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Genetic aspects of amyotrophic lateral sclerosis and progressive bulbar paralysis [1]

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At two universities of West Germany, in particular at the Institute for Human Genetics of the University of Münster, Westphalia, a thorough registration of a great number of pathological traits and clinical syndromes (that are considered to be caused by mutant genes) has been organized. This research program will supply data for statistical analyses, the material being collected from a population of about two million people. These extensive studies in the " Regierungsbezirk Münster ", comprising a good part of Westphalia, are carried out by a large staff of assistants, a team work of medical and other professional people (v. Verschuer, 1957).

Two of the conditions investigated for the last two years, are amyotrophic lateral sclerosis (first described by Charcot in 1865) and progressive bulbar paralysis (described by some French and German authors about a hundred years ago). This degenerative disease of the spinal cord and of the medulla, respectively, was known to be of a rather low frequency and thus seemed to be a model for this kind of research in population genetics.

Through systematic search in neurologic departments and mental hospitals of Westphalia, we found 251 index cases out of a population of about 250.000 neuropsychiatric patients observed during the last 30 years. Thus, the incidence of Charcot's disease within this large material is nearly 1 per 1000.

Our investigation is a family study, including a small twin series only. One out of four twin pairs seems to be concordant for bulbar paralysis (combined with congenital ptosis, incidentally).

So far, the field work of our research has been carried out for a representative sample of 100 cases collected within the district of Münster. All living probands (about one third of the material) are submitted to clinical examinations and anthropological tests; catamnestic data are obtained from relatives of deceased index cases. We had to have many other contacts, in particular with medical and official autho-

[1] This study is supported by the « Deutsche Forschungsgemeinschaft », Bad Godesberg, Germany.
[2] The author wishes to express his appreciation to Prof. O. Frhr. v. Verschuer, M. D., Director of this Institute, whose generous aid made this study possible.

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rities, to be able to check diagnoses and to get further information on our patients and on their families.

The clinical results of our study are in good agreement with those published by many other authors (Hemmer, 1951, 1953, 1955; Mulder, 1957; and others). There is one difference we want to indicate: a large part of our index cases showed some degree of emotional or mental disturbance. We may say that symptomatic cases and pseudo-forms of amyotrophic lateral sclerosis were excluded from our sample. We thus obtained a rather homogeneous material so that our diagnoses are considered to be clear-cut in every single case.

The histories of our probands do not suggest the presence of environmental influences playing a major role in the etiology of this disease. Both constitutional and peristatic factors must be taken into consideration to explain manifestation of amyotrophies. This etiologic concept is not inconsistent with those numerous findings of isolated cases, as reported in world literature; we cannot exclude the possibility of sporadic cases having some genetic basis.

A further way of judging the alternative " heredity versus environment " or of evaluating their part played in the etiology of certain diseases, is to determine the birth rank of probands within their sibship. In our sample there were relatively few first and last ranks, whereas the majority of our cases had birth ranks in between. These findings also suggest a predominantly genetic determination of Charcot's disease.

The age of onset of this condition was 42,5 years on the average of our cases, with limits of 16 and 66,5 years. The mean duration of illness of the deceased cases was 5,3, the average age at death of these probands was 48, 7 years (limits 24,5 and 70 years). These values are in good agreement with those published by other authors. The same holds true for the sex ratio of our cases: this value was 1,8 (or 64 per cent males to 36 per cent females).

Among our patients 13,5 per cent described a positive family history. These family histories clearly suggested a dominant inheritance of amyoytophic lateral sclerosis and progressive bulbar paralysis, as a number of authors have reported it previously (Mulder, Kurland, 1954, 1955, 1957; Haberlandt, 1958; and others). In qualifying this statement we may say that our pedigrees demonstrated an autosomal dominant mode of inheritance with incomplete penetrance, varying expressivity, and limitation to male patients in two thirds of our sample.

The pathogenetic mechanism of Charcot's disease is still unknown. It may be that some metabolic defect would account for the degenerative process. As some authors expressed it (prior to us), we presume that this inborn metabolic disturbance and the subsequent neurologic disease might originate in a gene mutation. This hypothesis would explain the frequent occurence of sporadic cases affected with this condition.

The genetic analysis of our material was extended to further evaluation of the following data collected, i. e., of blood groups and other hereditary traits examined in all living probands and secondary cases of our sample.

The distribution of the ABO and MN blood group systems in our material did not show significant differences, as compared with respective normal distributions of the German population. The same holds true for the Rh blood types, except for a few subgroups. These preliminary values, however, are not considered to be statistically significant (our sample still being too small to give conclusive results). Thus we are not able to calculate any possible correlations between distributions of blood factors and clinical types of Charcot's disease.

In examining our patients we used a further method for determination of genetic characters: the test with phenyl-thio-carbamide. As reported by Blakeslee and Fox (1932) as well as by Weber (1942), there are genetic differences in taste for P.T.C.: in about one two thirds of the general population the test is positive, i. e., they inherited this dominant trait. Our findings (59 per cent positive tests) are in good agreement with those mentioned above.

Further hereditary traits, as seen in our cases, were: a lesser degree of color-blindness (protanomaly and deuteranomaly) in four cases and of hemeralopia in three cases. As of yet, these data cannot be used for linkage studies.

With regard to the demographic aspects of amyotrophic lateral sclerosis, we want to refer to those remarkable observations in Micronesia, reported by Koerner (1952), Arnold (1953), Mulder, Kurland and coworkers (1954, 1956). From these investigations we know that in the Mariana Islands this condition is extremely prevalent. The frequency of the disease among the Chamorros (a mixed race living on Guam) is about one hundred times that of American and European populations, i. e., of some countries of the western civilization. We also learned from these studies that for a large percentage of the Guamanien series family histories were positive, athough the data available failed to prove a definite mode of inheritance.

If we compare the results of the Mayo Clinic, given by Kurland and Mulder (1957) for the population genetics of Charcot's disease in America with our own, we may say that the frequency of this condition, as calculated for the district of Münster, is equal to that of the United States (0,7 per 100.000).

Oldefey and Magun (1953) pointed out that some diseases, as for example amyotrophic lateral sclerosis, have increased in postwar times. This increase of degenerative processes is explained by the change of the German population, with regard to age distributions.

As to the social and economic status of our probands and of their families, our observations are in agreement with Mulder and Kurland's (1954) statement, that a „ lower class " is prevailing among these patients. We would not say, however, that this lower social and economic status of our cases might be a result or even a causative factor of the condition. We must mention here that in our material a large percentage of refugees from the German East is included.

As regards the occupation of our patients, skilled and unskilled labourers were most frequent (more than 50 per cent of our sample). This distribution was to be expected for the partly industrial, partly agricultural land of Westphalia. Only 11 per

cent of our cases were unmarried; the average number of children for the married patients was 2,7.

As we said before, the great number of sporadic cases might be the result of gene mutations. Such hypothesis can be corroborated by the value given as morbidity rate. This minimum value is not too far from that of spontaneous mutations in man, i. e., of about 1 per 50.000. So far, mutation rates of Charcot's disease have not been calculated.

Summary

In this preliminary report the question of the inheritance of amyotrophic lateral sclerosis is discussed. Through systematic search within the province of Westphalia and especially in the District of Münster, we found 251 index cases out of a population of about 250.000 neuro-psychiatric patients observed during the last 30 years. This material is being analysed from a clinical as well as from a genetic standpoint. The family study will be a basis for determination of the mode of inheritance. As for the sporadic cases of Charcot's disease, the effect of mutations must be taken into consideration.

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RIASSUNTO

Questa nota preventiva riguarda la questione dell'ereditarietà della sclerosi laterale amiotrofica. Abbiamo potuto raccogliere — nella Vestfalia e particolarmente nella provincia monasteriense — i casi di questa malattia, incorsivi negli ultimi tre decenni. Si tratta in tutto di 251, trascelti in un materiale di pazienti neuropsichiatrici ammontante a quasi un quarto di milione. Questo materiale viene elaborato sia clinicamente che geneticamente, attraverso ricerche estese ai relativi familiari. La questione relativa al meccanismo ereditario seguito dalla forma in quei casi che siano riferibili a gruppi familiari, o ad un'insorgenza mutazionistica in quei casi di riscontro sporadico, è oggetto della presente nostra indagine.

RÉSUMÉ

Dans cette communication préliminaire on a traité la question de l'hérédité de la sclérose latérale amyotrophique. Ayant registré cette maladie dans la province de Westfalie et surtout dans la région de Münster on a trouvé 251 cas observés dans les dernières trois décades dans un total d'un quart de million de malades neuropsychiatriques. L'étude de ce grand nombre de cas (atteints de la maladie de Charcot), et de leurs familles promet à donner des résultats cliniques et génétiques. Ainsi le problème du méchanisme héréditaire des cas familials est discuté. Finalement la question d'une mutation possible est posée pour les cas isolés.

ZUSAMMENFASSUNG

Diese vorläufige Mitteilung behandelt die Frage der Erblichkeit der amyotrophischen Lateralsklerose. Im Raume von Westfalen und besonders im Regierungsbezirk Münster wurde diese Erkrankung für die letzten drei Jahrzehnte erfasst: es sind 251 Fälle bei einer Bezugsziffer von einer viertel Million neuropsychiatrischer Patienten. Dieses Material wird nun einerseits klinisch bearbeitet und andererseits durch Familienuntersuchungen genetisch analysiert. Die Frage des Erbganges bei den familiären und die der Mutation bei dem sporadischen Fällen sollen in erster Linie geklärt werden.

https://doi.org/10.1017/S1120962300018801 Published online by Cambridge University Press