Survival and Disability in a Cohort of Neural Tube Defect Births in Dublin, Ireland

Marie Sutton,[1] Leslie E. Daly,[2] and Peadar N. Kirke[1]

[1]Child Health Epidemiology Unit, Health Research Board, Dublin, Ireland
[2]University College Dublin, School of Public Health and Population Science, Dublin, Ireland

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BACKGROUND: Neural tube defects (NTDs) are a major cause of death and disability. Periconceptional folic acid prevents up to 70% of these malformations but public health campaigns to increase use of supplements have had disappointing results: The proposed mandatory fortification of bread products in Ireland has raised concerns about possible side effects. We examined data collected on a cohort of children born with NTDs in an era before fortification/supplementation to illustrate the serious consequences in terms of survival and disability. **METHODS:** All 623 infants born with NTDs in the Dublin area between 1976 and 1987 were included. Information was collected on mortality and length of survival for those who died, and for those who survived at least 5 years, interview-based data were collected on age, place of residence, prevalence of hydrocephalus, degree of disability, schooling, and IQ. **RESULTS:** Seventy-four births (12%) were stillborn. Of the livebirths only 41% were alive at 5 years. Factors associated with mortality were type of lesion, level of lesion, presence of other defects, hydrocephalus, year of birth, and gestation. Of the children who survived to 5 years or more, 75% had a disability and 56% were severely disabled. Type of lesion and level of lesion influenced disability risk. Of the survivors, 51% of children had mobility limitations, 59% were incontinent, 42% had hydrocephalus, and 17% had intellectual disability. **CONCLUSIONS:** These findings illustrate the devastating consequences of NTDs and underline the importance of effective intervention programs with folic acid for prevention. *Birth Defects Research (Part A) 82:701–709, 2008.* © 2008 Wiley-Liss, Inc.

Key words: survival; spina bifida; myelomeningocele; meningocele; encephalocele; folic acid; disability; neural tube defects

INTRODUCTION

NTDs are major congenital malformations of the central nervous system (CNS) and are important causes of death and disability in children and adults. Spina bifida and anencephaly are the commonest forms of NTDs. Prevalence at birth varies by region and time, and despite declines in many countries in recent decades, NTDs are still common world-wide, occurring, for example, in the United States, Britain, and Ireland at a rate of approximately 1 in 1,000 births.

Folic acid taken periconceptionally can prevent up to 70% of these malformations (MRC Vitamin Study Research Group, 1991; Czeizel and Dudas, 1992; Berry et al., 1999), but public health campaigns encouraging women to take folic acid supplements have had disappointing results (Botto et al., 2005). Mandatory food fortification with folic acid has been associated with marked reductions in the birth prevalence rates of NTDs in North America (De Wals et al., 2007; Mersereau et al., 2004) and in Chile (Lopez-Camelo et al., 2005). However, plans to introduce mandatory fortification in Ireland and Britain (Food Safety Authority of Ireland, 2006; Scientific Advisory Committee on Nutrition, 2006) have been stalled by concerns about possible side-effects (Eichholzer et al., 2006; Cole et al., 2007), which have diverted attention from the essential and important public health reason for this intervention.

As part of our research program on NTDs we followed up all NTD births in the Dublin maternity hospitals during 1976–1987, collecting data on survival and disability, among other variables. This period was prior to any

*Correspondence to: Peadar N. Kirke, Child Health Epidemiology Unit Health Research Board, Knockmaun House, 42–47 Lower Mount Street, Dublin.
E-mail: pkirke@hrb.ie
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population programs of supplementation or of food fortification with folic acid to prevent NTDs. Against the background of the relative ineffectiveness of the supplementation approach and the current concerns being expressed about the proposed introduction of mandatory fortification, we examined these data to illustrate the severe sequelae of NTDs in a population not exposed to folic acid and for whom termination of pregnancy was not readily available. These data also provide a baseline for future evaluation of the impact of such interventions in terms of survival and disability of affected infants. The study examined birth outcome, survival in those who were liveborn, and disability in the survivors in an unselected cohort of 623 infants born with NTD lesions compatible with survival in Dublin during 1976–1987.

METHODS

Three types of NTD lesions that are compatible with survival beyond the neonatal period were included in this study: spina bifida cystica, encephalocele, and cranial meningocele. Spina bifida cystica lesions were categorized further as spinal myelomeningocele, spinal meningocele, and spina bifida, not otherwise specified (n.o.s.). In spina bifida cystica there is a cystic extension of meninges, with or without neural tissue, outside the vertebral (spinal) canal (Nevin and Weatherall, 1983). An encephalocele is a cystic expansion of meninges outside the cranium, containing brain tissue. A cranial meningocele is a cystic expansion of meninges outside the cranium that does not contain brain tissue. A spinal myelomeningocele contains both meninges and neural tissue, while a meningocele contains only meninges (Nevin and Weatherall, 1983). The study population included all infants born alive and all stillbirths with a diagnosis of one or more of these defects between 1976 and 1987 inclusive, in the four Dublin maternity hospitals. Most of the study mothers resided in the greater Dublin area but a small proportion lived outside this region. The distributions of the study variables were compared for the two groups (Dublin and non-Dublin residents) in our study cohort. Data analysis was undertaken including and excluding the non-Dublin residents to examine how their inclusion affected the results.

Infants born with anencephaly, with spina bifida and anencephaly combined, and with spina bifida occulta were excluded. Details of the birth defects were obtained from hospital medical records. Data were collected retrospectively between August 1989 and April 1990 on these infants and included date of birth, vital status at delivery, gender, type and level of lesion, presence of hydrocephalus, and the presence of other congenital malformations. For the survival analysis, date of death for children known to have died or date last known to be alive for the remaining children was ascertained from a combination of medical records and/or parental interview.

For the disability aspect of the study, the parents of the surviving children were interviewed in their home by a trained interviewer. Because disability could be more reliably assessed in children aged over 5 years, the surviving children who were less than 5 years at follow-up were excluded from this part of the study. Data collected were age, place of residence, degree of disability (mobility, incontinence, intellectual impairment, and the ability to dress and eat independently), the type of school attended, and the presence or absence of hydrocephalus. Intelligence was assessed by a number of methods. Formal IQ scores were assessed in 65% of the children and for the remainder IQ was inferred from schooling ability and in some cases from parents' or teachers' assessments also.

In order to assess the overall level of disability, a composite three-point scale based on the Lorber criteria (Lorber, 1971) was derived. On this scale, none denotes no abnormality detected. Moderate denotes one or more of the following: walks with calipers or aids, hydrocephalus not requiring a shunt or well controlled with a shunt, urinary incontinence only, or mild/moderate intellectual disability. Severe denotes one or more of the following: chairbound, hydrocephalus not well controlled with a shunt, doubly incontinent, or severe intellectual disability.

In the data analysis subjects were categorized according to the type of lesion already described (encephalocele, cranial meningocele, spinal myelomeningocele, spinal meningocele, and spina bifida n.o.s.). This categorization was chosen so that survival and outcome for cranial and spinal lesions could be examined and, as myelomeningocele lesions are more severe in terms of outcome than meningoceles, these were also analyzed separately. Infants whose lesion was documented as spina bifida, myelomeningocele, or meningocele but n.o.s., were assumed to have spinal lesions. Subjects were also classified by the anatomical level of the lesion and the highest level of the defect on the spine determined their category. Infants with an encephalocele or cranial meningocele who also had a spinal lesion were classified as cranial. Level of lesion was designated as unknown for subjects whose hospital chart did not provide sufficient information to determine the level.

Categorical factors related to stillbirth and disability were analyzed using the chi-square statistic with a p value of less than .05 accepted as statistically significant. Odds ratios (ORs) and their confidence intervals (CIs) were calculated to compare each level of the variable. Logistic regression using SPSS was performed to determine the independent effects of each variable on the stillbirth rate while controlling for the other variables and the adjusted ORs were determined from the model. Because of the high correlation between the type of lesion and level of lesion variables the regression model could only include one of these variables at a time.

Survival was analyzed using Kaplan Meier lifetable methods with the logrank test for determining significance (Daly and Bourke, 2000). The Cox proportional-hazards model was used to assess the independent effect of potential risk factors (Bland, 1995) and adjusted hazard ratios were based on this model. As in the logistic regression, the type of lesion and level of lesion variables had to be included separately in the model.

RESULTS

Data were collected on 623 infants born with spina bifida cystica, encephalocoele, and cranial meningocele in the four Dublin maternity hospitals (Fig. 1). Approximately 94% of births to residents of the greater Dublin area and one-third of all births in the Irish Republic occurred in these hospitals during the study period. There were 275,650 live- and stillbirths in the Dublin

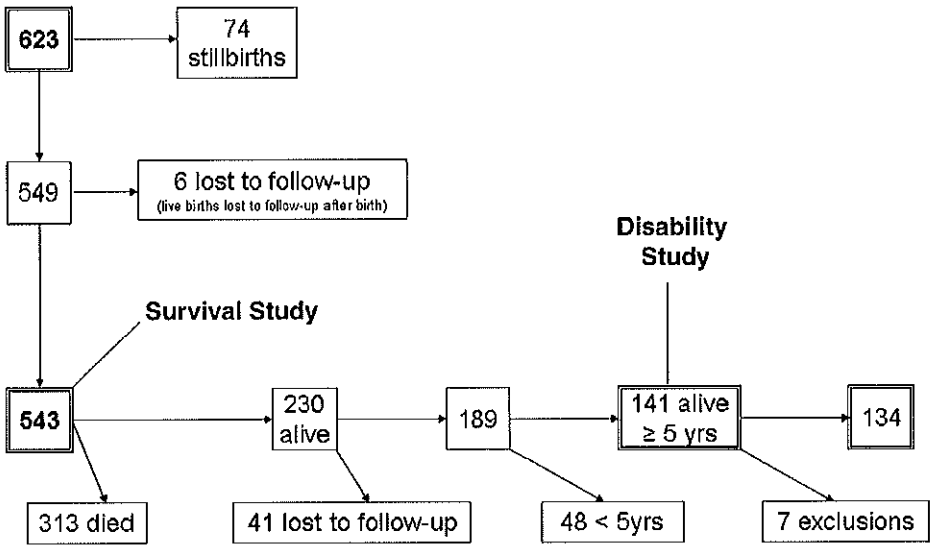

Figure 1. NTD births (n = 623). The number of participants available for different aspects of the study.

maternity hospitals, of which 623 had the NTD lesions included in the study, giving a birth prevalence rate of 2.3 per 1,000 births; the birth prevalence of all NTDs was 4.2 per 1,000 births. Of these 623 infants, 77 (12%) had an encephalocele; five (1%) had a cranial meningocele; 324 (52%) had a spinal myelomeningocele; 74 (12%) had a spinal meningocele; and in 143 (23%) the type of spina bifida lesion was not specified.

Many of the infants were stillborn or died shortly after birth. There were 74 stillbirths (12%) and the factors associated with stillbirth are shown in Table 1. Type of lesion influenced the stillbirth rate, with those in the spina

Table 1
Factors Associated with Stillbirth in a Cohort of 623 Infants Born with NTDs in Dublin, 1976–1987

	Stillbirth				
	n	%	Unadjusted p value	OR	Adjusted OR* [95% CI]
All subjects	74/623	11.9			
Type of lesion			<.001		
Spinal meningocele	2/74	2.7		1.00	1.00
Spinal myelomeningocele	18/324	5.6		2.12	2.01 [0.45–8.93]
Cranial meningocele	1/5	20.0		9.00	9.65 [0.70–132.48]
Encephalocele†	13/77	16.9		7.31	5.46 [1.16–25.77]
Spina bifida n.o.s.‡	40/143	28.0		13.98	12.66 [2.94–54.55]
Highest level of defect			.029		
Lumbosacral	16/240	6.7		1.00	1.00
Thoracic	18/128	14.1		2.29	2.17 [1.05–4.47]
Cervical	1/10	10.0		1.56	1.32 [0.15–11.71]
Cranial	14/82	17.1		2.88	2.19 [0.99–4.87]
Unknown	25/163	15.3		2.54	2.41 [1.23–4.72]
Gender§			.023		
Female	51/352	14.5		1.00	1.00
Male	23/270	8.5		0.55	0.53 [0.31–0.93]
Other birth defects			<.001		
NTD only	53/541	9.8		1.00	1.00
Multiple	18/61	29.5		3.85	3.30 [1.68–6.49]
Syndrome/possible syndrome	3/21	14.3		1.53	1.17 [0.31–4.43]

*Type and level variables each adjusted for gender and other birth defects. Gender and other birth defects variables adjusted for type of lesion only; results were similar when adjusted for level of defects variable (type and level variables were too highly correlated to be included in the same model).

†Eight cases with encephalocele had an additional spinal lesion and one encephalocele extended into the cervical spine.

‡Not otherwise specified.

§Excludes one indeterminate case.

Table 2
Lifetable Survival in a Cohort of 543 Infants Born Alive with NTDs in Dublin, 1976–1987 by Type of Lesion

	Livebirths	Survival at			
Type of lesion	no	1 day	28 days	1 year	5 years
Cranial					
Encephalocele*	64	70.3%	41.3%	32.9%	27.3%
Meningocele	4	100.0%	75.0%	75.0%	75.0%
All cranial	68*	72.1%	43.4%	35.2%	29.8%
Spinal					
Myelomeningocele	304	92.1%	73.3%	43.1%	39.3%
Meningocele	69	92.8%	91.3%	84.7%	84.7%
All spinal	373	92.2%	76.6%	50.4%	47.3%
Spina bifida n.o.s.†	102	70.6%	47.8%	25.5%	25.5%
All cases	543	85.6%	67.0%	43.7%	40.8%

*Eight cases with encephalocele had an additional spinal lesion and one encephalocele extended into the cervical spine.
†Not otherwise specified.

bifida n.o.s. category having the highest rate followed by infants with cranial meningocele and encephalocele. Infants born with lesions above the lumbosacral level had higher stillbirth rates than those with lumbosacral lesions. Rates were also higher in females than in males and in those with multiple birth defects compared to infants with NTD only. Year of birth and presence of hydrocephalus at birth were not associated with stillbirth (data not presented). The results of the logistic regression analysis indicated similar trends in stillbirth rates after adjusting for gender and other birth defects (Table 1).

There were 549 livebirths available for the survival analysis (Fig. 1). Six infants who were lost to follow-up immediately after birth were excluded. There were 313 deaths recorded in the survival analysis. Table 2 shows the survival of children to 5 years related to the type of lesion. The estimated lifetable probability of survival at 1 day was 86%, at 28 days 67%, at 1 year 44%, and at 5 years 41%. Five-year survival was lowest in children in the spina bifida n.o.s. category (26%) and in children with encephalocele (27%).

Table 3 shows 28 day and 1 year lifetable mortality related to various factors. There was a significant difference in mortality by year of birth ($p = .02$) with children born in the earlier years of the study having a higher mortality than those born in later years. Presence of hydrocephalus at birth, presence of other congenital anoma-

Table 3
Lifetable Mortality at 28 Days and 1 Year in a Cohort of 543 Children Born Alive with NTDs in Dublin, 1976–1987, Related to Various Factors

Factor	No. livebirths	28 day mortality	1 year mortality	Univariate log-rank*	Multivariate HR [95%CI]†
Year of birth				$p = .02$	
1976–1978	185	38.6%	58.5%		2.54 [1.69–3.80]
1979–1981	159	37.1%	62.1%		2.46 [1.64–3.69]
1982–1984	115	28.1%	56.2%		1.62 [1.05–2.49]
1985–1987	84	21.6%	40.6%		1.00
Hydrocephalus at birth				$p < .001$	
Present	305	37.3%	65.6%		1.95 [1.49–2.55]
Absent	235	28.5%	43.4%		1.00
Unknown	3	–	–		
Other birth defects				$P < .001$	
Syndrome/possible syndrome	18	88.9%	94.4%		3.95 [2.31–6.76]
Multiple	43	76.7%	86.0%		2.71 [1.89–3.89]
NTD only	482	27.4%	52.1%		1.00
Gestation				$P < .001$	
<37 weeks	60	63.5%	83.6%		2.76 [1.96–3.89]
≥37 weeks	483	29.6%	53.0%		1.00
Type of lesion				$P < .001$	
Spina bifida n.o.s.	102	52.2%	74.5%		7.06 [3.65–13.65]
Encephalocele‡	64	58.6%	67.1%		5.91 [3.03–11.52]
Cranial meningocele	4	25.0%	25.0%		2.07 [0.27–16.07]
Spinal myelomeningocele	304	27.4%	57.0%		3.31 [1.77–6.19]
Spinal meningocele	69	8.7%	15.3%		1.00
Highest level of lesion				$P < .001$	
Unknown	134	37.6%	61.9%		1.43 [1.05–1.94]
Cranial	68	56.6%	64.8%		2.03 [1.41–2.92]
Cervical	9	22.2%	33.3%		0.66 [0.21–2.08]
Thoracic	110	32.5%	65.4%		1.27 [0.93–1.73]
Lumbosacral	222	24.6%	46.6%		1.00
Gender				$p = .383$	
Male	244	30.7%	53.8%		0.98 [0.78–1.23]
Female	298	35.3%	58.0%		1.00
Unknown	1	–	–		

*Comparing entire lifetables.
†Type and level variables included separately in the model. The hazard ratio (HR) for the remaining variables taken from the model when type of lesion included. Four cases with missing data excluded from the Cox regression.
‡Eight cases with encephalocele had an additional spinal lesion and one encephalocele extended into the cervical spine.

Table 4
Description of Disability According to Whether the Lesion was Cranial or Spinal in a Cohort of 134* Children Born with NTDs in Dublin, 1976–1987, Who Survived for at Least 5 Years

	Encephalocele	Spinal lesions		Total
	no. (%)	Myelomeningocele no. (%)	Meningocele no. (%)	no. (%)
Mobility				
Walks without calipers or aids	12 (92.3)	21 (25.9)	32 (80.0)	65 (48.5)
Walks with calipers	0 (0.0)	32 (39.5)	7 (17.5)	39 (29.1)
Chairbound/bedbound	1 (7.7)	28 (34.6)	1 (2.5)	30 (22.4)
Incontinence				
Continent	12 (92.3)	16 (19.8)	27 (67.5)	55 (41.0)
Urinary incontinence only	1 (7.7)	7 (8.6)	7 (17.5)	15 (11.2)
Urinary and fecal incontinence	0 (0.0)	58 (71.6)	6 (15.0)	64 (47.8)
Hydrocephalus at follow-up†				
None	8 (61.5)	38 (46.9)	30 (75.0)	76 (56.7)
Hydrocephaly not requiring a shunt	2 (15.4)	8 (9.9)	5 (12.5)	15 (11.2)
Hydrocephaly requiring a shunt	3 (23.1)	33 (40.7)	5 (12.5)	41 (30.6)
Intelligence†‡				
Normal	8 (61.5)	60 (74.1)	34 (85.0)	102 (76.1)
Mild/moderate intellectual disability	3 (23.1)	17 (21.0)	2 (5.0)	22 (16.4)
Severe intellectual disability	1 (7.7)	0 (0.0)	0 (0.0)	1 (0.7)
Schooling†				
Mainstream school	8 (61.5)	43 (53.1)	33 (82.5)	84 (62.7)
Special school	5 (38.5)	36 (44.4)	6 (15.0)	47 (35.1)
All children	13 (100)	81 (100)	40 (100)	134 (100)

*Five children with spinal lesions for whom type of lesion unknown not tabulated and two children with cranial meningocele excluded.
†Children for whom information was missing excluded from these variables; percents may not add to 100.
‡Formal IQ scores were assessed for 65% of children and for the remainder IQ was inferred from schooling ability and in some cases from parents'/teachers' assessments also.

lies, and prematurity (less than 37 weeks gestation) were also significantly associated with mortality ($p < .001$). The type of lesion was significantly associated with mortality, with encephalocele and spina bifida n.o.s. lesions having the highest rates ($p < .001$). Mortality was also significantly associated with level of lesion, with cranial and thoracic lesions having the highest 1-year rates. Results from the multivariate Cox regression model confirmed that being born in the earlier years of the study, presence of hydrocephalus at birth, presence of other birth defects, and gestation less than 37 weeks were independently associated with mortality. For the diagnostic category spina bifida n.o.s. in the type of lesion variable there was a seven-fold increase in the hazard of death and for encephalocele a six-fold increase in the hazard of dying over the first year on multivariate modeling compared to spinal meningocele. Similarly, cases with cranial lesions had twice the hazard of death in infancy compared to the lumbosacral level.

There were 230 children alive at the review date. The status at the review date of 41 children could not be determined: 23 explained by unsuccessful contact attempts, nine were contacted but refused to take part, and nine had emigrated. All 41 were included in the survival analysis up to the date they were last known to be alive. A further 48 children who were less than 5 years at follow-up were also excluded from the analysis. Thus 141 children were available for the disability study. Seven of the 141 children were excluded from much of this analysis, five for whom the type of lesion was unknown and two with cranial meningocele because of small numbers.

The 141 children in the disability study had a mean age of 9.7 years and an age range of 5.0 to 13.8 years. At follow-up 99% of the children were living in their own home, with one child living in residential accommodation and one child spending some time in residential accommodation and some time at home. At follow-up, children had undergone a mean of 4.6 surgical procedures since birth or 0.5 surgical procedures per child per year. Surgical repair of the NTD lesion had been performed in 98% of the children and 39% had a shunt insertion.

Table 4 shows the degree of disability according to the type of lesion. Of this group ($n = 134$) 51% were unable to walk independently and 59% were incontinent. Seventy-five percent of those with incontinence relied on diapers or catheterization for urinary control, with catheterization accounting for 53%. Hydrocephalus was present in 42%, 17% had an intellectual disability, and 35% attended special schools. Sixty-six percent could dress independently and 96% could eat independently.

The overall level of disability in the surviving children was assessed using a composite scale of disability and was analyzed by type of lesion (Table 5): 56% of the 133 children had a severe disability, 20% a moderate disability, and 25% had no disability. Of children with spinal myelomeningocele, 79% had a severe disability compared to 21% of those with a spinal meningocele. In the case of spinal lesions, children with myelomeningocele had 1.7-times the risk of having a disability compared to those with meningocele and almost four times the risk of having a severe disability.

The factors influencing disability (moderate or severe) were analyzed (Table 6). The type of lesion ($p < .001$) and highest level of the lesion ($p = .04$) significantly influenced the risk of disability at follow-up. Of the 81 survivors with a spinal myelomeningocele, 72 (89%) had a disability compared with 8 of the 13 (62%) with an

Table 5
Disability in a Cohort of 133* Children Born with NTDs in Dublin, 1976–1987, Who Survived at Least 5 Years: Degree of Disability According to Whether the Lesion Was an Encephalocele or a Spinal Lesion

		Spinal lesions		
	Encephalocele	Myelomeningocele	Meningocele	Total
Degree of disability	*n* (%)	*n* (%)	*n* (%)	*n* (%)
None[†]	5 (38.5)	9 (11.1)	19 (48.7)	33 (24.8)
Moderate[‡]	6 (46.2)	8 (9.9)	12 (30.8)	26 (19.5)
Severe[§]	2 (15.4)	64 (79.0)	8 (20.5)	74 (55.6)
Total	13 (100)	81 (100)	39 (100)	133 (100)
	Chi Sq 47.5	4 df	$p < 0.0001$	

*Eight children excluded one who is mobile, continent, and does not have hydrocephalus but information is missing on intelligence, five for whom the type of lesion is unknown, and two children with cranial meningocele.
[†]No abnormality detected.
[‡]Any one or more of the following: walks with calipers or aids, hydrocephalus not requiring a shunt or well controlled with a shunt, urinary incontinence only or mild/moderate intellectual disability; includes three children with (moderate) disabilities other than those listed.
[§]Any more severe abnormality than listed above.

encephalocele and 20 of the 39 (51%) children with spinal meningocele.

A small percentage of mothers in the study (5.8%) were resident outside the Dublin area and as some of these may have been referrals because they had an NTD pregnancy, the comparability of the two groups (Dublin and non-Dublin residents) was examined for the study variables. Compared to Dublin residents the non-Dublin residents had a statistically significantly higher rate of encephaloceles ($p = .004$) and a higher stillbirth rate ($p = .002$). All of the data analysis was repeated excluding the non-Dublin residents and only one result changed. The significant gender difference ($p = .02$) in the stillbirth rate on the univariate analysis (Table 1) became marginally nonsignificant ($p = .06$). Therefore, the non-Dublin residents were included in the results.

DISCUSSION

This study documents the outcome in terms of survival and disability in a large, complete, and unselected cohort of infants born with NTDs in the greater Dublin area. This cohort was in a period of high prevalence (EUROCAT Working Group, 1991) and prior to any periconceptional supplementation or food fortification with folic acid in a country where pregnancy termination

Table 6
Factors Influencing Presence of Moderate or Severe Disability at Follow-Up, in a Cohort of 138* Children Born with NTDs in Dublin 1976–1987

Factor	Disability *n* (%)	R.R. (95% C.I.)	*p*
Year of birth			.907
1976–1978	37/49 (75.5)	0.99 (0.78–1.26)	
1979–1981	37/51 (72.5)	0.95 (0.74–1.21)	
1982–1984	29/38 (76.3)	1.00	
Type of lesion			<.001
Spina bifida n.o.s.	3/5 (60.0)	1.17 (0.54–2.55)	
Encephalocele	8/13 (61.5)	1.20 (0.71–2.03)	
Spinal myelomeningocele	72/81 (88.9)	1.73 (1.26–2.38)	
Spinal meningocele	20/39 (51.3)	1.00	
Highest level of lesion			.038
Unknown level	18/22 (81.8)	1.06 (0.84–1.33)	
Cranial	8/13 (61.5)	0.80 (0.51–1.25)	
Cervical	1/5 (20.0)	0.26 (0.04–1.50)	
Thoracic/thoracolumbar	15/19 (78.9)	1.02 (0.79–1.33)	
Lumbar/lumbosacral/sacral	61/79 (77.2)	1.00	
Gender			.497
Female	58/80 (72.5)	0.93 (0.77–1.13)	
Male	45/58 (77.6)	1.00	
Social class[†]			.469
5 and 6	28/41 (68.3)	0.87 (0.65–1.18)	
3 and 4	54/69 (78.3)	1.00 (0.78–1.28)	
1 and 2	18/23 (78.3)	1.00	

*Three children excluded one who is mobile, continent, and does not have hydrocephalus but information is missing on intelligence, and two children with cranial meningocele.
[†]A further five children excluded for whom social class was missing.

was not readily available. Therefore, this is one of the few studies that describes the natural history of survival of infants born with NTDs. It is the largest follow-up study of NTDs ever conducted in Ireland.

Only 8% of the study subjects were lost to follow up, with 92% followed for a sufficient length of time to allow analysis of the mortality and morbidity outcomes of the group and to evaluate the impact of several factors on the mortality and disability rates. The results show that only 41% of the children survived to 5 years and at follow-up survivors had undergone a mean of five surgical operations since birth, surgical repair having been performed in 98% and a shunt insertion in 39%. More than half of the survivors had a severe disability, with almost 80% of children with spinal myelomeningoceles having a severe disability. The findings of the present study have significant implications for any government evaluating the benefits of introducing a policy of mandatory fortification of food with folic acid to prevent NTDs.

The outcome of NTD births has been examined in many studies. Published survival and disability figures differ greatly depending on the time period, the cohort selection, the quality of the medical care available, and the availability of termination of pregnancy (Kalucy et al., 1994; Wong and Paulozzi, 2001; Bol et al., 2006; Mitchell et al., 2004). Much of the research on survival and disability follows infants who are referred to specialist treatment centers and therefore does not include stillbirths or children with very severe lesions who die without referral to tertiary care. Other studies include only myelomeningocele or are confined to spinal lesions and thus valid comparisons are difficult to make. More recently improved prenatal detection has increased the number of pregnancy terminations of what may well be the more severely affected fetuses (Kalucy et al., 1994; Wong and Paulozzi, 2001). Improved medical care and better medical management of the complications of NTD has influenced survival and disability in the survivors (Mitchell et al., 2004; Bol et al., 2006; Hunt and Poulton, 1995; Date et al., 1993; Kalucy et al., 1994, 1996). The introduction of clean intermittent catherization to improve the preservation of renal function, better management of hydrocephalus resulting in fewer episodes of shunt blockage, and development of antibiotics to treat cerebrospinal fluid infections have all contributed to improved survival and decreased disability (Kalucy et al., 1996; Date et al., 1993; Hunt and Poulton, 1995). Folic acid fortification has been associated with reductions in NTD rates (De Wals et al., 2007; Lopez-Camelo et al., 2005; Mersereau et al., 2004). Bol et al. (2006) reported that folic acid fortification in the US coincided with improved survival rates for infants with spina bifida and suggested that folic acid might lessen the severity of spina bifida.

Taking vitamin supplements when not pregnant was uncommon in Ireland during the study period. Prenatal vitamins were usually prescribed to pregnant mothers at their first hospital antenatal clinic visit in the Dublin maternity hospitals. In another study carried out in Dublin between 1986 and 1990 the median gestational age at this visit was 15 weeks, at which stage closure of the neural tube would be complete and hence any supplementation would be of no benefit in preventing NTDs (Kirke et al., 1993).

Althouse and Wald (1980) conducted a similar study of a cohort of spina bifida births in Oxford. The proportions of cases with cranial lesions and spinal meningocele were similar in both studies while the proportion of spinal myelomeningocele was higher in Oxford (66%, compared to 52% in the present study). This may be accounted for by a higher proportion of the spina bifida cases described as not otherwise specified in the Dublin study (23%) compared with the Oxford study (9%). In the spina bifida n.o.s. category in the Dublin study, 28% of these infants were stillborn and over half had died by 28 days. This poor survival suggests that these lesions are likely to be of a more severe nature, that is, myelomeningocele. The percentage of stillbirths was 12%, which is similar to that of other studies carried out around the same period (Adams et al., 1985; Althouse and Wald, 1980). The survival rate of 41% at 5 years in the present study is similar to that reported by Althouse and Wald (1980). The highest mortality occurred in the first year of life, which is in keeping with other studies (Althouse and Wald, 1980; Fitzgerald and Healy, 1974; Smith and Smith, 1973).

There was a significant association between survival and year of birth, with children born in the earlier years of the study having a higher mortality than those born in later years, as noted by others (Adams et al., 1985; Kalucy et al., 1994; Wong and Paulozzi, 2001). Survival was significantly affected by the presence of hydrocephalus at birth, the presence of other congenital anomalies, and level of the lesion, in keeping with the findings of earlier studies (Adams et al., 1985; Ames and Schut, 1972; Date et al., 1993; Kalucy et al., 1994; Lorber, 1971). Other factors affecting mortality were a gestational age of less than 37 weeks and type of lesion. Wong and Paulozzi (2001) found that prematurity was associated with reduced survival. Infants with encephalocele in this study experienced higher mortality than that reported in other studies (Haase et al., 1987; Kalucy et al., 1994). More females than males were affected in this study, similar to the findings of other cohort studies (Haase et al., 1987; Kalucy et al., 1994; Khoury et al., 1982).

A limitation of the present study is that the survival experience reported relates to 1976–1987 births and survival rates are likely to be considerably better for infants born in more recent years, as reported elsewhere (Bol et al., 2006; Nembhard et al., 2001). Our data do, however, give a picture of survival and disability in a cohort from the era preceding periconceptional supplementation and food fortification.

At follow-up of the children who survived at least 5 years, 49% could walk independently and 41% were continent, similar to the findings of Althouse and Wald (1980). In another cohort study in Western Australia 54% of school-aged children with spina bifida could walk unaided, but different methodologies for assessing continence and intellectual disability preclude valid comparisons with the results of the present study (Kalucy et al., 1996). In the Oxford study 37% of the children had some degree of intellectual disability, which is much higher than the 17% in the present study. However 67% of their survivors had hydrocephalus compared with 42% in this study. Hydrocephalus that requires treatment and complications thereof are known to be associated with intellectual disability (Date et al., 1993; Iborra et al., 1999; Lorber, 1971, 1972). It is possible that we underestimated the level of intellectual disability because only 65% of the children had been formally assessed for IQ scores. Stark and Drummond (1973) and Naglo and Hellstrom (1976)

reported that 20 and 16%, respectively, of their series of children with myelomeningocele had moderate or severe intellectual disability. Other studies reported higher levels of intellectual disability but all of these studies were confined to myelomeningocele only or based on children referred for specialist treatment (Lister et al., 1977; Richings and Eckstein, 1970; Lorber, 1971, 1972; Hunt, 1981).

Overall 25% of children in our study had no physical or intellectual disability. This is higher than the figure of 15% reported by Althouse and Wald (1980). Other studies that used a composite index of overall disability based on Lorber's criteria reported a lower proportion of children with no disability (Lorber, 1971; Rasmussen et al., 1993; Stark and Drummond, 1973), but again, these studies included only children with myelomeningocele. This cohort study may give a truer overall picture of the degree of disability in children with NTDs.

In this cohort children with encephalocele had a poor survival rate but for those that did survive, a greater proportion had no disability compared to children with thoracic or lumbar lesions. In a Danish study there were seven survivors at age 7 years with an encephalocele, only one of whom had a disability, compared to 78% of the spina bifida survivors (Haase et al., 1987). A greater proportion of children with spinal myelomeningocele had a disability at follow-up compared to those with spinal meningocele, in keeping with other studies (Date et al., 1993; Dougall et al., 1975; Laurence and Tew, 1967; Lorber, 1972; Lorber and Salfield, 1981).

Almost all of the children were being cared for by parents in their own home. Hunt (1973), in a study of children with myelomeningocele, gave an in-depth account of the problems encountered by both children and parents in the management and rearing of children with this condition, many of whom may be severely disabled. In keeping with other studies (Haase et al., 1987; Hagelsteen et al., 1989; Swank and Dias, 1992) we found that children with NTDs underwent multiple surgical procedures. Frequent hospitalizations and many surgical procedures place a significant burden on families, especially if there are other children to be cared for, and cause considerable disruption to the affected child particularly in terms of schooling (Hunt, 1973). Children with spina bifida continue to experience excess morbidity and mortality throughout adulthood (Mitchell et al., 2004) and medical management is ongoing and challenging.

These findings illustrate the very serious impact of NTDs on the affected individual, their family, and the community. The fact that these malformations can be prevented by taking folic acid periconceptionally emphasizes the importance of effective public health intervention strategies using folic acid for prevention. This means, in essence, having mandatory food fortification with folic acid, together with a national public health program to promote taking folic acid supplements. The second part of this dual strategy is especially important in Ireland because the proposed fortification level of 120 μg folic acid per 100 g of bread is estimated to reduce NTDs by only about 24% (Food Safety Authority of Ireland, 2006). The health promotion program to encourage all women of child-bearing age who are sexually active to take folic acid must be comprehensive and sustained and must pay particular attention to vulnerable groups, that is, women with unplanned pregnancies, low educational status, unsupported women, young women, and immigrants.

When considering a mandatory fortification policy the risks and benefits must be weighed. There are some concerns about possible adverse effects of increased folic acid intake, the most recent being the possibility of cancer promotion (Eichholzer et al., 2006; Cole et al., 2007). A frequently mentioned concern is that of masking the symptoms of vitamin B12 deficiency, but this only occurs at very high blood folate concentrations, most likely due to relatively high-dose supplementation and unlikely to result solely from food fortification.

When fortification is introduced, the health effects need to be adequately monitored and policy reviewed periodically. There is an urgent need to introduce the proposed strategy of mandatory food fortification as soon as possible in Ireland and to reinvigorate the public health campaigns to promote the periconceptional use of folic acid supplements. The study findings remind us of the benefits accruing to families and society from prevention.

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