Journal of Medical Genetics, 1979, **16**, 384–388

The sex ratio in spina bifida

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SUMMARY Published reports on the sex ratio of spina bifida have been reviewed. With one exception, there seems to be no evidence of variation in the sex ratio of spina bifida. In particular, unlike anencephaly, the sex ratio of spina bifida seems to be unrelated to the prevalence of the malformation: this (M/(M+F)) is of the order of 0·44 in respect of all spina bifida births (liveborn and stillborn). The sex ratio of spina bifida in Negroes does not seem to differ from that in whites (though the data on this point are not numerous). The exception noted above concerns spina bifida occurring in twins: these cases are disproportionately often female. The point stands in need of explanation.

There is considerable variation in the rates of anencephaly and of spina bifida. In this country, much of this variation seems to be environmental in origin, being associated with such variables as social class and season. In general, the rates of the two malformations vary in unison with these variables. For instance, in regard to UK data for 1958, Butler and Alberman (1970) found that the rates of both malformations at birth in social classes 4 and 5 were at least double the rates in classes 1 and 2. Rogers and Weatherall (1976) reported that for England and Wales 1964–1972, the two malformations had roughly equal amplitudes of seasonal variation, the month of highest risk having a rate about 15% higher than the month of lowest risk. Rogers and Weatherall (1976) also reported regional variations in the two malformations with maximum risks for both in Wales, and minimum risks in East Anglia: the range of risk was about two-fold for both malformations.

The two malformations have shown parallel secular trends in Dublin 1900–1965 (Elwood, 1973), in Berlin after the second world war (Lenz, 1965), in New York State 1945–1971 (Janerich, 1973), in Birmingham 1942–1949 (MacMahon *et al.*, 1951), and in Boston 1930–1965 (Naggan, 1969).

Furthermore, it is well established that cases of anencephaly and spina bifida tend to recur within the same sibships (Carter *et al.*, 1968; Smithells *et al.*, 1968), so the evidence is overwhelming that the two malformations share some cause(s).

It has been shown that the sex ratio of anencephalics correlates with the prevalence at birth of anencephaly both across populations (Knox, 1974) and within populations (James, 1979). It therefore seemed worth reviewing published reports to see whether this feature of anencephaly was also characteristic of spina bifida.

Received for publication 29 December 1978

Materials and methods

The sex ratio of spina bifida may be estimated from four different sorts of material: (1) data from studies which ascertain all affected cases in a specified population; (2) data from cases which have been born alive (for example, birth certificates, death certificates, or records of infant mortality); (3) data from cases which were stillborn; and (4) hospital records. It is important to separate these various sorts of data because of a source of bias in estimating the spina bifida sex ratio. As in anencephaly, the sex ratio (proportion of males) of liveborn spina bifida cases is higher than the sex ratio of stillborn cases: in other words, female cases are less likely to be born alive (Record and McKeown, 1949). Therefore, studies which are based on liveborn cases (and which thus fail to take account of stillborn cases) are likely to yield overestimates of the sex ratio of all cases. Similarly, studies based on stillborn cases tend to underestimate this sex ratio. It is not known that estimates based on hospital records are subject to bias, because it is not clear that the same proportion of stillborn and liveborn cases would be born in hospital. However, the possibility exists, so data of this sort have been kept separate.

The Tables give data from selected studies: the only basis for selection has been to limit the review to reasonably large samples.

Results

VARIATION OF SEX RATIO ACROSS SAMPLES

It seems that the best data for testing this variability are those in Table 1. In this Table, the values are arranged in order of the estimated prevalence rates. Visual inspection suggests that there is no correlation between these rates and the corresponding sex ratios, and this judgment is confirmed by the fact that the χ^2_{16} across the two columns of male and female frequencies takes the value 7·82, P≏0·9. Thus, there is no indication in these data that the sex ratio of spina bifida varies from one sample to another, even less with the prevalence rates. (It should be noted that all the samples in Table 1 are mutually exclusive.)

Table 2 gives the sexes of the hospital births. There is no significant variation between the sex ratios in the various samples in this Table ($\chi^2 = 1{\cdot}50$, df 3, $0{\cdot}7>P>0{\cdot}6$), and there is no significant difference between the overall sex ratio in this Table and that in Table 1 ($\chi^2 = 0{\cdot}8$, df 1, $0{\cdot}4>P>0{\cdot}3$).

Table 3 gives data on liveborn cases. There is significant variation between the sex ratios in this Table ($\chi^2 = 28{\cdot}90$, df 9, $P<0{\cdot}001$), and the overall sex ratio in this Table is significantly different from that in Table 1 ($\chi^2 = 7{\cdot}54$, df 1, P≏0·005).

The difference between the overall sex ratios in Tables 1 and 3 may reasonably be ascribed to the fact that female cases are more likely to be stillborn than male cases.

The only Table containing variation of sex ratio between samples is Table 3. It seems likely that part of this variation is the result of a variable level of selection when cases are chosen to be treated. Females are, in general, more severely affected than males, so (to varying degrees) they would be selected against in the decision to refer for surgery. Another possible cause of the variation in this Table is that variable health standards might be expected to alter the proportions of the severely affected (predominantly female) cases which are liveborn rather than stillborn. Lastly, since among the liveborn cases females are more severely affected than males, it follows that the subsequent 'deaths' (ascribed to the malformation) would be expected to contain a high proportion of females, because some of the survivors (mostly males) would escape from such records altogether to die eventually of some unrelated cause. Therefore, death certificates would be expected to contain a higher proportion of females than birth notifications.

Table 2 *Numbers of male and female spina bifida cases ascertained through hospital records*

Authors	*Males*	*Females*	*Sex ratio (% male)*
Stevenson *et al.* (1966)	161	192	46
MacMahon *et al.* (1953)	175	208	46
Collmann and Stoller (1962)	43	45	49
Book (1951)	16	27	37
	≶ 395	472	46

The data of Stevenson *et al.* (1966) were collected from 24 different reporting centres around the world. There is no evidence for heterogeneity (as tested by a χ^2 analysis) between the sex ratios of spina bifida reported by these different centres.

Table 1 *Numbers of male and female spina bifida cases ascertained in population studies*

Authors	*Place*	*Years*	*Males*	*Females*	*Sex ratio (% males)*	*Estimated rate of spina bifida per 1000 births*
Elwood and Nevin (1973)	Belfast	1964–68	76	109	41	4·5
Laurence *et al.* (1968)	S. Wales	1956–62	200	225	47	4·1
Smithells and Chinn (1965)	Liverpool	1960–63	117	139	46	3·5
Williamson (1965)	Southampton	1958–62	23	36	39	3·2
Wilson (1970)	Glasgow	1964–65	123	166	43	2·8
Record and McKeown (1949)	Birmingham	1940–47	167	221	43	2·5
Record and McKeown (1949)	Scotland	1939–45	654	858	43	2·3
Spellman (1970)	Cork	1961–66	32	38	46	2·1
Horowitz and McDonald (1969)	Quebec	1961–65	529	699	43	1·9
Rogers and Weatherall (1976)	England and Wales	1964–72	5697	7202	44	1·7
Czeizel and Revesz (1970)	Budapest	1963–67	211	287	42	1·6
Alter (1962)	Charleston, SC (white)	1946–55	22	22	50	1·5
Alter (1962)	Charleston, SC (Negro)	1946–55	5	5	50	0·6
Gittelsohn and Milham (1962)	New York State	1945–59	1304	1709	43	1·2
Field (1978)	New South Wales	1965–73	395	468	46	1·1
Naggan (1971)	Israel	1958–68	129	177	42	0·6
Granroth *et al.* (1977)	Finland	1965–73	111	127	44	0·4
			≶ 9795	12488	44	

(1) In addition to the population studies cited in the Table, two other authors seem to have obtained representative samples of spina bifida (liveborn and stillborn) without estimating the numbers of related normal births. These were Polman (1951), who ascertained 22 males and 24 females (48% males) in Groningen and Drenthe (Holland), and Timson (1969), who ascertained 25 males and 34 females (42% males) in Manchester and district.

(2) Data from Butler and Alberman (1970), in respect of England, Wales, and Scotland for March, April, and May 1958, and from Carter and Evans (1973), in respect of Greater London 1965–1968, are not included in Table 1 because some of these data are already included in the Table.

Table 3 *Numbers of male and female cases of liveborn spina bifida*

Authors	*Males*	*Females*	*Sex ratio (% male)*	*Source of data*
Ivy (1963)	399	397	50	Birth certificates
Conway and Wagner (1965)	502	533	48	Birth certificates
Ivy (1957)	414	449	48	Birth certificates
Hay (1971)	2372	2898	45	Birth certificates
Westlund (1969)	172	220	44	Death certificates
Doran and Guthkelch (1961)	145	162	47	Patients (presumably alive and being considered for surgery)
Siris (1936)	46	38	55	Live patients
Ingraham and Swan (1943)	250	296	46	Live patients
Schwidde (1952)	86	139	38	Live patients
Registrar General for Scotland 1961–1976	553	769	42	Infant deaths
	≶ 4939	5901		

VARIATION OF SEX RATIO WITHIN SAMPLES

Tables 4a, b, and c give the sexes of the stillborn cases reported in Scotland 1961–1976. The overall sex ratio of these cases is significantly different from those in Table 1 ($\chi^2 = 5{\cdot}3$, $P \simeq 0{\cdot}02$), but there are no detectable trends of sex ratio within these Tables. Table 4d gives the infant deaths (deaths in the first year) attributed to spina bifida in Scotland 1961–1976. It will be seen that even within this substantial sample, there is no discernible trend of sex ratio with social class.

Table 4a *Numbers of male and female spina bifida stillbirths by social class, Scotland 1961–1976*

	Social class *1*	*2*	*3*	*4*	*5*	*Total*
Male	4	12	82	26	26	150
Female	11	16	146	48	32	253
Sex ratio (% males)	27	43	36	35	45	37

Table 4b *Numbers of male and female spina bifida stillbirths by maternal age, Scotland 1961–1976*

	Maternal age *<20*	*20–24*	*25–29*	*30–34*	*35–39*	*40+*	*Total*
Male	25	57	44	22	13	4	165
Female	31	81	83	34	28	9	266
Sex ratio (% males)	45	41	35	39	32	31	38

Table 4c *Numbers of male and female spina bifida stillbirths by parity, Scotland 1961–1976*

	Parity *0*	*1*	*2*	*3*	*4+*	*Total*
Male	63	33	27	16	11	150
Female	106	55	36	29	26	252
Sex ratio (% males)	37	37	43	36	30	37

Table 4d *Infant deaths attributed to spina bifida by sex and social class, Scotland 1961–1976*

	Social class *1*	*2*	*3*	*4*	*5*	*Total*
Males	19	36	311	117	70	553
Females	21	52	436	148	112	769
Sex ratio (% males)	48	41	42	44	39	42

(1) When the data in this Table are pooled with those in Table 4a (thus comprising most of the spina bifida cases born in Scotland 1961–1976), the sex ratios (% males) of the cases born in social classes 1, 2, 3, 4, and 5 are 42, 41, 40, 42, and 40.
(2) The overall sex ratio in this Table (41%) is lower than that in Table 1: this is presumably because Table 4d includes no case who survived for more than one year after birth.
(3) The Registrar General for Scotland seems not to publish data on infant deaths by cause, sex, maternal age, or parity, so Tables 4b and c cannot be augmented in this way with infant deaths.

VARIATION OF SEX RATIO BY RACE AND TWINNING

The failure to find variation in the sex ratio of spina bifida raises the question of whether this sex ratio varies with any variable. Accordingly, data were reviewed in regard to race and twinning.

Race

Hewitt (1965) suggested, without offering supporting data, that spina bifida in Negroes has a ' distinctly masculine sex ratio' in contrast to that in whites. Table 5 summarises all the data I have been able to

Table 5 *Numbers of male and female Negro cases of spina bifida*

Authors	*Males*	*Females*	*Sex ratio (% males)*
Gittelsohn and Milham (1962)	17	25	40
Alter (1962)	5	5	50
Stevenson *et al.* (1966)	9	2	82
	≶ 31	32	49

Table 5 cites Gittelsohn and Milham (1962) who report data in respect of Upstate New York 1945–1959. Elsewhere (1965), they report on the data for Upstate New York 1950–1960. These latter data give 20 male and 22 female non-white cases of spina bifida.

locate on the point. There seems no strong evidence here for Hewitt's claim though, admittedly, the data are not numerous.

Twinning

Lorber and Rogers (in the Table privately circulated in supplement to their 1977 paper) cite data which suggest that, in both same-sexed and opposite-sexed twin pairs, the members affected with spina bifida are significantly more likely to be female than are singleton cases.

Comment

The general failure to find variability in the sex ratio of spina bifida is puzzling, bearing in mind (1) the known variation of the sex ratio of anencephaly with the prevalence of anencephaly, and (2) the strong evidence that the two conditions share a cause or causes.

This lack of variation seems to constitute evidence against the hypothesis of Knox (1974), and it points to the necessity of accounting for the differences between the epidemiologies of anencephaly and spina bifida.

The variation of the sex ratio of anencephaly with its prevalence has led me to speculate (James, 1979) that it has two sorts of cause: (1) an environmental cause which produces predominantly female cases; and (2) another cause (either environmental or genetic) which produces the two sexes in roughly equal numbers.

At first sight, it is tempting to suppose that since the sexes of cases of spina bifida are apparently of roughly equal numbers, spina bifida may be produced by the second of these two causes hypothesised to be responsible for anencephaly. The case against this supposition is that spina bifida, though it may perhaps not be subject to so much environmental variation as anencephaly, certainly does show a great deal of environmental variation. The inference seems to be that some environmental cause produces both anencephalics which are predominantly female, and spina bifida cases of both sexes in roughly equal numbers.

I suggest that the same environmental teratogen acts at slightly different times in gestation to produce these two sorts of effect, very early to produce anencephaly and slightly later to produce spina bifida. The different sex ratios would be accounted for by supposing that: (1) 'delayed' embryos are more susceptible to the teratogen; (2) initially, female zygotes are more 'delayed,' are formed later, than male zygotes (James, 1976; Roberts, 1978); and (3) zygotes which are initially delayed progressively 'catch up' during the course of gestation.

I am supported by the National Fund for Research into Crippling Diseases.

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Note added in proof

Since this paper was prepared, data on a large sample of liveborn Negro spina bifida cases have been published (Taffel, 1978). When these are pooled with the data cited above, there are 131 male and 109 female Negro spina bifida cases. Tested against a sex ratio of 0·46 (as suggested for liveborn cases in Table 3 above), these data yield a χ^2 of 7·12, $P<0·01$. So it seems that Negro cases are disproportionately often male.

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