NIH Public Access
Author Manuscript
Am J Ment Retard. Author manuscript; available in PMC 2008 June 8.

Published in final edited form as:
Am J Ment Retard. 2006 May ; 111(3): 193–198.

Mortality in Prader-Willi Syndrome

Stewart L. Einfeld and **Sophie J. Kavanagh**
University of New South Wales (Sydney, New South Wales)

Arabella Smith and
Children's Hospital at Westmead (New South Wales)

Elizabeth J. Evans
University of New South Wales

Bruce J. Tonge and **John Taffe**
Monash University (Clayton, Victoria)

Abstract

Persons with Prader-Willi syndrome have been known to have a high mortality rate. However, intellectual disability, which usually accompanies Prader-Willi syndrome, is also associated with a higher mortality rate than in the general population. In this study, the death rates in a longitudinal cohort of people with Prader-Willi syndrome are compared with those for an epidemiologically derived control sample of people with intellectual disability from other causes. We found that those with Prader-Willi syndrome had a higher mortality rate than did controls. After the protective effect of mild intellectual disability or average intellectual function was accounted for, the hazard ratio for Prader-Willi syndrome versus controls was 6.07. Obesity and its complications were factors contributing to the mortality identified in this study.

Evidence suggests that Prader-Willi syndrome carries a risk of significant morbidity and mortality. Whittington and colleagues (2001) calculated an approximate death rate of 3% per year for those with Prader-Willi syndrome compared to that of 1% per year for the general population. Smith, Loughnan, and Steinbeck (2003) followed-up 36 adults with genetically determined Prader-Willi syndrome who attended a clinic in Sydney; 28% died during the 10-year period of follow-up.

Causes of death in the Prader-Willi syndrome population have been reported in both children and adults (Nordmann, Eiholzer, l'Allemand, Mirjanic, & Markwalder, 2002; Oiglane, Ounap, Bartsch, Rein, & Talvik, 2002; Schrander-Stumpel et al., 2004; Schrander-Stumpel, Sijstermans, Curfs, & Fryns, 1998; Stevenson et al., 2004; Van Vliet, Deal, Crock, Robitaille, & Oligny, 2004; Vogels et al., 2004; Zaglia, Zaffanello, & Biban, 2005). Schrander-Stumpel et al. assessed the causes of death in 27 people with Prader-Willi syndrome who were not on growth hormone treatment. They noted that causes of death in infants and children included respiratory illness and sudden death associated with dysregulation of temperature, whereas death in adults was associated with obesity and its complications, including cardiovascular problems, diabetes mellitus, sleep apnea, and hypertension. Gastric dilation was also observed in adults. Vogels et al. (2004) reported a similar difference in causes of death in childhood and adulthood. Mortality in children is usually sudden and associated with respiratory infection and high temperature, whereas the cause of death in adults is circulatory or respiratory.

Requests for reprints should be sent to Stewart L. Einfeld, Primrose House, 190 Russell Ave., Dolls Point, NSW, 2219, Australia. E-mail: s.einfeld@unsw.edu.au.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In recent reports investigators have shown that growth hormone treatment, although having some positive outcomes in relation to decreasing weight for height index values and body fat mass (Allen & Carrel, 2004; Eiholzer & Whitman, 2004), may also be associated with sudden death in individuals with Prader-Willi syndrome (Sacco & Di Giorgio, 2005; Van Vliet, Deal, Crock, Robitaille, & Oligny, 2004). Further studies are needed on the possible association between growth hormone and sudden death.

However, intellectual disability is also characterized by increased risk of death compared to the general population (Forsgren, Edvinsson, Nystrom, & Blomquist, 1996; Hollins, Attard, von Fraunhofer, McGuigan, & Sedgwick, 1998; McGuigan, Hollins, & Attard, 1995). Forssman and Akesson (1970) reported the mortality rate for those with mild intellectual disability to be 1.7 times that of individuals in the general population. Prader-Willi syndrome is usually associated with mild intellectual disability, but IQs can vary from average function to moderate intellectual disability (Cassidy, Dykens, & Williams, 2000; Greenswag, 1987).

Given that high mortality rates have been reported in those with Prader-Willi syndrome, and in those with intellectual disability in general, it remains unclear whether Prader-Willi syndrome increases the risk of death beyond the risk associated with intellectual disability. Such information would assist in planning the best targets for health promotion efforts for individuals with Prader-Willi syndrome and in providing more accurate information on prognosis.

Method

Participants were recruited in 1989, as part of the Australian Child to Adult Development Study (ACAD). This study has two main cohorts: an epidemiological group (control group, described below) and a cohort of young people with syndrome-specific diagnoses, including Prader-Willi syndrome.

Prader-Willi Syndrome Group

Participants with Prader-Willi syndrome were recruited from specialist genetics clinics and parents' support associations. None of the Prader-Willi syndrome participants were infants when recruited to the ACAD study. Only the participants with a confirmed genetic diagnosis of Prader-Willi syndrome were included in the analyses. Genetic subtypes of the Prader-Willi syndrome group are presented in Table 1. None of these participants had been treated with growth hormone. The mean age at entry to the ACAD study was 17.7 years (*SD* = 8.1, range = 31.8)

Control Group

In 1989-1990, we identified all young people 4 to 18 years of age who had intellectual disability and lived in a number of geographically defined census regions in the Australian states of New South Wales and Victoria (Einfeld & Tonge, 1996a). Participants from these regions are a representative sample of young people with moderate and severe intellectual disability. In keeping with other population samples, those with mild intel-lectual disability are underrepresented. This is because some of these individuals have little dysfunction, so are not identified by service agencies. Details of this control group are provided in Einfeld and Tonge (1996a, 1996b). A detailed survey of the causes of intellectual disability in this cohort was reported by Partington, Mowat, Einfeld, Tonge, and Turner (2000). Briefly, causes of intellectual disability were divided into three main categories: known diagnosis (45%), descriptive diagnosis (28%), and unknown diagnosis (28%). A *known diagnosis* was defined as chromosomal (21%), for example, Down syndrome; monogenic (8%); either autosomal or X-linked; or environmental (16%). A *descriptive diagnosis* was defined as neurological (18%), such as cerebral palsy;

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

syndromic (4%); or autistic (6%). An *unknown diagnosis* was either nonsyndromic mental retardation (19%) or nonsyndromic with at least one other clinical abnormality (8%). A significant male excess in the sample was observed, particularly in the autistic, nonsyndromic groups, and those with an X-linked monogenic disorder. The mean age of the control group at entry to the ACAD study was 12.1 years (*SD* = 4.4, range = 18.3). The meanage of the control group with mild intellectual disability or average IQ was 11.6 years (*SD* = 4.0, range = 16).

Procedure

As part of the fourth wave of data collection in the ACAD study, questionnaires were mailed to all participants. Initial nonresponders were followed-up with a telephone call or letter from the researchers. Notifications from caregivers of deaths in the control group and in the Prader-Willi syndrome group were recorded. Cause of death was obtained from coroners' reports when possible.

Data Analysis

Cox proportional hazards regression in StataSE/8 (StataCorp, 2004) was used to estimate the hazard ratio (ratio of risks of death in Prader-Willi syndrome and control group), controlling for level of intellectual disability (moderate or below [the reference group] and mild or above). Survival time was age at death or age at end of followup (September 9, 2003), 13 to 14 years after the initial recruitment. Adjustment was made for the period at risk before the beginning of observation (i.e., for age at entry to the study).

Results

Information on status as alive or deceased and level of intellectual disability was available for 93% of the control group. Participation rate for the Prader-Willi syndrome group was 94%. Sample characteristics for both groups are presented in Table 2.

All 6 of the deaths that occurred in the Prader-Willi syndrome cohort happened in those with a mild intellectual disability. Only 2 of the 27 deaths reported in the control group were of those with mild intellectual disability. Death rates are presented in Table 3. Deaths in those with Prader-Willi syndrome occurred at a rate about 4 times that of the control group. When we compared the deaths in the Prader-Willi syndrome group to just the control group with mild intellectual disability or average IQ, we found that the Prader-Willi syndrome death rates were greater by a factor of 20. Figure 1 shows the survival rates for the control group (all levels of intellectual disability) and the Prader-Willi syndrome group. Figure 2 shows the survival curves separately, with 95% confidence intervals.

Results of the Cox regression analysis indicated that adjusting for the period of risk already survived at entry to the study, those with Prader-Willi syndrome are 6.07 (95% CI 1.87,19.73) times the risk (hazard) of death of the control subjects, after the protective effect of mild or normal IQ is accounted for. Those with mild or average IQ have a risk hazard ratio of 0.30 (95% CI 0.11, 0.78) compared with those who have moderate, severe, or profound intellectual disability levels, after the elevated risk associated with Prader-Willi syndrome is accounted for.

We also examined the effect of the genetic type of Prader-Willi syndrome, and gender on death rates, using odds ratios. Table 4 shows the gender, Prader-Willi syndrome status, and age of person at death for those with Prader-Willi syndrome. All individuals had mild intellectual disability. There were no significant difference in mortality rates depending on the genetic type of Prader-Willi syndrome or gender. However, the sample size did not offer sufficient power to detect any differences that may have been present.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Discussion

As stated earlier, the control participants underrepresented those with mild intellectual disability in the community. However, as previously described in detail (Einfeld & Tonge, 1996a), those with mild intellectual disability who were included in the control group were likely to be known to services because of an additional problem, such as epilepsy or psychopathology. If anything, they would be expected to have a higher death rate from such added complications than would those with mild intellectual disability in the community. This would have the effect of minimizing the resulting difference between death rates in the Prader-Willi syndrome group and control group.

All of our Prader-Willi syndrome subjects were identified in childhood. Therefore, these mortality rates do not reflect early deaths occurring in those with Prader-Willi syndrome from hypotonia, feeding difficulties, or other infant complications.

Results show the utility of Cox proportional hazards analysis. It is more useful than death rates because it accounts for intellectual disability level as well as Prader-Willi syndrome status and provides an estimate of the protective effect of higher IQ levels.

It would be of considerable interest to establish death rates in larger samples of people with Prader-Willi syndrome of the different genetic subtypes. If rates were found to be substantially different, it would potentially provide new insights into genetic mechanisms underlying appetite control.

Prader-Willi syndrome is a substantial risk factor for death, above the risk related to intellectual disability alone. Those with Prader-Willi syndrome have higher mortality rates than those with intellectual disability in general. They have a much higher estimated mortality ratio than a comparison group with mild or borderline intellectual disability. The pattern of death in those with Prader-Willi syndrome suggests that obesityrelated disease is a likely major risk factor. Management of caloric intake is truly a life-and-death issue for people with this syndrome.

Acknowledgements

This study was supported by the National Health and Medical Research Council Grant 113844.

References

Allen DB, Carrel AL. Growth hormone therapy for Prader-Willi syndrome: A critical appraisal. Journal of Pediatric Endocrinology 2004;17(Suppl 4):1297–1306.

Cassidy SB, Dykens E, Williams CA. Prader-Willi and Angelman syndromes: Sister imprinted disorders. American Journal of Medical Genetics 2000;97C:136–146. [PubMed: 11180221]

Eiholzer U, Whitman BY. A comprehensive team approach to the management of patients with Prader-Willi syndrome. Journal of Pediatric Endocrinology 2004;17:1153–1175.

Einfeld S, Tonge B. Population prevalence of psychopathology in children and adolescents with intellectual disability: I. Rationale and methods. Journal of Intellectual Disability Research 1996a;40 (Pt 2):91–98. [PubMed: 8731466]

Einfeld S, Tonge B. Population prevalence of psychopathology in children and adolescents with intellectual disability: II. Epidemiological findings. Journal of Intellectual Disability Research 1996b; 40(Pt 2):99–109. [PubMed: 8731467]

Forsgren L, Edvinsson SO, Nystrom L, Blomquist HK. Influence of epilepsy on mortality in mental retardation: An epidemiologic study. Epilepsia 1996;37:956–963. [PubMed: 8822694]

Forssman H, Akesson H. Mortality in the mentally deficient: A study of 12,903 institutionalized subjects. Journal of Mental Deficiency Research 1970;14:276–294. [PubMed: 4253022]

Greenswag LR. Adults with Prader-Willi syndrome: A survey of 232 cases. Developmental Medicine & Child Neurology 1987;29:145–152. [PubMed: 3582784]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Hollins S, Attard MT, Von Fraunhofer N, Mcyuigan S, Sedgwick P. Mortality In people with learning disability: Risks, causes, and death certification findings in London. Developmental Medicine & Child Neurology 1998;40:50–56. [PubMed: 9459217]

Mcguigan SM, Hollins S, Attard M. Age-specific standardized mortality rates in people with learning disability. Journal of Intellectual Disability Research 1995;39(Pt 6):527–531. [PubMed: 8746740]

Nordmann Y, Eiholzer U, L'allemand D, Mirjanic S, Markwalder C. Sudden death of an infant with Prader-Willi syndrome-Not a unique case? Biology of the Neonate 2002;82:139–141. [PubMed: 12169838]

Oiglane E, Ounap K, Bartsch O, Rein R, Talvik T. Sudden death of a girl with Prader-Willi syndrome. Genetic Counseling 2002;13:459–464. [PubMed: 12558118]

Partington M, Mowat D, Einfeld S, Tonge B, Turner G. Genes on the X chromosome are important in undiagnosed mental retardation. American Journal of Medical Genetics 2000;92a:57–61. [PubMed: 10797424]

Sacco M, Di Giorgio G. Sudden death in Prader-Willi syndrome during growth hormone therapy. Hormone Research 2005;63:29–32. [PubMed: 15583479]

Schrander-Stumpel C, Curfs LM, Sastrowijo-to P, Cassidy SB, Schrander JJ, Fryns JP. Prader-Willi syndrome: Causes of death in an international series of 27 cases. American Journal of Medical Genetics 2004;124a:333–338. [PubMed: 14735579]

Schrander-Stumpel C, Sijstermans H, Curfs L, Fryns JP. Sudden death in children with Prader-Willi syndrome: A call for collaboration. Genetic Counseling 1998;9:231–232. [PubMed: 9777348]

Smith A, Loughnan G, Steinbeck K. Death in adults with Prader-Willi syndrome may be correlated with maternal uniparental disomy. Journal Of Medical Genetics 2003;40:E63. [PubMed: 12746417]

Statacorp. Stata statistical software: Release 8.2. Author; College Station, TX: 2004.

Stevenson DA, Anaya TM, Clayton-Smith J, Hall BD, Van Allen MI, Zori RT. Unexpected death and critical illness in Prader-Willi syndrome: Report of ten individuals. American Journal of Medical Genetics 2004;124a:158–164. [PubMed: 14699614]

Van Vliet G, Deal CL, Crock PA, Robitaille Y, Oligny LL. Sudden death in growth hormone-treated children with Prader-Willi syndrome. Journal of Pediatrics 2004;144:129–131. [PubMed: 14722532]

Vogels A, Van Den Ende J, Keymolen K, Mortier G, Devriendt K, Legius E. Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. European Journal of Human Genetics 2004;12:238–240. [PubMed: 14679397]

Whittington JE, Holland AJ, Webb T, Butler J, Clarke D, Boer H. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK region. Journal of Medical Genetics 2001;38:792–796. [PubMed: 11732491]

Zaglia F, Zaffanello M, Biban P. Unexpected death due to refractory metabolic acidosis and massive hemolysis in a young infant with Prader-Willi syndrome. American Journal of Medical Genetics 2005;132a:219–221. [PubMed: 15523631]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

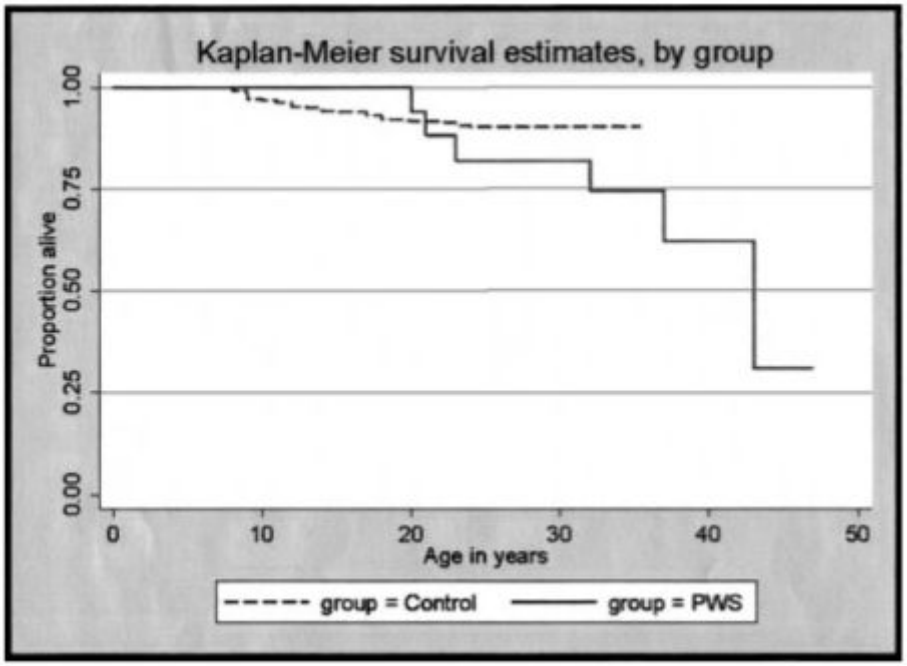

Figure 1.
Kaplan-Meier survival estimates for control group and Prader-Willi syndrome group.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

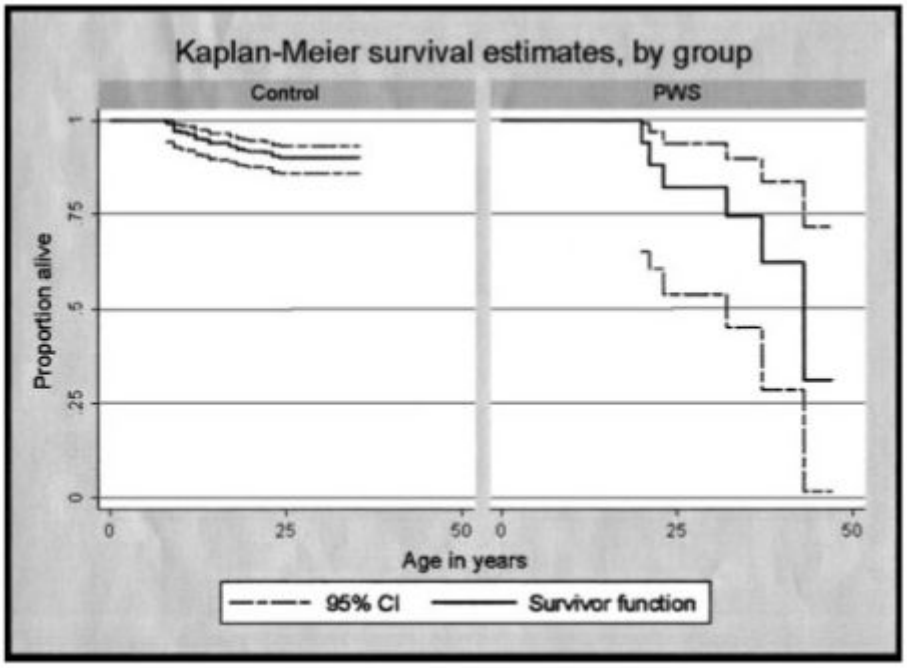

Figure 2.
Kaplan-Meier survival estimates for control group and Prader-Willi syndrome group with confidence intervals.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Genetic Subtypes of the Prader-Willi Syndrome Group

Genetic test result	*n*	%
Confirmed Prader-Willi syndrome	37	100
Paternal deletion	18	49
Maternal uniparental disomy	9	24
Imprinting mutation	1	3
Type unknown	9	24

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Sample Characteristics by Group

Characteristic	Control (*n* = 547)		Control with mild ID[a] or average IQ (*n* = 176)		Prader Willi (*n* = 37)	
	n	%	*n*	%	*n*	%
Male	316	58	102	58	23	62
ID[a]						
Average IQ or mild	176	32	176	100	32	86
Moderate	225	41	0	0	5	14
Severe	123	22	0	0	0	0
Profound	23	4	0	0	0	0

[a] Intellectual disability.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 3

Death Rates by Group

IQ	PWS[a]		Control		Deaths per 1000[b]		RR PWS/ Control[c]	95% CI[d] for RR
	No. deaths	*n* group	No. deaths	*n* group	PWS	Control		
All	6	37	27	547	16.4	4.3	3.8	(1.3, 9.5)
Mild	6	32	2	176	19.2	0.9	20.4	(3.6, 206.4)

[a] Prader Willi syndrome.

[b] Person years.

[c] Rate ratio.

[d] Confidence interval.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 4

Prader-Willi Syndrome (PWS) Participants Who Died

Gender	PWS status	Age at death	Cause of death
Male	Maternal uniparental disomy	20	Cardiorespiratory failure 4 weeks, morbid obesity
Female	Paternal deletion	21	Cardiomegaly, morbid obesity
Male	Paternal deletion	23	No death certificate available
Female	Proven PWS, type unknown	32	No death certificate available
Male	Maternal uniparental disomy	37	Adult respiratory distress syndrome, possible sepsis, possible aspiration, right ventricular failure
Female	Maternal uniparental disomy	43	Pneumonia, cerebro vascular accident, diabetes mellitus

Note. All individuals had mild intellectual disability.