European Journal of Public Health, Vol. 17, No. 2, 221–225

doi:10.1093/eurpub/ckl103 Advance Access published on July 19, 2006

The four ages of Down syndrome

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Background: Down syndrome (DS) affects ~1 per 650–1000 live births and is the most common known genetic cause of intellectual disability. A highly significant change in the survival of people with DS has occurred during the last two generations, with life expectancy estimates increasing from 12 to nearly 60 years of age. **Subjects and Methods:** Detailed information on 1332 people in Western Australia with DS was abstracted from a specialist statewide database for the period 1953–2000 and electronically linked with three other state or national health and mortality data sources and the state Birth Defects Registry. **Results:** Over the last 25 years the percentage of women over 35 years giving birth increased from 4.8 to 18.6%, accompanied by an increase in the overall prevalence of DS from 1.1 to 2.9 per 1000 births. Four life stages of DS were identified: prenatal, childhood and early adulthood, adulthood, and senescence. Although pneumonia, or other types of respiratory infections, was the most common cause of death across the entire lifespan, ranging from 23% of deaths in adulthood to 40% in senescence, each life stage exhibited a particular profile of comorbidities. Congenital heart defects were common causes in childhood (13%) and adulthood (23%), whereas in senescence coronary artery disease (10%) and cardiac, renal, and respiratory failure (9%) were leading causes of mortality. **Conclusions:** A major re-appraisal in attitudes towards DS is required to ensure that the medical and social needs of people with the disorder are adequately met across their entire lifespan. In particular, specific recognition of the comorbidities that can arise at different ages is needed, accompanied by the provision of appropriate levels of care and management.

Keywords: comorbidity, data linkage, Down syndrome, life expectancy, life stages, mortality

Introduction

Down syndrome (DS) is diagnosed in ~1 per 650–1000 live births,[1–3] and it the most common known genetic cause of intellectual disability, with an estimated 5500 infants with DS born annually in the United States.[4] Much of the research focus and information published on DS has related to the first decade of life. However, a combination of community living rather than institutional care, early and continuing access to clinical interventions, and overall improvements in population health has had a major positive impact on the lives of people with the disorder.[5] As a result, the survival prospects for people with DS have dramatically improved in developed countries, with 85% of cases born since 1980 living to 10 years of age,[6,7] increasing to >90% among children born after 1990.[7,8] At the same time, the estimated life expectancy of persons with DS has increased from just 12 years in the 1940s[9] to average ~60 years in the present-day populations of developed countries.[8,10]

Major transitions of this type require a substantial reappraisal in thinking, focusing on the medical and social needs of people with DS and their families. Rather than attempt to document and consider these needs across the entire extended DS lifespan, it is more appropriate to investigate the comorbidities and mortality patterns that occur at specific life stages. For the purposes of this study four life stages were separately identified: prenatal, childhood and early adulthood, adulthood, and senescence, with information on comorbidities and mortality drawn for analysis from a long-term, population-based specialist state database in Western Australia.

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Methodology

To complement published studies, an analysis was conducted of people with DS registered by the Disability Services Commission (DSC) of Western Australia (WA), which has been the primary support agency for people with intellectual disability in WA since 1952.[11] The records of 1332 people with DS maintained in the DSC database from 1953 to the end of 2000 were electronically linked with three additional data sources: (i) the WA Cancer Registry, which has recorded all cancer notifications in the WA population since 1981;[12] (ii) the WA Death Registry and the state Coroner's office, which together record all causes of death in Western Australia; and (iii) the National Death Index, which has recorded deaths in all states of Australia since 1980.[13] Information on overall DS survival trends for the WA population from 1980 to 2004 was additionally sourced from the WA Birth Defects Registry, which was established to collect information on birth defects (including DS) occurring in pregnancies and births in WA.[14]

Ethics approval for the study was obtained from the Confidentiality of Health Information Committee at the Department of Health WA, from the Human Research Ethics Committees of the Disability Services Commission and Edith Cowan University, and from the Australian Institute of Health and Welfare.

Results

The prenatal period

During the prenatal period DS pregnancies are associated with an elevated rate of spontaneous loss,[15] in particular among cases detectable by prenatal screening based on biochemical tests and

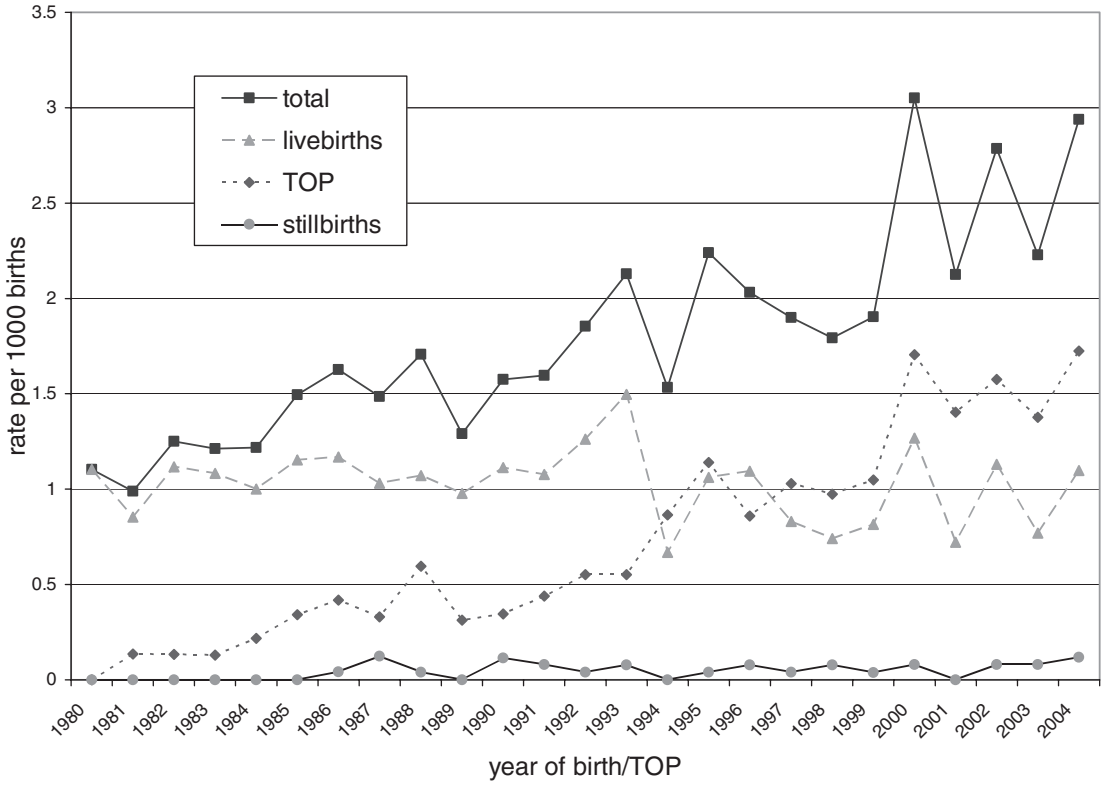

Figure 1 Down syndrome births, stillbirths, and terminations of pregnancy (TOP) per 1000 births in Western Australia 1980–2004.

ultrasound.[16] Although data on spontaneous losses during the first 2 months of pregnancy are unavailable, in a UK study 43% of DS pregnancies detected by chorionic villus sampling at 10 weeks gestation failed to reach term.[17]

Data on births and medical terminations of pregnancy (TOP) for DS have been available from the WA Birth Defects Registry since 1980.[18] The Registry data show that the overall prevalence of DS (live births, stillbirths, and TOP) per 1000 births increased from 1.1 per 1000 births in 1980 to 2.9 per 1000 births in 2004 (figure 1), which paralleled marked changes in maternal age.[19] In 1980, 4.8% of women giving birth in WA were aged 35 years or more but by 2004 this proportion had increased to 18.6% of women, with 11.7% being first-time mothers.[20] The prevalence of stillbirths with DS remained static over the study period, representing ~2.6% of all DS cases, and the numbers of DS live births also remained relatively steady at ~1.0 per 1000 births, although with some inter-year variation. During this time, pregnancy terminations for DS increased steadily in number and proportion and, by 2004, terminations occurred in 59% of DS pregnancies.

Until 1991 maternal age was the only criterion applied in WA to identify women at high risk of a DS fetus. Second trimester maternal serum screening was introduced from 1991, followed in 1999 by first trimester screening based on nuchal translucency and biochemistry. The introduction of first trimester screening could, therefore, have contributed to the increase in the number of DS pregnancies recorded since 1999, with the identification of fetuses that may previously have been lost spontaneously before 20 weeks gestation. Currently, about two-thirds of women in WA elect to have first trimester screening for DS.[21]

Childhood and early adulthood (0–18 years)

DS is associated with a high prevalence of cardiac, gastrointestinal, immunological, respiratory, sensory, and orthopaedic anomalies.[22–25] There is, also, recent evidence to indicate greater susceptibility to fatal sepsis.[26] Data from the WA Birth Defects Registry indicate that between 1980 and 2004, 6.5% of live-born infants with DS died within the first year. This proportion decreased from 13.0% of the live births with DS between 1980 and 1984 to 4.0% of live births with DS in 2000–2004. There is a strong correlation between the presence of congenital heart defects and death during the first 10 years of life,[2,7] but survival into early adulthood is increased significantly if corrective cardiac surgery for congenital heart conditions is performed in early childhood.[27–29]

The combined state and national Death Registries reported 298 deaths among the 1332 individuals with DS registered at DSC between 1953 and 2000. Almost half of these deaths (49.7%) were in persons aged <18 years, with 35.9% in children <5 years of age. The total number of deaths may be underestimated, since some DS infants may have died prior to registration with DSC. There were many assigned causes of death, with pneumonia and other respiratory infections (33.1%) and congenital heart defects (12.8%) the two main categories among the 148 persons who died aged 0–18 years (Table 1). A large majority of these deaths occurred in the 0–5 age group, with 31 deaths attributed to pneumonia and 13 to congenital heart defects.

Children with DS have a >20-fold increased risk of developing leukaemia in childhood,[22–24] and under 5 years of age the sex-standardized incidence ratio for leukaemia is 61.[30–33] Data from the WA Cancer Registry confirmed the very high risk of childhood leukaemia in the study cohort, accounting for 53.8% (14/26) of cancers recorded in people with DS. Twelve of the fourteen cases of leukaemia were diagnosed before 5 years of age and in four cases it was fatal.

Adulthood (19–40 years)

Many age-related disorders in DS commence earlier than in the general population. Analysis of the mortality data from the WA

DSC cohort indicated that 13.1% of the 298 deaths between 1953 and 2002 occurred in the 19–40 year age group. The main causes of death recorded were pneumonia and other respiratory infections (23.1%), cardiac, renal, and respiratory failure (10.2%), cancers (7.7%), cerebrovascular accident (5.1%), and coronary artery disease (2.6%). In 23.1% of cases the cause of death was attributed to a congenital heart defect, although many more individuals were known to have underlying defects of this nature.

Senescence (>40 years)

The phase of life from full maturity to death is characterized by the onset of physiological phenomena with increasing age, including an accumulation of metabolic products and deteriorative changes at the cellular and molecular levels.[34] Substantial individual variation is observed, but in most cases the age at onset is after 65 years. Senescence occurs much earlier in people with DS, as evidenced by symptoms of premature ageing,[35] reduced DNA-repair potential,[36] increased biological age,[37] and early mortality.[8,38–41]

In developed countries many of the current cohorts of people with DS will live to >60 years of age, especially those without congenital heart disease.[31] The DSC cohort data show that 29.9% (89/298) of registered clients were aged >50 years at the time of death, with 25.0% of cases dying between 57 and 62 years and the oldest person aged 73 years.[8] Information on cause of death was available for 97 of the 111 deceased persons >40 years of age. Pneumonia and other respiratory infections were the most common causes of death (39.6%), followed by coronary artery disease (9.9%), cardiac, renal, and respiratory failure (9.0%) cerebrovascular accident (6.3%), and cancers (5.4%). Alzheimer's dementia was listed as a contributory cause of death in only three cases.

Discussion

In Western countries many women are opting to delay childbearing to an age where the risk of a DS pregnancy is significantly raised. Under these circumstances, the prevalence of DS live births is in part determined by the prevailing national legislation on abortion and public attitudes towards medical termination of pregnancy, with religious and specific community beliefs acting as important additional influences. Earlier studies in the USA and UK indicated amniocentesis uptake rates of 79 and 75%, respectively, when a positive DS screening result had been obtained, with 85 and 92% of women in each country choosing termination for a DS pregnancy.[42] A more recent EUROCAT survey has suggested an overall divergence of the live birth prevalence of DS from the rising total prevalence associated with advancing maternal age, although country-specific variation was apparent, e.g. where termination of pregnancy is illegal.[43] This contrasts with countries such as Singapore[44] and Taiwan,[45] where there have been unequivocal, significant falls in the DS live birth rate.

In Western Australia the increasing age at which women are having their first pregnancy, and the wish of some women not to undergo prenatal screening or termination of pregnancy,[46] could explain the essentially stable prevalence of DS births indicated in figure 1, despite the ready availability of screening services. A similar overall situation has been described in the UK, with an increasing prevalence of DS pregnancies over time and, despite an increase in medical terminations, especially in women <35 years of age, no reduction in the number of DS live births has occurred.[47,48] There is, also, an increasingly positive image of DS among health professionals, with marked reductions in the discriminatory treatment previously experienced by people with DS, although further progress is needed.[49,50] Changing public attitudes also are apparent from the more critical approach of research ethics committees to prenatal screening for DS,[51] especially given the higher social competence scores obtained by children with DS by comparison with other genetic forms of intellectual disability.[52]

The age-associated morbidity and mortality patterns of DS that present in adulthood have not been widely discussed in medical literature, in part because of a general lack of information but also the sensitivity of many of the issues involved. In terms of general health, a case–control study in the UK showed that DS females, but not males, were more likely to be overweight or had a higher prevalence of obesity.[53] Similarly, the oral health of DS patients is often poor.[54] Many age-related disease states commence earlier in people with DS than in the general population and ~40% of cases are diagnosed with a thyroid disorder in adulthood.[24,55] Adult-onset epilepsy becomes common after 30 years of age.[24,56,57] Sensory losses are detected in 40–80% of DS individuals, usually related to hearing loss and cataracts. Testicular, liver and stomach cancers are more common as causes of death.[41] Conversely, females with DS appear to be less likely to develop breast cancer, possibly influenced by their shortened life expectancy or earlier menopause,[58] although a protective cell microenvironment that inhibits tumour angiogenesis also has been suggested.[59]

At autopsy, the presence of Alzheimer-type plaques and tangles has been reported in the brains of 7.5% of people with DS as early as the second decade, with a rapid rise in prevalence to 80% of cases by the fourth decade and 100% over 60 years of age.[60] The clinical presentation of Alzheimer disease with neurological changes may not be present at the time of death, but dementia involving memory loss, cognitive decline, and changes in adaptive behaviour have been diagnosed in at least 50% of DS cases >60 years.[61,62] As in the general population, in DS the apolipoprotein E2 allele is also associated with longevity and the preservation of cognitive functioning,[63–65] whereas the ApoE4 allele has an independent and strong relation to early mortality even in non-demented persons with DS.[66]

From a public health perspective the high levels of mortality due to pneumonia and other respiratory infections in both children and adults with DS is noteworthy (table 1). However, the dramatically improved survival figures among the last two

Table 1 Causes of death among people with Down syndrome at different life stages

Cause of death	Childhood and early adulthood (0–18 yr), % (*n*)	Adulthood (19–40 yr), % (*n*)	Senescence (>40 yr), % (*n*)
Congenital heart defects	12.8 (19)	23.1 (9)	0 (0)
Pneumonia and other respiratory infections	33.1 (49)	23.1 (9)	39.6 (44)
Coronary artery disease	1.4 (2)	2.6 (1)	9.9 (11)
Cerebrovascular accidents	1.4 (2)	5.1 (2)	6.3 (7)
Cardiac, renal and respiratory failure	11.5 (17)	10.2 (4)	9.0 (10)
Cancers	3.4 (5)	7.7 (3)	5.4 (6)
Other causes	36.5 (54)	28.2 (11)	29.7 (33)
Total (298 deaths)	100 (148)	100 (39)	100 (111)

generations of people with DS, the increasing frequency with which medical interventions are sought, and greater emphasis on community living, suggest that diseases of adult-onset will rapidly emerge as causes of morbidity and death in future years.

Although it is sometimes assumed that younger cohorts of people with DS will lead healthier lives than their counterparts in previous generations, this optimism seems to be based on access to improved medical technologies, since the adverse health consequences of the disorder are in large part genetic. Given continuing increases in life expectancy, it is equally probable that, in future years, people with DS will present with a higher incidence of adult-onset cancers and non-malignant disorders associated with advanced age. This trend has already been reported, e.g. with arthroplasty successively used to restore mobility to DS individuals with hip disease.[67,68] Therefore, from a wider perspective, it is important that equality of access to health care systems is ensured for people with intellectual disability.[69–72]

This poses challenges for genetic counselling, public education programmes, and for health care delivery systems in general. In the absence of appropriate understanding and assistance for people with DS, and additional help for carers, increasing life expectancy could result in greater emotional and financial burdens. These age-associated problems need to be urgently addressed if the interests of this vulnerable and growing section of society are to be adequately and appropriately met.

Acknowledgements

We wish to thank the Disability Services Commission of Western Australia for continuing support of our research. We also acknowledge the support from the National Health and Medical Research Council Program Grant #353514 and Fellowship (CB) #353628.

Key points

- From 1980 to 2004 the overall prevalence of DS in Western Australia (live births, stillbirths, and TOP) increased from 1.1 to 2.9 per 1000.
- A highly significant change in the survival of people with DS has occurred during the last two generations, improving life expectancy estimates from 12 to nearly 60 years of age.
- DS is associated with particular comorbidities at four distinct life stages: prenatal, childhood/early adulthood, adulthood, and senescence.
- Given their continuing significant increase in life expectancy, in future years people with DS will present with a higher incidence of morbidity, in particular adult-onset cancers and non-malignant disorders associated with advanced age.
- To achieve a high quality of life for people with DS, presenting comorbidities will require rapid detection, accompanied by the provision of appropriate levels of care and management.

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Received 13 January 2006, accepted 18 May 2006