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Birth prevalence of Prader-Willi syndrome in Australia

A Smith, J Egan, G Ridley, E Haan, P Montgomery, K Williams, E Elliott

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Early genetic testing for Prader-Willi syndrome (PWS) relies on recognition of the typical clinical features. In neonates with PWS, notable hypotonia, hypogonadism, and poor feeding are the main manifestations. In later childhood, features include gross obesity, hyperphagia, dysmorphic facial features, short stature, micromelia, and mental handicap. Without genetic testing, under diagnosis occurs in young children and over diagnosis occurs in obese retarded adolescents. If the diagnosis is missed in infancy it may be delayed into adulthood.

Genetic mechanisms resulting in the PWS phenotype include paternal deletion of the imprinted region on chromosome 15(q11–13), maternal uniparental disomy, or an imprinting defect for this region. Methylation analysis will accurately diagnose PWS, and fluorescence in situ hybridisation (FISH) and DNA polymorphisms will identify the mechanism of the genetic abnormality.

Inclusion in previous studies of individuals without genetic confirmation of the diagnosis of PWS and with ‘atypical PWS’, is likely to have led to over estimation of the frequency of PWS. No reliable estimates of birth prevalence are available for PWS from prospective studies. All published studies examined prevalence or estimate incidence retrospectively.

In this paper we report infants diagnosed with PWS in Australia over a three year period, the method of diagnosis, and provide an estimate of birth prevalence.

METHODS

Infants diagnosed with PWS were reported to the Australian Paediatric Surveillance Unit (APSU) between January 1998 and December 2000 inclusive by paediatricians and child health specialists. Clinicians on the APSU mailing list were asked to report ‘any child less than 15 years of age, seen in the last month with newly diagnosed Prader-Willi syndrome, in whom the diagnosis was made either clinically or following genetic investigation’. Clinicians were provided with the internationally recognised clinical diagnostic criteria for PWS. Clinicians reporting cases were then sent a reply paid questionnaire, requesting de-identified information including perinatal/neonatal history, clinical features, demographic data, growth, and genetic tests. Children diagnosed outside the study period, who had another diagnosis or were duplicate cases were excluded. In this report we have included only children diagnosed under the age of 1 year. Descriptive and comparative analyses were performed using SPSS for Windows version 10 and Epi Info version 6. Birth prevalence estimates and 95% confidence intervals were calculated using Stat Exact, and population data from the Australian Bureau of Statistics was used for the number of live births during the study period. The study was approved by the Children’s Hospital at Westmead Research Ethics Committee.

RESULTS

In the three year study period 126 notifications of children with PWS were received. Questionnaires were returned providing detailed information on 94 (75%) cases notified. Nineteen notifications were duplicates and 33 were reporting errors. In total, 42 cases of PWS were confirmed in children under 15 years. Thirty (71%) of these were infants. The median age of the infants at diagnosis was 1 month (interquartile range 0.51–4.98 months) and 18 (60%) of these were males. DNA testing, including methylation, FISH, and DNA polymorphisms confirmed the diagnosis of PWS in all infants. A deletion was identified in 21/30 (70%) infants and uniparental disomy in three (10%). In six infants the mechanism for PWS was not established; the methylation test was positive and FISH was not deleted, but no further testing was done. On the basis of the 30 cases diagnosed in infancy, the birth prevalence was 4 per 100 000 live births (95% CI 2.7 to 5.7) or ∼1/25 000 live births per annum.

DISCUSSION

The first attempt to estimate the prevalence of PWS, in 1968, involved identification of known cases in a small, well defined catchment area, and found a low frequency—1/280 000 males. Prevalence figures reported since then have varied widely depending on the population sampled and the study design. The most recent population based study, from a region in the UK, found a minimum prevalence of 1/52 000 and estimated a minimum birth incidence of 1/29 000. DNA studies had not been performed in all these patients. Unlike previous studies, PWS was confirmed by DNA testing in all children included in our report. Thus, we provide the first estimate of a national birth prevalence for DNA proven PWS. The rate of 1 case per 25 000 live births in Australia is comparable to the rate reported in the UK study.

We acknowledge that our figure is a minimum estimate of birth prevalence. Although the mean monthly return rate of cards to the APSU was 97% during the study period, a questionnaire was returned for 75% of notifications of children under 15 years. We have no information on the other 12 (25%) notifications, some of which may be true infant cases. However, cross checking with several laboratories throughout Australia did not identify additional cases of PWS of any age. Indeed, a considerable number of duplicate reports were received for some cases. Another potential reason for under estimating birth prevalence is that PWS may be missed clinically in infancy and not be diagnosed until well into adulthood.

There is only one other published series of PWS in Australia. In a group of 32 patients diagnosed clinically in Sydney in 1989, the age at diagnosis ranged from 1 week to 36
years with a mean of 3.8 years for males and 8.8 years for females. This contrasts with our study, in which 71% of reported cases were diagnosed in the first year of life and all were confirmed by genetic testing.

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**IMAGES IN PAEDIATRICS**

A Rapunzel with a difference

A n 8 year old girl with a severe language disorder and a background of fetal valproate syndrome presented with a three month history of abdominal pain, significant weight loss, and anorexia. Routine bloods and an abdominal ultrasound were normal. Upper gastrointestinal endoscopy revealed a mass of hair obstructing the pylorus with its extension into the duodenum (fig 1) necessitating surgical removal. A barium meal revealed a filling defect in the stomach (fig 2).

Trichobezoars are composed of huge amounts of entwined hair and undigested food. This forms an obstructive foreign body. They can extend into the small intestine, with a tail (Rapunzel syndrome). 1–3

Trichotillomania (pulling at one’s own hair) and trichophagia are closely related and can lead to a trichobezoar. They predominantly affect females in early childhood or adolescence. 5, 7 Our patient had developed a bald patch due to obsessive hair pulling. Trichobezoars cause abdominal symptoms, such as postprandial fullness, intermittent vomiting, and abdominal pain. Surgery is indicated to relieve obstruction and pressure necrosis. 9 A multidisciplinary approach should be adopted to prevent recurrence. In patients with learning difficulties and gastrointestinal symptoms a low threshold for upper gastrointestinal endoscopy should be maintained.

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