Risk of recurrence after two children with central nervous system malformations in an area of high incidence

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SUMMARY This study was undertaken to provide an estimate of the recurrence risk of central nervous system (CNS) malformation in families with two or more affected children. The hospital records and the records of the Genetic Counselling Clinics were examined for instances where a child born between 1962 to 1973 had spina bifida and anencephalus and was documented as having an affected elder sib; such children were taken as index patients. Parents of 76 families with 89 index patients were interviewed. Fifty-one index patients had younger sibs; of 85 younger sibs, 12 had spina bifida and six anencephalus (1 in 4.7). Little variation was observed in the proportion of subsequent children affected with the type of lesion in the index patient and the affected older sib. Ten index patients with two older affected sibs had 14 subsequent sibs of whom four had a CNS malformation (1 in 3.5). For the purpose of genetic counselling it was suggested that the risk after two and three children with CNS malformations in Northern Ireland was 1 in 5 and 1 in 4, respectively.

In the United Kingdom anencephalus and spina bifida (CNS malformations) show a marked geographical gradient, which steadily increases from the south and east to the north and west; the incidence (per 1000 total births) in south-east England is 2.95,¹ in Wales 7.6,² and in Northern Ireland 8.7.³ In England, after the birth of an affected child, the risk of a second affected child is 1 in 25, and after two affected children the risk of recurrence of another affected child is 1 in 8.⁴ It has been suggested that this risk probably varies from one area to another depending on the incidence in the particular population. The incidence of CNS malformations is extremely high in Northern Ireland; in Belfast (1964 to 1968), the incidence (per 1000 total births) was 4.2 for anencephalus and 4.5 for spina bifida,³ and in Northern Ireland (1974 to 1977) the corresponding figures were 3.1 and 4.0.⁵ We report the findings of a study of families designed to give an estimate of the recurrence risk after two affected children.

Material and methods

The hospital records of the major Northern Ireland maternity units and of the Spina Bifida Clinic, Royal Belfast Hospital for Sick Children were

examined for the years 1962 to 1973 for patients with spina bifida or anencephalus, who had at least one older sib with either of these malformations. The records of the Genetic Counselling Clinic, established in October 1967, were also used to identify similar families. Data on families with anencephalus and spina bifida were available also from a study in Belfast (1964 to 1968). The records were examined at the latest possible date and backwards through the earlier years. An index case was defined as any child with anencephalus or spina bifida or both recorded between 1962 and 1973 who had an affected older sib.

A total of 80 families was identified, but four families could not be traced. The parents of the 76 families were interviewed; there were 89 index patients in these sibships. A full family history, with particular reference to any subsequent sib born up to the last day of 1978, was documented. The information recorded at the interview was supplemented also from hospital records and from registration of deaths. Details of the sibships are given in the appendix.

Of the 89 index patients, 51 had younger sibs and so provided useful information. There were 85 children born after an index patient. These children were examined personally (NCN) or, if they were

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dead, any congenital abnormality confirmed from hospital records. Thirteen families had two index patients, of which seven had children born after the second index patient.

Results

The findings among the children born after the 51 index patients are shown in table 1, distinguishing between spina bifida and anencephalus in the index patient and their sibs. Of the 85 subsequent children, 12 had spina bifida and six had anencephalus, a proportion of 1 in 4.7. Of 41 subsequent brothers, 10 were affected (1 in 4.1), and of the 44 subsequent sisters, eight were affected (1 in 5.5). Considering only families in which the index patient was the second born, so that the mother had only affected children, the proportion of subsequent children affected was 3 in 19, that is 1 in 6.33. This figure is similar to that of the group where the index patient had only one older affected sib: of 65 subsequent children, 13 were affected, a proportion of 1 in 5.

There was little variation in the proportion of subsequent children with the same type of lesion as the index patient and the affected older sib. When the index patient and the affected older sib each had spina bifida, then of the subsequent 22 children, four had spina bifida, a proportion of 1 in 5.5. Similarly, when the index patient and the older affected sib had anencephalus, of the subsequent 15 children born, three were affected, a proportion of 1 in 5. Even when the index patient and the affected older sib had dissimilar lesions, the proportion of affected among subsequent born sibs was similar; of the subsequent 28 sibs, six were affected, a proportion of 1 in 4.67.

There were 10 index patients with two older affected sibs. Of the 14 subsequent sibs, four (three with spina bifida and one with anencephalus) were affected, a proportion of 1 in 3.5. One family with two index patients had 11 children, of whom five had spina bifida. The first index patient in this family had three older affected sibs; of the four subsequent sibs one had spina bifida. It so happened that after

the second index case, who had four affected older sibs, the two subsequent sibs were both normal.

Of the 85 sibs born after the index patient, only one had a congenital abnormality, Down's syndrome, other than a CNS malformation. Of the 163 children born before the index patient two had malformations other than those of the central nervous system; one had oesophageal atresia, tracheo-oesophageal fistula, common atrium, coarctation of the aorta, and hydro-nephrosis, and the other had talipes equinovarus.

Information was recorded also for cousins of index patients (table 2). Among 620 cousins on the maternal side, nine had spina bifida and four anencephalus, a proportion of 1 in 48. Among the 637 paternal first cousins, seven had spina bifida and two had anencephalus, a proportion of 1 in 70.8. Overall among the 1257 cousins, 16 had spina bifida and six had anencephalus, a proportion of 1 in 57. Thus, the incidence of CNS malformations among cousins is 2.5-fold that of the general population. In addition to the CNS malformations among cousins, one of mother's brother's daughters had hydrocephalus, and one of father's sister's daughters had spina bifida occulta. Eleven cousins had other congenital malformations: five had congenital heart defects, one had duodenal atresia, one had talipes equinovarus, one had mental retardation, one had Down's syndrome, and two had epilepsy.

The findings among the cousins in the families with two index patients is shown in table 3. Among

TABLE 2 Malformations among cousins of index patients

Relation	Total	Spina bifida	Anencephalus
Maternal			
Brother's sons	148	1	1
Brother's daughters	144	2	1
Sister's sons	164	3	0
Sister's daughters	164	3	2
Total	620	9	4
Paternal			
Brother's sons	158	0	0
Brother's daughters	155	2	0
Sister's sons	167	2	1
Sister's daughters	157	3	1
Total	637	7	2

TABLE 1 Children born after index patient

Abnormality in		No of index patients	No of children born after index patient					
Index patient	No of affected older sibs		Total		Spina bifida		Anencephalus	
			M	F	M	F	M	F
Spina bifida	1	26	22	24	3	4	3	0
Anencephalus	1	13	11	8	0	1	1	1
Anencephalus	2	2	3	1	0	0	1	0
Spina bifida	2	8	3	7	1	2	0	0
Spina bifida	3	1	2	2	1	0	0	0
Spina bifida	4	1	0	2	0	0	0	0
Total		51	41	44	5	7	5	1

TABLE 3 *Malformations among cousins of families with two index patients*

Relation	Total	Spina bifida	Anencephalus
Maternal			
Brother's sons	38	1	1
Brother's daughters	36	1	0
Sister's sons	41	0	0
Sister's daughters	44	1	0
Total	159	3	1
Paternal			
Brother's sons	48	0	0
Brother's daughters	36	1	0
Sister's sons	54	1	0
Sister's daughters	40	3	0
Total	178	5	0

TABLE 4 *Malformations among uncles and aunts of index patients*

Relation	Total	Spina bifida	Anencephalus
Maternal			
Uncles	187	2	0
Aunts	155	2	0
Total	342	4	0
Paternal			
Uncles	177	0	0
Aunts	156	2	0
Total	333	2	0

159 maternal cousins, three had spina bifida and one anencephalus, a proportion of 1 in 39.8. Among 178 paternal cousins, five had spina bifida, a proportion of 35.6. In all of 337 cousins, nine had CNS malformations, a proportion of 1 in 37.4, which is 3.8 times the general population incidence.

Data were collected on CNS malformations among uncles and aunts of the index patients, but these were far from complete as it was difficult to trace hospital records to confirm diagnoses, and death certificates often only recorded stillbirth or neonatal death without mention of congenital abnormalities. Of 675 uncles and aunts, six had spina bifida, a proportion of 1 in 112.5, which is similar to that for the general population and is clearly an underestimate.

Discussion

The risk of recurrence of anencephalus or spina bifida after the birth of two affected children is considered to be much higher than after one affected child. In England, the risk of recurrence after the birth of a single affected child is about 1 in 25.⁴ Lorber⁶ reported 13 families who had two children with spina bifida; of 67 subsequent births, 39 (58%) were affected. The author, however, was careful to point out that these families were highly selected, as families with a third or fourth affected child had been referred for treatment in a period when surgical treatment had been more generally recognised.

Smithells *et al*⁷ also found an unusually high recurrence rate after a second infant with anencephalus or spina bifida. Again, their study was biased towards sibships with two affected infants as their registry was established after the birth of the second. They found that half of the children born after the birth of the second infant had a CNS malformation. In Glasgow, Richards *et al*⁸ found the overall incidence of CNS malformations to be 4.9% after two affected children, a lower rate than found in other studies.

In a particularly well-designed investigation, Carter and Roberts⁴ interviewed, from various centres in England and Wales, 47 families which had children born after the birth of two affected children. Of 69 subsequent children, four had spina bifida and four had anencephalus, a proportion of 1 in 8.6. For the purpose of genetic counselling they suggested that the risk in England after two children with neural tube defects is 1 in 10.

Carter and Roberts⁴ suggested that the risk of recurrence might be expected to vary from one area to another, depending upon the incidence of these malformations in the particular population. As Northern Ireland has a very high incidence of neural tube defects, it was considered appropriate to investigate the risk of recurrence after two affected children, so that comparison could be made with the study of Carter and Roberts.⁴ Of 85 children born after two affected children, 12 had spina bifida and six had anencephalus, an overall recurrence risk of 1 in 4.7, which is almost twice that found by Carter and Roberts.⁴

In the study of Carter and Roberts,⁴ eight children were born after three affected children, and it so happened that all were normal. In our study there were 10 index patients with two older affected sibs. There was a total of 14 children born after the index patient, of whom four were affected (a proportion of 1 in 3.5). It is apparent that with each successive affected child, the risk of recurrence of neural tube defects rises steadily. For the purpose of genetic counselling in Northern Ireland, it would seem reasonable to advise a recurrence risk of 1 in 5 and 1 in 4, after the birth of two and three affected children, respectively.

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References

- ¹ Carter CO, Evans K. Spina bifida and anencephalus in Greater London. *J Med Genet* 1973;**10**:209–34.
- ² Laurence KM, Carter CO, David PA. Major central nervous system malformations in South Wales. *Br J Prev Soc Med* 1968;**22**:147–212.
- ³ Elwood JH, Nevin NC. Factors associated with anencephalus and spina bifida in Belfast. *Br J Prev Soc Med* 1973;**27**:73–80.
- ⁴ Carter CO, Roberts JAF. The risk of recurrence after two children with central nervous system malformations. *Lancet* 1967;**1**:306–8.
- ⁵ Nevin NC, McDonald JR, Walby AL. A comparison of neural tube defects identified by two independent routine recording systems for congenital malformations in Northern Ireland. *Int J Epidemiol* 1978;**7**:319–21.
- ⁶ Lorber J. The family history of spina bifida cystica. *Pediatrics* 1965;**35**:589–95.
- ⁷ Smithells RW, D'Arcy EE, McAllister EF. Outcome of pregnancies before and after birth of infants with nervous system malformations. *Dev Med Child Neurol (Suppl)* 1968;**15**:6–10.
- ⁸ Richards IDG, McIntosh HT, Sweeney S. A genetic study of anencephaly and spina bifida in Glasgow. *Dev Med Child Neurol* 1972;**14**:626–39.

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APPENDIX Index patients and sibs

*M, male; F, female; m, miscarriage; sb, stillbirth; * index patient; [], twins; (A), anencephalus; (S), spina bifida; (H), hydrocephalus.*

Serial No	Sibship	Date of birth	
		Mother	Father
A. SPINA BIFIDA (INDEX PATIENT): SPINA BIFIDA (OLDER SIB)			
Two child families			
010	M(S)3/71sb;*M(S)1/72;ml/73;m4/75,ml/76	1949	1947
011	M(S)3/71;*M(S)11/72	1954	1952
021	M(S)5/70;*M(S)9/71	1947	1944
083	F(S)7/61;*M(S)4/62sb;m5/66;m5/67	1938	1933
Three child families			
001	F8/69;F(S)8/70;*F(S)4/73	1946	1942
012	F(S)7/67sb;M3/69;*F(S)3/72	1942	1943
022	M(S)7/69;*M(S)2/71;F2/72	1947	1947
039	M10/66;m-/67;m-/68;F(S)7/69;m-/70;*F(S)7/71	1947	1944
044	M(S)12/64;m5/65;M6/66;*M(S)2/69	1943	1940
051	M(S)4/66;m-/67;*M(S)2/68;F5/72;m3/73	1940	1942
060	F(S)1/61;F9/64;*M(S)4/66sb;m6/72	1941	1940
061	M(S)1/59;F5/61;*F(S)7/66	1936	1939
Four child families			
023	M(S)6/69;ml/70;*F(S)1/71;M11/73;F9/78	1950	1946
076	M11/54;F7/56;F(S)9/61;*F(S)1/64;m5/67	1934	1931
Five child families			
002	F3/68;F6/69;m9/71;F(S)1/73;*F(S)11/73sb;F12/74	1938	1928
045	m3/63;M(S)2/64;M2/65;M6/66;M5/67;*M(S)6/69;m11/71	1941	1935
056	F(S)1/61;M3/62;M2/65;*F(S)5/67;F2/69	1935	1933
062	M(S)11/63;m12/63;M1/65;*F(S)3/66;M2/67;F1/70	1942	1943
072	F1/62;M(S)3/63;M7/64;*F(S)11/65;F4/69	1940	1940
073	M9/63;M(S)4/64;*F(S)12/65;m-/67;m-/69;M5/70;M3/72	1941	1941
Six child families			
025	M3/66;F5/67;F9/69;M(S)11/70;*M(S)12/71;M5/73	1945	1943
026	M11/61;m-/62;F10/64;M(S)12/65;M5/66;M5/68;*F(S)3/71	1942	1942
027	M12/61;M11/64;[M(S)10/67;F(S)10/67];F8/70;*M(S)2/71	1942	1940
052	M8/64;F(S)12/65;M3/66;*M(S)9/68;F5/69;M12/70sb;m10/71;F2/74;m8/75	1944	1943
074	M4/56;M11/57;F(S)2/60;M4/63;*F(S)6/65;M(S)8/66 No 064	1936	1939
085	M(S)11/52;m-/53;M-/54;F4/55;F5/56;M-/59;*M(S)1/62	1935	1935
Seven + child families			
040	m10/63;M(S)12/64;M1/66;m6/66;F8/67;F7/68;*M(S)4/70;M(S)8/71 No 028;F(S)1/74	1940	1932
079	m5/56;M3/57;m12/57;F(S)1/59;M6/60;m12/60;M7/62;m5/63;*M(S)9/64;m-/65;F7/66;F11/69	1935	1929
086	F10/54;F12/55;M2/56sb;M1/58;F(S)4/59;M8/60;m4/61;*F(S)2/62;M(S)7/64 No 078;F10/69	1935	1933
B. ANENCEPHALUS (INDEX PATIENT): ANENCEPHALUS (OLDER SIB)			
Two child families			
003	M(A)5/70sb;m12/72;*F(A)11/73sb	1936	1938
004	m5/71;F(A)2/72sb;*F(A)11/73sb	1945	1946
029	m5/68;F(A)6/69sb;*F(A)7/71sb	1946	1945
087	M(A)7/59sb;m4/60;*F(A)12/68sb	1939	1935
Three child families			
005	F(A)2/72sb;*F(A)1/73sb;M2/74	1950	1953
006	F(A)4/72sb;*F(A)3/73sb;M1/75	1950	1947
014	F(A)2/71;m-/71;*M(A)11/72sb;M(A)11/73 No 007	1945	1947
075	F(A)10/58sb;M3/62;*M(A)8/65sb;m-/70	1939	1932
Four child families			
030	m-/69;F(A)6/70sb;*F(A)10/71sb;M8/74;F10/76	1945	1945
046	F(A)8/66sb;m11/66;M9/67;*F(A)12/69;F3/72	1946	1947
053	F(A)10/64sb;F10/65;*M(A)2/68sb;F6/69	1939	1938
054	F(A)10/65sb;F9/66;m-/67;*M(A)7/68sb;M1/77	1945	1946
Five child families			
032	M(A)1/70sb;*M(A)5/71sb;m9/71;F1/73;F(S)1/74sb;m1/76;M11/76	1943	1945
047	F(A)8/66sb;F5/68;*F(A)6/69;F(A)11/71sb No 031;M10/78	1941	1940
Seven + child families			
033	M11/62;m6/64;M4/67;F(A)11/69sb;*F(A)3/71sb;M1/73;F8/74	1938	1937
C. ANENCEPHALUS (INDEX PATIENT): SPINA BIFIDA (OLDER SIB)			
Two child families			
055	F(S)9/67;*M(A)8/68	1935	1938
Three child families			
015	m12/68;M12/69;F(S)12/70;*F(A)4/72sb	1949	1948
068	M(S)9/65;*F(A)8/66sb;F2/70	1944	1946
Four child families			
034	M9/66;m-/67;F12/67;M(S)3/70sb;*M(A)6/71sb	1939	1942
035	F(S)7/67;M12/68;*M(A)4/71sb;M10/72	1934	1939
036	M(S)5/69;m12/69;*F(A)12/71;M4/74;M5/77	1949	1950
041	M6/64;M(S)4/67;M12/68;*F(A)4/70sb	1937	1938

APPENDIX continued

Serial No	Sibship	Date of birth	
		Mother	Father
D. SPINA BIFIDA (INDEX PATIENT): ANENCEPHALUS (OLDER SIB)			
Two child families			
008	F(A)9/71;*F(S)10/73	1950	1946
042	M(A)7/67;*F(S)6/70sb	1939	1945
Three child families			
016	F(A)5/69;m-/70;*F(S)4/72sb;M3/75	1946	1948
017	F6/67;F(A)1/71sb;*F(S)2/72	1936	1940
037	M(A)4/69sb;*F(S)6/71;M3/73	1938	1943
048	F(A)6/66sb;F3/67;*M(S)11/69	1936	1936
Four child families			
018	F8/71;F(A)11/72sb;*F(S)12/73;M4/75	1935	1934
038	F2/71;F(A)1/72sb;*M(S)4/73;M3/74	1950	1949
049	F6/63;M(A)9/64sb;M9/65;*M(S)5/69	1932	1935
081	F(A)9/61sb;M8/62;*M(S)2/64sb;m7/65;M(A)4/67 No 058	1939	1934
084	m1/62;M(A)10/62sb;*M(S)10/64;F(S)10/66 No 063;m12/67;m8/68;F2/70	1938	1935
Five child families			
069	m-/62;M(A)10/63sb;M11/64;*M(S)4/66;F7/68;F(S)11/72 No 019	1939	1939
070	M2/63;F(A)11/64sb;*M(S)1/66;F7/68;F1/70	1939	1937
Six child families			
020	F4/70;F(A)2/71sb;*M(S)12/72;M1/73;m-/73;F2/74;F8/75	1949	1949
059	M9/64;F(A)1/66;*M(S)7/67;M3/69;M6/71;M4/74	1934	1936
Seven + child families			
043	M(A)9/63sb;F2/65;F5/67;*M(S)9/70;F(S)2/73 No 009;F2/75;M10/77	1936	1936
071	M2/64;M(A)8/65sb;*M(S)9/66;[M(A)5/69 No 050;M5/69];F11/70;M(A)5/76	1941	1940
E. ANENCEPHALUS (INDEX PATIENT): TWO AFFECTED OLDER SIBS			
Three child families			
007	F(A)2/71;m-/71;M(A)11/72sb No 014;*M(A)11/73	1945	1947
Four child families			
058	F(A)9/61sb;M8/62;M(S)2/64sb No 081;m7/65;*M(A)4/67	1939	1934
Five child families			
031	F(A)8/66sb;F5/68;F(A)6/69 No 047;*F(A)11/71sb;M10/78	1941	1940
Seven + child families			
050	M2/64;M(A)8/65sb;M(S)9/66 No 071;[*M(A)5/69;M5/69];F11/70;M(A)5/76	1941	1940
F. SPINA BIFIDA (INDEX PATIENT): TWO AFFECTED OLDER SIBS			
Three child families			
080	F(S)10/48;m-/49;M(A)-/50;*F(S)3/63	1922	1921
Four child families			
063	m1/62;M(A)10/62sb;M(S)10/64 No 084;*F(S)10/66;m12/67;m8/68;F2/70	1938	1935
077	m-/58;M(S)9/60;F(S)10/61;m-/63;*F(S)12/64;F(S)4/71 No 024	1932	1937
Five child families			
013	M(S)12/59sb;F(S)10/60;F9/63;M7/66;*M(S)12/72	1937	1934
019	m-/62;M(A)10/63sb;M11/64;M(S)4/66 No 069;F7/68;*F(S)11/72	1939	1939
088	M(S)9/59;M(S)12/60;*F(S)10/62;M1/65;M(S)5/66 No 089	1935	1934
Six child families			
064	M4/56;M11/57;F(S)2/60;M4/63;F(S)6/65 No 074;*M(S)8/66	1936	1939
Seven + child families			
009	M(A)9/63sb;F2/65;F5/67;M(S)9/70 No 043;*F(S)2/73;F2/75;M10/77	1936	1936
028	m10/63;M(S)12/64;M1/66;m6/66;F8/67;F7/68;M(S)4/70 No 040;*M(S)8/71;F(S)1/74	1940	1932
065	F2/56;F(S)6/57;M1/59;M(S)9/61sb;F3/62;M7/65;*M(S)10/66	1940	1934
066	M1/50;F1/52;M11/52;F(S)9/53;M12/54;M10/56;M(S)-/59sb;F/60;[m-/64;m-/64];*F(S)4/66;F6/70	1926	1928
067	M11/48;F1/51;M5/52;F(S)9/53;m11/54;M12/55;M10/57;M(S)2/60;m8/60;F2/62;m3/63;m6/64;m9/64;m3/65;*F(S)6/66;m-/67;m-/68;F6/70	1926	1922
078	F10/54;F12/55;M2/56sb;M1/58;F(S)4/59;M8/60;m4/61;F(S)2/62 No 86; *M(S)7/64;F10/69	1935	1933
G. SPINA BIFIDA (INDEX PATIENT): THREE AFFECTED OLDER SIBS			
Four child families			
024	m-/58;M(S)9/60;F(S)10/61;m-/63;F(S)12/64 No 077;*F(S)4/71	1932	1937
Five child families			
089	M(S)9/59;M(S)12/60;F(S)10/62 No 088;M1/65;*M(S)5/66	1935	1934
Seven + child families			
082	m-/55;F(S)1/56sb;F(S)9/56sb;M10/57;m-/58;M7/59;M(S)9/60;m-/61;F9/62;*F(S)6/63sb;m-/64;M2/66;M(S)7/67 No 057;F12/68;F1/72	1937	1935
H. SPINA BIFIDA (INDEX PATIENT): FOUR AFFECTED OLDER SIBS			
Seven + child families			
057	m-/55;F(S)1/56sb;F(S)9/56sb;M10/57;m-/58;M7/59;M(S)9/60;m-/61;F9/62;F(S)6/63sb No 082;m-/64;M2/66;*M(S)7/67;F12/68;F1/72	1937	1935