

In 1977 when we were collecting the clinical information which resulted in our publication in 1982, motor nerve conduction velocity measurement was considered useful in distinguishing between demyelinating and neuronal neuropathies, that is, hereditary motor and sensory neuropathies types I and II. However, theoretical objections, as pointed out by Heimans and Lindhout, and practical application in our study showed motor velocities to be of no use in separating affected from normal in families with neuronal disease. Indeed Buchthal and Behse, in the publication referred to, found that sensory conduction abnormalities related better than motor velocities to the clinical state of the patients and biopsy appearance of the sural nerve in both neuronal and demyelinating neuropathies.

Furthermore, when the full range of possible genetic heterogeneity in the Charcot-Marie-Tooth neuropathies is taken into account to include autosomal and X linked, dominant and recessive modes of inheritance, it is clear that comprehensive electrophysiological testing is necessary both to resolve the mode of inheritance and to ascertain which family members are actually affected. This is particularly important when the proband appears to be an isolated male case because of clinically asymptomatic but mildly affected females in autosomal dominant families and the possible existence of X linked forms. It may well be that studies using the H reflex in addition to motor conduction velocity measurement and sensory conduction studies may help to resolve these problems.

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Evidence against a female specific class of neural tube defect

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The fact that the sex ratio (male/female) of anencephalic babies varies inversely with the population frequency has led to the suggestion that "some environmental factor causes predominantly female anencephalics and that another factor affects the sexes almost equally".¹ Since the sex ratio in spina bifida does not vary with population prevalence, even though spina bifida and anencephaly show similar epidemiological variations, it was inferred that the factor that caused predominantly female anencephalics caused spina bifida in roughly equal numbers.² According to this hypothesis, one would expect proportionately more females (and

thus a lower sex ratio) among the anencephalic sibs of female anencephalic probands than among the anencephalic sibs of male probands, since the former group would contain many more cases 'caused' by the female specific environmental factor. Because of the clinical implications of the hypothesis with respect to the possible effect of maternal vitamin supplementation on the frequency of neural tube defects within a family,³ we attempted to test it, using data available in the literature.

Family studies of neural tube defects were selected in which the data on probands and sibs were reported by sex and by type of defect.⁴⁻¹¹ To these we added updated data from our own study.¹² The results are summarised in the table. Patients with both anencephaly and spina bifida are classified as anencephalic (AN), and those with encephalocele as having spina bifida (SB). A family was counted once for each proband.

TABLE *Sex ratios of affected sibs in families of probands with anencephaly (AN) or spina bifida cystica (SB).*

Sibs	Proband			
	Male AN	Female AN	Male SB	Female SB
Male sibs with AN	3	15	13	8
Female sibs with AN	14	34	21	28
Sex ratio, AN sibs	0.21	0.44	0.62	0.28
Male sibs with SB	5	21	30	29
Female sibs with SB	7	23	33	22
Sex ratio, SB sibs	0.71	0.91	0.91	1.32
Unaffected male sibs	423	1027	924	1066
Unaffected female sibs	419	896	769	976
Sex ratio, unaffected sibs	1.01	1.15	1.20	1.09
Frequency of AN in sibs	2.0	2.4	1.9	1.7
Frequency of SB in sibs	1.4	2.2	3.5	2.4
Frequency of NTD in sibs	3.3	4.6	5.4	4.1

Contrary to the hypothesis, the sex ratio of the AN sibs of female AN probands (0.44, column 2) is not lower than that of the AN sibs of male AN probands (0.21, column 1). In fact the difference is in the opposite direction, though not significantly so. The sex ratio of the AN sibs of female SB probands is lower than that of male SB probands (0.28 vs 0.62) but again the difference is not significant, and the numbers are too small to carry much weight.

There is an excess of males among the unaffected sibs in all categories. While the excess in the sibs of female AN probands could reflect selective prenatal loss of female AN embryos, a similar argument would have to apply to the unaffected sibs of male SB probands. These data, therefore, provide no support for the James hypothesis.

It is interesting that the sibs of AN probands have a slightly higher frequency of AN (66/2887=2.3%) than of SB (56/2887=1.9%), whereas the sibs of SB probands have a higher frequency of SB (114/3919=2.9%) than of AN (70/3919=1.8%), suggesting that in addition to the factors contributing to the familial tendency of neural tube defects there may be one or more factors influencing the type of neural tube defect. This finding supports that of Cowchuck *et al*¹³ for cases diagnosed prenatally in the United States.

Despite numerous attempts to make sense of the familial and epidemiological variations in frequency of neural tube defects, no clear understanding emerges. Perhaps clarification will depend on better documentation of the selective prenatal loss that is undoubtedly obscuring the picture.

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