Expectation of life and unexpected death in open spina bifida: a 40-year complete, non-selective, longitudinal cohort study

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AIM The aim of our study was to investigate survival and causes of death in a complete cohort of open spina bifida at the mean age of 40 years.

METHOD We conducted a community-based, prospective study of 117 consecutive infants (50 males, 67 females) with open spina bifida whose backs were closed non-selectively within 48 hours of birth between 1963 and 1971 at Addenbrooke's Hospital, Cambridge, UK. Of those who survived to age 1 year, 89% (82 out of 92) had a cerebrospinal fluid shunt. In 2007, all survivors were surveyed by postal questionnaire backed up by telephone interview. Details of deaths were obtained from the Office for National Statistics, medical records, and autopsy reports, and Kaplan–Meier survival curves were constructed.

RESULTS One in three of the cohort (40/117) died before the age of 5 years. A further 26% (31/117) died during the next 35 years, over 10 times the national average. Half the deaths (16/31) after the age of 5 were sudden and unexpected. All occurred in the community and were followed by a coroner's autopsy. The most frequent causes of these unexpected deaths were epilepsy, pulmonary embolus, acute hydrocephalus, and acute renal sepsis. The prognosis for survival was strikingly poor in those with the most extensive neurological deficit. Only 17% (7/42) of those born with a high sensory level (above T11) survived to the mean age of 40 years, compared with 61% (23/38) of those with a low sensory level (below L3; p=0.001).

INTERPRETATION Doctors and care planners need to be aware that, contrary to previous suggestions, there is continuing high mortality throughout adult life in individuals with open spina bifida, and many deaths are unexpected.

More than 4500 pregnancies in the European Union and 3000 in the USA each year are affected by neural tube defects.[1,2] In parts of India and China the incidence is particularly high: around 6 per 1000 live births[3] compared with 1 per 1000 in Europe.[1] Before use of the cerebrospinal fluid (CSF) shunts in the 1960s, most children with spina bifida and hydrocephalus died in infancy.[4] Neurosurgical intervention increased survival at 1 year from 20% to 80%, but no-one knew what the long-term outcome would be, and, as the children grew older, their physical and intellectual disabilities became more evident.[5–7] Although there have been many reviews of outcome in children and young adults with spina bifida[8–13] data from long-term reviews are sparse and incomplete. In three studies, the maximum age of survivors was less than 25 years,[10–12] and in one cohort 20% were lost to follow-up.[10] It has been widely suggested that, after the initial hazardous years, survival in spina bifida is near normal,[14–16] but there is no empirical evidence to support this. A prognosis for survival that lacks information on the mortality in older individuals may be over-optimistic.

Reliable data on life expectancy and lifestyle in open spina bifida are crucial for parents, clinicians, and care planners. They need an estimate of the likely degree of disability if the child survives, and the prospects for an independent life as an adult. The prerequisite for such predictions is a follow-up into adulthood of every consecutive case treated unselectively from birth after full and detailed examination. In 1963, in Cambridge, UK, a prospective study was set up which fulfilled these requirements. The cohort of 117 consecutive individuals born with open spina bifida has previously been reviewed six times, with no loss to follow-up.[17–21] The aim of this review, conducted in 2007, was to investigate survival and causes of death in a complete and unselected cohort of open spina bifida at the mean age of 40 years.

METHOD

Participants

The cohort comprised 117 consecutive infants (50 males 67 females) with open spina bifida who were treated unselectively from birth in the Neurosurgical Department at Addenbrooke's

Hospital, Cambridge, UK, between 1963 and 1971. After a meticulous neurological examination, their backs were closed within 48 hours of birth.[17] In four infants, the open lesion was found at operation to be a simple meningocele. A cerebrospinal fluid (CSF) ventriculoatrial shunt was inserted when required, i.e. in 89% (82/92) of those who passed their first birthday.

When first surveyed at a mean age of 4 years, the cohort had been classified into four groups according to neurological deficit in terms of sensory level to pinprick recorded in infancy.[17] Sensory level was used as it was found to relate more closely to outcome in terms of mortality and disability than motor or external level, and remained stable over time.[17] It ranged from T5 in the severest cases to no sensory loss in the mildest.

Data collection

In 2007, all survivors and/or their carers were surveyed by confidential postal questionnaire and telephone interview. The protocol was reviewed by the Huntingdon Research Ethics Committee (reference 07/Q0104/11), and survivors or carers gave informed consent. They were asked about health, disability, and lifestyle, including mobility, continence, medical treatment, hospital admissions, pressure sores, visual problems, and need for daily care.[19] They were also asked about achievements in terms of living independently, driving a car, and working in open employment.[22] Causes of death for all those who had died were obtained from the Office for National Statistics (reference MR 564) backed up by medical records, interviews with carers, and autopsy reports. We defined 'unexpected deaths' after the age of 5 years as those referred by the local coroner for an autopsy. This is the usual procedure for deaths of initially uncertain cause in the UK. Unexpected deaths before the age of 5 years were not routinely referred for a coroner's autopsy, and were defined as sudden deaths that were not expected by either clinicians or parents.

Statistical analysis

We used Kaplan–Meier survival analysis for the complete spina bifida cohort. For comparison, we obtained survival rates for the UK 1967 birth cohort from the Office for National Statistics and adjusted them for the ratio of males to females found in the study. We also compared spina bifida survival rates between different sensory levels using Kaplan–Meier analysis and the log-rank test.

RESULTS

Of the original cohort of 117, there were 46 survivors (39%); 21 were male, 24 female, and one had undergone a sex change from male to female. Between June and October 2007, all were followed up. Twenty-five of them (54%) returned postal questionnaires. In addition, 38 survivors, and the carers of the remaining eight, were interviewed by telephone.

Mortality

There were 71 deaths (61%): 40 deaths (34%) occurred before the fifth birthday and 31 (26%) during the following 35 years.

What this paper adds

- The death rate from age 5 to 40 years in people with treated open spina bifida is 10 times the national average.
- Many deaths are sudden and unexpected.
- Survival to age 40 can be predicted from the neurological deficit at birth.
- Infants with intact sensation down to the knee (sensory level below L3) have a better long-term outcome.

The mortality rate per decade was 9% (7/77) at age 5 to 14, 13% (9/70) at age 15 to 24, and 15% (9/61) at age 25 to 34. Figure 1 shows that, between the ages of 5 to 40 years, the death rate in our cohort was over 10 times that of the total UK cohort born in 1967 (26% versus 2.0%).

Unexpected deaths

Of the 71 deaths, 23 (32%) were unexpected and sudden. Eighteen per cent (7/40) of deaths before the age of 5 years were unexpected, compared with 52% (16/31) at ages 5 to 43 (Table I). All 16 unexpected deaths at age 5 or over occurred in the community, and in all cases an autopsy was carried out at the request of the local coroner. The most frequent causes of these unexpected deaths were epilepsy, pulmonary embolus, acute hydrocephalus, and acute renal sepsis (Table II).

Survival and neurological deficit

Figure 2 shows that the survival rate was highest among those born with the least neurological deficit (log-rank test, p=0.001). Among those with intact sensation down to the knee (sensory level below L3), 40-year survival was 61% (23/38), in

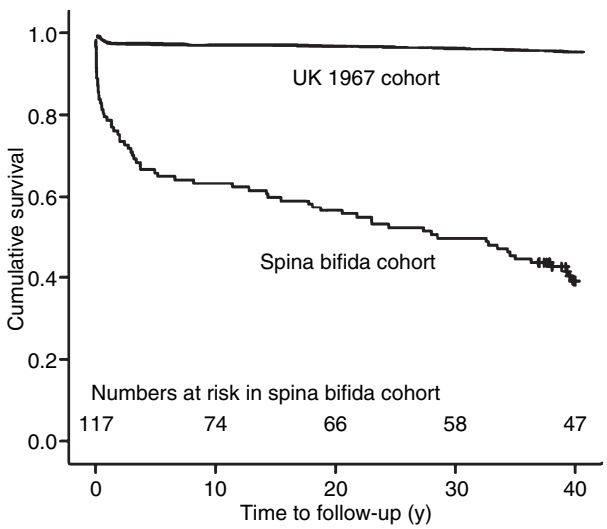

Figure 1: Forty-year survival of a complete cohort of 117 patients with open spina bifida born 1963–1971 compared with the UK 1967 birth cohort (Office for National Statistics data). Spina bifida cohort: no loss to follow-up. Data censored if participant was not yet 40. One further death occurred after the current cut-off at age 40. The median survival time was 28.5 years.

Table I: Unexpected deaths by age group at death in a complete cohort of 117 patients with open spina bifida

	Age group (y)					
	0–4	5–14	15–24	25–34	35–43	All ages
Total deaths	40	7	9	9	6	71
Unexpected deaths (%)	7 (18)	2 (29)	5 (56)	5 (56)	4 (67)	23 (32)

Table II: Causes of 23 unexpected deaths in a complete cohort of 117 patients with open spina bifida

Cause of death	Number of unexpected deaths	Comments
Age <5y: 7 deaths (18% of 40 deaths)		
Acute bronchopneumonia	3	
Inhaled vomit	2	
Pulmonary embolus	1	
Cot death	1	
Age 5–43y: 16 deaths (52% of 31 deaths)		
Epileptic seizure	3	All were taking anticonvulsants
Pulmonary embolism	3	One with ventriculoatrial shunt, one related to venous hypostasis, one fat embolism
Renal sepsis	3	Two acute on chronic pyonephrosis, one perinephric abscess with diabetes
Acute hydrocephalus	3	One after shunt removed, one collapsed at a night club, one died asleep at night
Acute asthma	2	
Central nervous system infection	1	Erosion and infection of the scar of myelomeningocele repair
Haemorrhagic pneumonia	1	

The causes of the remaining 48 (non-sudden) deaths were renal, *n*=17; cardio-respiratory, *n*=14; central nervous system infection, *n*=9; hydrocephalus, *n*=7; and thrombocytopenic purpura, *n*=1.

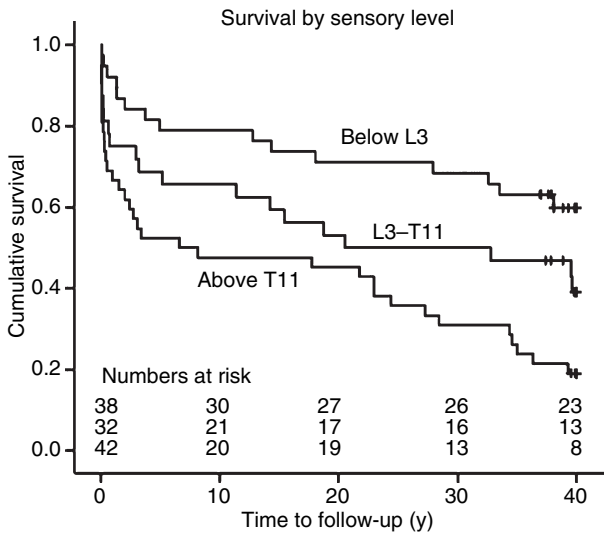

Figure 2: Survival in 112 individuals with spina bifida up to 40 years' follow-up (excludes five with asymmetrical sensory level). Data censored if participant was not yet 40. No loss to follow-up. Log-rank test for comparison of sensory levels was p=0.001.

those with sensory level L3 to T11 survival was 41% (13/32), but in those with no sensation below the umbilicus (sensory level above T11) survival was only 17% (7/42).

Characteristics and lifestyle of survivors

The mean age of the 46 survivors was 40 years (range 37–43y). Fourteen, all with a low sensory level, could walk more than 50m, 37 had an IQ of 80 or more (when assessed at school age), 38 had a CSF shunt, and nine were continent of urine and faeces without pads, catheters, or appliances. Fifteen worked in open employment and 21 drove a car. However, 16 needed daily care.

DISCUSSION

Principal findings

At the mean age of 40 years, 39% of the cohort was still alive, mainly those least severely affected at birth. Contrary to previous suggestions,[14–16] the death rate from age 5 to 40 was over 10 times the national average. Half these deaths were sudden and unexpected.

Strengths and weaknesses

There are four major strengths of this study. First, it is community based and, unlike other studies,[10,23,24] has no loss to follow-up. Most of the cohort no longer attended hospital and were cared for by their general practitioner. Second, it comprised an unselected cohort with a wide range of disability from no disability to very severe, with careful recording of clinical details at birth. Other series are likely to have been treated selectively by termination of affected pregnancies or

differential rates of active intervention after birth. Third, it is the first study to follow up participants prospectively from birth for 40 years, and all reviews were carried out by the same independent observer (GMH). No other study has such a long duration of follow-up; hence, this is the first to establish clearly the high risk of unexpected death. Finally, there is full ascertainment of all causes of death, with a coroner's autopsy report on all cases of sudden death after the age of 5 years.

The main limitation is that treatment has improved greatly in the four decades since the study began.[8,11,13] The high mortality before the age of 5 years is typical of the outcome in the period 1963 to 1975.[4,5,9] Improvements in treatment have resulted in reduced mortality in childhood,[12,13] and ventriculoperitoneal shunting has reduced shunt-related death rates. It is likely that the high ongoing mortality in adulthood in our cohort may be less applicable to infants born with open spina bifida today, but further robust follow-up studies are needed. However, modern management may have a smaller impact on disability, as this relates to the severity of the original neurological deficit.[7,12,13,21] Although this was a small cohort, it is similar in size to other studies.[10,11] Finally, our findings may not be applicable to non-white ethnic groups or to countries with higher prevalences of spina bifida or different systems of medical care. However, our data may serve as a baseline with which to compare the results of other series.[10,24–26]

Comparison with other studies

No other study of spina bifida has complete data on deaths in the community. Typical loss to follow-up ranges from 20% to 45%.[10,23,24,26] In our cohort, none of the 16 individuals who died unexpectedly between the ages of 5 and 40 years reached hospital alive. Their deaths were notified to the local coroner but were unlikely to be entered in their hospital records. We received the details via the Office for National Statistics tagging system. Missing these deaths in a hospital-based study could have greatly underestimated the apparent death rate in this age group. However, occasional sudden deaths have been described,[26] with causes including shunt malfunction[10,24] and suicide.[23] Renal-related deaths remain common.[23,27] Other series may include cases of spina bifida occulta or skin-covered meningocele, which tend to have lower mortality and disability.[14]

Implications

The high death rate throughout adulthood questions predictions of normal life expectancy in open spina bifida following early surgical treatment.[14–16] Improvements in management mean that about 75% of individuals now reach early adulthood,[8,10] and it is likely that future studies will show greater long-term survival. However, our cohort is the first to be followed up to the fifth decade, the first with complete ascertainment, and the first to show continuing high mortality in adulthood and a high rate of unexpected death. General practitioners and community nurses who had cared regularly for participants in the cohort were often shocked when their patient died suddenly. Apparently, minor symptoms such as headache, neck ache, drowsiness, visual disturbances, or vague chest or abdominal discomfort may need to be taken seriously.

There are many reasons why people with treated spina bifida remain at increased risk. A CSF shunt may become blocked, infected, or detached; this can happen after a prolonged quiescent period[10,24] and may also cause blindness. Motor deficit may lead to immobility, obesity, venous stasis, and risk of thrombosis and pulmonary embolism. Sensory deficit with lack of pain sensation may leave individuals liable to pressure sores, burns, and delayed diagnosis of painless abdominal emergencies, sepsis, or injury.[18] A neuropathic bladder may rupture, and a neuropathic bowel may become acutely obstructed. In addition, cognitive disability, such as forgetfulness, lack of organizational skills, and poor communication, can lead to neglect of medical problems and difficulty accessing care. Individuals with spina bifida may be cared for by a wide range of specialists, including paediatricians, neurosurgeons, urologists, and orthopaedic surgeons. Alerting both general practitioners and hospital doctors to potential complications, and providing ready access to specialist medical services,[8,10,26] might help to reduce the high death rate.

Despite unambiguous evidence of the benefit of periconceptional folate, the prevalence of neural tube defects in Europe has not declined substantially over the past decade.[1] In the USA, over 1300 infants are born with spina bifida each year.[2] Too many parents still face the difficult decisions about termination of an affected pregnancy or treatment of open spina bifida after birth. For them, data on prognosis are crucial. They need to consider the enormous commitment of looking after a disabled child and the possibility of continued dependency into adult life. Based on previous reviews of this cohort,[19,21,27] their doctors can tell them that an infant who cries at a heel prick blood test (sensory level S1 or below) has a high probability of surviving and being able to walk and live independently as an adult. However, doctors and care providers planning for the long-term needs of people with treated open spina bifida need to be aware of the novel findings of continuing high death rates throughout adulthood and the previously unrecognized high risk of sudden death.

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