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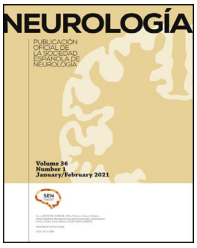

ORIGINAL ARTICLE

Red flags in patients with hereditary transthyretin amyloidosis at diagnosis in a non-endemic area of Spain

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KEYWORDS
Transthyretin;
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Abstract
Introduction: Hereditary transthyretin (hATTR) amyloidosis with polyneuropathy is a rare multisystemic disease characterised by onset during adulthood and associated with poor prognosis if untreated. A set of signs and symptoms, commonly known as ''red flags,'' have been proposed to assist in early detection of the disease; presence of red flags may suggest underlying hATTR amyloidosis in patients with progressive sensorimotor polyneuropathy.
Material and methods: We analysed the frequency of red flags at the time of diagnosis in 30 patients with hATTR amyloidosis in a non-endemic area of Spain; onset was late in the majority of patients.
Results: The frequencies of the red flags were as follows: bilateral carpal tunnel syndrome in 15 patients (50%), early autonomic dysfunction in 17 (56%), gastrointestinal problems in 14 (46.6%), unexplained weight loss in 8 (26.6%), heart disease in 12 (40%), asymptomatic cardiac findings in 13 (43.3%), kidney disease in one (3.3%), vitreous opacities in none, family history of neuropathy in 21 (70%), family history of heart disease in 15 (50%), and family history of gastrointestinal problems in 3 (10%). All patients presented at least one red flag at diagnosis, with a median of 4 red flags.
Conclusion: Red flags were common at the time of diagnosis, even in patients with late-onset hATTR amyloidosis. Presence of red flags in a patient with symmetrical sensorimotor polyneuropathy should serve as a warning sign, and lead to targeted diagnosis to rule out hATTR amyloidosis, independently of age of onset.

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PALABRAS CLAVE
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Red flags

«*Red flags*» en pacientes con polineuropatía amiloidótica familiar relacionada con transtiretina (hATTR) en el momento del diagnóstico en un área no endémica de España

Resumen
Introducción: La polineuropatía relacionada con el depósito de amiloide por transtirretina (hATTR, por sus siglas en inglés) es una enfermedad poco común, multisistémica, de inicio en la edad adulta con un pronóstico ominoso sin tratamiento. Para reconocer la enfermedad en la etapa más temprana posible, se ha propuesto un grupo de signos y síntomas, comúnmente conocidos como ïred flags¨, y su presencia puede sugerir la presencia de un hATTR subyacente en pacientes con polineuropatía sensitivo-motora progresiva.
Materiales y métodos: Se analizó la frecuencia de ïred flagsën el momento del diagnóstico en 30 pacientes hATTR de un área no endémica de España, con una mayoría de pacientes de inicio tardío.
Resultados: Las frecuencias de ïred flagsfueron las siguientes: síndrome del túnel carpiano bilateral (STC) 15/30 (50%); disautonomía temprana en 17/30 (56%); síntomas gastrointestinales en 14/30 (46,6%); pérdida inexplicable de peso en 8/30 (26,6%); enfermedad cardiaca en 12/30 (40%); hallazgos cardiacos asintomáticos en 13/30 (43,3%); enfermedad renal en 1/30 (3,3%); opacidades vítreas en 0/30 (0%); neuropatía familiar en 21/30 (70%); cardiopatía familiar en 15/30 (50%) y antecedentes familiares gastrointestinales en 3/30 (10%). Todos los pacientes presentaron al menos una bandera roja en el momento del diagnóstico, con una mediana de cuatro banderas rojas.
Conclusión: Las ïred flags¨ incluso en los pacientes de inicio tardío, fueron hallazgos comunes en el momento del diagnóstico, y su presencia en un paciente con polineuropatía sensitivo-motora simétrica debería alertarnos y conducir el diagnóstico a lo largo del hATTR hasta excluirlo, independientemente de la edad de inicio o de la región endémica.

Introduction

Hereditary transthyretin amyloidosis (hATTR), first described by Andrade[1] in 1952, is a rare, adult-onset, multisystem disease that dramatically reduces the life expectancy of affected patients. In hATTR, amyloid deposition preferentially involves the peripheral nervous system and heart, causing progressive autonomic and sensorimotor peripheral neuropathy and restrictive cardiomyopathy.[2] Other common sites of amyloid deposition are the kidneys, eyes, and central nervous system.[3] If left untreated, prognosis is poor, with death within 9—10 years after diagnosis.[2] To date, over 120 *TTR* mutations have been described,[4] with Val30Met (also known as p.Val50Met) being the most common in both endemic and non-endemic areas worldwide.[5]

Early diagnosis requires a high level of suspicion, and the disease is often associated with a diagnostic delay of 2—5 years. The availability today of disease-modifying therapies has improved the prognosis of these patients, especially when treatment is started early.[6—9] Early diagnosis is therefore essential.

With a view to facilitating the early detection of the disease, a series of red flag signs and symptoms have been proposed to alert clinicians to the possibility of underlying hATTR in patients with progressive sensorimotor polyneuropathy.[10] However, these red flags were originally described in endemic areas, in patients with early-onset disease (EOD) associated with the Val30Met (V30M) mutation. Therefore, their diagnostic value in patients from non-endemic areas, with non-V30M mutations, or with late-onset disease (LOD) has been questioned, mainly due to variations in the clinical expression of the disease in these populations.[11—13]

This study aims to establish the incidence of hATTR red flags at diagnosis in patients from a non-endemic area of Spain, the majority of whom presented LOD.

Material and methods

Patients

All patients were recruited at the neuromuscular diseases unit of Hospital Clínico San Carlos in Madrid. This university hospital receives patients with suspected or confirmed hATTR from central Spain, considered a non-endemic region. The study was conducted in accordance with the good clinical practice guidelines and with the legislation in force on the protection of patient data.

Study design

We conducted a retrospective, observational, single-centre study based on the review of clinical records collected prospectively over a 10-year period (2008—2018). With a view to minimising selection bias, the sample included all patients with a definitive diagnosis of hATTR and assessed at our centre during the study period. Definitive diagnosis of hATTR was defined as the presence of clinical and neurophysiological signs of sensorimotor polyneuropathy plus genetic confirmation of heterozygous presence of a pathogenic or probably pathogenic variant in the *TTR* gene, according to the guidelines of the American College of Medical Genetics and Genomics/Association for Molecular Pathology.[14]

Table 1 Clinical and demographic characteristics of patients with hereditary transthyretin amyloidosis.

Total ($n = 30$)	
Sex, n (%)	
Men	17 (56.7)
Women	13 (43.3)
Age at symptom onset (mean [SD])	62.47 (12.6)
Red flags at diagnosis, n (%)	
Bilateral CTS	15 (50)
Unilateral CTS	2 (6.7)
Autonomic dysfunction	17 (56.7)
Gastrointestinal symptoms	14 (46.7)
Unintended weight loss	8 (26.7)
Cardiac symptoms	12 (40)
Asymptomatic cardiological alterations	13 (43.3)
Kidney disease	1 (3.3)
Vitreous opacification	0 (0)
Family history of neuropathy	21 (70)
Family history of heart disease	15 (50)
Family history of gastrointestinal symptoms	3 (10)
Red flags at diagnosis, n (%)	
1	2 (6.7)
2	1 (3.3)
3	8 (26.7)
4	10 (33.3)
5	5 (16.7)
6	2 (6.7)
7	1 (3.3)
8	1 (3.3)
Age of onset, n (%)	
Early onset ($\leq$ 50 years)	6 (20)
Late onset (> 50 years)	24 (80)
Mutation, n (%)	
p.Val30Met	18 (60)
Other	12 (40)

CTS: carpal tunnel syndrome.

Table 2 Comparison of initial manifestations between patients with early and late onset and between patients with the V30M mutation and with other *TTR* mutations.

	Early onset ($\leq$ 50 years) ($n = 5$)	Late onset (> 50 years) ($n = 22$)	*P*	V30M ($n = 16$)	Other *TTR* mutations ($n = 11$)	*P*
Weakness	0	1	> .1	1	0	> .1
Dyspnoea	0	3	> .1	2	1	> .1
Atrial fibrillation	0	1	> .1	0	1	> .1
Dysautonomia	3	1	.018	2	2	> .1
Pain	2	3	> .1	3	2	> .1
Paraesthesia	0	9	0.09	7	2	> .1
Weight loss	0	2	> .1	0	2	> .1
CTS	0	1	> .1	1	0	> .1

CTS: carpal tunnel syndrome.

Table 3 Comparison of red flags at diagnosis between patients with early and late onset and between patients with the V30M mutation and with other *TTR* mutations.

Red flags at diagnosis	Early onset (≤ 50 years) (*n* = 6)	Late onset (> 50 years) (*n* = 24)	*P*	V30M (*n* = 18)	Other *TTR* mutations (*n* = 12)	*P*
Bilateral CTS	3	12	.67	7	8	.132
Dysautonomia	5	12	.156	9	8	.301
Gastrointestinal symptoms	3	11	.605	9	5	.471
Cardiac symptoms	2	10	.545	6	6	.296
Asymptomatic cardiological alterations	1	12	.133	8	5	.664
Unintended weight loss	0	8	.126	4	4	.396
Kidney disease	0	1	.800	1	0	.600
Vitreous opacification	0	0	—	0	0	—
Family history of neuropathy	6	15	.091	12	9	.472
Family history of heart disease	4	11	.326	7	8	.132

CTS: carpal tunnel syndrome.

Data collection

For all patients with hATTR, the following data were systematically recorded at the baseline clinical assessment and during follow-up: sex, date of birth, age of onset, type of mutation, and presence and number of red flags at the time of definitive diagnosis.

Red flags

The following clinical characteristics were considered red flags for hATTR in patients with progressive sensorimotor polyneuropathy[10]: family history (first-degree relatives) of peripheral neuropathy; autonomic dysfunction (including orthostatic hypotension, sexual dysfunction, urinary retention, sweating abnormalities, or abnormal findings from autonomic tests [sympathetic skin response, variability of RR interval]); cardiac symptoms; gastrointestinal symptoms (including diarrhoea, constipation, and alternating episodes of diarrhoea and constipation); unintentional weight loss; bilateral carpal tunnel syndrome (CTS); renal involvement (laboratory findings suggesting kidney failure); and vitreous opacification. In addition to these signs, the following were also considered red flags: family history (first-degree relatives) of heart, gastrointestinal, or kidney disease; abnormal electrocardiography (ECG), DPD-scintigraphy, or echocardiography findings without cardiac symptoms; and unilateral CTS.

Data analysis

We initially conducted a descriptive analysis of the clinical, neurophysiological, and genetic characteristics of all patients included in the study ($n = 30$). Secondly, we analysed the frequency of red flags among patients with hATTR in our cohort. Finally, we compared the frequency of red flags between patients with EOD (age of onset $\leq$ 50 years) and those with LOD (> 50 years) and between carriers of the V30M mutation and non-V30M mutations.

Categorical variables are expressed as numbers and percentages. Contingency tables were analysed using the Pearson chi-square test or the Fisher exact test; where appropriate, we also calculated odds ratios with 95% confidence intervals. Non-parametric data are expressed as medians and quartiles 1 and 3 (Q_1—Q_3) and were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test. All tests were 2-tailed; statistical significance was set at $P < .05$. Statistical analysis was conducted using the SPSS software, version 25 (IBM Corp.; Armonk, NY, USA).

Results

The study included a total of 30 patients with confirmed hATTR. Of these, 6 (20%) had EOD and 24 (80%) had LOD. Median age of onset was 65 years (Q_1—Q_3, 54.8—72.3). Median age in the EOD group was 42 years (Q_1—Q_3, 37.8—47), compared to 67.5 years (Q_1—Q_3, 61.5—73.0) in the LOD group. Median diagnostic delay (symptom onset to genetic confirmation) was 1.25 years (Q_1—Q_3, 0.87—3). Eighteen patients (60%) were carriers of the V30 M mutation. Table 1 lists patients' clinical and molecular genetics characteristics.

The initial symptom was determined in 27 cases. By order of frequency, symptoms were distributed as follows: positive sensory symptoms (paraesthesia) (9/27; 33.3%), symptoms of heart failure or arrhythmia (7/27; 25.9%), neuropathic pain (5/27; 18.5%), dysautonomic symptoms (4/27; 14.8%), unintended weight loss (2/27; 7.4%), uni- or bilateral CTS (1/27; 3.7%), and limb weakness (1/27; 3.7%). The initial symptom could not be precisely determined in 3 patients. Table 2 compares the initial symptoms in patients with EOD and LOD. Dysautonomic symptoms were the most common form of presentation in EOD, occurring in 50% of patients.

At the time of diagnosis, the distribution of red flags was as follows (Table 1): unilateral CTS (2/30; 6%); bilateral CTS (15/30; 50%); early autonomic dysfunction (17/30; 56.7%); gastrointestinal symptoms (14/30; 46.7%); unintended weight loss (8/30; 26.7%); cardiac symptoms (12/30; 40%); asymptomatic ECG, echocardiography, or DPD-scintigraphy alterations (13/30; 43.3%); kidney failure (1/30; 3.3%); vitreous opacification (0/30; 0%); family history of peripheral neuropathy (21/30; 70%); family history of heart disease (15/30; 50%); and family history of gastrointestinal disease (3/30; 10%). No patient had family history of kidney disease. Overall, every patient presented at least one red flag at diagnosis (median of 4; Q_1—Q_3, 3—5). All 6 patients with EOD and 22 patients with LOD (22/24; 92%) presented 3 or more red flags at diagnosis.

Table 3 shows the distribution of red flags at diagnosis for the total patient cohort ($n = 30$), comparing data between patients with EOD and LOD and between those with the V30M mutation and with non-V30M mutations.

Discussion

The main findings of this study show that red flags were relatively common among all patients, with the majority presenting more than 3 red flags, independently of age of onset or time from onset to diagnosis. Comparisons between groups revealed no statistically significant differences between patients with LOD and those with EOD in terms of the number of red flags at diagnosis. We also found no significant differences in the number of red flags between patients with the V30M mutation and with non-V30M mutations.

Therefore, our results seem to contradict the findings of previous authors, who suggest that these red flags are not reliable diagnostic markers in patients with LOD or in non-endemic areas.[13]

Regarding the initial manifestation, dysautonomia was the only symptom showing a statistically significant difference between groups, appearing as the initial symptom in 50% of patients with EOD and only 0.21% of those with LOD. While only 3 patients with EOD (50%) presented the V30M mutation in our series, previous studies report that dysautonomia tends to be the initial symptom in patients with EOD presenting this mutation, in approximately 50% to 60% of cases.[11,15] This is probably due to greater loss of unmyelinated fibres in V30M patients with EOD than in those with LOD, which would explain the earlier onset of dysautonomia in this group.[16]

Therefore, due to the phenotypic variability and heterogeneous presentation of hATTR, the presence of red flags may differ between endemic and non-endemic regions.

Our series presents limited statistical power due to the small sample size; nonetheless, hATTR is a rare disease, and this small sample was expected. Therefore, our results should be interpreted with caution, in the context of a small series, and should not be the basis for definitive assumptions.

Conclusion

Red flags were common at the time of diagnosis, even in patients with LOD. Presence of red flags in a patient with symmetrical sensorimotor polyneuropathy should serve as a warning sign, and lead to targeted diagnosis to rule out hATTR, independently of age of onset or geographical region. This is particularly important considering that early treatment appears to be associated with a better response.[17]

Conflicts of interest

Dr Silva-Hernández has consulted for Pfizer. Dr Lucía Galán has received lecture honoraria and consulting fees from

Pfizer, Alnylam, Akcea, and Grunenthal, and financial assistance to attend scientific meetings from Pfizer, Alnylam, and Akcea. Dr Alejandro Horga has received consulting fees from Pharnext.

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References

1. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain. 1952;75:408—27.
2. Planté-Bordeneuve V, Kerschen P. Transthyretin familial amyloid polyneuropathy. Handb Clin neurol. 2013;115:643—58.
3. Maia L. Emerging CNS involvement in FAP-TTR long survival patients. Orphanet J Rare Dis. 2015;10 Suppl 1:I14.
4. Ando Y, Coelho T, Berk JL, Waddington-Cruz M, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31—8.
5. Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants, 2003. Amyloid. 2003;10:160—84.
6. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. Amyloid. 2006;13:236—49.
7. Coelho T, Maia LF, Martins da Silva A, Waddington-Cruz M, Planté-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79:785—92.
8. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:22—31.
9. Adams D, González-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11—21.
10. Conceiçao I, González-Duarte A, Obici L, Schmidt H, Simoneau D, Ong ML, et al. ''Red flag'' symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv System. 2016;21:5—9.
11. Koike H, Misu K, Ikeda S, Ando Y, Nakazato M, Ando E, et al. Type I (transthyretin Met30) familial amyloid polyneuropathy in Japan: early vs late-onset form. Arch Neurol. 2002;59:1771—6.
12. Buades-Reinés J, Raya-Cruz M, Gallego-Lezaún C, Ripoll-Vera T, Usón-Martín M, Andreu-Serra H, et al. Transthyretin familial amyloid polyneuropathy (TTR-FAP) in Mallorca: a comparison between late- and early-onset disease. J Peripher Nerv System. 2016;21:352—6.
13. Adams D, Cauquil C, Labeyrie C. Familial amyloid polyneuropathy. Curr Opin Neurol. 2017;30:481—9.
14. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standars and guidelines for the interpretation of sequences variants: a joint consensus recommendation of the American College of Medical Genetics and the Association for Molecular Pathology. Genet Med. 2015;17:405—24.
15. Koike H, Misu K, Sigiura M, Iijima M, Mori K, Yamamoto M, et al. Pathology of early -vs late-onset TTR Met30 familial amyloid polyneuropathy. Neurology. 2004;63:129—38.
16. Conceiça˜o I, De Carvalho M. Clinical variability in type I familial amyloid polyneuropathy (Val30Met): comparison between late- and early-onset cases in Portugal. Muscle Nerve. 2007;35:116—8.
17. Planté-Bordeneuve V. Update in the diagnosis and man-agement of transthyretin familial amyloid polyneuropathy. J Neurol. 2014;261:1227—33.