OPEN

OPHTHALMOLOGIC INVOLVEMENT IN PATIENTS WITH HEREDITARY TRANSTHYRETIN AMYLOIDOSIS

JORGE RUIZ-MEDRANO, MD, PHD,*† MARILUZ PUERTAS, MD,* ELENA ALMAZÁN-ALONSO, MD,* MARINA FERNÁNDEZ-JIMÉNEZ, MD,* IGNACIO FLORES-MORENO, MD, PHD,* CLARA SALAS ANTÓN, MD, PHD,‡ PABLO GARCÍA-PAVÍA, MD, PHD,§¶ JOSÉ M. RUIZ-MORENO, MD, PHD*†**††‡‡

Purpose: The aim of this study was to determine the ophthalmologic involvement in patients with hereditary transthyretin amyloidosis and its correlation with the mutations described in the literature.

Methods: Cross-sectional, noninterventional study. Fifty-two eyes of 26 consecutive patients diagnosed with hereditary transthyretin amyloidosis who visited the Puerta de Hierro-Majadahonda University Hospital from September 2019 to March 2022. All patients underwent complete ophthalmologic examination and multimodal imaging. Cardiologic, neurologic, digestive, and renal examinations were also recorded.

Results: Eighteen eyes of the total (34.61%) showed amyloid-related ocular involvement, vitreous amyloid deposits being the most common ocular manifestation (18/52). Statistically significant differences were found for the presence of vitreous amyloid deposits ($P < 0.01$), crystalline amyloid deposits ($P < 0.05$), parenchymal amyloid deposits ($P < 0.01$), and vascular alterations ($P < 0.01$) when comparing affected and unaffected eyes. Moreover, affected eyes showed worse best-corrected visual acuity ($P < 0.01$).

Conclusion: Ocular manifestations are present in a substantial number of patients with ATTR that could potentially lead to devastating consequences to patients' best-corrected visual acuity and quality of life. Therefore, it is important to emphasize the importance of multidisciplinary management and ophthalmologic assessment, follow-up and surgical treatment when necessary. To the best of our knowledge, this represents the largest series in Spain of amyloidosis' ophthalmologic involvement.

RETINA 43:49–56, 2023

The amyloidosis are a heterogeneous group of disorders in which a pathologic deposition of an insoluble fibrillar material, termed amyloid, slowly and progressively infiltrates and impairs the functioning of the different organs.[1] Amyloid production may result from altered amyloid precursor proteins, as in hereditary amyloidosis and systemic amyloidosis because of light chain deposition; or from excessive amyloid production as a consequence of systemic inflammation (AA amyloidosis) or ageing (senile amyloidosis or wild type (wt)-transthyretin amyloidosis).[2]

Hereditary transthyretin amyloidosis (hATTR) is the most common type of hereditary amyloidosis. ATTR is an autosomal dominant disease caused by genetic variants in the *TTR* gene.[1] There are currently more than 130 disease-causing genetic variants described, including Val30Met, which is endemic in Portugal, Brazil, Sweden, and Japan.[3]

TTR, also referred to as prealbumin, is a homotetrameric protein synthesized mainly by the liver, and by the choroidal plexi of the brain, retinal pigment epithelium, and pancreas.[4] Some of its roles include the transport of thyroxine and vitamin A by participating in its binding to the retinol-binding protein.[5]

Mutations described in hATTR lead to a conformational change that destabilizes TTR and enhances the deposition of misfolded subunits within the different organs.[6] Widespread deposits cause a broad spectrum of clinical manifestations in hATTR, including neurologic involvement, mainly as peripheral sensorimotor neuropathy and dysautonomia; cardiac, mostly in the form of heart failure; ophthalmologic; and renal.[7]

Given the wide range of ophthalmologic manifestations in hATTR, the unspecificity of many of them, variability in phenotypes depending on the type of mutation, and limited literature on the subject, ophthalmologic involvement in these patients may be underdiagnosed despite the potential impact on their daily lives.[8] The foregoing, together with the scarcity of studies on the Spanish population, make this research aim to highlight the importance of ophthalmologic follow-up in hATTR and to describe the ocular manifestations associated with the different *TTR* mutations in a cohort of Spanish hATTR patients under multidisciplinary follow-up by the Ophthalmology, Cardiology and Neurology Departments at Puerta de Hierro-Majadahonda University Hospital in Madrid.

Methods

This cross-sectional, noninterventional study included 58 eyes from 29 patients with hATTR under follow-up at the Inherited Cardiac diseases Unit of Puerta de Hierro-Majadahonda University Hospital. The study was conducted in adhesion to the Tenets of the Declaration of Helsinki for research involving human subjects. Local Research Ethics Committee approval was obtained, and all patients signed the appropriate informed consent form.

Patients included in the present study met the following inclusion criteria: 18 years or older, carriers of pathogenic or likely pathogenic hATTR variants, and the will to participate in the study. Patients with non-hATTR amyloidosis were excluded.

All patients underwent a complete ophthalmologic examination including: best-corrected visual acuity (BCVA), slit-lamp anterior segment examination, optical biometry (IOL Master 500, Carl Zeiss Meditec AG, Jena, Germany), intraocular pressure with Goldman tonometry, pachymetry and endothelial cell count (Tomey EM-3000, Nagoya, Japan), indirect fundus ophthalmoscopy and multimodal imaging (color fundus photography, swept-source optical coherence tomography (OCT), optical coherence tomography angiography, and fundus autofluorescence) using DRI-OCT Triton plus (Topcon Corporation, Japan) and Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). Structural OCT protocol included radial 12-mm scans centered at the fovea and containing 1,024 axial scans. All examinations were conducted in both eyes if they met the inclusion criteria.

The systemic involvement data were recorded based on the patients' clinical records, according to the scales and parameters usually collected and relevant for each affectation.

Vitrectomy and cataract surgery was performed in one eye with subsequent anatomopathologic study of the vitreous. Once the vitreous humor was extracted, it was introduced in physiologic saline solution for transport and centrifugation. After processing the fluid, a kerosene block was made, in which hematoxylin-eosin and immunohistochemical markers were performed to establish the protein phenotype.

In addition, a literature review of the ophthalmologic involvement in hATTR described to date was performed. For this purpose, the terms "TTR amyloidosis," "ophthalmologic amyloidosis," and "ophthalmologic involvement in ATTR" were searched in PubMed.

Statistical Analysis

All analyses were performed using a statistical analysis program (SPSS, version 26.0, IBM-SPSS, Chicago, IL). A two-tailed *P*-value <0.05 was considered as statistically significant. Descriptive statistics were provided for normal distributed variables using the mean and SD for quantitative and n (percentage) for categorical variables. To assess the normality or nonnormality of the variables, the Kolmogorov–Smirnov test was performed (all our variables were normally distributed). Demographic data, BCVA, and axial length were compared between groups using independent Student t-test for normally distributed variables, Chi-square test for normally distributed, or Fisher's exact test for nonparametric categorical variables. Pearson correlation was used to determine the correlations for normally distributed variables. The results were expressed in r and *P*-value.

From the *Department of Ophthalmology, Puerta de Hierro-Majadahonda University Hospital, Madrid, Spain; †Instituto de Microcirugía Ocular (IMO), Madrid, Spain; ‡Department of Pathologic Anatomy, Puerta de Hierro-Majadahonda University Hospital, Madrid, Spain; §Department of Cardiology, Puerta de Hierro-Majadahonda University Hospital, IDIPHISA, CIBERCV, Madrid, Spain; ¶Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; **VISSUM Corporation,Alicante, Spain; ††Department of Ophthalmology, Castilla La Mancha University, Albacete, Spain; and ‡‡Spanish Ministry of Health, Instituto de Salud Carlos III, Madrid, Spain.

J. M. Ruiz-Moreno disclosed receipt of the following financial support for the research, authorship, and/or publication of this article from: Topcon, Co. The sponsor had no role in the design or conduct of this research.

None of the authors has any financial/conflicting interests to disclose.

Reprint requests: Jorge Ruiz-Medrano, MD, PhD, Puerta de Hierro-Majadahonda University Hospital, C/Manuel de Falla 1, 28222 Majadahonda, Madrid, Spain; e-mail: jorge.ruizmedrano@gmail.com

Results

Of the total, 42% of patients were women (n = 11/26) and mean age was 57.8 ± 13.7 (range, 42–81) years old. The demographic characteristics of the full cohort are shown in Table 1.

Ophthalmologic Involvement

18 eyes of the grand total (34.61%) showed amyloid-related ocular involvement, vitreous amyloid deposits being the most common ocular manifestation, which was in fact present in all affected eyes (34.61%, n = 18/52). Ophthalmologic involvement is more common in women (66.7%, n = 12/18; $P < 0.05$).

Among other signs, the presence of amyloid deposits in crystalline lens (22.2%, n = 4/18), retinal vessels (22.2%, n= 4/18), and in retinal parenchyma (55.6%, n = 10/18) was noteworthy. After the amyloid deposition in retinal vessels, atrophy secondary to vascular occlusion was found in inner retinal layers in all patients with vessel deposits (100%, n = 4/4) (Figures 1 and 2). Furthermore, amyloid vitreous–retinal tractions were identified causing an advancing retinal schisis in one eye (Figure 3). Data regarding ophthalmologic involvement are summarized in Table 2.

Table 1. Demographic Data of 26 hATTR Patients

Demographic Characteristic	Data
Gender, n. (%)	N=26
Male	15 (57.7)
Female	11 (42.3)
Age (years)	
Mean ± SD (range)	57.8 ± 13.7 (42–81)
Ethnic group, n. (%)	N=26
Caucasian	23 (88.5)
African/Afro-American	1 (3.8)
Unknown	2 (7.7)
Diagnostic mehtod of hATTR, n. (%)	N=26
EMB	4 (15.4)
Non-invasive	22 (84.6)
hATTR mutation, n. (%)	N=26
Val30Met	8 (30.8)
Val122Ile	8 (30.8)
Glu89Lys	7 (26.9)
Ser23Asn	3 (11.5)
Time from diagnosis to ophthalmologic assessment (months)	
Mean ± SD (range)	29 ± 40.6 (0–194)
hATTR treatment, n. (%)	N=26
Yes	20 (76.9)
No	6 (23.1)
Time under treatment until ophthalmologic assessment (weeks)	
Mean ± SD (range)	56 ± 43 (1.3–126)
Systemic hATTR involvement, n. (%)	N=26
Ophthalmologic	9 (34.6)
Neurologic	22 (84.6)
Cardiac	22 (84.6)
Digestive	10 (38.5)
Renal	1 (3.8)
Ophthalmologic history, n. (%)	N=26
Personal	8 (33.3)
Family	7 (29.2)

EMB, endomyocardial biopsy.

Affected eyes showed a statistically worse BCVA ($P < 0.01$). Moreover, statistically significant differences were found for the presence of crystalline amyloid deposits ($P < 0.05$), vitreous amyloid deposits ($P < 0.01$), parenchymal amyloid deposits ($P < 0.01$), vascular alterations ($P < 0.01$), and altered fundus autofluorescence ($P < 0.05$) when comparing affected to unaffected eyes. Time from diagnosis and time under hATTR treatment had no statistically significant influence in the appearance of ophthalmologic signs ($P > 0.05$).

Regarding hATTR mutations found in these patients: Vall30Met and Vall22Ile mutations were present in 30.8% (n = 8/26) each respectively, Glu89Lys mutation was identified in 26.9% (n = 7/26), whereas Ser43Asn mutation was more uncommon being identified in 11.5% (n = 3/26).

Glu89Lys mutation was the most prevalent with respect to vitreous amyloid floccules (58.8%, n = 10/17) and retinal amyloid deposits (70%, n = 7/10).

Despite the former data, none of the four mutations found showed any statistically significant differences concerning ophthalmologic involvement ($P > 0.05$).

Surgery and Anatomopathologic Study

A patient's eye underwent combined vitrectomy and cataract surgery because of severe visual acuity loss secondary to amyloid deposits in vitreous presenting a BCVA before surgery of 20/2000 (Figure 4). Hematoxylin–eosin showed the presence of amorphous acellular material with the classic amyloid quartering. There was no presence of cells in the vitreous in addition to this material, as expected. IHC staining showed positivity for TTR (prealbumin) and negativity for amyloid A and immunoglobulin light chains (kappa and lambda). With all this, the diagnosis of "vitreous humor occupied by TTR+ amyloid" was established (Figure 5).

One day after surgery the patient showed a visual acuity of 20/25 (Fig. 4).

Systemic Involvement

Patients with ocular amyloidosis showed greater neurologic ($P < 0.05$) and cardiac ($P < 0.05$)

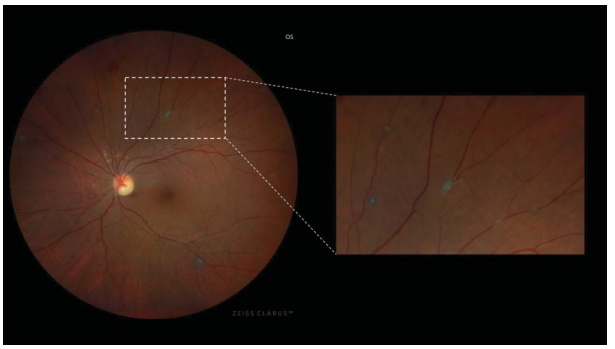

Fig. 1. Left eye wide-field retinography with amyloid deposits in the retinal vessels and parenchyma, some of these deposits producing vascular stops with consequent ischemia.

involvement. Ocular amyloidosis was associated with troponin ($P < 0.05$) and creatinine ($P < 0.01$) levels, both considered prognostic parameters for amyloidosis cardiac involvement.

Furthermore, neurologic and cardiac affection were related to each other ($P < 0.05$) and to digestive involvement ($P < 0.05$). Women were more likely to show neurologic and cardiac impairment ($P < 0.05$).

Cardiac involvement was more prevalent in older patients ($P < 0.05$) and was related to prognostic parameters such as: NTproBNP ($P < 0.01$), CDK-EPI ($P < 0.01$), and creatinine ($P < 0.01$), as well as to LVEF ($P < 0.01$). Patients under treatment for hATTR showed less cardiac involvement than those without treatment ($P < 0.05$). In addition, the greater the patients' cardiac involvement, the worse their BCVA ($P < 0.01$) and the thinner mean RNFL papillary thickness ($P < 0.05$). Patients' systemic data are compiled in Table 3.

Discussion

Ophthalmologic impairment in hATTR was first described in 1953 as the presence of vitreous opacities and scalloped pupils in patients with lower limb neuropathy.[5] Since then, numerous ocular features have been described in relation to this disease, which can affect nearly every component of the eye. Vitreous amyloid opacities are the most common ophthalmologic manifestations in hATTR; keratoconjunctivitis sicca, secondary glaucoma, and retinal and choroidal microangiopathy are some of the most remarkable ocular findings.[7–10]

Pathophysiology of ophthalmologic involvement in hATTR was originally presumed to be the same as for cardiac and neurologic disease and that it was because of a local deposition of abnormal TTR from the liver. However, with the subsequent

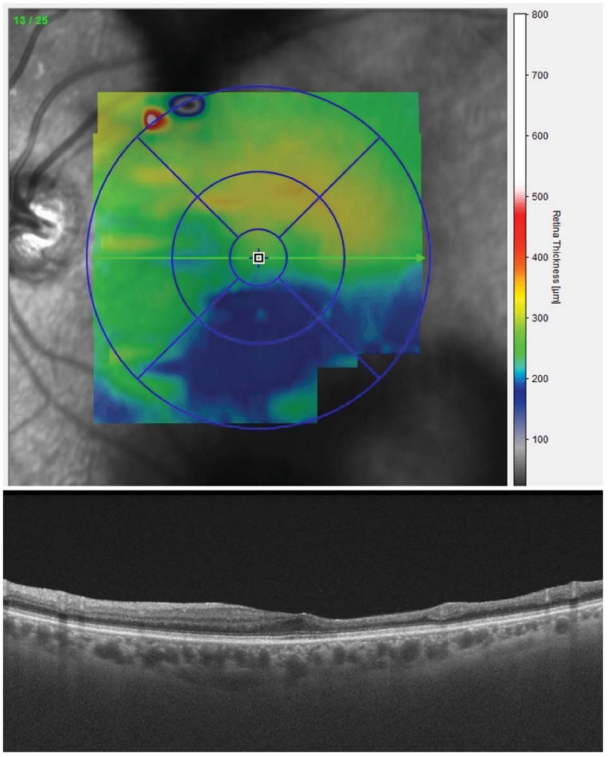

Fig. 2. Fifty-seven year-old woman diagnosed of hereditary-TTR amyloidosis with multiple vascular amyloid deposits. Macular thickness map image with a marked decrease in thickness, predominantly in the inferior macular location (up). B-scan OCT image revealing severe retinal atrophy at the expense of the inner layers secondary to ischemia after amyloid deposition (down).

introduction of liver transplantation as a potential treatment for hATTR, it became a clear that the ophthalmologic involvement in patients undergoing transplantation not only did not improve but worsened significantly. Therefore, it is currently assumed that the abnormal TTR causing the ocular manifestations in hATTR is that produced by the retinal pigment epithelium.[10]

Currently, more than 120 mutations are known that can cause hATTR; and even though transmission is autosomal dominant, the penetrance is variable.

Given the great geographic diversity, accurate prevalence is difficult to establish; being estimated below one per 100,000 population in Europe and not few among those patients could suffer ophthalmologic alterations that can potentially lead to irreversible vision loss.[3,6,8] The results of this study show vitreous involvement to be the most common finding in these patients (34.6%) followed by lens deposits (22.2%), retinal vessel involvement (16.7%), and deposits in retinal parenchyma (55.6%), with rest of the manifestations being summarized in Table 2. Women were more prone to show involvement with signs appearing in 66% of them.

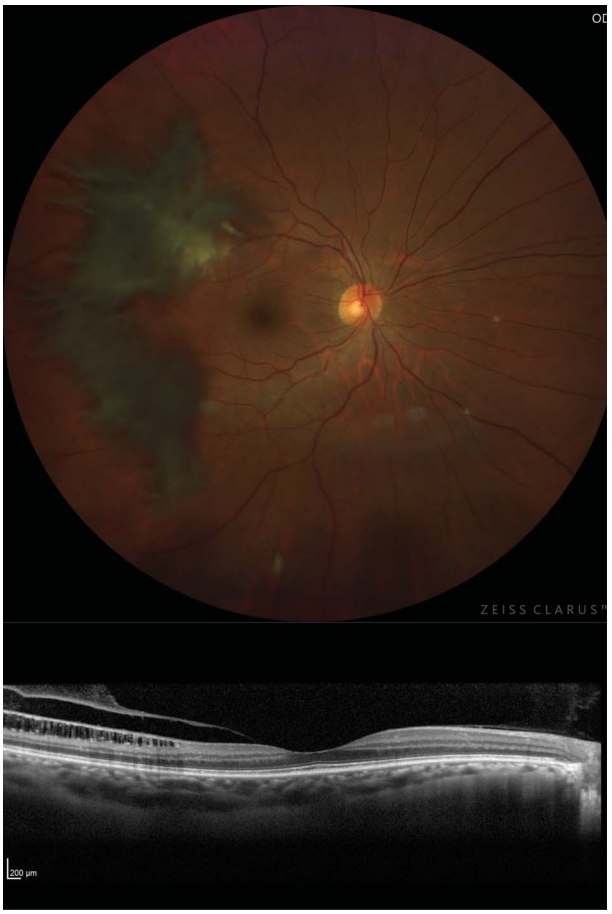

Fig. 3. Wide-field retinography of a 45-year-old woman patient showing a dense amyloid deposit involving the posterior hyaloid in the temporal sector (up). Structural OCT imaging reveals the presence of progressive vitreo-retinal traction secondary to amyloid deposits (down).

Some of these conditions pose a threat to patients' vision and quality of life and their identification is key, as some of them can be treated, with pars plana vitrectomy being able to restore 20/20 vision in some patients with decreased visual acuity caused by vitreous deposits.[8] However, vascular deposits may cause focal arterial occlusions that lead to irreversible inner retinal atrophy, BCVA loss, and visual field alterations (Fig. 1).

One of the patients included showed progressive vitreous–retinal tractions causing an advancing retinal schisis. This complication has not been previously described in hATTR, at the current rate of progression will most certainly require pars plana vitrectomy surgery (Fig. 2).

These results are in line with previous reports[3,5,8,11,12] with variations of different signs prevalent probably because of the different distribution of genetic variants in different geographic areas.

It is important to note that, although cardiac and neurologic manifestations tend to be the first signs to appear in hATTR patients causing the greatest morbidity and being more common, other systems usually

Table 2. Ophthalmologic Data

	Data		
Ophthalmologic Findings	Mean	SD	Range
BCVA (decimal)	0.7	±0.3	0.0–1
AL (mm)	23.7	±1.9	20.7–32.7
IOP (mmHg)	14	±2.9	8–20
Pachymetry (µm)	531.6	±32.6	454–600
EC (cells/mm^2)	2,613	±224.5	2,152–3,185
Macular ETDRS			
Central	289	±77	218–725
Upper (inner/outer)	335/292	±46/±25	190–558/203–350
Bottom (inner/outer)	332/284	±35/±23	180–411/191–318
Nasal (inner/outer)	345/311	±67/±38	227–695/257–509
Temporal (inner/outer)	332/289	±63/±38	193–665/182–465
Subfoveal choroidal thickness (µm)	227.8	76.5	107–408
RNFL			
General	99	±14	65–126
Upper (nasal/temporal)	109/134	±30/±28	34–189/72–181
Bottom (nasal/temporal)	109/141	±30/±38	50–164/37–321
Nasal	80	±22	35–155
Temporal	71	±22	37–171

	n. (%) N=52
Crystalline lens	
AD	4 (7.7)
Cataract	6 (11.5)
Corneal amyloid deposits	1 (1.9)
Vitreous	
Amyloid floccules	18 (34.61)
Optic nerve papilla	
Excavated	4 (7.7)
Atrophic	2 (3.8)
Macula	
AD	2 (3.8)
Drusen	2 (3.8)
RPEA	4 (7.7)
Amyloid vitreous–retinal traction	1 (1.9)
Parenchyma	
AD	10 (19.2)
Drusen	6 (11.5)
Vascular involvement	
Vascular amyloid sheathing	4 (7.7)
AD in vascular arcades	4 (7.7)
Pathologic OCT RNFL	4 (7.7)
FAF	
RPEA	7 (13.5)
Hypoautofluorescence	2 (3.8)
Ischemia in AFG	2 (3.8)

FAF, fundus autofluorescence.

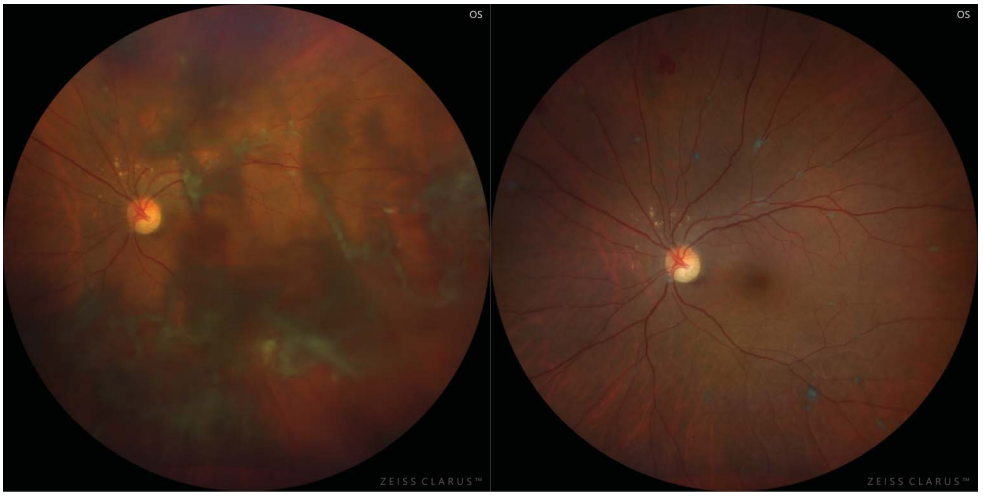

Fig. 4. Wide-field fundus retinography before and after combined vitrectomy and cataract surgery. On the left, wide-field fundus photography showing dense vitreous amyloid deposits that barely allow visualization of the eye fundus (BCVA 20/2000). On the right, wide-field fundus photography after surgery showing multiple vascular deposits (arterial and venous) and in retinal parenchyma, with clear media (BCVA 20/25).

show alterations in time. Digestive and ocular involvement are often the next down the line with renal signs appearing later in the natural course of this disease.[13] That is why there are many patients with cardiac disease and no ocular symptoms. Looking at our sample specifically, there are eight eyes from four patients with no cardiac nor ophthalmologic disease, whereas four eyes belong to patients with exclusive neurologic involvement. This highlights the importance of routine ophthalmologic examinations in hATTR patients because many may show no signs of involvement at first, but may develop a wide variety of alterations as the disease evolves, many of them being treatable.

Prospective studies will be important to evaluate the actual efficacy of systemic treatments on ocular involvement, where the ophthalmologist's role will be key to assess any sign of affection. Blood–retinal barrier could potentially pose an obstacle to them, whereas local production of amyloid at the level of the retinal pigment epithelium may keep local deposits to persist or even advance, as has previously been described.[5,6]

Larger studies will be necessary to establish which genetic mutations show a higher tendency to lead to ocular involvement, and differences in sign prevalence among them, because some of them do not seem to affect the eye, whereas others show alterations aplenty with clear threat to BCVA.

Limitations

Our study shows several limitations: this was a cross-sectional study and follow-up of these patients is

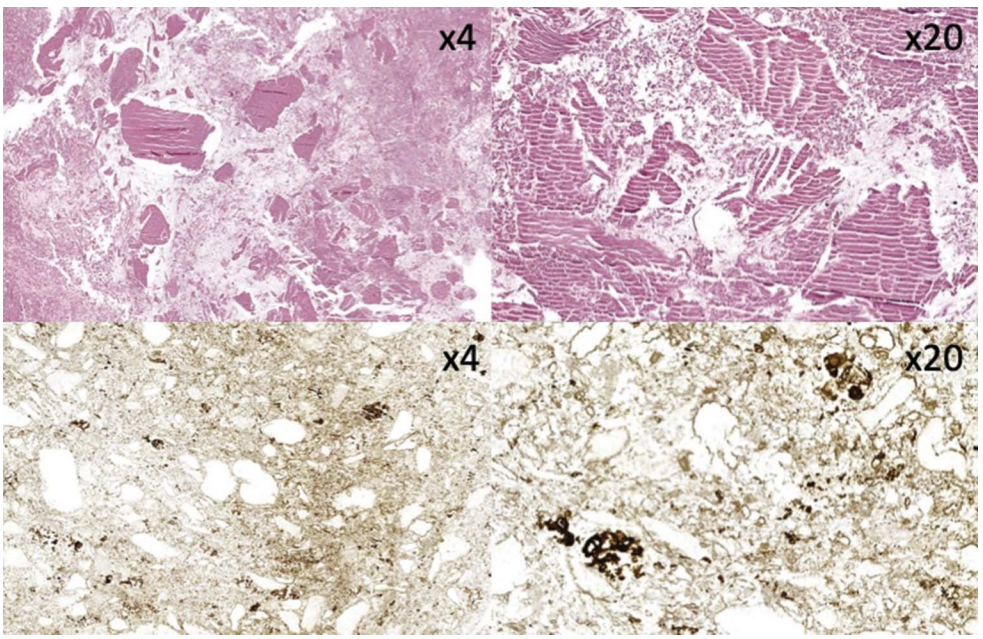

Fig. 5. Presence of acellular amorphous material, quartered inside the vitreous humor HEX200 (up), immunopositivity of the material for TTR, which confirmed the diagnosis (down).

Table 3. Systemic hATTR Involvement Data

Systemic hATTR Involvement	Data	
	n. (%)	Findings
Ophthalmologic	N = 52	Corneal amyloid deposits
	18 (34.6)	Retinal amyloid deposits
		Vitreous floccules
		Vascular sheaths
		Vascular amyloid deposits
Neurologic	N = 26	Paresthesias
	22 (84.6)	Bilateral carpal tunnel syndrome
		Sensory-motor polyneuropathy of lower limbs/lower limbs + upper limbs
		Lumbar canal stenosis
		Dysautonomia (orthostatism, erectile dysfunction, urinary incontinence, dyshidrosis)
Cardiac	N = 26	Heart failure
	22 (84.6)	Decrease in LVEF (%)
		Restrictive cardiomyopathy
		Rhythm disorders
Digestive	N = 26	Constipation
	10 (38.5)	Diarrhea
Renal	N=26	Kidney failure
	1 (3.8)	

	n. (%) N=26
HBP	7 (26.9)
DM	3 (11.5)
CTS	9 (34.6)
Polyneuropathy	12 (46.2)
PND score	
I	11 (42.3)
II	2 (7.7)
IIIa	—
IIIb	1 (3.8)
Dysautomia	17 (65.4)
NYHA	
I	9 (34.6)
II	13 (50)
III	4 (15.4)
IV	—
Atrial fibrillation	
Paroxysmal	7 (26.9)
Permanent	1 (3.8)
Restrictive pattern	6 (23.1)

	Mean	SD	Range
LVEF (%)	57.3	±11	32–78
NTproBNP (pg/mL)	1829	±2,364.7	16–8,594

(*continued on next page*)

Table 3. (*Continued*)

	Mean	SD	Range
Troponine Ic (ng/mL)	0.06	±0.08	0.02–0.3
Creatinine (mg/dL)	0.9	±0.4	0.4–1.8
eGFR (mL/minute/1.73m^2)	76.9	±18.5	40–106.7

HBP, high blood pressure; DM, diabetes mellitus; CTS, carpal tunnel syndrome; PND score, Polyneuropathy Disability score; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.

not reported. Although prevalence of hATTR amyloidosis is rare, sample size is small and some mutations are not sufficiently represented so as to draw significant conclusions. Further studies will be necessary to establish associations between a given mutation and specific ophthalmologic alterations. However, contrary to some studies, our sample represents a wider than usual variety of patients and mutations because our hospital is currently a national referral center for amyloidosis, receiving patients from across our country and so being less population biased. To the best of our knowledge, this series represents the largest sample in Spain of amyloidosis' ophthalmologic involvement.

In conclusion, hATTR is a systemic disease that could potentially lead to severe ocular involvement with devastating consequences to our patients' BCVA and quality of life, where ophthalmologic assessment is paramount to identify, follow, and in some cases treat the alterations that tend to appear in time in different parts of the eye.

Key words: amylodosis, ophthalmology, TTR, hereditary, amyloid, ocular.

References

1. Aroch I, Ofri R, Sutton GA. Ocular manifestations of systemic diseases. Slatter's Fundam Vet Ophthalmol 2008;46:374–418.
2. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641–2654.
3. Liu T, Zhang B, Jin X, et al. Ophthalmic manifestations in a Chinese family with familial amyloid polyneuropathy due to a TTR Gly83Arg mutation. Eye 2014;28:26–33.
4. Buxbaum JN, Reixach N. Transthyretin: the servant of many masters. Cell Mol Life Sci 2009;66:3095–3101.
5. Sandgren O. Ocular amyloidosis, with special reference to the hereditary forms with vitreous involvement. Surv Ophthalmol 1995;40:173–196.
6. Manganelli F, Fabrizi GM, Luigetti M, et al. Hereditary transthyretin amyloidosis overview. Neurol Sci 2020. Online ahead of print. doi:10.1007/s10072-020-04889-2
7. Rousseau A, Terrada C, Touhami S, et al. Angiographic signatures of the predominant form of familial transthyretin amyloidosis (Val30Met mutation). Am J Ophthalmol 2018;192:169–177.

8. Reynolds MM, Veverka KK, Gertz MA, et al. Ocular manifestations of familial transthyretin amyloidosis. Am J Ophthalmol 2017;183:156–162.
9. Dammacco R, Merlini G, Lisch W, et al. Amyloidosis and ocular involvement: an overview. Semin Ophthalmol 2020;35:7–26.
10. Buxbaum JN, Brannagan T, Buades-Reinés J, et al. Transthyretin deposition in the eye in the era of effective therapy for hereditary ATTRV30M amyloidosis. Amyloid 2019;26: 10–14.
11. Leung KCP, Ko TCS. Ocular manifestations in hereditary transthyretin Gly67Glu amyloidosis. Amyloid 2019;26:171–172.
12. Bunod R, Adams D, Cauquil C, et al. Conjunctival lymphangiectasia as a biomarker of severe systemic disease in Ser77-Tyr hereditary transthyretin amyloidosis. Br J Ophthalmol 2020;104:1363–1367
13. Swiecicki P, Zhen D, Mauermann M, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid 2015;22:123–131.