4/100 000 (95% CI 0.3-0.5) children aged <15 years.

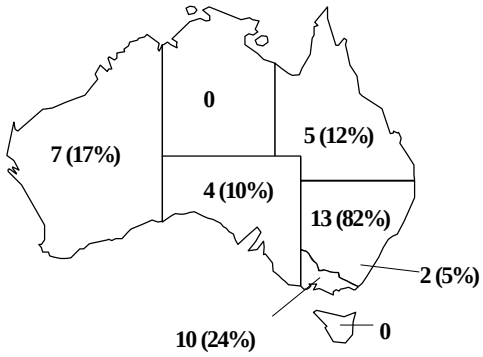
Figure 7 PWS notifications, Jan 1998-Dec 2000



Nationwide distribution of patients

Data was available for 41 of the 42 confirmed cases. Their distribution by state or territory is shown in Figure 8.

Figure 8 Geographic distribution of confirmed cases of PWS, 1998-2000



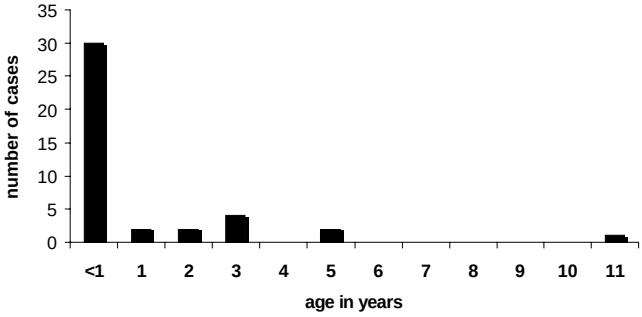
Clinical features of PWS

The major and minor clinical features in children with PWS, according to age, is shown in Table 15. Twenty-six children were male and 15 were female. The age at diagnosis ranged from one day to eleven years, with over 70% diagnosed before twelve months of age (Figure 9).

Table 15 Clinical features of PWS by age, Jan 1998-Dec 2000

Clinical features	Age < 1yr	Age > 1yr
Major features		
Severe neonatal hypotonia	25/30 (83%)	6/11 (55%)
Unusual facial features	26/30 (87%)	8/11 (73%)
Never breastfed	18/30 (60%)	4/11 (36%)
Undescended, small testes	21/30 (70%)	7/11 (63%)
Minor features		
Decreased fetal movement	16/30 (53%)	4/11 (36%)
Breech presentation	5/30 (17%)	5/11 (46%)
Polyhydramnios	2/30 (7%)	1/11 (9%)
Excessive sleepiness	15/30 (50%)	5/11 (46%)
Eye abnormalities	9/30 (30%)	2/11 (18%)
Behavioural problems	N/A	4/11 (36%)
Food obsession	N/A	5/11 (46%)
Small hands	10/30 (30%)	6/11 (55%)
Small fee	11/30 (37%)	6/11 (55%)

Figure 9 Age at diagnosis of PWS



Diagnostic testing for PWS

DNA testing was used in all 41 patients. The methods used included:

- *Chromosomal testing: a* routine cytogenetic test used to check for deletions in the patient's DNA
- *Methylation testing:* identifies the absence of the paternal copy of chromosome 15 (q11-13), responsible for PWS
- *Fluorescence in situ hybridisation (FISH):* detects deletions within the PWS region of chromosome 15 (q11-13)

The frequency with which each method was used in the diagnosis of PWS is shown in Table 16. Although chromosomal testing was used in all but four patients, this test is the least specific in identifying patients with PWS and hence should be used in combination with methylation or FISH testing to confirm the diagnosis.

Table 16 Diagnosis of PWS

Diagnostic test	Patients tested
Chromosomal alone	3
Chromosomal + methylation	5
Chromosomal + FISH	13
Chromosomal + methylation + FIS	5
Methylation alone	1
Methylation + FIS	14
Total	**41**

Mechanism of genetic abnormality

The probable mechanism of the genetic abnormality in the 12/41 (29%) children, who had an abnormal methylation test *and* a normal FISH test, is uniparental disomy (UPD). DNA deletion was the probable mechanism in 22/41 (54%) children. Thirteen of these children were identified using chromosomal + FISH testing, two using chromosomal + methylation testing, five using chromosomal + methylation + FISH testing and two using methylation + FISH. For 7/41 (17%) children, the genetic mechanism was unclear. The results were unavailable in four of these cases and in three cases, the tests performed did not allow a mechanism to be defined. Five (12%) children had a muscle biopsy and two of these were abnormal.

Genotype and phenotype correlation

The major and minor clinical features of children with PWS are shown in relation to the genetic mechanism in Table 17. Excessive sleepiness was the only clinical feature that was shown to be significantly more common in patients with uniparental disomy as compared to those with a DNA deletion (Fisher statistic = 5.649; p< 0.017).

Table 17 Clinical features of PWS by genetic mechanism, 1998-2000

Genetic Mechanism	UPD	Deletion	Unknown
Mechanism frequency	12(29%)	22(54%)	7 (17%)
Males	8(67%)	15(68%)	3(43%)
Females	4(33%)	7(32%)	4(57%)
Major Clinical features			
Severe neonatal hypotonia	8(67%)	16(73%)	7(100%)
Unusual facial features	9(75%)	20(91%)	5(71%)
Never Breastfed	8(67%)	10(46%)	4(57%)
Hypogonadal	9(75%)	17(77%)	2(29%)
Minor Clinical Features			
Decreased Fetal movements	6(50%)	11(50%)	3(43%)
Breech/ transverse presentatio	4(33%)	5(23%)	3(43%)
Polyhydramnios	1(8%)	2(9%)	0
Excessive sleepiness	9(75%)	7(32%)	4(57%)
Eye abnormalit	1(8%)	6(27%)	4(57%)
Behavioural problems	3(25%)	1(5%)	0
Food related problems	2(17%)	2(9%)	1(14%)
Small hands	4(33%)	8(36%)	4(57%)
Small feet	6(50%)	7(31%)	4(57%)
Other features			
Caesarean Section delivery	8(67%)	8(36%)	2(29%)
Resuscitation at birt	5(42%)	4(18%)	2(29%)
Hypopigmentation	3(25%)	7(31%)	2(29%)

Conclusion

Our study provides the first estimate of a national incidence of PWS confirmed by genetic testing. This estimate (0.4/100 000 children aged <15 years) is lower than previous estimates of national prevalence of PWS, based on clinical assessment. Although under-ascertainment is possible, the condition may also have previously been over diagnosed clinically. Over 70% of patients reported to the APSU were diagnosed during the first year of life.

DNA testing of some form had been performed on all 41 children with PWS. We recommend that the methylation test, believed to be the "gold-standard" in PWS diagnostic tests, should be performed first, followed by FISH. Use of these two tests in combination will also help identify

the genetic mechanism in children with PWS.
This study has clearly identified the frequency of the major and minor clinical features of PWS. Excessive sleepiness is the only PWS phenotype that was significantly associated with a particular genetic mechanism. However, the sample size was small (34 had UPD or a DNA deletion) and a larger group of children with PWS needs to be studied to support this finding.

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