Trends in the Epidemiology of Spinocerebellar Ataxia Type 3/Machado-Joseph Disease in the Azores Islands, Portugal

Maria Andrade de Araújo1#, Mafalda Raposo1-3#, Nadiya Kazachkova1, João Vasconcelos1, Teresa Kay5, and Manuela Lima1-3*

1Departamento de Biologia, Universidade dos Açores, Portugal
2Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal
3Instituto de Biologia Molecular e Celular (IBMC), Universidade do Porto, Portugal
4Serviço de Neurologia, Hospital do Divino Espírito Santo, Portugal
5Departamentode Genética Clínica, Hospital de D. Estefânia, Portugal

#Both authors contributed equally to this work

Abstract

Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD) is the most common form of autosomal dominant ataxias worldwide. In Portugal, the epidemiological situation of the Azores Islands, known to be a worldwide cluster for this disorder, needs to be regularly monitored. The present work aims to characterize the epidemiological situation of MJD in the Azores Islands, updating values of prevalence and establishing a temporal trend for its evolution from 1980 until the present day.

The prevalence value for the Azores archipelago by the end of 2015 was 39/100 000; prevalence values in the different islands are highly dependent on population size differences within the archipelago. An increase of prevalence from 1981 to 2015 was evidenced in the present study, values ranging from 23 to 39 patient's per 100 000 inhabitants, respectively. MJD is recognised worldwide as a rare disease; this study confirms that the Azorean islands still represent an important cluster for this disorder. Given the local burden associated with the high prevalence of SCA3, regional-specific measures need to be reinforced, targeting the improvement of the life-quality of patients and families.

ABBREVIATIONS

SCA3: Spinocerebellar Ataxia Type 3; MJD: Machado-Joseph Disease; SCA: Spinocerebellar Ataxia; CAG: Cytosine-Aadenine-Guanine; PT: Predictive Test; DNA: Deoxyribonucleic Acid; HDES: Hospital do Divino Espirito Santo

INTRODUCTION

With a pooled average of 2.7 patients per 100000 individuals, autosomal dominant cerebellar ataxias are globally considered rare disorders [1]. Amongst the dominant cerebellar ataxias, SCA3/MJD is considered as one of the three most prevalent SCA types [2] http://www.orpha.net/.orphacon/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf. In mainland Portugal, 56% of all the dominant ataxias correspond to MJD [3], representing a prevalence of 3.1 per 100000 individuals. MJD reaches in the Portuguese Islands of the Azores particularly high values of prevalence; the available systematic epidemiological study of MJD in the Azores dates from 1997, reporting 41.6 patients per 100000 individuals [4]. The Azorean cluster of MJD patients is linked to the original descriptions of the disease, which targeted three distinct families originating from these islands [5-7]. The extensively studied Azorean pedigrees have allowed the development of studies on several aspects of this disease (Table 1).

MJD is an autosomal dominant neurodegenerative disorder that involves the cerebellar, ocular, pyramidal, extra pyramidal and peripheral motor systems [8]; the disease is characterized by a wide range of clinical manifestations, usually starting around 40 years of age, which include ataxia, progressive external ophthalmoplegia, pyramidal and extra pyramidal signs, dystonia with rigidity and distal muscular atrophies [9,10]. Survival time for MJD has been reported to be approximately
of 20 years [revised in [11]]. The causative MJD gene, ATXN3, presents a CAG repeat expansion at exon 10 that is polymorphic, consensually ranging from 13 to 44 CAGs in normal chromosomes [12]. When the CAG tract at the ATXN3 gene contains above 50 repeats [13], the corresponding protein, ataxin-3, gains a toxic function, triggering a cascade of pathogenic events, including the formation of aggregates, failure of cellular protein homeostasis, impairment of axonal transport, transcriptional dysregulation, mitochondrial dysfunction and oxidative stress, as well as abnormal neuronal signaling (revised in [14]).

Based on the determination of the (CAG) length at the ATXN3 gene, a direct molecular test is currently available for MJD. Molecular testing warrants differential diagnosis, since in probable MJD patients overlapping of clinical features with other SCAs is widely acknowledged. Testing of healthy at risk individuals is also available, in the context of PT and genetic counselling programs. In the Azores the PT is available in the Azores Islands since 1998 [15-17].

MJD remains an untreatable disorder; patient’s management is supportive, as no medication has yet proven effective to either prevent disease or slowdown the progression of symptoms. Double - blind, randomized, placebo controlled clinical trials have been initiated, but those terminated have been inconclusive [18,19]. Noteworthy, several compounds tested in a pre - clinical setting have been providing promising results [20,21] and are likely candidate for future interventional trials.

The present work aims to characterize MJD’s epidemiological situation in the Azorean islands, by updating values of prevalence and establishing a temporal trend for its evolution. Given the impact that MJD has in the Azores Islands, reliable estimates of the overall prevalence of this disease should be important for planning and delivering the appropriate provision of health and social care to patients and families. In a more global scenario, MJD in the Azores Islands can provide insights into the paradigm of population clusters of otherwise rare diseases.

PATIENTS AND METHODS

Patients

Individual data on MJD patients was available at the Department of Neurology at the HDES. All Azorean pedigrees (which included data from 4 generations) were revised and updated by the last day of 2015. In all MJD pedigrees considered, a molecular diagnosis of MJD was available for at least one family member. Data concerning a total of 222 patients was compiled: for 56% (125/222) of these patients only a clinical diagnosis of MJD was available; for the remaining a clinical as well as a molecular diagnosis and the respective genotype were available.

The present study is part of a larger project on MJD in the Azores (PRI - “Projeto Regional Integrado sobre a DMJ”) approved by the Ethics Committee of the HDES at Ponta Delgada, São Miguel, Azores.

Genetic and clinical variables

For the patients considered in the up - dating of prevalence (prevalence estimation for 2015), the number of CAG repeats, age at onset and disease duration were available. Furthermore, age at onset adjusted for CAG repeats was estimated. The size of the CAG tract at ATXN3 was determined as in Bettencourt and colleagues [22], using DNA from blood samples of patients, extracted using the standard procedures. Age at onset was defined as the age of appearance of the first symptoms (normally gait disturbance). This information was self - reported by the patients or by the caregivers, during the neurological exam. Disease duration was defined as the time elapsed between age at clinical diagnosis and age calculated at the time of the present study (last day of 2015).

Epidemiological analysis of MJD in the Azores

Prevalence update of MJD in the Azores Islands: Patients alive by the last day of 2015 and with known residency in the Azores were considered in the updating of prevalence. Values for the total Azorean population were obtained from the last population census [23].

Temporal trend of prevalence (1981-2015): Patients alive by the last day of 1981, 1991, 2001 and 2011 with known residency in the Azores, were considered for prevalence
calculation in each of these years. Values for the total Azorean population were obtained from the population census of 1981, 1991, 2001 and 2011 [23].

Statistical analysis

Age, CAG repeats number of normal and expanded allele, age at onset and disease duration of patients from São Miguel and Flores were compared using the student t-test. Estimated age at onset was calculated by an ANCOVA procedure, in which CAG repeat was treated as covariate. Ap-value of 0.05 was considered as statistically significant. All the analyses were carried out using procedures of the IBM SPSS statistics version 22.

RESULTS AND DISCUSSION

Prevalence update of SCA3 in the Azores Islands

The 97 MJD patients ascertained by the end of 2015 are distributed by 7 of the 9 Azorean islands, with a clear concentration of cases in Flores and S. Miguel (Figure 1). For the total cohort, constituted by 51 females and 46 males, the average age was of 52 ± 15 [mean ± standard deviation] years (Table 2). Genetic and clinical data for the subset of patients from São Miguel and Flores Islands, representing 78% of the total cohort, are displayed in Table (2). Azorean patients presented earlier age at onset (37 ± 12) when compared to patients from EUROSCA study (N = 403, 40 ± 12), USA (N = 110, 40 ± 11), Japan (N = 126, 41 ± 15) and France (N = 44, 44 ± 12) [24,25]. The number of CAGs repeats in expanded allele in the Azorean cohort was statistically different from all abovementioned cohorts, with the exception of the USA cohort [24,25]. In the Azorean cohort, the number of CAGs in the expanded allele explains 68% of the onset variance, a value which is 18% higher than that of the EUROSCA cohort [24,25]. This finding could be related with the use of a mixed population sample in the work of Tezenas and colleagues, which enrolled patients from different genetic backgrounds, weakening genotype - phenotype correlations.

Age at onset was significantly lower for patients from São Miguel when compared with patients from Flores Island (p < 0.05, (Table 2)). However, taking into account as covariate in the ANCOVA model the CAG repeats size in the expanded allele; differences of estimated age at onset between São Miguel and Flores were not statistically significant. Therefore, the average size of the CAG tract, which is lower in Flores than in São Miguel Island, explains the difference in age at onset between patients from these two islands.

Values of prevalence by island are shown in Figure (1). The updated overall prevalence of MJD in the Azores (Figure 1) is 39/100000, a value similar to the previously reported by Lima and colleagues (1997) [4]. It is known, however, that values presented by Lima et al., (1997) were overestimations; in fact, due to the lack of a molecular confirmation until 1998, cases representing other spinocerebellar ataxias, clinically undistinguishable from MJD, were included in the previous prevalence estimations [4]. Coutinho and colleagues, in 2013, reported values of prevalence for mainland Portugal of 3.1 per 100 000 population, although Azores was not included (Coutinho et al., 2013). In Azores, therefore, the number of identified MJD patients is more than 10 times comparatively to mainland Portugal, confirming Azores, namely Flores Island as a MJD cluster.

Prevalence values are highly dependent on population size differences within the archipelago; in the small island of Corvo, with only 430 inhabitants, 1 in each 143 is affected (Figure 1). Patients from Corvo, however, are originally from the island of Flores, whose particularly high prevalence of MJD is confirmed in this study (633/100 000).

Temporal trend of prevalence (1981-2015)

Data collected allowed the assessment of the number of patients in Azores at five different moments - 1981, 1991, 2001, 2011 and 2015. Figure (2) evidences the tendency for the increase of prevalence. This tendency should be primarily related with the growing awareness about the disease, both in a medical and social context, overall allowing a better referral of patients to the clinicians. Furthermore, the availability of the predictive test has, by itself, promoted the early identification of asymptomatic carriers. In fact, the adherence to the PT in the Azores was reported as being of 20.7%, a value which is considered high, when compared to levels in other similar disorders (16); because subjects identified as carriers in the PT are usually engaged in follow - up visits, the time lag between onset and the referral to the neurologist is shortened. The large survival time, a common feature of MJD patients, should also have contributed to the tendency for the increase of prevalence observed in the Azores in the period analysed.

<table>
<thead>
<tr>
<th>Gender, Female/Male</th>
<th>N</th>
<th>Total</th>
<th>São Miguel</th>
<th>N</th>
<th>Flores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>97</td>
<td>51/46</td>
<td>52</td>
<td>29/23</td>
<td>24</td>
</tr>
<tr>
<td>Mutant allele, (CAG)n size</td>
<td>87</td>
<td>71 ± 3 [64-79]</td>
<td>47</td>
<td>71 ± 3 [65-78]</td>
<td>21</td>
</tr>
<tr>
<td>Age at onset, yrs</td>
<td>92</td>
<td>37 ± 11 [16-71]</td>
<td>50</td>
<td>36 ± 1 [16-71]</td>
<td>24</td>
</tr>
<tr>
<td>Estimated age at onset*, yrs</td>
<td>86</td>
<td>36 ± 2</td>
<td>47</td>
<td>37 ± 1</td>
<td>21</td>
</tr>
</tbody>
</table>

Yrs=years; all continuous variables are described as mean ± standard deviation [minimum-maximum], exceptionally for estimated age at onset; *age at onset was estimated (mean ± standard error) using an ANCOVA model, for which the CAG repeats size in mutant allele was set as covariate [71 CAGs]; #p-value lower than 0.05
CONCLUSION

MJD is recognised, worldwide, as a rare disease; this study confirms that the Azorean islands represent an important cluster for this disorder. Given the fact that Azorean MJD patients share genetic and environment conditions, the study of non-CAG factors underlying disease variability should be facilitated.

More importantly, given the local burden associated with the high prevalence, regional - specific measures need to be reinforced, targeting the improvement of the life - quality of patients.

REFERENCES


7. Nakano KK, Dawson DM, Spence A. Machado disease. A hereditary...
Lima et al. (2016) Email: lima.m.m.lima@uauc.pt


23. Instituto Nacional de Estatística
