Letter to the Editor

Estimation of survival in Spinocerebellar Ataxia type 2 Cuban patients

To the Editor:

Spinocerebellar Ataxia type 2 (SCA2) is a neurodegenerative disorder that reaches the world’s highest prevalence in Holguín, Cuba (1). Despite the early morbidity and mortality of SCA2, there are insufficient data assessing the affect of the disease on patient survival. Here, we make use of this large sample of affected SCA2 families to evaluate disease and expanded CAG repeat number impacts on patient survival.

Clinical and molecular data were obtained in the course of a nationwide survey for SCA2 families (1). The protocol was approved by the institutional board and an informed consent was obtained from each participant. A dataset was assembled consisting of two age and sex matched groups: affected individuals with molecular and clinical diagnosis whose age at death or current age could be established (n = 606, 53.3% male), and unaffected non-carrier siblings (n = 614, 47.6% male). All individuals were born between 1915 and 1991. In the affected group the age at onset had a mean of 30.3 ± 14.1 years. Corresponding figures for overall survival – years from birth to death – and survival after disease onset – years from onset to death – were 52.0 ± 17.7 and 21.8 ± 9.3 years, respectively. The expanded CAG repeat varied between 32 and 79 with a mean of 41.4 ± 5.7 units. The diagnosis was made on the basis of clinical examination and molecular testing (1). Data were processed by the Kaplan–Meier method, log-rank statistics and Cox regression. Statistics were computed in SPSS software (2).

There were 177 deaths among the 606 SCA2 affected individuals (429 censored), and 23 events among their 614 unaffected siblings (591 censored). Expected survival estimates for the affected and unaffected individuals are show in Table 1. The median overall survival estimate for the affected individuals was lower than that obtained for unaffected individuals (Table 1). The survival curves corresponding to the affected and unaffected groups were significantly different from each other as a whole and by sex (Fig. 1). There were no significant differences for survival curves between male and female in the affected and unaffected groups (p > 0.70).

No comparison between survivals in SCA2 affected individuals and in unaffected relatives has ever been reported, and even survival estimates for SCA2 patients were limited by the small number of individuals tested (3, 4). Previous studies overestimate the effect of SCA2 on life expectancy as they ignore the contribution of living patients to an increased survival time. It is expected that a case–control design as well as the present use of unaffected non-carriers siblings as a comparison group, improves the objectivity of the estimations of disease impact on patients’ survival. Also, the life expectancy of contemporaries of SCA2 patients in the general population was 77.97 years of age – 76.0 years for men and 80.02 years for women – (5), which is very similar to what we found for control individuals, corroborating the external validity of our study.

In a subset of 546 affected individuals with information regarding CAG repeat size and age at onset, CAG repeat number significantly influenced overall survival, with an HR of 1.46 (95% CI: 1.40–1.52) for each additional repeat. A similar picture was obtained for the age at onset with each additional year representing an HR of 0.87 (95% CI: 0.86–0.89). For survival, after disease onset significant associations with expanded alleles and age at onset were obtained, with HR’s of 1.14 (95% CI: 1.10–1.17) and 0.99 (95% CI: 0.973–0.999), respectively. Again, sex was not significantly associated with survival. These findings differ from a previous report on SCA2 patients stating that female sex markedly increased the risk of entering advanced disease stages or
Table 1. Overall survival and survival after disease onset estimates by clinical status

<table>
<thead>
<tr>
<th>Clinical status</th>
<th>Affected</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>N</td>
<td>323</td>
<td>283</td>
</tr>
<tr>
<td>Events (%)</td>
<td>87 (26.93)</td>
<td>92 (32.51)</td>
</tr>
<tr>
<td>Overall survival (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Q_1) (95% CI)</td>
<td>74 (71.9–76.1)</td>
<td>78 (75.4–80.6)</td>
</tr>
<tr>
<td>([\text{Median}] Q_2) (95% CI)</td>
<td>69 (65.8–72.2)</td>
<td>68 (65.6–70.4)</td>
</tr>
<tr>
<td>(Q_3) (95% CI)</td>
<td>57 (52.6–61.4)</td>
<td>53 (48.7–57.3)</td>
</tr>
<tr>
<td>Survival after disease onset (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Q_1) (95% CI)</td>
<td>30 (25.9–34.1)</td>
<td>28 (22.9–33.1)</td>
</tr>
<tr>
<td>([\text{Median}] Q_2) (95% CI)</td>
<td>23 (20.9–25.1)</td>
<td>22 (20.5–23.5)</td>
</tr>
<tr>
<td>(Q_3) (95% CI)</td>
<td>18 (16.6–19.5)</td>
<td>17 (15.3–18.7)</td>
</tr>
</tbody>
</table>

\(Q_1\), age by which 25% of individuals will be alive; \(Q_2\), age by which 50% of individuals will be alive; \(Q_3\), age by which 75% of individuals will be alive.

of death (6). This apparent contradiction could be due to heterogeneous genetic and environmental settings of populations under study.

In conclusion, SCA2 conferred a significant decrease in survival to the affected individuals compared with their unaffected siblings, and this effect was modulated by the CAG repeat number and age at onset.

Acknowledgements

We are grateful to the affected patients and relatives, and Cuban Ministry of Health for their cooperation with this research. This work was supported by a research grant by the Cuban Ministry of Public Health to L. A.-M.

LE Almaguer-Mederos,†
R Aguilera Rodríguez,†
Y González Zaldivar
D Almaguer Gotay
D Cuello Almarales
J Laffita Mesaa
Y Vázquez Mojena
P Zayas Feria
G Auburger
S Gispert
L Velázquez Pérez

†These authors contributed equally to this work.

References

2. SPSS Inc. SPSS for Windows (version 15.0), 2006.

Correspondence:
Luis Enrique Almaguer-Mederos
Edif. 7, Apt.17, Rpto. Nuevo Holguín
Holguín CP 80100, Cuba
Tel.: +53 024 424090
Fax: +53 024 463579
e-mail: leam@cristal.hlg.sld.cu