Transthyretin familial amyloid polyneuropathy (TTR-FAP) in Mallorca: a comparison between late- and early-onset disease

Juan Buades-Reinés¹, Manuel Raya-Cruz¹, Cristina Gallego-Lezaún¹, Tomás Ripoll-Vera², Mercedes Usón-Martín³, Hernán Andreu-Serra⁴, and Eugenia Cisneros-Barroso⁵

¹Department of Internal Medicine, Son Llàtzer Hospital, Carretera de Manacor; ²Department of Cardiology, Son Llàtzer Hospital, Carretera de Manacor; ³Department of Neurology, Son Llàtzer Hospital, Carretera de Manacor; ⁴Department of Digestive Medicine, Son Llàtzer Hospital, Carretera de Manacor; and ⁵Clinical Research Coordinator A-TTR Group, Son Llàtzer Hospital, Carretera de Manacor, Palma, Spain

Abstract

The age of onset (AO) of hereditary ATTR amyloidosis (hATTR) is known to vary between populations, with differing characteristics reported according to AO in endemic/non-endemic foci. This was a retrospective study of patients with early AO (<50 years) and late AO (≥50 years) hATTR at our center in Mallorca. Data were collected on patient demographics, clinical disease manifestation, and physical symptoms. A total of 95 patients were analyzed, with mean follow-up of 9 years from diagnosis. The early AO group included 53 patients (33 male) and the late AO group included 42 patients (21 male). Neurologic involvement was the most common initial symptom, although it was significantly more frequent in the late AO vs. early AO group (p = 0.015). Autonomic involvement was observed in 26% of patients in the early AO group, but was rarely observed in the late AO group (5%). During follow up, cardiologic symptoms, renal involvement, and ophthalmologic symptoms were significantly more common in the late AO group (p < 0.05). This retrospective study demonstrates the variation in disease presentation and progression according to AO of hATTR at our Mallorcan center.

Key words: age of onset, early onset, familial amyloidosis with polyneuropathy, late-onset, neurologic involvement

Introduction

Hereditary TTR amyloidosis (hATTR) is a systemic disease resulting from the extracellular deposition of insoluble transthyretin (TTR) amyloid fibrils in various organs and tissues (Ando et al., 2013). The deposition of TTR fibrils results from misfolding of the native TTR protein, which is promoted by familial mutations in the TTR gene (Hammarstrom et al., 2002; McCutchen et al., 1993) and the Val30Met is the most common variant in patients with hATTR (Connors et al., 2003).

The mean age of onset (AO) is different depending on the endemic focus, with large variations observed across different populations. The AO in our treatment center in Mallorca has previously been reported as 50 years (Reines et al., 2014), although earlier AO was observed in other regions (e.g., mean AO of 34 years in Portugal) (Sousa et al., 1995).

In previous observational studies of endemic foci associated with early AO (<50 years), such as
Patients and Methods

This was a retrospective, single-center study (Son Llàtzer Hospital Palma de Mallorca, Spain) from 2003 to 2014 to compare clinical features between patients with early AO (<50 years) and late AO (≥50 years) hATTR. In patients with symptoms suggestive of disease but without a previous DNA diagnosis, diagnosis of hATTR was confirmed by presence of the Val30Met TTR mutation, identified by polymerase chain reaction amplification of exon 2 of the TTR gene from genomic DNA, and subsequent sequencing. Where possible, a tissue biopsy was performed to demonstrate amyloid deposits. Symptomatic onset was defined as the time point within the follow-up period, which shows pathological findings in additional tests or appearance of symptoms not present previously. The study was approved by the Research Committee of the hospital and confidentiality of the data collected was guaranteed.

Clinical assessments

Demographic data collected included age, gender, age at diagnosis by identification of Val30Met mutation, family history, and familial transmission. Patients were assessed at baseline and follow up for the following clinical features: sensory-motor complaints, autonomic involvement, cardiac abnormalities, renal disturbances, or ocular abnormalities. Physical examinations included body mass index (BMI) and laboratory findings (serum albumin).

Statistical analyses

The statistical analyses were primarily descriptive, calculating frequencies of each of the qualitative variables, and the mean and standard deviation (SD) or median and interquartile range for quantitative variables. The categorical data were assessed using Pearson’s chi-squared test or Fisher’s exact test. Continuous variables were analyzed using a Student’s t-test or Mann-Whitney U test for non-parametric variables. A p-value of <0.05 was used to show statistically significant associations. All statistical analyses were based on SPSS (IBM) version 17.0 or later.

Results

Data from 95 patients (54 males and 41 females) were analyzed. All patients had the TTR Val30Met mutation. Overall, the median age at onset (AO) was 47 (range: 23–79) years and the mean follow up was 9 ± 6 years from onset.

Patient characteristics at diagnosis

The baseline characteristics of the early and late AO groups are shown in Table 1. Diagnosis by genetic test (Val30Met) was delayed by a mean ± SD of 1 ± 5 and 0.4 ± 6 years in the early and late AO groups, respectively. Diagnosis was confirmed by biopsy in 87% cases in the early AO group and 67% cases in the late AO group. In the early-onset group, 77% patients had a family history of hATTR, with 23 cases maternally transmitted and 18 cases paternally transmitted. Compared with the early AO group, the proportion of cases with family history was significantly lower in the late AO group (p = 0.001). In this group, transmission was maternal or paternal in 10 and 8 cases, respectively.

Sensory-motor abnormalities were the most frequent initial symptoms in both groups (Table 1). However, the overall proportion of patients with sensory-motor involvement was significantly lower in the early AO group compared with the late AO group (55% vs. 79%, respectively; p = 0.015). Conversely, the proportion of patients with autonomic involvement was significantly higher in the early AO group (26% vs. 5%, respectively; p = 0.01). Digestive symptoms were observed in 12 (27%) and 2 (5%) patients in the early and late AO groups, respectively. Impotence was reported in three patients (two with early AO and one with late AO), and cardiac involvement in one patient (early AO group). In 15 cases, the diagnosis of hATTR was made based on previous family history during an asymptomatic stage (nine patients in the early AO group and six in the late AO group). In these patients, neurologic involvement was the initial symptom in seven of nine cases in the early AO group and five of six cases in the late AO group; dysautonomic symptoms were observed first in the remaining cases (early AO [n = 2]; late AO [n = 1]).
Clinical features during follow up

Of the clinical characteristics monitored during follow up, renal involvement, dyspnea, chronic heart failure, dry eye, and vitreous opacity were significantly more common in the late AO group compared with the early AO group (Table 2). Syncope was significantly less common in the late AO group. There were no statistically significant differences between the two groups for any of the other symptoms assessed (Table 2). During follow up, 8% patients died in the early AO group and 36% died in the late AO group (p = 0.001). Of these deaths, 50% in the early AO groups were related to hATTR, compared with 73% deaths in the late AO group that were considered a consequence of this disease (p = 0.002).

During the follow-up period, orthotopic liver transplantation was performed in 38 patients (49%) in the early AO group and 18 (42%) in the late AO group.

Discussion

This retrospective, single-center study demonstrated that clinical characteristics at presentation and follow up differ between patients with early AO (<50 years) and late AO (≥50 years) hATTR from a Mallorcan community. This variation in clinical presentation of disease according to AO is consistent with previous reports (Misu et al., 1999; Koike et al., 2002; Conceição and De Carvalho, 2007; Koike et al., 2012); however, we have also demonstrated that differences in symptom prevalence persist during 9 years of follow up. Our data indicate that neurologic involvement at diagnosis is more common in patients with late AO than early AO disease, but suggest that cardiologic and eye symptoms occur more frequently during follow up in the late AO group. An improved understanding of the features associated with early- and late-onset hATTR may aid diagnosis and management of this disease.

In this study population the median AO was 35 and 64 years in the early and late AO groups, respectively. For the early AO group, this median AO is similar to the mean AO observed in the main endemic areas of Portugal (Sousa et al., 1995) and Japan (Ikeda et al., 2002). By comparison, the age of patients in the late AO group is similar to that noted in French and Swedish patients with hATTR (Plante-Bordeneuve et al., 2003; Sousa et al., 1993). A Swedish study suggested that AO is higher in patients with paternal compared with maternal transmission (Drugge et al., 1993), yet in the current data set the proportion of patients with paternal inheritance was not higher in the late AO group.

In this study, there was predominance of males with early AO, whereas an equal split was seen between sexes in the late AO group. An assessment of patients with early AO and late AO in Japan showed an increased proportion of male patients in both cohorts (Koike et al., 2002; 2012). However, a similar study in Portugal revealed a near 1 : 1 male : female ratio in both early and late AO patients (Conceição and De Carvalho, 2007). Overall, the discrepancies between our data and those from other countries suggest that unknown genetic or environmental factors may influence the phenotypic expression of disease.

Delay in the time to diagnosis is a major obstacle to the optimal management of TTR-FAP. With the exception of those with a clearly diagnosed familial history of FAP, patients still invariably wait several years between the emergence of first clinical signs and accurate diagnosis (Adams et al., 2016). Indeed, the delay of only 0.4 years in patients with late AO is shorter than that reported in other series (Koike et al., 2004). The speed of diagnosis relates in part to the fact that this is an endemic community, and we have collected the pedigree of families affected as part of family screening. Also, hATTR is included in differential diagnosis of many diseases in our center, not only in cases of neurologic involvement, allowing us to make an early diagnosis and initiate appropriate monitoring and treatment of these patients.

At presentation, the most common symptoms were neuropathic in both groups. However, whilst...
Table 2. Clinical features during follow-up

| Feature                  | Early AO (<50 years) | Late AO (≥50 years) | p-value |
|--------------------------|-----------------------|----------------------|---------|
| Neurologic involvement   | 45 (85)               | 36 (86)              | NS      |
| Autonomic dysfunction    | 39 (74)               | 35 (83)              | NS      |
| Digestive involvement    | 38 (72)               | 28 (67)              | NS      |
| Renal involvement        | 8 (15)                | 13 (31)              | 0.05    |
| Cardiac involvement      |                       | 16 (38)              | NS      |
| Syncope                  | 12 (23)               | 5 (12)               | 0.01    |
| Dyspnea                  | 0 (0)                 | 8 (19)               | 0.01    |
| Chronic heart failure    | 2 (4)                 | 10 (24)              | 0.004   |
| Ophthalmologic involvement| 9 (17)               | 13 (31)              | NS      |
| Dry eye                  | 2 (4)                 | 7 (17)               | 0.03    |
| Vitreous opacity         | 7 (13)                | 12 (29)              | 0.05    |

AO, age of onset; NS, non-significant difference between early and late AO groups.

Autonomic involvement was also seen in approximately one-quarter of patients in the early AO group, it was rare in patients with late AO. Indeed, neurologic involvement was almost the only initial symptom in the late AO group. This variation in initial clinical affection, with evidence of mixed involvement in early AO patients but predominance of neurologic involvement in late AO patients, is in general agreement with previous studies (Misu et al., 1999; Koike et al., 2002; Conceição and De Carvalho, 2007; Koike et al., 2012). However, it should be noted that autonomic involvement was observed in patients with late AO disease in a small German study (Dohrn et al., 2013). Overall, these data support the consideration of hATTR in elderly patients with unexplained neurologic affection, yet importantly it also suggests that younger patients with autonomic symptoms (e.g., diarrhea and impotence) should also trigger suspicion of hATTR.

During follow-up in our study the proportion of patients with neurologic involvement or autonomic dysfunction was not statistically significantly different between the early and late AO groups, although the severity of these symptoms was not compared. However, when individual cardiologic symptoms were assessed, syncope, dyspnea, and chronic heart failure were more common in the late AO group. In addition to cardiac symptoms, renal, and ophthalmologic symptoms were also more common in the late AO group in this study, with the proportion of patients with dry eye and vitreous opacities significantly increased. These symptoms have classically been considered a signal of a potential severe systemic disease (Seca et al., 2014). The rate of mortality was greater in the late AO group, and a slightly higher proportion of these deaths were related to hATTR compared with the early AO group; these data are fitting with the reduced survival expected in late AO patients (Koike et al., 2012). As the OLT not performed in our center, there could be the possibility that monitoring be carried out in an irregular way compared to commonly followed in our center.

Acknowledgements

The authors received editorial assistance from Adelphi Communications Ltd, funded by Alnylam Pharmaceuticals. We would especially like to acknowledge Ricardo de Frutos, Pritesh Gandhi, and Angela Partisano for their help in reviewing the manuscript.

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