Multiple sclerosis and birth order

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SUMMARY Studies on the birth order of patients with multiple sclerosis have yielded contradictory conclusions. Most of the sets of data, however, have been tested by biased tests. Data that have been submitted to unbiased tests seem to suggest that cases are more likely to occur in early birth ranks. This should be tested on further samples and some comments are offered on how this should be done.

Considerable interest attaches to the question of whether patients suffering from multiple sclerosis tend to occupy non-random positions in their sibships. This stems from the hypothesis that multiple sclerosis, perhaps like poliomyelitis, may be dependent on an infection that is harmless in early childhood but pathogenic if it first occurs later in life. If this were so then one would expect later born members of sibships to be less at risk, having been exposed to such infection by an older sibling who had contacted it at school. For this reason, published data on birth order and multiple sclerosis will be briefly reviewed.

The data

Six studies were located (based on nine samples of patients) relating multiple sclerosis to birth order.¹⁻⁶ Table 1 summarises the results of these studies. Significant excesses and significant deficit of early born patients have both been reported.

Discussion

In this note a "positive" birth order effect refers to a tendency for patients to be born late in their sibships; and a "negative" effect will refer to patients being

Table 1 Results of studies of birth order and multiple sclerosis

Authors	Sample size	Result	Significance	Test
Pratt ¹	67	Slight positive effect	Not stated	Turner & Penrose ^a
Cendrowski ²	240	Slight positive effect	NS	Slater ^a and Turner & Penrose ^a
	147	Slight positive effect	NS	Slater ^a and Turner & Penrose ^a
Alperovitch <i>et al</i> ³	107	Positive effect	0.01	Slater ^a
Isager <i>et al</i> ⁴	46	Negative effect	0.05	Case control
Visser <i>et al</i> ⁵	2119	Slight positive effect in large sibships	NS	Greenwood & Yule ⁷
	65	Negative effect	0.05	Case control
Cripps <i>et al</i> ⁶	175	No appreciable effect		Slater ^a
	36	No appreciable effect		

NS=Not significant.

(1) The significance level cited in respect of the smaller sample of Visser *et al*⁵ is calculated thus. This was a study of 65 cases each matched with a control. Each individual was assigned to the category "early born" (ranks 1 or 2) or "later born" (ranks 3+). Of the 65 pairs, in 36 the case and the control were in the same category. Of the remaining 29, in 19 the case was early born and the control later born and in 10 the case was later born and the control early born. The chi-squared on these two values of 10 and 10 is 2.8, and this is just significant (one-way) at the 0.05 level.

(2) It is not clear whether Isager *et al*⁴ controlled for family size. If they did not, then their significant result suggests *either* that cases occur in early birth ranks *or* that cases are more likely to occur in small sibships (or both). Any of these interpretations seem to support the hypothesis outlined in the introduction.

born early. I should like to suggest a reason for the contradictory nature of the findings reviewed here. It is that all of the samples interpreted as exemplifying a positive effect were tested in one way; and those interpreted as exemplifying a negative effect were tested in another. The samples interpreted as suggesting a positive birth order effect had all been submitted to the tests of Greenwood and Yule,⁷ Turner and Penrose,⁸ or Slater.⁹ All these tests are based on the assumption that if a subject within a given age range is chosen at random from a sibship of size N, then his probabilities of being 1st, 2nd, 3rd . . . Nth-born are all identical and equal to 1/N. Though this assumption is intuitively true, it is in fact itself dependent on the assumption that the population family size distribution remains stable through time. This latter assumption is false: family sizes have declined considerably during the present century. The point may be appreciated by considering a randomly ascertained person who comes from a sibship of size 10: today he is much more likely to be the last born than the first born, being the survivor of a sort of sibship that is disappearing. The point is further illustrated in hypothetical data (table 2) and in empirical data presented by Hare and Price.¹⁰ In particular these authors found that at present the population contains more later born than early born. This is simply because family size has decreased during the present century.

Table 2 Hypothetical data (after Hare & Price¹⁰)

1	2	3	4	5	6	7
1	2	3	4	5	6	
	1	2	3	4	5	
		1	2	3	4	5
			1	2	3	4
				1	2	3

Each row represents the siblings (in rank order) born to families begun at a particular period. Successive rows represent families born at later periods and are progressively smaller in size. The individuals between the vertical lines represent those sampled within a given age range. Those to the left are too old, and those to the right too young. The sample contains an over representation of the later born members of large families and an under representation of the later born in small families.

Accordingly I suggest that the positive birth order effect reported in respect of some samples of patients with multiple sclerosis is due to test bias rather than to any feature of the disease. The only two samples of such patients that were not subjected to a potentially biased test were that of Isager *et al.*,³ and one of those of Visscher *et al.*⁵ It is noteworthy that they both yielded suggestions of a negative birth order effect. Bearing in mind the support it offers to the hypothesis mentioned above this result is well worth efforts to replicate. Two suggestions may be made about how to avoid test bias in such a project. Berglin proposed that the patients' birth rank distributions should be

contrasted with control data derived from demographic sources.¹¹ Such a method has the merit of obviating the expense of a control group. It seems to me, however, that this method is subject to the criticism that in a disorder such as multiple sclerosis, which may be associated with social class, the distributions of birth ranks would be expected to differ from those in the parent population anyway, even if the null hypothesis were true. Accordingly I suggest that the birth ranks of samples of patients with multiple sclerosis should be contrasted with the birth ranks of controls matched for age, sex, and social class. At the same time researchers should satisfy themselves that the family size distributions of the two samples are similar. This provision is necessary because if the family size distributions are not similar then one would not expect the birth rank distributions to be similar even if the null hypothesis were true. If the family size distributions of the two samples differ then the distributions of birth ranks of patients and controls should be contrasted separately for each family size. It would be useful also to test whether the durations of birth intervals preceding cases exceed those preceding controls (for a given birth rank in a given sibship size).

References

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