




# Monitoring the Patient with Retinal Angiopathy Associated with Hereditary Transthyretin Amyloidosis: Current Perspectives

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**Abstract:** Retinal angiopathy associated with hereditary transthyretin amyloidosis (ATTRv), if untreated, may lead to irreversible vision loss. Our purpose was to systematically review the clinical and imaging features of retinal angiopathy associated with ATTRv and assemble a monitoring approach for these patients. All types of original research studies reporting clinical and imaging findings on retinal angiopathy associated with ATTRv were included. The most common clinical findings were tortuous retinal vessels, microaneurysms, retinal hemorrhages, sheathing of retinal vessels, whitish amyloid deposits along retinal arteries, obliteration of retinal vessels, vitreous hemorrhage, retinal and iris neovascularization. The most relevant imaging findings were hyperautofluorescence of perivessel amyloid deposits; delayed arterial filling, vascular leakage, and retinal ischemia on fluorescein angiography; late hypercyanescence along the choroidal arteries on indocyanine green angiography; perivascular hyperreflective material, needle-shaped deposits on the retinal surface and macular edema on optical coherence tomography (OCT) and attenuated retinal vascular network on OCT-angiography. ATTRv patients should be strictly followed to detect and treat retinal angiopathy, avoiding complications. Both panretinal photocoagulation and intravitreal anti-vascular endothelial growth factor have been used to treat retinal angiopathy in ATTRv. In an individual that presents with retinal angiopathy of unknown etiology, ATTRv should be considered as in the differential diagnosis, even out of the initial core countries. The prognostic value of subclinical findings, namely in OCT-A, is not yet established.

**Keywords:** amyloidosis, transthyretin amyloidosis, retinal angiopathy, fluorescein angiography, retinal ischemia

## Introduction

Tissue deposition of misfolded protein fibrils leads to organ dysfunction and causes a group of diseases called systemic amyloidoses.<sup>1</sup> The most common form of primary or genetic amyloidosis is caused by a mutation in transthyretin (ATTRv). The prevalence of ATTRv amyloidosis is estimated to be between 5526 and 38,468 individuals worldwide, distributed in and out of the initial clusters.<sup>2</sup> Despite large genotypic variability, the substitution of methionine for valine at position 30 is the most frequent mutation world-wide.<sup>3</sup> It is characterized by sensitive and motor neuropathy, autonomic neuropathy, cardiomyopathy, nephropathy and oculopathy. ATTRv also shows phenotypic heterogeneity, with incomplete penetrance and variable age of onset.<sup>4</sup>

The ocular manifestations of hereditary transthyretin-mediated amyloidosis (ATTRv) vary: abnormal conjunctival vessels, keratoconjunctivitis sicca, glaucoma, deposition of amyloid in the anterior capsule of the lens and at the pupillary border, scalloped iris, vitreous opacities and retinal angiopathy.<sup>5</sup> These manifestations become more frequent with time,<sup>5,6</sup> and, if untreated, retinal angiopathy can lead to vision loss due to macular ischemia or neovascular glaucoma.

Our purpose was to systematic review all studies about retinal angiopathy in ATTRv patients, analyze the retinal imaging modalities used and describe the manifestations of each specific TTR mutation.

## Materials and Methods

To find all relevant published data on retinal angiopathy associated with ATTRv, a systematic literature review was performed on the following databases: Cochrane library, Embase and PubMed, using a search strategy with the terms ((retinal) OR (retina)) AND (transthyretin amyloidosis). A manual search using bibliographies and reference lists of previous studies was also conducted.

All-time original human English and Portuguese-language studies such as descriptive case-reports and case-series, as well as prospective studies on patients with genetically confirmed ATTRv, with report of retinal findings, both clinical and with imaging modalities, were included. Reviews were excluded. Animal and in-vitro studies were both excluded.

The materials were collected, analyzed, and summarized. Relevant findings were grouped considering different TTR mutations and specific retinal imaging modalities.

## Results

After eliminating repeated results, our search strategy found in 41 publications. Of these, 14 items were excluded because they reported no findings on retinal vessels; 2 were pictures either with incomplete or no description of retinal vascular changes; 2 were reviews; 2 studies were ex vivo and 1 was inaccessible.

Therefore, for analysis, 20 studies were included, comprising 7 case-reports, 8 small descriptive case-series (less than 50 patients), 3 large descriptive case-series and 2 cross-sectional case-control studies. No study was longitudinal, and no study reported prognostic factors regarding retinal angiopathy. Only three studies reported quantitative data on OCT and OCT-A, however the values were not comparable due to different OCT-A device and scan size used.<sup>7–9</sup> One study further found associations between retinal angiopathy and the severity of systemic neuropathy in ATTRv patients.<sup>10</sup>

Table 1 details the studies that were included for analysis together with the imaging modalities used and the TTR mutations present in the patients included.

## Fundoscopy and Retinography

The standard ophthalmological examination including dilated fundus examination with a 90D lens can detect most of the vascular changes associated with ATTRv. The main vascular clinical findings described in ATTRv patients were:

- tortuous retinal vessels<sup>7,11–13</sup>
- microaneurysms<sup>10,12</sup>
- retinal hemorrhages<sup>5,7,10,14–18</sup>
- sheathing of retinal vessels<sup>7,14,17,18</sup>
- whitish amyloid deposits along retinal arteries<sup>7,12,15,19–21</sup>
- obliteration of retinal vessels<sup>5,7,15,20</sup>
- pre-retinal neovascularization<sup>10</sup>
- vitreous hemorrhage<sup>18,22</sup>
- iris neovascularization<sup>10,22</sup> (anterior segment biomicroscopy).

One study reported better visualization of amyloid deposits along the vessels with red-free confocal retinography, versus conventional retinography.<sup>19</sup> Ultra-widefield retinography may be useful to detect and document peripheral lesions.<sup>7</sup>

## Retinal Autofluorescence

Autofluorescence (AF) is a non-invasive imaging technique that uses the fluorescent properties of lipofuscin (a metabolite of the retinal pigmented epithelium) after excitation at a specific wavelength. Two studies showed hyperautofluorescent deposits over the retinal surface and hyperautofluorescent areas of focal cuffing along retinal arterioles that corresponded to amyloid deposits.<sup>7,14</sup> Therefore, not only lipofuscin but also amyloid may be responsible for hyperautofluorescence in ATTRv patients.

**Table 1** Studies Included of Analysis Regarding Retinal Angiopathy Associated with Hereditary Transthyretin Amyloidosis

Authors of the Study	Year of Publication	Retinal Imaging Modalities	Number of Patients Included	TTR Mutations Included
Falls et al <sup>15</sup>	1955	Fundoscopy	6	Unknown
Noble et al <sup>21</sup>	1998	Retinography, fluorescein angiography	1	Val30Met
Kawaji et al <sup>23</sup>	2005	Retinography, fluorescein and indocyanine angiography, histopathological study	1	Tyr114Cys
Veronese et al <sup>14</sup>	2013	Retinography, autofluorescence and fluorescein angiography	1	Glu54Lys
Zou et al <sup>17</sup>	2013	Retinography	11	Ala36Pro
Sandhu et al <sup>18</sup>	2013	Retinography and fluorescein angiography	1	Glu89Lys
Liu et al <sup>20</sup>	2014	Retinography	12	Gly83Arg
Lv et al <sup>19</sup>	2014	Red-free confocal retinography, autofluorescence	1	Ile107Met
Santos et al <sup>13</sup>	2014	Retinography, fluorescein angiography and OCT	1	Val30Met
Beirão et al <sup>5</sup>	2015	Fundoscopy under mydriasis	477	Val30Met
Reynolds et al <sup>11</sup>	2017	Retinography	13	Asp18Glu, Glu54Gly, Ala36Pro, Val30Met
Rousseau et al <sup>10</sup>	2018	Retinography, fluorescein and indocyanine angiography	18	Val30Met
Latasiewicz et al <sup>7</sup>	2019	Retinography, autofluorescence, OCT and OCT-A	8	Ile107Met, Val30Met, Glu89Lys
Bunod et al <sup>24</sup>	2020	Fluorescein and indocyanine angiography	24	Ser77Tyr
Tasiopoulou et al <sup>16</sup>	2021	Retinography, OCT and fluorescein angiography	1	Val30Met
Kakihara et al <sup>25</sup>	2021	OCT	120	Val30Met
Marques et al <sup>8</sup>	2021	OCT-A	24	Val30Met
Kakihara et al <sup>22</sup>	2022	Fluorescein and indocyanine angiography	51	Val30Met
Patil et al <sup>12</sup>	2022	Retinography and fluorescein angiography	1	Asp18Glu
Choi et al <sup>26</sup>	2022	Retinography and OCT-A	6	Glu89Lys, Asp38Ala, Thr59Lys
Marta et al <sup>9</sup>	2022	Choroidal imaging with OCT	166	Val30Met

**Note:** Use the references list to find the full author's list and titles of the publications.

**Abbreviations:** OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography.

## Fluorescein Angiography

In fluorescein angiography (FA), the dye is injected intravenously and reaches the retinal vessels, a blue light (wavelength 465–490 nm) is projected on the retina and is absorbed by fluorescein molecules. The molecules fluoresce, emitting light with a longer wavelength in the yellow-green spectrum (520–530nm) that is captured by a camera. Images are acquired immediately after injection and continued for ten minutes. Intravenous fluorescein remains largely bound to proteins in the blood and, in normal eyes, the retinal vascular endothelium and the retinal pigment epithelium act as barriers and avoid diffusion of the dye to the extravascular space.

In ATTRv patients, FA may be superior to funduscopy at detecting microaneurysms,<sup>14,23</sup> telangiectasia<sup>12</sup> and vascular closure.<sup>23</sup> More importantly, FA is the only imaging modality that may detect delayed arterial filling,<sup>12</sup> vascular leakage,<sup>10,12,23</sup> and retinal ischemia.<sup>14</sup> It may also reveal macular edema,<sup>14</sup> but OCT is a less invasive examination for this purpose. Rousseau et al<sup>10</sup> observed that, in some patients, retinal angiopathy was not seen with funduscopy or retinography, whereas it was obvious on FA, suggesting that the latter may be more sensitive to detect vascular changes. Additionally, they found an association between systemic polyneuropathy disability scores and ischemic retinal angiopathy.<sup>10</sup>

## Indocyanine Green Angiography and Choroidal Changes

Indocyanine green angiography (ICG) is mainly used to study the choroid. The main differences to FA are that ICG emits fluorescence in near-infrared (790–805 nm) range (that penetrates better the pigmented retinal epithelium and possible media opacities) and that ICG leaks less from the choriocapillaris because of higher bounding to proteins and thus it will remain longer in choroidal vessels.

Rousseau et al initially described choroidal amyloid angiopathy with ICG with variable patterns of late hypercyanescence along the choroidal arteries: diffuse, focal and punctiform.<sup>10</sup> Two other studies with ICG confirmed these changes in ATTRv patients.<sup>23,24</sup> Marta et al evaluated the choroidal vascularization with OCT in ATTRv patients.<sup>9</sup> They found higher stromal area, a lower choroidal thickness, and lower choroidal vascularity index, compared with a control group of age-matched healthy patients. This could be the result of choroidal vascular lumen reduction due to stromal amyloid deposition.

## Optical Coherence Tomography

Macular optical coherence tomography (OCT) is a non-invasive diagnostic method that captures an in vivo depth-resolved cross-sectional view of the retina, using the concept of light interferometry. Regarding retinal vascular changes in ATTRv patients, OCT showed perivascular hyperreflective material (probably related to amyloid deposition) and some cases of macular edema.<sup>13,14</sup> A recent study described characteristic needle-shaped deposits on the retinal surface present in most of the vitrectomized eyes of patients with ATTRv.<sup>25</sup>

## Optical Coherence Tomography Angiography

Optic coherence tomography angiography (OCT-A) relies on how repeated OCT scans of the same region change with time to detect blood cells' movement and, therefore, microscopic vessels, with no need for intravenous contrast administration. Furthermore, OCT-A allows for automatic quantitative measurements that can be objectively compared, such as foveal avascular zone dimensions and macular capillary density.

In ATTRv patients, one study reported decreased vascular flow due to perivascular cuffing of the amyloid deposits.<sup>26</sup> Another study in ATTRv patients without clinical visible angiopathy lesions but with scalloped pupils found an attenuated retinal vascular network when compared to contralateral non-scalloped pupil eyes, namely larger foveal avascular zone (FAZ) area, decreased foveal vascular density, superficial and deep plexus vascular density. The FAZ acircularity index was superior, representing an abnormal FAZ morphology.<sup>8</sup>

## Specific TTR Mutations

The included studies report retinal vascular changes in patients with 10 different mutations. However, no feature was unique to a specific mutation.

## Discussion

This is the first systematic review focusing on retinal angiopathy associated with hereditary transthyretin amyloidosis. The retinal vasculopathy observed in all studies, both in fundus examination and in ancillary imaging examinations, is compatible with previous histological findings.<sup>23,27</sup> Paton et al described in 1966 extensive ocular vascular involvement in ATTRv patients: initially amyloid deposited in the *muscularis* of the small arteries. Later, the entire wall of the arteries and arterioles, as well as veins and capillaries, were replaced by amyloid, both in the retina and in the choroid. This led to the hypotheses that retinal ischemia and weakening of vessel walls caused by the deposition of amyloid were etiological

factors behind the observed retinal vascular findings. Beirão et al observed that the prevalence of retinal angiopathy in ATTRv patients is lower than other ocular manifestations of the disease but it increases with time.<sup>5</sup>

More than 100 TTR mutations associated with amyloidosis have been reported in the literature. Of these, 32 mutations have been associated with ophthalmic disease.<sup>28</sup> The current study reveals that at least 10 mutations are associated specifically with retinal angiopathy; however, no mutation seems yet to be associated with a unique finding. In contrast, systemic manifestations often correlate with the specific mutations: some are traditionally associated with a neurologic phenotype with progressive peripheral sensory-motor polyneuropathy while others like Val122Ile present with cardiomyopathy.

Regarding subclinical retinal angiopathy (a stage where no clinical lesions were visible in fundus examination), only two studies have reported changes: one found retinal microaneurysms and choroidal angiopathy seen only in fluorescein and indocyanine angiography, respectively.<sup>10</sup> However, these subclinical changes were observed in a single patient of their series of 18 patients, which suggest that, in most cases, the earliest retinal vascular changes may be seen clinically through a dilated pupil or in a widefield retinography. The other study reported subclinical vascular changes using OCT-A, but the lack of a longitudinal analysis and the inexistence of a database of normal OCT-A values precludes so far the transition to clinical practice. Unfortunately, no longitudinal or prognostic data exists regarding the retinal vasculopathy associated with ATTRv.

ATTRv eyes suffer from an ischemic environment with elevated VEGF levels.<sup>17,29</sup> Retinal ischemia is the precedent for neovascularization, in both the posterior and the anterior segment, which can cause irreversible visual loss such as neovascular glaucoma and tractional retinal detachment. In fact, there are reports of ATTRv patients presenting with neovascular glaucoma.<sup>30,31</sup> The use of panretinal photocoagulation and intravitreal antiVEGF may be used to treat retinal ischemia/neovascularization in ATTRv patients.<sup>30,32</sup> Moreover, treatment with panretinal photocoagulation may decrease the endocular production of mutant TTR by the pigmented retinal epithelium.<sup>32</sup> Therefore, patients with retinal angiopathy must be promptly diagnosed and strictly followed.

Given the long-term risk of ocular involvement and potential for blindness, Beirão et al suggested the following visit schedule for ATTRv patients without retinal angiopathy: 1) initial ophthalmological visit at the time of genetic diagnosis; 2) repeated evaluations every 2 years in asymptomatic carriers; and 3) annual evaluation in symptomatic patients. This visit should include a complete ophthalmological examination and funduscopy under mydriasis. If available, a retinography should be performed to document the findings. Autofluorescence should be considered as it may improve the detection of amyloid deposits in retinal vessels. Ultra-widefield modalities should be preferred as, in some patients, the disease begins in the peripheral retina.

In the presence of clinical retinal angiopathy, we recommend that patients undergo fluorescein angiography (consider ultrawide-field OCT-A when available) at diagnosis and that they should be reevaluated every 3 months.

The time intervals shown should be adapted in the presence of concomitant ocular disease such as scalloped pupils, ocular hypertension, secondary glaucoma, significant vitreous opacities, and severe systemic polyneuropathy, as it may be associated with more severe retinal ischemia.

The ophthalmologist's approach to ATTRv patients should be independent of their systemic therapy as the ocular manifestations seem to progress despite liver transplantation or treatment with tafamidis or with inotersen.<sup>14,33–35</sup>

On the other side, in an undiagnosed patient that presents with retinal angiopathy of unknown etiology, ATTRv should be considered as differential diagnosis. Symptoms of dysautonomia (hypotension, intolerance to antihypertensive medications, alternating diarrhea and constipation), sensitive and motor polyneuropathy and cardiomyopathy should be investigated. Other ocular signs of ATTRv should be explored. Interestingly, there is a reported case of isolated retinal angiopathy as the first manifestation of ATTRv,<sup>36</sup> suggesting that it may be undervalued and sub-diagnosed.

A comprehensive evaluation of each exam should be implemented in ATTRv patients because artefacts, shadow effects and errors in segmentation in OCT are more frequent in ATTRv patients in the presence of vitreous amyloidosis or amyloid deposits in the vitreoretinal interface.

Ocular comorbidity associated with ATTRv is complex. Despite extensive experience with ATTRv patients in our center, longitudinal studies should be completed to better document the natural history of these patients. Moreover, prospective studies regarding the treatment of retinal angiopathy associated with ATTRv are missing.

## Conclusion

Despite no longitudinal data on retinal angiopathy caused by ATTRv, the current literature shows consistent findings in the ophthalmological examination and ancillary imaging examinations. The presence of retinal angiopathy in ATTRv patients should motivate the screening of retinal ischemia and its timely treatment to avoid irreversible complications. The prognostic value of subclinical findings, namely in OCT-A, is yet to be unveiled and should motivate future research.

## Disclosure

The authors report no conflicts of interest in this work.

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