Genetic and clinical patterns of heritable cerebellar ataxias in adults. I Genetic analyses

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SUMMARY Family data on 299 probands with spinocerebellar types, 163 with late cortical cerebellar atrophies (LCCA), and 180 with olivopontocerebellar atrophies (OPCA) were analysed. Spinocerebellar types included cases with cerebellar ataxia combined with spasticity. Their family history was not compatible with sex linked inheritance. There were few recessive cases occurring before 24 years of age. The majority of cases were products of non-consanguineous marriages in which one partner was affected. The genetic ratio was 0.5 for each decade at onset between 20 and 59, suggesting that these cases were dominant. The proportion of these familial cases, however, decreased with increasing age at onset, and there were quite a few sporadic cases among the elderly. LCCA and OPCA were considered to represent extremes of a correlated disease spectrum. Although they were weakly familial, single gene heredity was rejected. Sib recurrence rate was 7.5% for LCCA and 9.4% for OPCA. When calculated for different age groups at onset, the rates decreased with increasing age in the two diseases. The rates increased to 25% and 20%, respectively, given two sibs already affected, and to 37.5% and 22.2% when three were affected. These patterns were incompatible with single gene mechanisms and were similar to those in multifactorial diseases with a threshold effect.

Although familial onset characterises spinocerebellar degenerations (SCD), the genetic mechanisms of the diseases have been controversial. Because of the lack of specific metabolic abnormalities in abiotrophic varieties, clinical-genetic entities of SCD had to be established by defining clinical syndromes which corresponded to a certain pattern of heredity. Unfortunately, however, delineation of the entities in this way was often seriously hampered in SCD because of poor correlation between the clinical picture and the pathological picture, with mixed or intermediate cases between two given types, different modes of heredity for the same clinical entity, seemingly different clinical forms occurring in the same family, etc.

The present report summarises the results of genetic analyses in 844 probands with SCD recently collected in Japan. Although the analyses included all recognisable types of SCD, special emphasis was placed on abiotrophic cases showing cerebellar ataxia starting in adult life, whose patterns of heredity were particularly obscure. The cases included, among others, olivopontocerebellar atrophies, late cortical cerebellar atrophies, and cases

of spinocerebellar types or cerebellar ataxias combined with spasticity.

Materials and methods

There were 844 probands who were selected from about 1000 cases of the diseases reported to the SCD Research Committee on the basis of adequate clinical description and pedigree data. The committee was organised by the authors in 1975.

METHODS OF COLLECTION

Cases directly observed by any of 16 committee members and 31 selected neurologists encompassing the whole country were reported to the committee. The probands, therefore, were hospital cases who were examined at various stages of the disease, and not cases ascertained in a defined population at a given time.

DIAGNOSIS AND CLASSIFICATION

Each case was diagnosed by the reporting neurologists, but the present authors re-evaluated the diagnosis from clinical information provided, according to the following criteria.

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Spinocerebellar types

This disease comprised, in the present study, cases of abiotrophic, predominantly cerebellar ataxia associated with pyramidal signs, but with no other major neurological disorders. Hyperreflexia alone and pathological reflexes alone were accepted as pyramidal signs although most cases showed both, particularly in the lower extremities. Ocular signs, tremors, sensory changes, muscular atrophies, and congenital defects ranging from retinitis pigmentosa and deafness to minor anomalies were noted in many cases accepted, but these were not conditions for acceptance.

Late cortical cerebellar atrophies (LCCA)

Cases with chronic, progressive, abiotrophic, predominantly cerebellar ataxia were accepted as LCCA when there was no indication of acquired or underlying causes such as chronic alcoholism, malnutrition, malignant disease, etc. Since such 'pure' cases were very few, cases showing one or two of the following signs occasionally or to a minor extent were included: horizontal nystagmus, disturbed ocular movements, hyperreflexia, non-intention tremors, etc. However, when these were marked, or when a symptom such as dementia, other types of nystagmus, pathological reflexes, intention tremors, involuntary movements, epileptic seizures, rigidity or other types of hypertonicity, or autonomic disorders including severe orthostatic hypotension, was observed, the case was not accepted.

Olivopontocerebellar atrophies (OPCA)

Cases with abiotrophic, predominantly cerebellar ataxia were accepted as OPCA when they had two or more of the following: organic dementia, rigidity or dystonia, involuntary movements or tremors, and various types of autonomic disturbances, thus showing clinical evidence of a multisystemic involvement. Nystagmus, disturbed ocular movements, spasticity and other pyramidal signs, muscular atrophies, and sensory changes featured in many cases accepted, but these were not conditions for acceptance. A few cases with features of the so-called Shy-Drager syndrome were accepted, even though autonomic disturbances preceded other neurological symptoms.

In diagnosing these three diseases, age of onset and family information were not considered, so that no bias would be introduced into the genetic analyses and age-specific calculations of various parameters.

CASES ACCEPTED

Table 1 summarises the 844 probands, 509 males and 335 females, accepted for the present analysis.

TABLE 1 Numbers of probands

Clinical or phenotypic entities	Male	Female	Total
Well established clinical entities inherited through a known single gene mechanism			
Ataxia-telangiectasia	4	3	7
Marinesco-Sjögren syndrome	2	2	4
Friedreich's ataxia	26	26	52
Hereditary spastic diplegias	43	29	72
Ramsay-Hunt syndrome	6	1	7
Roussy-Lévy syndrome	3	1	4
Bassen-Kornzweig syndrome	1	0	1
Congenital cerebellar degenerations			
Behr's syndrome	2	1	3
	0	1	1
Predominantly cerebellar ataxias in adult life			
Spinocerebellar types*	165	134	299
LCCA*	111	52	163
OPCA*	115	65	180
Unclassified†	31	20	51
Total	509	335	844

*Diagnostic criteria are given in the text.

†Accepted as cases of abiotrophic spinocerebellar degenerations but classified as none of the diseases shown in the table.

Only 151 were cases of established entities or genetic syndromes inherited through known single gene mechanisms. There were 299 cases of spinocerebellar types, 163 of LCCA, and 180 of OPCA. Of 163 cases of LCCA, there were about 50 'pure' cases showing no neurological abnormality other than cerebellar ataxia. In 51 cases, clinical classification was not possible although they were acceptable as cases of SCD of abiotrophic nature. Of these, about 40 were atypical cases of cerebellar ataxias conforming to none of the three diseases according to our criteria.

FAMILY DATA AND GENETIC ANALYSIS

Sex, age at last contact, and affection with a similar condition to the proband were recorded for the parents and all sibs of the proband. Parental consanguinity was also recorded. In quite a few cases the family study included direct examination of these relatives, but in other families information about affected relatives was obtained by asking the probands or their relatives.

Genetic analysis required a somewhat artificial approach at the expense of rigorous statistical requirements, because, despite efforts to define each disease clinically as uniformly as possible, they still appeared heterogeneous genetically. The first part of the genetic analysis was a test to evaluate whether the patterns of familial onset were dependent on sex. Negative results in this test indicated that sex linked heredity was not relevant, and the data on both sexes could be pooled for further analysis, with due caution regarding the possible sex difference of some parameters such as penetrance. In the next

part, we tested whether autosomal recessive inheritance could explain the entire family pattern, or at least part of the data. Autosomal dominant inheritance was then considered and, finally, whether family patterns in a given disease could reasonably be explained by one or a combination of these three modes of single gene transmission. In the cases where single gene transmission appeared inapplicable, other mechanisms were considered.

Results

Genetic analyses were performed for three diseases; spinocerebellar types, LCCA, and OPCA. We found that Marinesco-Sjögren syndrome, ataxia-telangiectasia, and Friedreich's ataxia clearly showed a recessive mode of transmission. Hereditary spastic diplegias were heterogeneous. Patterns in some pedigrees of Ramsay-Hunt syndrome and Roussy-Lévy syndrome were not clear cut.

PROBANDS

The numbers of probands in the three disease categories are shown in table 2 by sex and age at onset. In all three, males predominated over females but it was uncertain whether or not this was a

reflection of the greater likelihood of male patients to visit hospitals. Age patterns were identical in LCCA and OPCA but in spinocerebellar types they were different. In LCCA and OPCA, the disease never became manifest before 20. The age distributions were unimodal in the two sexes in these two diseases, with peaks in the sixth decade of life. Spinocerebellar types included a few younger cases at onset and ages at onset were more varied with a plateau in middle age. In all three diseases, average ages at onset were comparable between the two sexes.

The proportion of probands with affected parents or sibs or both were 57.9%, 27.6%, and 23.3%, respectively.

SPINOCEREBELLAR TYPES

Familial aggregation was a prominent feature in this disease compared with the other two.

X linked inheritance was rejected because there were 71 instances of father-to-son transmission, which never occurs in X linked recessive heredity. There were 74 male and 52 female sporadic cases whose parents were normal; again this does not occur in X linked recessive heredity. In X linked dominant inheritance, all the daughters but none of the sons of affected fathers are affected, but in our cases affected fathers transmitted the disease equally to sons and daughters.

Evidence for a small number of autosomal recessive cases was as follows. The proportion of second cousin matings and closer consanguinity was 18% among parents who were normal, but 11.2% when one of the parents was affected. The former figure was apparently raised but the latter was predictable for marriages in Japan where inbred mating used to be common. For further verification of recessive transmission in some cases, a genetic ratio was calculated by the method explained in table 3. In 20 sibships with normal and inbred

TABLE 2 Numbers of probands with spinocerebellar types, LCCA, and OPCA by sex and age at onset

Age	Spinocerebellar		LCCA		OPCA	
	Male	Female	Male	Female	Male	Female
0-9	1	1				
10-19	24	14				
20-29	40	31	5	3	3	3
30-39	48	30	21	4	18	9
40-49	31	31	26	16	43	21
50-59	19	26	42	22	43	26
60+	2	1	17	7	8	6
Total	165	134	111	52	115	65
Average age at onset	34.0	36.8	49.1	50.0	48.0	48.6

TABLE 3 Genetic ratios in spinocerebellar types, male only, with non-consanguineous parents one of whom is affected

Age at onset	-19	20-29	30-39	40-49	50+	All ages
No of sibships with a male proband: N	8	19	26	8	4	65
Total of male sibs, probands excluded: $\Sigma(s-1)$	15	48	62	24	11	160
Total of affected male sibs, proband excluded: $\Sigma(r-1)$	5	16	20	10	4	55
Genetic ratio (%): p or $\Sigma(r-1)/\Sigma(s-1)$	33.3	33.3	32.3	41.7	36.4	34.4
Standard error of p : $\sqrt{p(1-p)/\Sigma(s-1)}$	1.5	0.5	0.4	1.0	2.1	0.1
Corrected genetic ratio (%): p/y	48.8	48.8	47.3	61.1	53.3	50.4
$(0.5-p/y)/\sqrt{p/y}$	0.141	0.252	0.675	-1.608	-0.331	-0.142

s is number of sibs in a sibship and r is number of affected sibs in a sibship. y is a penetrance parameter because of delayed onset¹⁵ defined as $y = \int_z f(z)g(z)dz$ where $f(z)$ is the frequency of age at death or at last contact among normal and affected sibs with the probands excluded, and $g(z)$ is the cumulative frequency of onset at age z among affected sibs. If all sibs are old enough, y is 1.0. The corrected ratio is p/y , which must be compared with p_0 or the expected ratio. $y = 0.683$ for the data for all ages. This value was also used for the correction of age specific ratios. Corrected genetic ratio p/y did not differ significantly from the expected ratio 0.5 under dominant heredity ($p < 0.05$).

parents the crude ratio was 14.5%, but it was 15.8% based on 12 sibships with an age at onset of 29 or less. It increased to 18.2% for 11 sibships with probands aged 24 or less at onset. The age corrected value for the cases aged 24 or less was 0.27, which is equal to the expected value under the recessive hypothesis. There was a total of 16 cases, including secondary cases, aged 24 or less at onset. Autosomal recessive inheritance was, therefore, not excluded, at least in cases occurring at younger ages whose parents were normal and inbred.

Evidence for a large number of autosomal dominant cases was as follows. In a rare and deleterious dominant disease, patients are either new mutants who are sporadic, or heterozygotes who received the gene from one of the parents who is affected. The proportion of probands whose father or mother was affected was more than 50% for the cases with onset at 49 years or less, but 37.5% for those with onset over 50. This suggested that a considerable proportion of the cases occurring before the age of 49, and probably some of the later cases as well, could be inherited by autosomal dominant transmission.

For a further test of this possibility, the genetic ratio, or *p*, was calculated for sibs whose parents were unrelated, but one of them was affected. For sibs who already satisfied two criteria for autosomal dominant heredity, one more criterion was evaluated. Autosomal dominant heredity is a mechanism which affects both sexes equally, but in diseases showing variable and relatively mild symptoms penetrance is sometimes reduced, often to different extents in the two sexes.

In order to evaluate whether both sexes had an equal risk of having spinocerebellar types when either the father or the mother was affected, the numbers of secondary cases were counted by sex among the multiplex sibships with one affected parent, because these cases were considered unbiased. Of 127 secondary cases, 79 were males but only 48 were females, showing a great deficiency of female cases from the expected 1:1 ratio. This suggested, under the autosomal dominant hypothesis, that penetrance was reduced among female heterozygotes to 48/79, or about 60%, given that penetrance in male heterozygotes was total.

Genetic analysis, therefore, was undertaken for males only and all females were excluded from the family data. Relevant figures are presented in table 3, which shows that the corrected values of *p* are compatible with this form of heredity for various age groups at onset.

In summary, autosomal dominant inheritance, with reduced penetrance in females, was highly

likely in cases whose parents were affected. It may be that there were new mutants in addition to these cases, as well as a few dominant cases whose gene was transmitted through non-penetrant mothers.

In any dominant disease there are some sporadic cases resulting from new mutations, but there were too many sporadic spinocerebellar cases to explain in this way. Moreover, the proportion of sporadic cases was larger among the elderly, suggesting that there were some age-related mechanisms other than single gene heredity which caused sporadic occurrence at older ages, but to a lesser extent at younger ages. The large numbers of sporadic spinocerebellar cases aged 20 to 59 at onset is shown in the appendix. The proportion of sibships containing a non-segregating sporadic case was 39.1%. For cases aged 50 to 59 at onset, as many as a half of the sibships were non-segregating sporadic cases.

LCCA AND OPCA

Familial aggregation was less prominent in these diseases. The family patterns were almost identical and are presented jointly.

The various single gene transmissions were evaluated as described for spinocerebellar types and were immediately rejected. Details are not presented here to avoid redundancy.

The sib recurrence rate is shown in table 4. The overall crude rates were 7.5 and 9.4%, respectively, given that one sib was already affected. When calculated for decades of life, the values were largest during the decade 40 to 49, but decreased with age. On the other hand, the overall rates given that two sibs were affected were 25 and 20%, and 37.5 and 22.2% given that three sibs were affected for LCCA and OPCA, respectively.

Familial aggregation was less prominent in cases occurring at older ages, the diseases always being sporadic over 60 years, and the risks increased when a larger number of sibs in the same sibship were already affected. These patterns were totally incompatible with single gene inheritance in which each sib has a fixed probability of being affected, for

TABLE 4 Crude sib recurrence rates in LCCA and OPCA, male only

	LCCA	OPCA
Rates given one brother affected (%)		
All ages	7.5	9.4
20-39	7.4	9.3
40-49	10.9	13.9
50-59	7.1	7.1
60+	0	0
Rates given two brothers affected (%)		
All ages	25.0	20.0
Rates given three brothers affected (%)		
All ages	37.5	22.2

example, 0.5 in dominant transmission, independent of other sibs and regardless of age.

For an idiopathic disease with unclear familial clustering which cannot be attributed to single gene heredity, a multifactorial hypothesis must be considered, since irregular dominant inheritance, among others, can be confused with this mechanism.

It is likely that some sporadic traits are caused when a multifactorially determined susceptibility to an undesirable trait crosses a threshold. That is, an all-or-none type affection in some obscure diseases may be explained in terms of an underlying continuous characteristic determined multifactorially. Given an obscure familial disease, however, it is difficult to establish that the disease is caused in this way. Several theoretical expectations were derived by Carter,^{1,2} Edwards,³ and Neel,⁴ among others, which may be used as tests of whether observed patterns of a given disease are compatible with the stated mechanism.

Table 5 summarises patterns expected together with those observed in LCCA and OPCA. Of these, the first three and the last patterns could not be tested because of lack of data or other technical difficulties.

The correlation of increased risk with younger age of onset was proposed by Neel⁴ when he discussed multifactorial hypotheses in diabetes mellitus, a disease showing such a pattern. This was predicted because subjects having more causative genes would manifest the disease sooner, and the risk would be increased because the relatives would also have more of these genes. This pattern was observed in cases of LCCA and OPCA aged 40 and over at onset, as seen in table 4.

An increased risk with increasing numbers of sibs already affected was proposed by Carter.² He observed this pattern in several congenital malformations and proposed it as one of the bases of a multifactorial hypothesis. This pattern was observed in LCCA and OPCA, as seen in table 4.

An increased risk in sibs of probands of the sex less often affected was predicted by Carter¹ and shown convincingly in congenital pyloric stenosis. He assumed that the threshold for females was higher than that for males and thus female patients were more extreme deviants who carried more risks to their relatives. This pattern was evaluated in LCCA and OPCA and observed in LCCA only. In this disease, only 16 of 214 brothers of male probands were affected (7.5%), but 15 of 81 brothers were affected (18.5%) when the probands were females ($\chi^2 = 5.91$). In OPCA, the proportions were not related to sex ($\chi^2 = 0.64$).

Viewing these patterns, multifactorial aetiologies appear likely in these diseases.

TABLE 5 Expected patterns under a multifactorial liability hypothesis with a threshold effect, and patterns observed in LCCA and OPCA

Expected patterns	LCCA	OPCA
Sib recurrence rate is about the root of the prevalence rate	?	?
Risk decreases with decreasing blood relations	Yes?	Yes?
Concordance rate is higher in monozygotic than dizygotic twins	?	?
Risk increases when ages at onset are younger	Yes	Yes
Risk increases when more sibs are already affected	Yes	Yes
Risk increases in sibs of probands with less affected sex	Yes	No
Risk increases when probands have severer symptoms	?	?

This table represents overall answers to the expected patterns. See text for the theoretical basis for the expected patterns and statistical evidence supporting the answers.

Discussion

This report is a summary of statistical analyses of family data in a clinical series of 844 cases with SCD, especially in three major groups showing cerebellar ataxia.

FEASIBLE APPROACHES TO THE GENETICS OF ABIOTROPHIC SCD

For various reasons which are difficult to overcome, abiotrophic neurological diseases such as SCD pose problems for neurologists and clinical geneticists. Even abiotrophic cases, which represent the majority of SCD, are not well-defined. Various additional requirements for adequate family surveys and analyses make the situation worse when a genetic study is attempted for these diseases.

In these circumstances, one reasonable method is to collect and analyse pedigrees of well-documented cases with pathological information. The observations of Schut⁵ are examples of such an approach. However, the usefulness of such an approach is largely limited because of biases through haphazard ways of sampling cases, for example, because of the tendency of physicians and editors to report 'interesting' or 'unusual' cases or 'large families' more eagerly than ordinary cases.

Alternatively, a statistically more adequate method is to collect the proband cases in a systematic and unbiased way and analyse the family patterns. A good method would be where complete ascertainment is achieved in a defined population at a defined time and diagnosis is made by a single investigator using rigid criteria. In reality, however, various technical difficulties interfere with the feasibility of such statistical and epidemiological

approaches. For example, pathological verification in every proband case collected is usually impossible, and clinical diagnostic criteria usually have to be relied upon. In rare diseases like SCD, the collection of probands and family surveys are necessarily indirect and biases result in various aspects of the study. The works of Bell and Carmichael⁶ or Sjögren,⁷ among others, which contributed greatly to current knowledge of the genetics of SCD, were not above such criticism.

Unfortunately, as already emphasised, even the clinical and pathological spectrum has yet to be established in abiotrophic cerebellar ataxias, and this was the major target of this study. Therefore, it appeared advisable to apply comprehensive diagnostic criteria and simple or robust methods of genetic analysis.

GENETIC MECHANISMS OF SPINOCEREBELLAR TYPES

Spinocerebellar types, though fairly uniform clinically, are rather complex genetically. We found that there were (1) practically no X linked cases, recessive or dominant; (2) few recessive cases occurring at younger ages, probably 20 or less; (3) about 50% dominant cases with reduced penetrance in the female; and (4) an excess of sporadic cases in increasing proportion with increasing age at onset, which could not be attributed to new mutation.

It must be stressed, however, that the delineation of spinocerebellar types in this study was somewhat arbitrary and artificial and included clinical cases of predominantly cerebellar ataxia associated with pyramidal signs, but with no other major neurological disorders.

The original concept of 'cerebellar heredoataxia' proposed by Marie in 1893⁸ was quickly criticised by others, particularly by Holmes,⁹ who pointed out that the cases had no uniform pathological basis. Subsequent workers, for example Hassin and Harris,¹⁰ claimed that the pathological features in most cases were basically those of OPCA. Greenfield,¹¹ in his big review of SCD, was unable to give support to Marie's thesis, and the pathological lesions in the 22 families he reviewed appeared to conform to type A or Menzel type, or type B or Holmes type. He also pointed out that the clinical picture in the majority of cases of Marie's ataxia corresponded to the family described by Brown.¹² The disease, because of these and other criticisms, has gradually come to be regarded as a merely clinical syndrome, essentially as described by Marie.⁸

In the light of the present results, at least three groups of cases, recessives, dominants, and non-segregating sporadics, appear to be separable

genetically in a comprehensive group of spinocerebellar types basically equivalent to 'Marie's ataxia'.

GENETIC MECHANISMS OF LCCA AND OPCA

These showed identical family patterns, which indicated that the diseases were less familial than spinocerebellar types and none of single gene heredities could be involved, and that the sib recurrence rate pointed to a multifactorial causation of the diseases.

The genetics of these diseases has not really been seriously investigated. There has been discussion on how sporadic cases of LCCA are related to familial cases,¹³ and how sporadic cases of OPCA are related to familial cases.¹⁴ Most pathologists, including Greenfield,¹¹ were unable to distinguish between sporadic and familial cases pathologically. This is quite understandable for a geneticist because, in any given disease, it is basically a matter of probability whether a patient is an isolated case or whether one or more relatives are affected through the same causative mechanism, and division of the cases into an isolated group and a familial group is hardly an aetiological division.

LCCA and OPCA are known to represent the extremes of the same, or a closely related, disease spectrum from both the clinical and pathological points of view. It was, therefore, predictable and extremely important that the present study indicated identity of their family patterns, because this supports the view that the two diseases are a continuum resulting from the same, or at least a closely related, aetiological mechanism.

In the past it has been suggested that familial cases are dominantly inherited and that isolated cases are not hereditary. This is an artificial combination of two untenable hypotheses. The present analysis suggests that these diseases may have a multifactorial cause. More evidence is obviously necessary, but this new hypothesis appears a better working explanation for these diseases.

PROBLEMS EMERGING FROM THE PRESENT RESULTS

It is not certain how the three genetic subgroups within the spinocerebellar types are distributed, what subtle clinical differences characterise these subgroups, and how techniques such as electronystagmography or computerised tomography can discriminate between these subgroups.

Similar questions are relevant to LCCA and OPCA. While we feel that they represent a spectrum of the same disease, there are others who would prefer to split the diseases into several types or varieties. It is useful to reconsider such nosological debates, viewing all available information together.

The question remains as to how sporadic spinocerebellar types are related to LCCA or OPCA. Pathologists have claimed that most cases of 'Marie's ataxia' are in fact OPCA, but this view has not been fully explored in the light of genetics, electrophysiology, and computerised tomography.

These and other problems will be discussed in a later report.

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APPENDIX *Excess of sporadic cases in spinocerebellar types*

It is usually meant by sporadic, solitary, or isolated occurrence of a disease that a case occurs in the absence of another relative with the same disease. Morton¹⁵ distinguished two different kinds of sporadic occurrence. One is the chance isolation of a single gene hereditary disease in a child of parents who are genotypically causative. The other situation is observed in diseases other than segregating single gene diseases, such as new mutations, chromosome aberrations, multifactorial traits, extrinsic phenocopies, etc, which repeat in the same family with a very low probability. The latter will be called non-segregating sporadic occurrence. When clinically indistinguishable non-segregating sporadic cases are combined with segregating cases, there is a greater excess of sporadic cases than would be expected from Mendelian inheritance.

In sibships of size s , numbers of affected sibs may be $s, s-1, \dots, r, \dots, 1, 0$ with a probability distribution $p^s + sp^{s-1}q + \dots + \frac{s!}{r!(s-r)!} p^r q^{s-r} + \dots + spq^{s-1} + q^s$, where p is the genetic ratio and q is $1-p$. The proportion of sibships with an isolated affected case is $sp^{s-1}q$. If the ascertainment is single, the probability of being ascertained is, multiplying each term by the number of those affected, $s \cdot p^s + (s-1) \cdot sp^{s-1}q + \dots + 1 \cdot s \cdot pq^{s-1} + 0 \cdot q^s = sp(p+q)^{s-1} = sp$. Thus, dividing each term by sp , the proportion of sibships ascertained having $s, s-1, \dots, 1$ affected cases among sibships of size s can be given.

A rough idea of the excess of sporadics in spinocerebellar types is shown in table 6. In the right hand columns, the expected numbers of ascertained sibships are given for all possible values of r and $s = 2, 3, 4$, and 5 , together with the observed numbers, assuming dominant transmission of the disease. The totals of the expected and the observed sporadic sibships were, by adding values for $r = 1, 32 \cdot 13$ and 77 , respectively, indicating an excess of

TABLE 6 *Expected and observed numbers of sporadic cases by single ascertainment, sibships with male probands with spinocerebellar types aged 20-59 at onset, all female sibs excluded*

No (s) in each sibship	No of sibships (n_s)	No of affected sibs (r)	$rf(r)$ — sp	No of ascertained sibships	
				Expected	Observed
2	38	2	p	19.00	6
		1	q	19.00	32
3	35	3	p^2	8.75	1
		2	$2pq$	17.50	12
		1	q^2	8.75	22
4	28	4	p^3	3.50	0
		3	$3p^2q$	10.50	9
		2	$3pq^2$	10.50	3
		1	q^3	3.50	16
5	14	5	p^4	0.88	0
		4	$4p^3q$	3.50	0
		3	$6p^2q^2$	5.25	4
		2	$4pq^3$	3.50	3
		1	q^4	0.88	7
Total	115			115.01	115

See appendix for explanations. $f(r)$ is $prq^{s-r}s!/r!(s-r)!$. Expected number of ascertained sibships is $n_s f(r)/s \times 0.5$.

observed sibships. Excess sporadic sibships were $77-32 \cdot 13$, or $44 \cdot 87$, or $39 \cdot 1\%$ of all sibships, which could not be attributed to the segregation in dominant inheritance. In this type of heredity, there are a few additional sporadics as a result of a new mutation, but such a gross excess cannot be explained by this mechanism alone.

The same calculation was made for each decade from 20 to 59 years of age at onset of the probands. The proportion of excess sporadics was $36 \cdot 4\%$ for ages 20 to 29, $38 \cdot 2\%$ for ages 30 to 49, and $49 \cdot 1\%$ for ages 50 to 59. Therefore, the older the age at onset, the more likely sporadic cases of spinocerebellar types are to occur.

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