Incidence, prevalence, and gene frequency studies of chronic childhood spinal muscular atrophy

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SUMMARY A total population study of chronic childhood spinal muscular atrophy (arrested Werdnig-Hoffmann disease, Kugelberg-Welander disease, SMA type II and III) was undertaken in north-east England to establish gene and carrier frequencies, incidence, and prevalence. The incidence of this disease was 1 in 24 100 live births. Prevalence was 1.20 per 100 000 of the general population. A technique for estimating an autosomal recessive gene frequency in the known presence of dominant new mutations (or phenocopies), using data from a segregation analysis, is described. Gene frequency was in the range 0.00451 to 0.00659 (95% confidence limits), with a working estimate of 0.0055. Carrier rates for the autosomal recessive gene concerned were 1 in 76 to 1 in 111 (95% confidence limits), with a working estimate of 1 in 90 for genetic counselling purposes.

It is general clinical and genetic counselling experience that chronic childhood spinal muscular atrophy (SMA) is one of the more common fatal autosomal recessive diseases of childhood. Gene and carrier frequency rates for this condition are required for genetic counselling purposes. Accurate data would also be of value in the broader context of appraisals of monogenic disorders in general (Carter, 1977).

Previous attempts to obtain an estimate of the gene frequency of this condition have been frustrated for 3 reasons. Firstly, index cases of the disease have been impossible to identify because of nosological difficulties with other diseases involving anterior horn cell degeneration. Secondly, though the bulk of cases is known to be the result of an autosomal recessive gene (Winsor *et al.*, 1971; Emery *et al.*, 1976), until recently the proportion of dominant new mutations or phenocopies hidden in case series of index patients has been difficult to estimate. Thirdly, case referral and selection practices for this type of chronic childhood neurological illness have made published case series difficult to interpret from the point of view of disease incidence and prevalence. Most case series have been drawn from primary populations whose size and demographic composition is quite unknown.

Several recent studies have resolved these interpretational difficulties. It is now possible to identify index cases of acute fatal infantile SMA, called type I (Emery, 1971; Emery *et al.*, 1975), and adult onset SMA (Emery, 1971; Pearn, 1974a), both of which are now known to be due to different genes. By excluding such index cases from an otherwise consecutive unselected series, a body of index patients with chronic childhood SMA can be defined. Two recent studies (Bundey and Lovelace, 1975; Pearn, 1978) have provided estimates of the proportion of index cases in clinical series of chronic childhood SMA which are due to dominant new mutations, or which are indistinguishable non-genetic phenocopies; these 2 studies have given many similar results. Bundey and Lovelace (1975) estimated that a quarter of all index patients might fall into this group, and Pearn (1978) gave a bracket (95% confidence limits) of 20 to 33%. Thus, it is now possible to correct for these non-autosomal recessive cases in a gene frequency survey. Finally, a gene frequency study of the acute fatal infantile form of SMA (Pearn *et al.*, 1973; Pearn and Wilson, 1973a) established that the special demographic and topographical properties of north-east England could be exploited for incidence and prevalence studies of human disease where total population surveys are needed (Pearn, 1973).

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This paper reports the results of a total population study from north-east England over the 10-year period 1960 to 1969, to determine incidence and prevalence figures, and to provide estimates of gene and carrier frequencies for this disease.

Methods

INDEX PATIENTS

These were defined as those cases with chronic childhood SMA, who, being independently ascertained from any tracing source, brought the family to the notice of the survey. Chronic childhood SMA was defined as a progressive degenerative disease of anterior horn cells with initial proximal muscle selectivity, with clinical onset between birth and 8 years, and which did not, of itself, cause death before 18 months of age (Pearn *et al.*, 1978).

TERMINOLOGY

This disease is also called arrested Werdnig-Hoffmann disease, amyotonia congenita, chronic proximal SMA (Bundey and Lovelace, 1975), and many other names. The 4 major genetic studies of chronic SMA in childhood have failed to show more than one type of autosomal recessive disease among these patients (Winsor *et al.*, 1971; Bundey and Lovelace, 1975; Emery *et al.*, 1976; Pearn, 1978). For this reason, 'chronic childhood SMA' includes, variously, those cases earlier described as type II and type III SMA (Emery *et al.*, 1975), chronic generalised SMA (Pearn and Wilson, 1973b), and Kugelberg-Welander disease.

GEOGRAPHICAL REGION

The survey area has been defined previously (Pearn, 1973). The region includes the counties of Northumberland, Tyne and Wear, Durham, Cleveland, and part of Cumbria. This corresponds, before the 1973 administrative renaming of the region, to the county of Northumberland, the city and county of Newcastle-upon-Tyne, the county of Durham, the Teesside conurbation of North Yorkshire, and the county of Cumberland (Department of Health and Social Security, UK, 1975). The survey region was wholly within the catchment area of the Regional Neurological Centre, and was part of the Newcastle Hospital Region as officially defined. The diagnostic, clinical management, and topographical features within this Region meant that every case of this disease diagnosed in the period 1956 to 1972 was traced in initial case finding. For the gene frequency studies, the decade 1960 to 1969 was selected because demographic data were complete for these years. The year 1971 was used for prevalence studies, as all living patients were able to be traced and personally re-examined, and accurate census data were available.

DEMOGRAPHIC DATA

Information about the general population, from which index patients were drawn, has been previously reported (Pearn, 1973). Census Data (1971) were also used and, in addition, the 10 Medical Officers of Health for the 5 counties concerned provided exact numbers of live births, by year, for the period of the survey. A correction for these raw live birth figures was required to take into account those children dying from causes other than chronic SMA. It is now known that 99% of index patients are diagnosed before their 5th birthday (Pearn *et al.*, 1978). An age-specific death rate for each year of the study was estimated from the Registrar General's infant mortality tables (Registrar General, 1972a), and from a combination of live birth figures (Registrar General, 1972b) and actual numbers of deaths by age at death and by year (Registrar General, 1972c). In addition, supplementary unpublished data were given by each of the 10 Medical Officers of Health concerned. These death rates, specific for the region of the study, were obtained for each year of age up to the 5th birthday. From these estimates, figures were obtained of the number of children born in each year of the survey who were still alive at their 5th birthday, when the disease, if present, would have been diagnosed. Though there are observed differences in the infant mortality rate between rural and urban communities (Donaldson, 1971), these were considered of minor importance overall in the current context.

The incidence of the disease was defined as the number of cases per estimated number of live births. Prevalence was defined, also by convention, as the number of affected patients (both index and secondary cases) alive at any one time per 100 000 of the general population.

GENETIC DATA

A correction factor was also required to take into account children who were born in later years of the study who may not have had time to present with their disease. A similar point was made by Danks *et al.* (1965) in connection with gene frequency studies of cystic fibrosis. Cumulative frequency curves for age at presentation are now available for this condition (Pearn *et al.*, 1978), allowing the appropriate correction factor at any age to be applied.

For that component of all chronic childhood SMA cases in which autosomal recessive inheritance had been formally established (Bundey and Lovelace, 1975; Pearn, 1978):

$$q = \sqrt{I},$$

where q = the gene frequency of the condition, and I incidence expressed as one SMA case per 'x' live births (birth incidence). The carrier frequency is $(\approx 2q)$.

Results

Exact numbers of live births and age-specific death rates by year are shown in Table 1. Corrections applied to obtain (a) the estimated number of all children, born in the stated year and still alive at their 4th birthday, and (b) corrected numbers of childhood SMA patients, including those not yet traced because of incomplete 'risk period' passed, are also shown. There were 15 patients (9 females and 6 males) traced from the geographical area surveyed. All came from different families. One child of parents from Bangladesh was also traced, but was not included. The data in Table 1 give corrected totals of 15.14 chronic childhood SMA patients from an estimated 365 166 live births. The incidence of the condition is thus 1 in 24 119 live births in this population.

A summary of the gene and carrier frequency

studies is shown in Table 2. The range for the corrected birth incidence figures, for true recessive cases only, was 1 in 30 154 to 1 in 36 012 live births. This bracket was established using two extreme estimates for the proportion of non-recessive cases, obtained from a segregation analysis of this condition (Pearn, 1974a). The initial estimate of the carrier frequency range was thus 1 in 87 to 1 in 95. Gene frequency was $q = 0.00526$ to 0.00574 . The range established here was the result of estimates of the proportion of non-recessive patients hidden in the series, and not due to sampling error. As each of these raw estimates was associated with its own standard error, it was necessary to calculate a final true bracket (necessarily wider), using 95% confidence ranges of each polar estimate. This gave a range for true gene frequency of $q = 0.00451$ to 0.00659 , with a corresponding true carrier frequency range of 1 in 76 to 1 in 111. For

Table 1 Raw and corrected live birth figures for the total population and for chronic childhood SMA cases by year. Northern Region (UK) excluding Cumbria.

Year	Total no. of births*	Age-specific death rate† (0-4 y per 1000 live births estimated)	Estimated no. of children, born in stated year, still alive at 4th birthday	No. of patients born in stated year	Corrected no. of patients‡
1960	39 569	25	38 580	1	1.00
1961	39 174	25	38 195	1	1.00
1962	40 194	24	39 229	1	1.00
1963	39 716	24	38 763	1	1.00
1964	39 597	23	38 686	2	2.00
1965	38 892	23	37 997	2	2.00
1966	37 276	22	36 456	1	1.00
1967	35 581	22	34 798	1	1.00
1968	32 469	21	31 787	1	1.01
1969	31 333	21	30 675	3	4.13
Total	373 801	—	365 166	15	15.14

* Raw figures from local Medical Officers of Health.
† Age-specific death rate estimate obtained from combination of infant mortality rates and 1 to 4 year death rates. Various sources included Registrar General's figures and local Medical Officers of Health annual reports for the period 1960 to 1969.
‡ Correction for patients who had not yet presented with chronic childhood SMA; correction factor obtained from cumulative frequency tables for age at presentation (Pearn, 1974a).

Table 2 Gene and carrier frequencies for chronic childhood SMA

Estimate of non-recessive component*	Corrected no. of recessive cases	Birth incidence estimates for autosomal recessive cases	Carrier frequency	Gene frequency (q)
20%	12-11	1 in 30 154	1 in 87	0.00574
33%	10-14	1 in 36 012	1 in 95	0.00526

* 95% confidence range for the proportion of new dominant mutations, or phenocopies, present among index cases (Pearn, 1974a).

Table 3 Prevalence of chronic childhood SMA by sex and by county (Northern Region, UK)

County	Living population at June 1971	No. of patients with chronic childhood SMA alive at June 1971		Prevalence (no. of patients per 100 000 of general population)
		Male	Female	
Tyne and Wear	221 845	1	3	1.80
Northumberland	505 720	1	1	0.39
Durham	1 408 640	6	9	1.06
Cumbria (pre-1973 Cumberland component)	220 605	1	2	1.36
Cleveland	132 000	2	4	4.55
Total	2 488 810	11	19	1.20

genetic counselling purposes, a 'working' carrier rate of 1 in 90 is thus appropriate.

Table 3 shows the results of the prevalence studies. A total of 30 patients were alive on 30 June 1971 (8 familial and 22 sporadic patients). It can be seen that the overall prevalence of chronic childhood SMA in north-east England was 1.20 per 100 000 of the general population. The differences (Table 3) between different geographical regions were interesting, with a range of 0.39 per 100 000 for Northumberland to 4.55 per 100 000 for Cleveland (formerly Teesside). There is a suggestion that these differences may have taken the form of a gradient with low prevalence in the north, with a progressive increase as more southerly populations were sampled. I believe that it is unlikely that this is due to sociological factors, and is further evidence for significant genetic differences among the sub-populations of north-east England.

Discussion

This study confirms the impression that chronic childhood SMA is the result of a relatively common autosomal recessive gene. A gene frequency of 0.0055 means it is slightly less common than the gene causing SMA type I, which has an estimated frequency for the same population of 0.0063 (Pearn, 1973).

Reference to standard tables (Maynard-Smith *et al.*, 1961) shows that if the working estimate of 1 in 90 for the carrier frequency is correct, the expected incidence of first cousin marriages among parents of index cases would be less than 5%. This assumes that only one autosomal recessive gene is present. In a large study of 124 consecutive index patients with this disease, only one case of parental consanguinity was established (Pearn, 1974b). This provides two independent approaches to this problem which give data which are not inconsistent. The United States study of Bunday and Lovelace (1975), however, revealed two examples of consanguinity among parents of 33 index patients, which implies that the gene might be rarer in the population from which their cases were drawn. There were 10 consanguineous marriages among the parents of 389 index cases in the International Collaborative Study of the SMAs (Emery *et al.*, 1976), but, as the authors point out, the interpretation of this is difficult in the absence of a defined baseline rate for the parent population as a whole. A similar interpretational difficulty exists with other incidences of parental consanguinity in published reports (Forbus and Wolf, 1930; Hutchison and McGirr, 1956). Unfortunately, this means that such cases cannot be collected and used as a composite series for gene frequency studies using this method.

Another independent estimate of gene frequency

will come from extended studies which include index patients with affected first cousins. In a chronic illness like chronic childhood SMA, such information is reasonably reliable. As early as 1935, Hurwitz and Gerstle reported such a kindred with affected first cousins. Two index patients in the large study of Pearn *et al.* (1978) were also first cousins (no consanguinity was established), and one case in the series of Bunday and Lovelace (1975). The relative rarity of such cases, however, means that their accumulation has been slow. If the provisional estimate of carrier frequency (1 in 90) is correct, then only 1 in 720 first cousins of index patients, on average, would be affected, assuming random mating.

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