Sexes of affected cases in sibships containing two or more members with anencephaly or spina bifida

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SUMMARY A study has been made of the sexes of the affected within sibships containing two or more members with anencephaly or spina bifida (ASB). There is no clear evidence for variation between ASB-prone women in their propensity to bear affected cases of one sex rather than the other. It is suggested that the point should be regarded as open until further data have settled the issue.

It is well established that across populations (Knox, 1974), and within populations (Knox, 1974; James, 1979), the prevalence of anencephaly at birth correlates with the sex ratio of the affected, higher prevalences being associated with female cases. So one might try to explain the aetiology of anencephaly by proposing that it has two sorts of cause, *viz* (1) an environmental cause which affects predominantly females, and (2) another cause which may be genetic or environmental and which affects the sexes in roughly equal numbers.

If this were so, then it may be supposed that women who are known to be at high risk of bearing anencephalics are, in general, at risk on account of only one of these two sorts of cause and not both. If that were so then we might expect anencephalic-prone women to be of two sorts, those inclined to bear cases of both sexes in about equal numbers, and those inclined to bear female cases. And if that were so, then the distribution of the sexes of the affected in sibships with more than one case would not be binomial, but would show Lexis variation (Edwards, 1960). For instance, if attention were confined to sibships containing exactly two anencephalics, there would be excesses of MM and FF pairs, and a deficit of MF pairs, as contrasted with chance expectation. It seemed worth testing this deduction.

Materials and method

Published reports were scanned for family histories containing two or more cases of anencephaly or spina bifida (ASB). Also, letters were despatched to

workers who (to judge from their papers) might have unpublished data of this sort.

Care has to be exercised in the analysis of such data. If we denote anencephaly by A, and spina bifida by S, then the sex combinations within the three sorts of sibship AA, AS, and SS have to be examined separately. This is because it is known that (1) anencephaly has a lower sex ratio than spina bifida, and (2) the same malformation tends to recur within sibships (Smithells *et al.*, 1968; Richards *et al.*, 1972; Carter, 1974).

Unless the data are separated in the manner suggested, any observed Lexis variation might simply be attributed to excesses of male-male spina bifida pairs and female-female anencephaly pairs.

To assess whether the observed distributions departed from binomial expectation, the simplified maximum likelihood method of Robertson (1951) may be used.

Consider a sample of N sibships, each containing exactly n affected, where $n = m + f$ and m is the number of males affected and f the number of females affected. Then each sibship is assigned a score

$$K = \frac{1}{2} \left[\frac{f(f-1)}{q^2} + \frac{m(m-1)}{p^2} - \frac{2fm}{pq} \right]$$

where p is the proportion of males among affected in the sample, and $q = 1 - p$. Now take

$$\Sigma I = \frac{Nn(n-1)}{2p^2q^2}.$$

Let the sum of the N values of K be ΣK : then Robertson showed that $\Sigma K / \Sigma I$ is distributed

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normally with sampling variance $1/\Sigma I$. For the present type of data, K is a particularly convenient statistic because $\Sigma \Sigma K / \Sigma \Sigma I$ is also distributed normally with sampling variance $1/\Sigma \Sigma I$, where summation may be carried out over sibships with different numbers of affected (and with different values of p and q). Hence, one can test a whole range of material for a tendency towards over- or under-dispersion.

Results

Tables 1, 2, and 3 give the frequencies of MM, MF, and FF pairs of affected within sibships. Table 1 suggests that (1) overall there is some tendency for anencephalics to be of the same sex within sibships, but that (2) this tendency is largely (if not wholly) because of the varying sex ratios of the affected across samples (corresponding, presumably, to the known variation in sex ratio of anencephalics across the country).

On the face of it, one might draw a similar inference from Table 2. However, there is little

Table 1 *Combinations of sexes of affected within sibships containing exactly 2 anencephalics*

Source	MM	MF	FF
Carter <i>et al.</i> (1968)	0	3	5
Carter and Evans (1973)	2	7	9
Williamson (1965)	0	1	1
Polman (1951)	0	1	2
Fuhrmann <i>et al.</i> (1971)	1	0	0
MacMahon <i>et al.</i> (1953)	2	0	5
Murphy (1936)	1	2	2
Czeizel and Revesz (1970)	0	1	1
Richards <i>et al.</i> (1972)	3	5	10
Ismail (1966)	0	5	1
Professor Carter	0	2	6
Mrs Fedrick	0	3	2
Professor Harris	0	5	4

For the pooled data in this Table, $\Sigma I = 2187$, $\Sigma K = 32.5$, $z = 0.7$: not significant. When the distributions are treated separately, $\Sigma \Sigma I = 2775.7$, $\Sigma \Sigma K = -4.93$, $z = -0.09$: not significant.

Table 2 *Combinations of sexes of affected within sibships containing exactly 2 spina bifidas*

Source	MM	MF	FF
Carter <i>et al.</i> (1968)	8	11	2
Carter and Evans (1973)	3	5	3
Williamson (1965)	0	1	1
Penrose (1946)	0	3	2
MacMahon <i>et al.</i> (1953)	4	3	3
Murphy (1936)	0	2	1
Czeizel and Revesz (1970)	0	3	2
Richards <i>et al.</i> (1972)	4	5	10
Professor Carter	0	4	11
Dr Lorber	16	32	19
Professor Harris	3	4	3

For the pooled data in this Table, $\Sigma I = 2758$, $\Sigma K = 81.48$, $z = 1.55$, $P = 0.06$ (one-tailed). When the distributions are treated separately, $\Sigma \Sigma I = 3817$, $\Sigma \Sigma K = 10.95$, $z = 0.18$: not significant.

Table 3 *Combinations of sexes of affected within sibships containing exactly one spina bifida and one anencephalic*

Source	MM	MF	FF
Carter <i>et al.</i> (1968)	1	4	11
Carter and Evans (1973)	2	13	6
Williamson (1965)	0	0	1
Penrose (1946)	0	1	1
Polman (1951)	0	2	0
MacMahon <i>et al.</i> (1953)	3	6	8
Murphy (1936)	0	1	1
Czeizel and Revesz (1970)	0	2	1
Richards <i>et al.</i> (1972)	2	8	4
Book and Rayner (1950)	0	1	0
Professor Carter	1	6	6
Dr Lorber	5	11	16
Mrs Fedrick	0	1	1
Professor Harris	1	19	6

For the pooled data in this Table, $\Sigma I = 2973$, $\Sigma K = -61.3$, $z = -1.12$: not significant. When the distributions are treated separately, $\Sigma \Sigma I = 3283$, $\Sigma \Sigma K = -57$, $z = -0.99$: not significant.

evidence that the sex ratio of spina bifida varies between samples. If it does not, then it would be legitimate to pool all the data in Table 2. If that is done, then the evidence for overdispersion may be assessed from a z score of 1.55 , $P = 0.06$ (one-tailed). Thus, even after pooling, the evidence is not strong.

The data in Table 3 are not of any obvious relevance to the aetiology of ASB. Since the sex ratio of anencephaly is lower than that of spina bifida, the distribution of the combinations of the sexes of pairs of affected (one spina bifida and one anencephalic) within sibships is subject to Poisson variation (not to be confused with Poisson distributions) (Edwards, 1960). It is a standard result in probability theory that Poisson variation is associated with a lower variance than the binomial with the same mean. Therefore, the subnormal dispersion of the distributions in Table 3 (and in the pooled data in that Table) may be ascribed to this.

Discussion

It is noteworthy that the test failed to detect significant Poisson variation in the distributions in Table 3. This suggests that the failure to find significant Lexis variation in Table 1, at any rate, may be because of the weakness of the test, rather than the absence of the variation. We may be failing to find a needle that is in the haystack.

It seems likely that this problem will not be solved until more data are forthcoming. Accordingly, I should be grateful if anyone with further data on this point would send them to me.

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