Machado–Joseph disease (MJD), one of the most prevalent autosomal dominant cerebellar ataxias, is a neurodegenerative disease that starts during adulthood, with patients showing difficulties in gait, later becoming bedridden, and ultimately presenting premature death. There is, however, scarce data quantifying disease impact on patient survival. We investigated the overall survival of a large series of MJD patients and compared it with the survival of their asymptomatic relatives. A total of 412 affected and 413 unaffected individuals were ascertained from a consecutive sample of 82 families with a molecular diagnosis of MJD. Estimated mean survival time was 63.96 years [95% confidence interval (CI), 62.09–65.83] for the affected group and 78.61 years (95% CI, 74.75–82.47) for the unaffected group (p < 0.001). For a subset of 366 patients, mean age at onset was 36.37 years (95% CI, 35.21–37.53) and survival after disease onset was estimated as 21.18 years. Early onset and large CAG length predicted shorter overall survival times. This study presents quantitative data on the impact of MJD on overall survival, a phenomenon that is related to CAG length, age at onset, and year of birth.

Methods
The present study was approved by the ethics committee of our institution (Hospital de Clínicas de Porto Alegre). After consent, an interview was conducted with patients and their relatives aged 18 or older whose families had a molecular diagnosis of MJD. All cases belonged to MJD families already registered in our hospital. Each informant was personally interviewed and provided data on his/her relatives (children, siblings, parents, uncles, cousins, and grandparents of the affected lineage) by following a structured questionnaire about each family member. Data were double-checked by a second (or a third, and so on) informant of the same family; only concordant information was included. Rio Grande do Sul, the southernmost state of Brazil, was the geographical...
origin of all families (4). All studied cases were carriers of the A-C-A haplotype (5).

Individuals were classified into two groups as follows: MJD affected cases, if they were molecularly diagnosed or if they were reported as symptomatic by the informants, and unaffected individuals, if no disease symptoms were reported by the informants. Only healthy brothers and sisters of affected individuals could be recruited in the unaffected group. Variables, such as year of birth, gender, disease onset, and CAGn (in the affected group), were also determined.

Survival was estimated through the Kaplan–Meier product-limit method and compared using a log-rank test. Cox regression model was employed for inclusion of covariates and calculation of hazard ratios (HR). Proportional hazard assumptions were tested by plotting log-minus-log survival curve and Schoenberg residuals for individual covariates against time.

Results

One hundred and eighty-two informants agreed to participate in this study. Reliable information on birth and survival was available for 825 individuals from 82 families; all individuals were born between 1903 and 1996. There were 142 deaths among the 412 individuals presenting MJD and 15 events among their 413 unaffected relatives. Estimated mean survival time was 63.96 years [95% confidence interval (CI), 62.09–65.83] for the affected group and 78.61 years (95% CI, 74.75–82.47) for the unaffected group (p < 0.001). Compared with the unaffected individuals, patients with MJD showed an increased risk of death (HR, 4.92; 95% CI, 2.86–8.46; Fig. 1).

Year of birth showed to be a risk factor for death in the entire population. Stratification revealed that each additional year increased the HR by 1.03 (95% CI, 1.02–1.05) only in the affected group, whereas in the unaffected group, there was a trend towards protection. For a subset of 105 patients with information regarding number of CAG repeats, tract length also influenced survival, each extra repeat representing an HR of 1.80 (95% CI, 1.22–2.65). Gender did not significantly alter results and was not included in the final model.

Age at disease onset was available for 366 individuals and was estimated as 36.37 years (95% CI, 35.21–37.53). As we expected, early onset predicted a shorter survival time with an HR of 1.15 (95% CI, 1.12–1.18) for each year. Survival after disease onset was calculated for each individual, and the mean period between onset of symptoms and death was 21.18 years (95% CI, 19.85–22.51). Although year of birth and age at disease onset were not significant predictors of survival time after disease onset (p = 0.288 and 0.130, respectively), the number of CAG repeats remained a risk factor for disease survival time (HR, 1.35; 95% CI, 1.09–1.68).

Discussion

This study brings further evidence of a reduced survival in MJD, as well as on the role of CAG repeats and age at onset on the survival of patients with MJD. To our knowledge, no comparison between life expectancy in MJD patients and in unaffected relatives has ever been published. This quantitative data measure the impact of MJD on overall survival and survival after disease onset, investigating the influence of CAG length, age at onset, and year of birth.

Previous studies have estimated mean survival time after disease onset in series of cases that included only deceased patients, with results ranging from 14 to 17 years (3, 6, 7). However, these figures overestimate the effect of MJD as they ignore the contribution of living patients to an increased survival time. Klockgether et al. (8) performed a sophisticated graphic analysis of the natural history of degenerative ataxias and reported survival times after disease onset ranging from 21 to 25 years for patients with SCA1, SCA2 and SCA3. Unfortunately, the authors did not

![Fig. 1. Kaplan–Meier overall survival curves by affection status. Survival probabilities were significantly different between individuals affected by Machado–Joseph disease and their unaffected relatives (log-rank test, p < 0.001).](image-url)
provide objective estimates for survival times in MJD. For a sample of 110 MJD patients, they observed that age at disease onset was a risk factor for disease progression and death, and that CAGn was a risk factor for disease progression (no analysis was performed for the outcome of death), whereas gender did not have any significant influence on progression or survival.

A comparison of survival between disease and control groups has evident advantages because it truly evaluates the impact of the disease in a given community. The present strategy of using unaffected siblings as a comparison group aimed at reducing the interference of confounding variables while measuring the magnitude of the disease impact. Also, external validity was corroborated by the comparability between the unaffected mean survival time and the life expectancy of the MJD individuals’ contemporaries in the general population [76.59 years of age according to the latest Brazilian census (9)].

We acknowledge that among asymptomatic individuals, there might be some pre-symptomatic carriers of the MJD mutation. These individuals could possibly represent milder cases of MJD and, therefore, potentially increase the survival estimates of the affected group. To assess this limitation, we performed an additional analysis including only individuals older than 45 years, a subgroup in which the proportion of pre-symptomatic carriers would be reduced. Results were similar to those obtained with the entire sample (data not shown).

The risk imparted to MJD-affected individuals by their year of birth deserves some comments. Whereas each additional year exhibited a trend towards protection in the control group, it increased the HR of death in the affected group. This finding probably reflects the lack of specific treatment for MJD and the large time span included in this study, in which the anticipation phenomenon could be operating, that is, recently born individuals would present the disease earlier and, thus, have shorter survival times. Interestingly, neither year of birth nor age at disease onset was associated with different survival times after disease onset, which indicates that these variables could be reducing overall survival time mostly by reducing disease-free survival time. This was not the case regarding CAG repeats (which are risk factors for reduced overall survival and survival after disease onset).

In conclusion, MJD conferred an almost five-fold increase in the risk of death to the affected individuals compared with their unaffected relatives, and this effect was modulated by CAG length, year of birth and age of symptoms onset. We believe that, according to the results presented herein, estimates of the magnitude of premature death among MJD patients will assist clinicians in counseling patients regarding the nature of their disease and will guide researchers in the evaluation of the long-term impact of future therapies.

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References