Scientific letters

Hereditary transthyretin amyloidosis caused by p.Ser43Asn variant. A new endemic variant in Ecuador

Amiloidosis hereditaria por transtirretina causada por la variante p.Ser43Asn. Una nueva variante endémica en Ecuador

To the Editor,

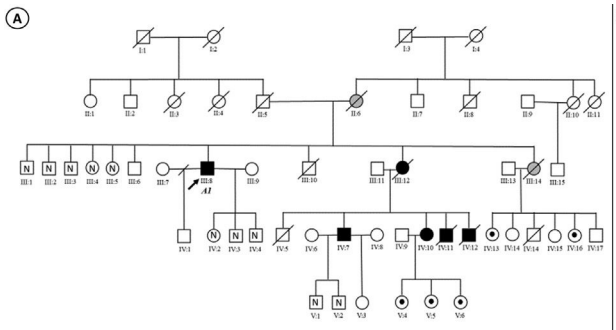
Hereditary transthyretin amyloidosis (ATTRv) is a multisystemic disease with autosomal dominant inheritance and variable penetrance, caused by mutations in the *TTR* gene. More than 120 genetic variants associated with the disease have been described, some of them considered endemic to certain geographic areas and with a strong genotype-phenotype correlation.[1,2] The heart and nervous system are the organs most often affected in ATTRv. The cardiac manifestations are usually heart failure, conduction disturbances, or atrial fibrillation, whereas the neurological features include symmetrical and distal sensory-motor polyneuropathy, often associated with dysautonomia symptoms.[1,2] Until recently, the only therapeutic option for ATTRv was liver transplant; however, specific drugs proven to increase survival are now available for these patients.[3]

The p.Ser43Asn variant of the *TTR* gene is a very rare cause of ATTRv, reported in only 7 cases to date.[4–6] Because it is so uncommon, the available information does not suffice to predict the expected clinical course of the disease or the type of follow-up management to use in carriers of the variant.

After identification of 3 independent families affected by ATTRv caused by the p.Ser43Asn variant, we endeavored to study the characteristics and clinical course of this condition, and determine possible geographic areas where the variant could be endemic.

A retrospective observational study was carried out in all carriers of the p.Ser43Asn variant followed up in our center. The study was approved by the Puerta de Hierro Hospital Ethics Committee, which did not require informed consent from the participants. The variant was detected by sequencing the 4 exons of the *TTR* gene in index cases and the affected exon in relatives. Cardiac involvement was established based on left ventricular thickness ≥12 mm or Perugini grade 2 or 3 uptake of 99mTc-DPD on cardiac scintigraphy, after exclusion of blood cell dyscrasia.[3] Neurological involvement was determined by the presence of neurological symptoms consistent with the disease, together with abnormal neurological test findings.[1] The variables collected included the patients' clinical characteristics and results of complementary tests in the first evaluation, and the clinical course and events that occurred during follow-up. Quantitative variables are presented as the median [interquartile range] and categorical variables as the number and percentage.

Eight individuals from 3 independent families (3 probands and 5 relatives: 4 men; age, 29-60 years) were identified as carriers of the p.Ser43Asn variant (figure 1A-C). The characteristics of these individuals are shown in table 1. The 3 families were not related, but were all originally from southern Ecuador, and more specifically from the Loja region. In the first evaluation, all probands were found to have both cardiac and neurological involvement, whereas among the relatives, only 1 showed a mixed phenotype, 2 had neuropathy alone, 1 cardiomyopathy alone, and 1 was an asymptomatic carrier. In addition, 4 patients reported a history of carpal tunnel syndrome in the first evaluation. Median age at disease onset was 49.8 [44.0-58.8] years. The heart condition in all probands was characterized by advanced symptoms (New York Heart Association II-III). None of the patients had atrial



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Marker	D18S66	D19S49	L1	D18S36	L4	TTR 18:31595244 (GRCh38)	L8	L9	D18S47	D18S1133	D18S57	D18S451
Physical distance, kilobases	5044.662	879.662	102.144	10.99	2.32		105.16	115.538	606.071	2923.443	4879.708	6363.137
Allele frequency in control population	0,00	0,28	0,28	0,28	0,39		0,33	0,17	0,44	0,28	0,00	0,28
FAMILY A	252	98	236	135	266	Ser43Asn	291	307	198	198	93	89
	254	92	236	135	266		295	307	198	190	91	91
FAMILY B	252	98	236	135	266	Ser43Asn	291	307	198	198	93	89
	242	92	238	141	266		283	318	198	196	93	87
FAMILY C	252	98	236	135	266	Ser43Asn	291	307	198	198	93	89
	258	102	238	141	266		291	324	192	196	89	85

Figure 1. Genealogic trees of the families included (A-C) and haplotype study (D). Squares indicate men and circles women. White symbols represent healthy individuals, black symbols individuals with a diagnosis of ATTRv, and gray symbols individuals with suspected ATTRv. White symbols with a central dot are asymptomatic carriers. White symbols with an *N* represent individuals testing negative for Ser43Asn. Individuals *A1*, *B1* and *C1* are the probands in each family. Diagonal lines indicate those who have died. ATTRv, hereditary transthyretin amyloidosis.

Table 1
Characteristics of patients with ATTRv due to the Ser43Asn variant included in the study

Patient	A1	B1	B2	B3	B4	B5	B6	C1
Sex	Man	Woman	Woman	Woman	Man	Man	Woman	Man
Age at diagnosis, y	50	47	60	58	51	47	29	41
Country of origin	Ecuador	Ecuador	Ecuador	Ecuador	Ecuador	Ecuador	Ecuador	Ecuador
Age at onset of symptoms, y	50	47	61	59	52	—	—	40
Cardiologic involvement	Yes 99mTc-DPD (+)	Yes 99mTc-DPD (+)	No 99mTc-DPD (–)	No 99mTc-DPD (–)	Yes 99mTc-DPD (+)	Yes 99mTc-DPD (+)	No	Yes 99mTc-DPD (+)
Functional class	NYHA II	NYHA II	—	—	NYHA I	NYHA I	—	NYHA III
Neurologic involvement	PND I, NIS 11	PND I, NIS 2	PND I, NIS 4	PND I, NIS 11	PND I, NIS 0	No	No	PND I, NIS 2
Other manifestations	Unilateral CTS	—	Bilateral CTS	—	Bilateral CTS	—	—	Unilateral CTS
Treatment	Tafamidis	Tafamidis	Tafamidis	Tafamidis	Tafamidis	—	—	Patisiran
Follow-up, mo	36.1	17.0	15.6	8.1	18.9	3.3	4.4	10.8
Events	HF admissions, de novo AF, complete AVB	HF admissions, de novo AF, Shock/HF	—	—	HF admission	—	—	HF admission, complete AVB

AVB, atrioventricular block; AF, atrial fibrillation; HF, heart failure; NIS, Neuropathy Impairment Score; NYHA, New York Heart Association; PND, Polyneuropathy Disability score; CTS, carpel tunnel syndrome; 99mTc-DPD, scintigraphy with 99m technetium and 3,3-diphosphono-1,2-propanedicarboxylic acid

fibrillation or pacemaker implantation before the first evaluation. All those with neurological involvement showed isolated sensory symptoms (Polyneuropathy Disability score [PND] I), with a median Neuropathy Impairment Score (NIS) of 3 [2-11].

For first-line treatment, 5 patients received tafamidis and 1 started patisiran, as the diagnosis was made in an advanced phase of the disease. After a median follow-up of 13.2 [6.2-17.9] months, 4 patients required hospital admission for heart failure, 2 developed de novo atrial fibrillation, and 2 required pacemaker implantation due to complete atrioventricular block. One of the patients progressed to refractory cardiogenic shock and required biventricular mechanical circulatory support as bridging therapy to heart transplant. The patient had a poor clinical response following transplant and died due to infectious complications during the postoperative period. The PND score did not worsen in any patient during follow-up. A haplotype study performed with DNA samples from the 3 families showed concordance in 11 genetic markers around the p.Ser43Asn variant, indicating that the families likely arose from a recent common ancestor (12.4 generations; 95% confidence interval [95%CI], 5.4-28.9) (figure 1D).

Despite the limitations of an observational study with a small patient sample and short follow-up, the findings obtained here indicate that ATTRv due to the p.Ser43Asn variant is associated with a mixed cardiologic and neurologic phenotype with onset after the age of 40 years. These results contrast with those of the previously reported cases[4–6] in which neurological involvement was less prevalent, and highlight the importance of conducting an in-depth neurological evaluation to enable prompt initiation of disease-modifying treatment. As was seen in the previous descriptions, the cardiologic condition determines the prognosis, with aggressive progression to advanced heart failure, whereas the neurological condition is mild. In light of the aggressive clinical course and documented age of onset, close follow-up is recommended for carriers of the variant, starting at age 30 to 35 years.

From the epidemiological viewpoint, the variant was identified in 3 independent families from the province of Loja, Ecuador, with a concordant haplotype study, which suggests an endemic focus associated with a founder effect. Some of the reported cases also come from Latin America (Ecuador and Peru),[4,5] in line with our findings. We believe that detection of the cases described here outside the country of origin may be related to limited access to a clinical diagnosis and genetic testing for ATTRv in Ecuador. Although additional studies are needed to determine the prevalence of ATTRv due to p.Ser43Asn in Ecuador, the findings reported here should raise suspicion of this condition in patients from the Loja region or from Ecuador showing signs and symptoms consistent with ATTRv.

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AUTHORS' CONTRIBUTIONS

E. Porres-López and F. de Frutos are the first authors.

E. Porres-López and F. de Frutos collected and analyzed the data, and wrote the first draft. L. Silva-Hernandez, L. Galán, and E. González-Lopez collected the data, reviewed the work undertaken, and made relevant intellectual contributions. Pablo Garcia-Pavía supervised the study, obtained funding, and participated in writing the manuscript.

CONFLICTS OF INTEREST

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Fluid-dynamic impact of commissural alignment in transcatheter aortic valve implantation

Impacto fluidodinámico del alineamiento comisural en implante percutáneo de válvula aórtica

To the Editor,

New commissural alignment techniques in transcatheter aortic valve implantation (TAVI) can facilitate coronary reaccess, if needed, and prevent coronary obstruction in valve-in-valve TAVI procedures. These techniques could also reduce central aortic regurgitation, gradient progression, and subclinical thrombosis, which would improve durability, all of which are crucial in low-risk patients. However, in specific patients it is impossible to determine differences between an implant with correct neocommissural alignment and one with misalignment. Computational fluid dynamics models have been widely validated for the cardiovascular system[1] and could help to predict the impact of different degrees of commissural misalignment on transvalvular gradients[2] and the degree of platelet activation in specific patients.[3] Based on computed tomography (CT) scans of the patients included in this study, we estimated the central axis of the aorta and predicted the degree of clockwise/counterclockwise rotation required by the delivery system (self-expanding) or the prosthesis at crimping (balloon expandable) for correct commissural alignment using a previously described technique.[4] After implantation, CT/angiography was used to assess the degree of alignment. Based on the patients' anatomical and pressure data, computational fluid dynamics simulations were performed using the calculated velocity fields (figure 1A; video 1 of the supplementary data), with the valve fully open, by parametric study of the influence of the commissural alignment angle, rotating the valve in incremental 1-degree steps from perfect alignment (0°) up to 119°. These simulations were performed for two situations: *a)* an unrealistic completely uniform flow at the ventricular outflow tract, as simulated in current models (figure 1C); and (b) a helical flow similar to that used in MRI studies (figure 1D). The platelet activation model used was the same as the one validated in an in-vitro model of coronary bifurcation.[3]

Forty patients with severe aortic stenosis, trileaflet aortic stenosis, severe calcification, and an aortic annulus area of 478 ± 101 mm^2 (age, 81.4 ± 4.9 years; STS risk score, 5.2 ± 2.9) were treated with TAVI with commissural alignment. Ventricular function was $57.5 \pm 11.9\%$ and mean gradient was 51.1 ± 18.5 mmHg, increasing to 6.3 ± 2.1 mmHg at 30 days, with no differences related to alignment (0% mortality). Mean commissural misalignment was 9.2° (ie, moderate; $< 30°$) in all patients. Significant differences in alignment were found between self-expanding prostheses (Acurate neo [Boston Scientific, EE. UU.] and Evolut [Medtronic, EE. UU.]: $7 \pm 3.2°$; n = 28) and balloon expandable prostheses (SAPIEN-3/Ultra [Edwards, EE. UU.] and MyVal [Meril, India]: $11.2° \pm 4.9°$; $P = .001$; n = 12). Analysis of the 2 fluid dynamics simulations, as described above, (figure 2A), showed high sensitivity to ventricular outflow conditions, such that in the more realistic (helical) flow model an association was found between the absence of moderate or severe commissural misalignment (around 30° or less) and higher ventricular energy efficiency (lower line, red). However, in the uniform flow model, no association was found between better commissural alignment and reduced shear stress (upper line, blue). No differences were found between the 2 conditions (helical or uniform) in the degree of platelet activation according to previously validated models (figure 2B).