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Sib risk of neural tube defect: is prenatal diagnosis indicated in pregnancies following the birth of a hydrocephalic child?

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SUMMARY Recurrence frequencies of central nervous system malformations in sibs of probands with anencephalus or spina bifida range between 1% and 7%. The frequency of hydrocephalus among sibs of such probands is low (0·21%) but, nevertheless, is increased 2 to 5-fold when compared to general population frequencies. Anencephalus and spina bifida cystica were observed in 1·65% of sibs of children with hydrocephalus, a 2- to 8-fold increase over the population frequencies. These data indicate that some aetiological factors may be common to all three malformations. The risk figure of 1·65% for anencephalus and spina bifida in sibs born after the birth of a hydrocephalic proband constitutes sufficient indication for prenatal diagnosis by alphafetoprotein determination of the amniotic fluid.

An increased frequency of sibs with either anencephalus or spina bifida exists following the birth of a proband with either of these conditions. However, little has been published concerning hydrocephalus in sibs of children with anencephalus or spina bifida, and, conversely, the occurrence of the latter two malformations after the birth of a hydrocephalic proband (Tables 1, 2, 3). Mid-trimester alphafetoprotein levels of amniotic fluid at present serve as a prenatal indicator of 'open' malformations of the fetal central nervous system (CNS), that is, anencephalus and spina bifida cystica. Therefore, the risk to sibs of hydrocephalic children of having an open CNS malformation is of great practical importance.

Methods

Estimates of these risks have been obtained from pertinent data in published reports as summarised in Tables 1, 2, and 3. These data represent the published surveys which include detailed information on sibs of probands with CNS malformations. Naturally the studies are not completely comparable since methods of authors differed. In these studies, when definitions were stated, the 'anencephalus' group was defined as those patients with and without spina bifida and also iniencephalus; the 'spina bifida' group as those patients with and without hydrocephalus and also encephalocele, but not occult spina bifida; and the 'hydrocephalus' group as the patients with hydrocephalus apparent in the perinatal period and without spina bifida. Stillbirths were included by some authors. The population incidence of CNS malformations (Tables 1, 2, 3) sometimes refers only to anencephalus and spina bifida. Though Yen and MacMahon (1968) stated that their data included former data of MacMahon *et al.* (1953), both surveys were included, since the former contains detailed information on the hydrocephalic sibs of probands.

Affected sibs were not classified as being born before or after the birth of the proband, since such information was sometimes lacking. The χ^2 test of heterogeneity (Snedecor, 1956) was calculated on the total number of healthy and affected sibs in each survey.

Results

Morbidity among sibs of probands with anencephalus and spina bifida is shown in Tables 1 and 2. The frequency of CNS malformations among sibs of children with anencephalus is 1 to 6% (Table 1) and with spina bifida is 2 to 7% (Table 2). The occurrence of hydrocephalus in sibs of probands with either CNS malformation is 0 to 0·8%. However, since not all authors included hydrocephalus as a CNS malformation, and some included it among 'other malformations', the frequency may be higher. The χ^2 test of heterogeneity of healthy and affected sibs

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Table 1 *Morbidity among sibs of anencephalic probands*

Survey	*Population incidence*		*No. of probands*	*No. of affected sibs*				*% of affected sibs*	
	CNS malformations (%)	*Anencephalus (%)*		*Total*††	*Anencephalus*	*Spina bifida*	*Hydrocephalus*	*Total*	*Hydrocephalus only*
Böök and Rayner (1950), Lund	—	0·06	67	1/88	0	1	0	1·14	0
MacMahon *et al.* (1953), Rhode Island	0·54	0·19	162	6/119	2	3	1	5·04	0·84
Frézal *et al.* (1964), Paris	—	0·05	254	9/423	5	3	1	2·13	0·24
Williamson (1965), Southampton	0·60	0·20	27	2/41	2	0	0	4·88	0
Carter *et al.* (1968), Wales	0·81	0·35	245	15/424	7	8	0	3·54	0
			116	15/284	9	5	1	5·28	0·35
Smithells *et al.* (1968), Liverpool	—	—	598	44/887	26	13	5	4·96	0·56
Yen and MacMahon (1968), Rhode Island	—	—	452	26/573	14	12	5/1263*	4·54	0·40
Czeizel and Révész (1970), Budapest	0·37	0·11	151	7/186	3	4	1/579*	3·76	0·17
Richards *et al.* (1972), Glasgow	0·56	0·28	146	26/454	18	8	0	5·73	0
Carter and Evans (1973), London	0·30	0·14	392	43/754	24	17	2†	5·70	0·26

*, no. of hydrocephalics among sibs of probands with anencephalus or spina bifida;
†, listed in 'other malformations';
††, χ^2 test of heterogeneity between affected and non-affected sibs in 11 studies, $\chi^2 = 13{\cdot}76$, df = 10, P = 0·1855.

is high for spina bifida (Table 2; P = 0·002) indicating that the results of the morbidity surveys in sibs of spina bifida patients are not homogeneous. On the other hand, the results of sibs of probands with anencephalus (Table 1; P = 0·186) and hydrocephalus (Table 3; P = 0·347) are homogeneous. Sibs of children with hydrocephalus often have hydrocephalus (0 to 4%), but also may have anencephalus or spina bifida (0 to 3%) (Table 3). However, the possibility should be considered that some patients, both probands and sibs, diagnosed as hydrocephalics in fact had hydrocephalus secondary to spina bifida which was either not recognised or not recorded in the medical notes. Subgroups within Table 3, that is, sibs affected with anencephalus and/or spina bifida among all sibs, and those affected with hydrocephalus among all sibs, do not deviate from homogeneity (P = 0·370 and P = 0·404, respectively).

The frequency of affected sibs for each of the three CNS malformations, as calculated from the above data (Table 4), shows that the highest risk to sibs is for the same malformation as observed in the proband: anencephalus 2·6%, spina bifida 3·0%, and hydrocephalus 1·6%. The frequency of hydrocephalus among sibs of probands with anencephalus or spina bifida (21/9794) is 0·21%. Though this figure is low, it is still two to five times greater than the population frequencies. The frequency of anencephalus and spina bifida among sibs of children with hydrocephalus (16/1972) is 1·6%, two to eight times the population frequencies.

Conclusions

These results lead to two conclusions:

(1) Common aetiological factors may exist in all

Table 2 *Morbidity among sibs of probands with spina bifida*

Survey	*Population incidence*		*No. of probands*	*No. of affected sibs*				*% of affected sibs*	
	CNS malformations (%)	*Spina bifida (%)*		*Total*†	*Anencephalus*	*Spina bifida*	*Hydrocephalus*	*Total*	*Hydrocephalus only*
MacMahon *et al.* (1953), Rhode Island	0·54	0·25	215	11/166	5	6	0	6·63	0
Lorber (1965), Sheffield	0·50	—	539	85/1256	22	54	9	6·77	0·72
Williamson (1965), Southampton	0·60	0·32	59	7/119	1	6	0	5·88	0
Carter *et al.* (1968), Wales	0·81	0·41	276	35/518	15	20	0	6·76	0
			147	17/336	5	12	0	5·06	0
Smithells *et al.* (1968), Liverpool	—	—	729	33/903	20	11	2	3·65	0·22
Yen and MacMahon (1968), Rhode Island	—	—	585	32/690	14	18	5/1263*	4·64	0·40
Czeizel and Révész (1970), Budapest	0·37	0·18	292	9/393	0	9	1/579*	2·29	0·17
Richards *et al.* (1972), Glasgow	0·56	0·28	172	25/450	6	19	0	5·56	0
Carter and Evans (1973), London	0·30	0·15	478	25/730	12	13	0	3·42	0

*, no of hydrocephalics among sibs of probands with anencephalus or spina bifida;
†, χ^2 test of heterogeneity between affected and non-affected sibs in 10 studies, $\chi^2 = 26{\cdot}47$, df = 9, P = 0·0022.

Table 3 *Morbidity among sibs of hydrocephalic probands*

Survey	*Population incidence*		*No. of probands*	*No. of affected sibs*				*% of affected sibs*	
	CNS malformations (%)	*Hydrocephalus (%)*		*Total**	*Anencephalus*	*Spina bifida*	*Hydrocephalus*	*Total*	*Anencephalus and spina bifida*
MacMahon *et al.* (1953), Rhode Island	0·54	0·09	86	1/54	0	0	1	1·85	0
Lorber and Bassi (1965), Sheffield	—	—	51	4/90	1	2	1	4·44	3·33
Williamson (1965), Southampton	0·60	0·09	15	1/31	0	0	1	3·22	0
Lorber and De (1970), Sheffield	—	—	187	13/338	4	4	5	3·85	2·37
Carter *et al.* (1968), Wales	0·81	0·04	26	2/57	0	0	2	3·51	0
			19	1/52	1	0	0	1·92	1·92
Smithells *et al.* (1968), Liverpool	—	—	111	10/206	4	0	6	4·85	1·94
Czeizel and Révész (1970), Budapest	0·37	0·08	91	0/144	0	0	0	0	0

*, χ^2 test of heterogeneity between affected and non-affected sibs in 8 studies, $\chi^2 = 7{\cdot}85$, df = 7, P = 0·3466.

Table 4 *CNS malformations: summary of frequencies in sibs*

Malformation in proband	*Population incidence (%)*	*Affected sibs*					
		Total no.	*%*		*Anencephalus*	*Spina bifida*	*Hydrocephalus*
Anencephalus	0·05–0·35	194/4233	4·58	no.	110	74	10
				%	2·60	1·75	0·24
Spina bifida	0·15–0·41	279/5561	5·02	no.	100	168	11
				%	1·80	3·02	0·20
Hydrocephalus	0·04–0·09	32/972	3·29	no.	10	6	16
				%	1·03	0·62	1·65

three CNS malformations, as indicated by the high frequency of spina bifida among sibs of anencephalics and vice versa, and by the increased frequency of hydrocephalus among the sibs of probands with anencephalus and/or spina bifida and vice versa.

(2) For practical purposes, the results in Table 4 show that the frequency of anencephalus and spina bifida among 972 sibs of children with congenital hydrocephalus was 1·65%. Since a risk figure of 1% is usually considered adequate to suggest prenatal diagnosis by amniocentesis, we propose that alphafetoprotein determination in amniotic fluid is indicated in mothers of children with hydrocephalus.

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