Causes of Death in Machado-Joseph Disease

A Case-Control Study in the Azores (Portugal)

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Background: Machado-Joseph disease (MJD) is an autosomal dominant cerebellar ataxia of adult onset with a high prevalence in the islands of Azores (Portugal). The genetic epidemiological studies presently under way in these islands are based on the genealogical reconstruction of the affected families, thus partially depending on the reference of patients using family history. A considerable effort has been made to obtain genealogies that are as complete as possible, making use of different types of data. The utility of the death causes contained in the death registers of the patients with MJD was determined in this study.

Objectives: To estimate the extent to which the cause of death reported in the death register can confirm other reports of an individual's status for the disease (ie, oral information), and to determine the accuracy of the death certificates in listing MJD in patients whose disease was clinically diagnosed.

Design: Case-control study.

Methods: The death registers of 113 patients with MJD (82 whose disease was identified by history and 31 whose disease was clinically diagnosed) were examined and compared with those of controls matched by sex and date and place of death.

Results: There were significant differences in the causes of death between cases and controls, both for those whose disease was identified by history ($\chi^2 = 51.69$, $P < .001$) and for those whose disease was identified by examination ($\chi^2 = 27.78$, $P = .004$). However, the cause of death was in accord with the presence of the disease in only 40% of the cases reported as being identified only by family history. In the cases in which the disease was clinically diagnosed, only nearly 38% of the registers provided reliable information as to MJD being the direct cause of death.

Conclusions: The fact that only nearly 40% of the patients with clinically confirmed MJD had a cause of death compatible with MJD precludes the use of cause of death as a means of identifying affected individuals in the Azorean MJD pedigrees.

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MACHADO-JOSEPH disease (MJD) is a late-onset, progressive, neurodegenerative disorder that involves the cerebellar, ocular motor, pyramidal, extrapyramidal, and peripheral motor systems. The mean age at onset is 40.5 years. The estimated median survival time is 20 years.[1] There is no treatment to delay or halt the progression of the disease. The *MJD* gene, which has been linked to chromosome 14,[2] consists of an unstable triplet (CAG) expansion at 14q32.1.[3]

Machado-Joseph disease was first described in North American patients who had emigrated from the Portuguese islands of the Azores.[4-6] For this reason, the disease's origin was believed to be Azorean, and the entity was temporarily referred to in the literature as an "Azorean disease of the nervous system."[7-9] To date, 34 affected families have been identified in the Azores, where the current estimated prevalence of the disease is 1/2402.[10] To understand the origin and spread of the mutant gene in these islands, a multidisciplinary research program was developed that aims to study MJD from a genetic, epidemiological, and demographic perspective. The data used for the analysis were obtained from the database "Willy," which includes detailed genealogical and demographic information on all the Azorean MJD families. These studies are based on the reconstruction of the MJD families and therefore rely on the quality of the genealogies obtained. In similar studies, the accuracy of the data contained in the genealogies has proved to be crucial in understanding the mechanisms responsible for the representation of deleterious genes in specific populations.[11] Therefore, a considerable effort has been made to obtain MJD genealogies that are as complete as possible by collecting and making use of different types of data.

The data contained in death registers are often criticized, mainly because of their lack of accuracy.[12,13] Our intention, however, is not to address this issue but to evalu-

PATIENTS AND METHODS

A list of deceased individuals identified as having had MJD was obtained from the database on the MJD Azorean families (Willy). Willy contains the genealogies of all Azorean MJD families, consisting of more than 8500 individuals and 3200 unions. The database and the software have been described in detail elsewhere.[10] We selected the affected individuals with date and cause of death listed in the death register from these MJD families. The individuals were then classified into 2 different groups: group 1 (G1), individuals who were identified by close relatives as having had MJD but who died without a clinical diagnosis (disease identified by history); and group 2 (G2), individuals with clinically confirmed MJD (disease identified by examination). The diagnosis of MJD was determined by clinical examination by an experienced neurologist, using established diagnostic criteria.[14]

Only individuals who died between 1911 and 1990 were included, since it is only from 1911 on that cause of death has been registered. In 1990, legislation aiming to ensure the confidentiality of cause of death was issued, preventing it from being referred to in the registers. Therefore, because cause of death stopped being reported in the death registers after 1990, this year defines the upper limit of our study. During most of the period analyzed, only 1 cause of death is listed. In the few cases in which more than 1 diagnosis was listed, we retained the 1 representing the primary cause of death.

The sample analyzed consisted of a group of 82 individuals (51 men and 31 women) in G1 (disease identified by history) and a group of 31 individuals (18 men and 13 women) in G2 (disease identified by examination). Data available from death registers consisted of sex, date of birth, place of birth, date of death, place of death, and cause of death (primary cause). The 2 sexes were not considered separately in the analysis, because the number of individuals included was too small to show possible differences between them. For each individual in G1 and G2, one control was selected from a group reported as "not affected" from the same database (Willy), using sex, place of death (island), and date of death within 10 years as matching variables. The control individuals consisted of nonaffected individuals who were part of the large MJD genealogies. These controls were selected from branches of the MJD families in which no reference to affected individuals existed, at least 2 generations before the individuals chosen. This methodology aimed to decrease the chances of including at-risk individuals (50% risk) in the control group. Although not matching for age at death, and considering the fact that MJD is a late-onset disease, only adults (older than 20 years) were sampled as controls. The mean ± SD age at death among those in G1 was 60.3 ± 14.6 years and 53.4 ± 20.3 years among the controls (C1). The average age at death among those in G2 was 62.2 ± 13.6 years and 68.4 ± 16.4 years among the controls (C2).

The causes of death were grouped into 12 general categories, numerically coded. Although the grouping contained some ambiguity, it was necessary, in view of the variability of the causes of death. The proportional mortality ratio (number of deaths from a specific cause over the total number of deaths) was calculated for cases and controls. A χ^2 test was used to determine the significance of the differences in the distribution of causes of death between cases and controls and between the 2 groups of cases.

ate whether determining the cause of death can help to detect affected individuals in large MJD Azorean pedigrees. There were 2 main aims for the analysis. First, we estimated the extent to which the cause of death reported in the death register could confirm other reports of an individual's having the disease (ie, oral information). This is an important objective, since one of the problems associated with the organization of a database for the Azorean MJD families has been the ascertainment of the disease status of the individuals who were reported as being affected by close relatives but who died without a clinical diagnosis. The second aim was to determine the accuracy of the death certificates in listing MJD in patients whose disease was clinically diagnosed. The information contained in the death certificates, if proved accurate, could improve the quality of the genealogies and therefore allow an estimation of the prevalence of this disease in past generations, providing a better understanding of the present epidemiological situation of MJD in the Azores.

RESULTS

DISTRIBUTION OF DEATH REGISTERS

The distribution of the registers analyzed, by decade of death, is shown in **Figure 1**. There was a concentration of the "disease identified by history" in the period 1961 to 1971. The cases of clinically confirmed MJD were most frequent in the period 1971 to 1991. This finding is in accord with the fact that the disease was not specifically diagnosed until 1972,[4] becoming recognizable as a specific clinical entity in the Azores only by the end of the 1970s.[15]

PROPORTIONAL MORTALITY RATIO

Table 1 presents the proportional mortality ratio in individuals with MJD (G1 and G2) compared with controls (C1 and C2, respectively). For the G1 group, category 4 is clearly the most frequently represented, with 38.7% of the deaths attributed to a neurological disease. In control group C1, no death attributed to a neurological cause was reported. Neurological disorders are listed as a cause of death in only 12 (38.7%) of the 31 clinically confirmed cases of MJD (G2); there was no death attributed to a neurological disorder reported in the controls (C2).

DIFFERENCES IN CAUSES OF DEATH BETWEEN CASES AND CONTROLS

The large value for cardiovascular disorders (second in rank of occurrence in G1, as shown in Table 1) agrees with the overall trend in the Azorean population. In control group C1, heart disease (category 6) is the major cause of death, which also is in accordance with the general trend in the population. In this control group, 25.8% of the registers give no information on the reasons that led

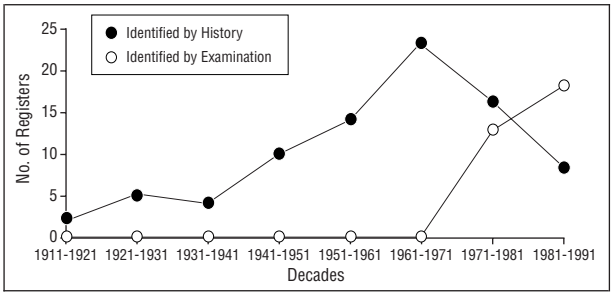

Figure 1. *Distribution, by decade of death, of the death registers for the 2 groups of cases (identified by history and identified by examination).*

Table 1. Proportional Mortality Ratio in Patients With Machado-Joseph Disease and Controls*

Categories of Causes of Death	Proportional Mortality Ratio G1 (n = 82)	C1 (n = 82)	G2 (n = 31)	C2 (n = 31)
1. Respiratory disease	3.2	9.7	4.9	10.9
2. Cancer	6.5	6.4	3.6	8.5
3. Intestinal disease	0.0	0.0	4.9	10.9
4. Neurological disease	38.7	0.0	37.8	0.0
5. Trauma	0.0	3.2	1.4	4.9
6. Heart disease	3.2	25.8	3.6	15.8
7. Infectious disease	3.2	3.2	8.5	12.2
8. Nonspecified	6.5	12.9	9.7	14.6
9. Bone disease	3.2	0.0	4.9	4.0
10. Stroke	32.3	19.4	8.5	8.5
11. Chronic disease†	3.2	6.5	6.1	1.2
12. Unknown	0.0	12.9	6.1	8.5

**G1 indicates group whose disease was identified by history; C1, control group for G1; G2, group whose disease was identified by examination; and C2, control group for G2.*

†Other than neurological.

to the individual's death, either because the description used was too ambiguous to allow specific classification (12.9%) or because the cause of death is listed as unknown (12.9%).

The results of the χ^2 test are shown in **Table 2**. We limited the analysis to individuals who died within the same time interval (1970-1990) and whose disease was identified either by history or by examination. There were statistically significant differences in the distribution of the causes of death between cases and controls in all 4 groups (ie, G1 and C1 and G2 and C2). No significant difference was found between the 2 groups of cases.

CAUSES OF DEATH WITHIN THE NEUROLOGICAL DISORDERS CATEGORY

The specific causes of death listed in the registers within category 4 (neurological disorders), for individuals whose disease was identified by history (38.7% of the cases) and for those whose disease was identified by examination (37.8% of the cases), are shown in **Figure 2**. In G1, tabes, sclerosis, ataxia, and paralysis were almost equally common. Multiple sclerosis was reported twice as a specific cause of death in G1. No death attributed to MJD was recorded in this group, since the specific diagnosis could not be made

Table 2. Distribution of Cause of Death Categories Between Patients With Machado-Joseph Disease and Controls and Between the 2 Groups of Patients

Groups*	χ^2	*df*	*P*
G1/C1	51.69	11	<.001†
G2/C2	27.78	11	.004†
G1/G2	11.79	11	.38

**G1 indicates group whose disease was identified by history; C1, control group for G1; G2, group whose disease was identified by examination; and C2, control group for G2.*

†Significant difference at 5%.

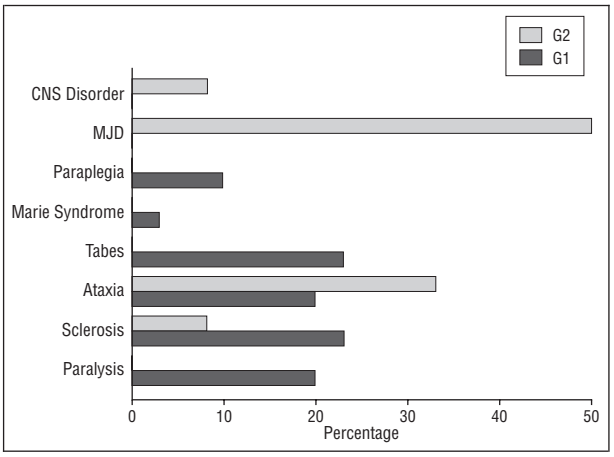

Figure 2. *Causes of death within category 4 (neurological disorders) for patients whose disease was identified by history (G1) and for patients whose disease was identified by examination (G2). CNS indicates central nervous system; MJD, Machado-Joseph disease.*

until the end of the 1970s. On the other hand, in G2, MJD was the most frequent specific cause of death, followed by ataxia. No specific reference to multiple sclerosis was made in this group. Parkinson disease was not listed as a specific cause of death in either G1 or G2.

OTHER CAUSES OF DEATH ASSOCIATED WITH MJD

Because the concomitant complications of MJD (eg, bronchopneumonia, often due to aspiration caused by dysphagia) could be recorded as the cause of death in clinically confirmed cases of MJD,[9,14] we would expect that respiratory diseases would be second in order of occurrence in G2. This was not the case in our study, in which only 4.9% of the patients with clinically confirmed MJD died of a respiratory complication (Table 1). Other causes of death known to be associated with MJD, such as decubital ulcer or catheter-related sepsis, were classified within the infectious diseases group and were also observed at a low frequency (8.5%).

COMMENT

For G1, all the discriminated causes included in the neurological disorders category (Figure 2) are highly compatible with a diagnosis of MJD, ataxia being the most reliable indicator. Marie syndrome was at that time the general

diagnosis for dominant ataxias. Tabes dorsalis, although related to syphilis, was often associated with ataxia in degenerative disorders. Sclerosis could be related to multiple sclerosis, a diagnosis that even nowadays is still occasionally made in cases of MJD. Finally, paralysis and paraplegia possibly describe the motor incapacity in MJD. We can therefore conclude that an indication of the presence of the disease could be obtained in approximately 40% of the patients in G1, this percentage corresponding to the individuals for whom neurological disorders have been reported as the cause of death.

Regarding the clinically confirmed cases of MJD, 3 groups of causes of death could be compatible with death occurring as a result of the natural course of the illness (neurological, respiratory, and infectious diseases, in this order of importance). The fact that higher frequencies for the categories of respiratory diseases or infectious diseases were observed in the control group leads us to infer that no association exists between these groups of causes of death and MJD. Therefore, we concluded that only 37.8% of the cases in G2 have a cause of death potentially in accordance with MJD (Table 1); in the remaining cases, no reliable indication of the presence of the disease was given. The clinical variability of MJD can be attributed to the fact that a reduced proportion of deaths were the result of a neurological disorder. A later form of the disease, corresponding to type 3 described by Coutinho and Andrade,[15] demonstrates a slow evolution of symptoms, allowing the affected individuals to reach a considerable age.[16] Therefore, in patients with type 3 MJD, the registered cause of death is likely not to be MJD. One additional factor could be responsible for the nonreporting of MJD as the cause of death in some cases: if the individuals die of an unrelated illness (eg, cancer) at the beginning of the natural course of the disease, it is probable that there will be no reference to MJD when the cause of death is listed. The fact that statistically significant differences were found in the distribution of causes of death in the patients with MJD compared with controls seems to indicate that, to some extent, death causes can be used when determining the status for the disease (affected/nonaffected) in an individual belonging to an MJD family. In the control groups, the absence of deaths that were attributable to a neurological disorder could be explained by the fact that we were dealing with small numbers, and not with the general population. From the results mentioned above, and aiming at ascertaining the status of the disease in deceased individuals belonging to MJD families, we can establish the following categories, in order of decreasing reliability: (1) MJD listed as cause of death (corresponding to the most reliable category); (2) other neurological diseases compatible with MJD (eg, ataxia, tabes, sclerosis, or paralysis) listed as cause of death; and (3) nonneurological disorders frequently associated with MJD (eg, bronchopneumonia). According to our results, the latter category cannot be used to confirm the presence of the disease.

In conclusion, the fact that not more than nearly 40% of the patients with clinically confirmed MJD had a cause of death compatible with MJD precludes the use of cause of death as a means of identifying affected individuals, even in the large Azorean pedigrees. Although these results cannot be generalized to all the remaining populations, they should be taken into consideration in other Portuguese cases. In the mainland of Portugal, where 34 families with MJD have been identified,[17] new kindreds have recently been described (P.C., oral communication, January 25, 1998). The genealogical reconstruction of these families is presently being undertaken. Therefore, even if our study results are not generalizable, they should provide further indications concerning the collection of data for reconstructing previous generations of the Portuguese MJD kindreds.

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