Influence of Vitrectomy on Ahmed Glaucoma Valve Success for Glaucoma Secondary to Hereditary Transthyretin Amyloidosis

A Influência da Vitrectomia no Sucesso da Válvula de Ahmed no Glaucoma Secundário à Amiloidose Hereditária por Transtirretina

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ABSTRACT

INTRODUCTION: Our purpose was to assess the role of previous pars plana vitrectomy (PPV) on the surgical outcomes of patients with hereditary transthyretin amyloidosis (hATTR) who had undergone Ahmed glaucoma valve (AGV) implantation.

METHODS: A retrospective cohort study was performed enrolling consecutive patients with a diagnosis of hATTR secondary glaucoma who underwent primary AGV implantation in our department over the last decade. Previous PPV was used to split the patients in two groups (PPV versus non-PPV). The primary outcome was success, defined as intraocular pressure (IOP) ≥ 6 mmHg and ≤21 mmHg with or without medication, with no need for further glaucoma surgery during 60 months of follow-up. Secondary outcomes included postoperative IOP and medication score, early and late surgical complications, as well as the frequency of hypertensive phase and hypotony.

RESULTS: The study included 100 eyes of 79 patients, of which 45 eyes had had PPV. No significant differences were found between groups for age at the time of surgery, hATTR diagnosis or symptoms onset, gender, liver transplant or use of Tafamidis®. Vitrectomized eyes presented worse vision (0.46±0.51 *vs* 0.22±0.22 logMAR, p=0.002) and had a higher proportion of pseudophakia (40% *vs* 7%, p<0.001). Preoperative IOP and medication score were not significantly different between groups. The success rate of AGV surgery was 81% at 60 months, with non-PPV presenting a higher success rate at each timepoint. The PPV group presented a higher hazard (HR 2.73 (95%CI 1.07-6.97), p=0.035) for glaucoma surgery failure than the non-PPV group. No differences were found in postoperative IOP and medication at all timepoints nor for postoperative complications or frequency of hypertensive phase or hypotony.

CONCLUSION: The management of glaucoma secondary to hATTR is very complex. In our cohort, patients previously submitted to PPV had lower success after AGV surgery.

KEYWORDS: Amyloid Neuropathies, Familial; Glaucoma/surgery; Glaucoma Drainage Implants; Intraocular Pressure; Vitrectomy.

RESUMO

INTRODUÇÃO: O nosso objetivo foi avaliar o papel da vitrectomia via *pars plana* (PPV) prévia nos resultados cirúrgicos de pacientes com amiloidose hereditária por transtirretina (hATTR) submetidos a cirurgia de glaucoma com válvula de Ahmed (AGV).

MÉTODOS: Foi realizado um estudo de coorte retrospetivo incluindo pacientes consecutivos com diagnóstico de glaucoma secundário a hATTR que foram submetidos a cirurgia de glaucoma primária com AGV no Centro Hospitalar Universitário de Santo António. Os doentes foram divididos em dois grupos conforme os antecedentes de PPV (PPV *versus* sem-PPV). O *outcome* primário foi o sucesso, definido como pressão intraocular (PIO) ≥ 6 mmHg e ≤ 21 mmHg com ou sem medicação tópica e sem necessidade de nova cirurgia de glaucoma durante 60 meses de seguimento. Os outcomes secundários foram o valor da PIO e o *score* de fármacos hipotensores, complicações precoces e tardias e a frequência de fase hipertensiva e hipotonia.

RESULTADOS: Este estudo incluiu 100 olhos de 79 pacientes, dos quais 45 olhos tinham sido previamente submetidos a VPP. Não foram encontradas diferenças significativas entre os grupos relativamente à idade no momento da cirurgia, diagnóstico de hATTR ou início dos sintomas, género, transplante hepático ou uso de Tafamidis®. Os olhos vitrectomizados apresentaram pior acuidade visual (0,46±0,51 *vs* 0,22±0,22 logMAR, p=0,002) e uma maior proporção de pseudofaquia (40% *vs* 7%, p<0,001). A PIO pré-operatória e o score de fármacos hipotensores não foram significativamente diferentes entre os grupos. A taxa global de sucesso da AGV foi de 81% aos 60 meses, com o grupo PPV apresentando uma taxa de sucesso superior em cada avaliação pós-operatória. O grupo VPP apresentou um maior *hazard* (HR 2,73 (IC 95% 1,07-6,97), p=0,035) para insucesso da cirurgia de glaucoma do que o grupo de não-vitrectomizados. Não foram encontradas diferenças na PIO ou *score* de fármacos hipotensores nos diferentes momentos de avaliação pós-operatória nem complicações pós-operatórias ou na frequência de fase hipertensiva ou hipotonia.

CONCLUSÃO: A orientação do glaucoma secundário à ATTRh é sobremaneira complexa. Na nossa coorte, os pacientes previamente submetidos a VPP tiveram um menor sucesso da cirurgia de glaucoma com AGV.

PALAVRAS-CHAVE: Implantes para Drenagem de Glaucoma; Neuropatias Amiloides Familiares; Glaucoma/cirurgia; Pressão Intraocular; Vitrectomia.

INTRODUCTION

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant inherited disorder characterized by the deposition of abnormal transthyretin protein aggregates in peripheral nerves and several organs.[1] In the eye, it can lead to medium opacities by the deposition of the mutated transthyretin (TTR) in the vitreous and anterior lens capsule[2,3]; secondary open-angle glaucoma[4,5]; irregular pupil[6]; abnormalities in conjunctival, retinal and choroidal vascular networks[7-9]; and impairment of nerve function manifested as corneal hypoesthesia leading to keratoconjunctivitis sicca and neurotrophic corneal ulcers, pupillary light-near dissociation, and optic neuropathy.[10-12]

Secondary glaucoma is one of the leading causes of blindness in hATTR patients, but its pathophysiology is far from being fully understood. Deposition of TTR in the intertrabecular space and Schlemm's canal may impair aqueous humor outflow pathway whereas perivascular deposition of amyloid in the conjunctival and episcleral tissue may increase episcleral venous pressure.[13,14] One special feature of hATTR ocular involvement is continuous production of TTR in retinal and ciliary pigment epithelia[13,15] regardless of systemic treatments,[16] leading to a relentless deposition of amyloid. This feature emphasizes the challenges imposed by the ocular manifestations of the pathology.

The management of glaucoma secondary to hATTR is often surgical. In one series, 75% of the eyes required surgery for intraocular pressure (IOP) control.[13] Glaucoma development or progression after pars plana vitrectomy (PPV) has been reported.[14,17] It was hypothesized that the vitreous provides a meshwork for amyloid deposition and its removal leads to higher deposition of amyloid in the aqueous outflow pathway.[14] In addition, vitrectomy also increases the free circulation of oxygen imposing oxidative stress on the trabecular meshwork.[14] Favoring these hypotheses, it was demonstrated that eyes submitted to complete vitrectomy had a higher rate of glaucoma development that those in whom an incomplete vitreous removal was performed.[14]

Beyond the impact on glaucoma development and progression, it is warranted to understand the role of vitrectomy

on the success of surgical glaucoma techniques as conjunctival manipulation is a common feature and several patients will be needing both procedures during their lifetime. In this study, we aimed to assess the influence of previous PPV on the success of primary Ahmed glaucoma valve (AGV) implantation for glaucoma secondary to hATTR.

METHODS

This is a retrospective cohort study that enrolled consecutive adult patients with a diagnosis of glaucoma secondary to hATTR who were submitted to primary AGV implantation in the Department of Ophthalmology of Centro Hospitalar Universitário de Santo António, Porto, Portugal. This study was conducted following the tenets of the Declaration of Helsinki[18] and complied with the requirements of the institute's committee on human research. Patients anonymity was carefully protected. Informed consent was signed for all procedures, following the guidelines required by the institution with which all the authors are affiliated.

PARTICIPANTS AND SURGERIES

Indications for surgery included uncontrolled IOP despite maximum tolerated topical therapy with documented progression. The inclusion criteria were as follows: glaucoma patients with a diagnosis of hTTR confirmed by laboratory tests and collaborative ability to provide IOP evaluation with Goldmann applanation tonometry without history of glaucoma surgeries. Patients with less than a year of follow-up were not enrolled. Two groups were formed according to previous PPV (PPV and non-PPV groups). All PPV were performed with 23-gauge (G) devices. AGV implantation was performed as previously described.[5]

PARAMETERS

Demographic characteristics, full ophthalmological examination, AGV implantation alone or combined with phacoemulsification, preoperative and postoperative evaluations over time, early (within 1 month) and late (>1 month) surgical complications and the need for further glaucoma surgery were recorded. Central endothelial cell counts (ECC) were performed with specular microscopy (EM 4000® (Tomey GmbH)). All patients were scanned with Spectral-Domain OCT (SD-OCT) using Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) for assessement of peripapillary nerve fiber layer in a circular B-scan with 3.4 mm of diameter. All scans were reviewed, and segmentation errors were manually corrected.

For statistical purposes, "counting fingers" was classified as 0.01, "hand movement" as 0.005 and "light perception" as 0.0005.[19] Best-corrected visual acuity (BCVA) registered in decimals was converted to the logarithm of the minimum angle of resolution (LogMAR) equivalent.[20] Intraocular pressure (IOP) was measured by Goldmann applanation tonometry. Antiglaucoma medication score was calculated for each eye by assigning 2 points for topical fixed combined eyedrops and 1 point for topical single medication eyedrops and oral carbonic anhydrase inhibitor.

OUTCOMES

Our main outcome is the cumulative survival rate during 60 months of follow-up after AGV implantation. Surgical success was defined as an IOP ≥ 6 mmHg and ≤ 21 mmHg with no need for further glaucoma surgery or laser trabeculoplasty. In the Kaplan-Meier analysis, deviation from the above criteria or loss of light perception were considered as failure.

As secondary outcomes, postoperative IOP and medication score, early and late surgical complications and the frequency of hypertensive phase and hypotony were assessed and compared between groups. Hypertensive phase was defined as the presence of an IOP ≥ 22 mmHg in the assessments of the first 3 months (excluding cases of tube obstruction).

STATISTICAL ANALYSIS

All statistical analyses were performed using Stata software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Continuous variables are presented through means and standard deviations (SD) or 95% confidence interval (CI) for data with Gaussian distribution, or medians and interquartile ranges (IQR) for variables with a skewed distribution. Categoric variables are described as absolute and relative frequencies. Parametric or nonparametric tests were used for continuous variables comparison between groups according to the normality of data. Kaplan–Meier survival curve was plotted to depict the cumulative probability of surgical success. A Cox proportional hazard model was used to assess the effect of previous PPV on surgical success of AGV implantation. Statistical significance was defined as $p<0.05$.

RESULTS

One hundred eyes of 79 patients with glaucoma secondary to hATTR were enrolled, of which 45 eyes had been submitted to PPV. Thirty-eight (48.1%) patients were women and the mean±SD ages of hATTR diagnosis and symptoms onset were 30.5±11.1 and 33.2±9.5, respectively. Most patients had been submitted to liver transplantation (n=74, 93.4%) and pacemaker implantation (n=66, 83.5%) with these procedures occurring 7.6±6.3 and 9.8±6.8 years after hATTR diagnosis, respectively. Primary AGV implantation was performed 20.6±7.9 years after diagnosis and 17.6±6.8 years after symptoms onset, at a mean±SD age of 50.6±7.2 years. The median (IQR) time of follow-up was 48.3 (29.5 – 60.0) for PPV group and 59.9 (48.4 – 60.0) for non-PPV group.

Table 1 presents the demographic and ophthalmological characteristics at baseline. No significant differences between groups were found for demographic or systemic characteristics. Vitrectomized eyes had worse BCVA

Table 1. Demographic and ophthalmological characteristics of population at baseline.

	PPV	No PPV	*p*-value
Number of patients / eyes	35 / 45	44 /55	
Female sex	18 (51.4%)	20 (45.4%)	0.598
Age at hATTR diagnosis, y	30.5 ± 11.0	30.4 ± 11.3	0.912
Age at hATTR onset, y	32.8 ± 8.5	33.5 ± 10.3	0.342
Age at AGV implantation, y	50.9 ± 6.6	50.3 ± 7.6	0.800
Age at PPV, y	48.7 ± 6.8	-	
Liver transplantation	33 (94.3%)	41 (93.2%)	0.841
Age, y	37.3 ± 8.1	36.3 ± 7.3	0.808
Pacemaker implantation	28 (80.0%)	38 (86.4%)	0.449
Age, y	38.3 ± 7.1	39.6 ± 9.4	0.610
Tafamidis meglumine	3 (8.6%)	3 (6.8%)	0.770
Age, y	49 [39 – 58]	66 [48 – 67]	0.154
BCVA, logMAR	0.46 ± 0.51	0.22 ± 0.22	**0.002**
IOP, mmHg	27.3 ± 5.9	29.2 ± 7.8	0.200
Medication score	3.9 ± 0.7	4.0 ± 0.7	0.469
Pseudophakia	18 (40.0%)	4 (7.3%)	**<0.001**
Type of surgery			
AGV alone	28 (62.2%)	38 (69.1%)	0.528
AGV + CS	17 (37.8%)	17 (30.9%)	
ECC	2799.3 ± 530.6	2328.4 ± 536.6	**<0.001**
NFL thickness	87.9 ± 18.5	76.4 ± 16.6	**0.008**

Data shown as number (percentage), mean ± standard deviation and median [interquartile range].

AGV, Ahmed glaucoma valve; BCVA, best-correct visual acuity; CS, cataract surgery; ECC, endothelial cell count; hATTR, hereditary transthyretin amyloidosis; IOP, intraocular pressure; NFL, nerve fiber layer; PPV, pars plana vitrectomy.

(*p*=0.002) and had a higher proportion of pseudophakia (*p*<0.001). Preoperative IOP and the medication score were not significantly different between groups (*p*=0.20 and *p*=0.47, respectively).

Table 2 presents the success rates between groups for each timepoint and Fig. 1 depicts the Kaplan-Meier probability estimates. PPV group presented a hazard for failure almost 3-times higher than the non-PPV group (HR 2.73 (95%CI 1.07-6.97), *p*=0.035). Overall, the success rate was 81%, with non-PPV presenting a higher success rate at each timepoint (Table 2). Twelve (26.7%) patients of PPV group and 7 (12.7%) patients of non-PPV group needed further glaucoma procedures to achieve IOP control. Of those, ten

Table 2. Success rates of AGV implantation over time.

Months	PPV		No PPV	
	N	Success rate	N	Success rate
0 - 12	45	93.3%	55	100%
12 - 24	42	81.9%	55	98.2%
24 – 36	35	79.3%	52	94.3%
36 – 48	27	76.2%	48	90.3%
48 – 60	23	68.4%	44	85.3%
60	19	68.4%	37	85.3%

AGV, Ahmed glaucoma valve; PPV, pars plana vitrectomy.

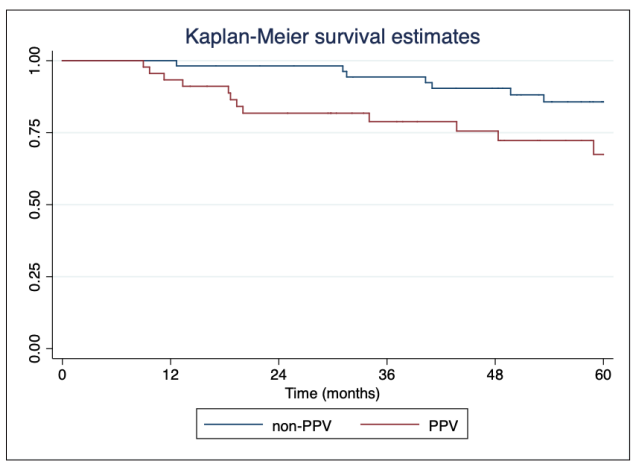

Figure 1. Kaplan-Meier estimates of the cumulative probability of success for Ahmed glaucoma valve implantation.

(83.3%) eyes of PPV group and 6 (85.7%) eyes of non-PPV group were submitted to transscleral cyclophotocoagulation with the remaining 2 (16.7%) and 1 (14.3%) eyes of each group, respectively, being treated with selective laser trabeculoplasty. No patient lost light perception during the 60 months of analysis. Overall, 8 (8.0%) patients died during follow-up (4 in each group) and 17 eyes (10 in PPV group and 7 in non-PPV group) did not have a complete follow-up period of 60 months due to recent surgery. Despite these

losses of follow-up, groups remain comparable in all moments of assessment, with exception of the differences already present in the baseline.

Considering the secondary outcomes, no differences were found between groups in postoperative IOP (Fig. 2) or medication score (Fig. 3) at all timepoints. Compared with baseline, both groups presented significantly lower values of IOP and medication score at all postoperative timepoints (all $p<0.001$). Twenty-seven patients of each group (60.0% for PPV *vs* 49.1% for non-PPV, $p=0.276$) developed a hypertensive phase. Table 3 describes the early and late-onset complications. The occurrence of any early (17.8% *vs* 18.2% for PPV and non-PPV, respectively) or late-onset (8.9% *vs* 10.9%) complications was similar between groups. Hypotony with or without athalamia was more frequent in the non-PPV group.

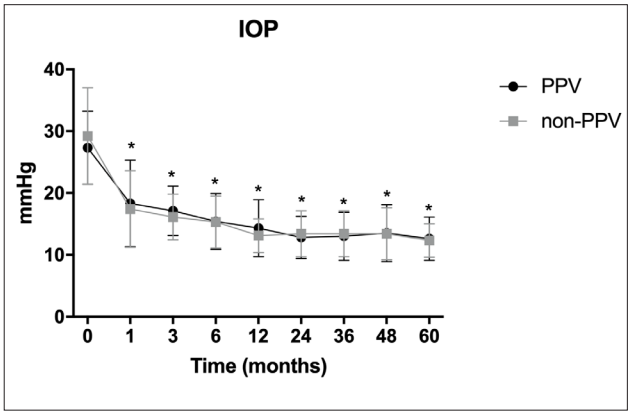

Figure 2. Intraocular pressure (IOP) values during the follow-up.

* corresponds to $p<0.001$ for the comparison with baseline IOP (time=0).

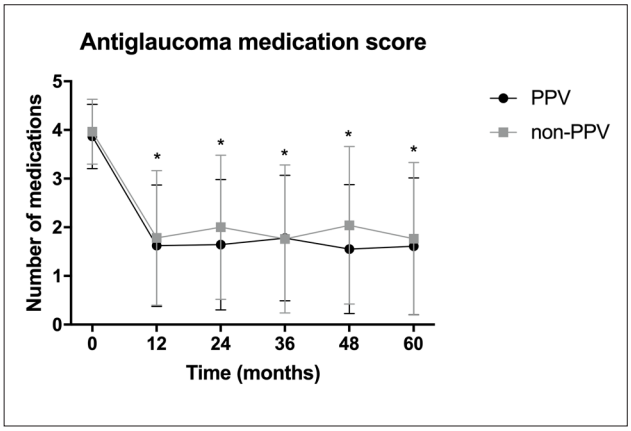

Figure 3. Medication scores values during the follow-up.

* corresponds to $p<0.001$ for the comparison with baseline IOP (time=0).

Table 3. Early and late-onset complications after AGV implantation over time.

Early-onset complications	PPV (n=45)	Non-PPV (n=55)
None	37 (82.2%)	45 (81.8%)
Choroidal detachment	1 (2.2%)	0 (0.0%)
Corneal ulcer	1 (2.2%)	0 (0.0%)
Hypotony ± athalamia	1 (2.2%)	7 (12.7%)
Mild hyphema	2 (4.4%)	1 (1.8%)
Suprachoroidal hemorrhage	1 (2.2%)	0 (0.0%)
Vitreous hemorrhage	2 (4.4%)	0 (0.0%)
Tube obstruction	0 (0.0%)	2 (3.6%)
Late-onset complications		
None	41 (91.1%)	49 (89.1%)
Corneal decompensation	1 (2.2%)	3 (5.5%)
Bleb encapsulation	1 (2.2%)	0 (0.0%)
Tube exposure	1 (2.2%)	2 (3.6%)
IOL subluxation	1 (2.2%)	1 (1.8%)

AGV, Ahmed glaucoma valve; IOL, intraocular lens.

DISCUSSION

Glaucoma is one of the leading causes of blindness in hATTR patients that imposes a challenge to ophthalmologists as it tends to be refractory to medical and often surgical management. Several patients will need surgery and aqueous humor drainage devices assume an important role in this scenario as they are an useful resource for refractory glaucoma, either as a primary or secondary procedure.[21] It is accepted that previous PPV increases the chances of glaucoma development. Additionally, one recent small series has demonstrated that eyes with a history PPV presented a trend towards lower survival rate after trabeculectomy.[22] To our best knowledge, this is the first study demonstrating that eyes previously submitted to 23G PPV present a higher hazard for failure after primary AGV implantation.

Surgical results of glaucoma secondary to hATTR have been reported with several techniques including implantation of glaucoma drainage devices such as AGV5 and Baerveldt glaucoma valve (BGV),[23] trabeculectomy,[22] suture (SLOT)[24] and microhook[25] *ab interno* trabeculotomy, Ex-PRESS® Filtration Device implantation using a modified technique with scleral pocket[26] and transscleral cyclophotocoagulation (TSCPC).[27] The latter technique was shown to be an effective and safe secondary approach after AGV failure.[27] Ex-PRESS® Filtration Device using the modified technique was demonstrated to control the IOP without further topical medication in almost 70% of patients.[26] On the other hand, the majority of patients submitted to glaucoma drainage devices implantation, *ab interno* trabeculotomies and trabeculectomy can only achieve IOP control with additional topical antiglaucoma medication, with its use being implemented early in the follow-up.[5,22,24,25] In fact, most of these studies define success as IOP control with or without topical medication and we followed that definition in this study. In a long-term cohort study of our center, the surgical success without the need of antiglaucoma eyedrops was

below 20%.[5] These facts highlight that glaucoma secondary to hATTR is a challenging condition and that surgical treatment aims to control IOP and glaucoma progression and not to wean patients out of drops.

In this study, all patients enrolled have been submitted to a primary glaucoma surgery with AGV implantation. This fact is one of the main differences from other studies that assessed the role of vitrectomy in glaucoma surgeries success. Previous cataract surgery was not exclusion criteria. Some authors hypothesized that phacoemulsification could increase glaucoma development given the proximity of the trabecular meshwork to the surgical site, although they found no evidence supporting their conjecture.[17] In our study, PPV group presented a higher proportion of pseudophakia which is justified by the previous vitrectomy as it accelerates cataract progression. Posterior capsule opacification or a higher severity of ocular involvement may explain the lower visual acuity in that group. No differences between groups were found considering the history of systemic disease, implying that groups were well balanced, and that disease duration could not explain the higher failure rate after AGV surgery. Thus, PPV group might have a more severe ocular involvement justifying the earlier vitrectomy. At time of AGV implantation, patients of PPV group had a higher count of endothelial cells and a higher nerve fiber layer (NFL) thickness. These differences, mostly the thicker NFL, suggest that patients of PPV group were submitted to surgery at an early stage of glaucoma than those of non-PPV. Despite the age at time of AGV surgery was similar, the glaucoma of PPV group could have a faster progression, justifying the earlier intervention. Thus, a higher severity of ocular involvement could explain why these patients had lower visual acuity, an earlier vitrectomy, a glaucoma surgery with lesser loss of NFL than the non-PPV group and also a higher failure after AGV implantation.

Conjunctival manipulation and subsequent scarring may also explain our results. In this study, previous PPV was performed with 23G equipment for all surgeries and sclerotomies suture was at surgeons' discretion. Both the size of equipment and the resource to sutures increase the likelihood of conjunctival scarring. In addition, an increased episcleral pressure due to higher perivascular conjunctival and episcleral amyloid deposition could also contribute to the results hereby presented if these patients actually present a more severe ocular phenotype. Kitahara *et al*[22] assessed the long-term results of trabeculectomy for hATTR secondary glaucoma and compared them according to the history of small gauge (25- or 27-gauge) vitrectomy. Despite the reduced conjunctival scarring due to the small gauge equipment, patients with previous PPV presented a trend to worse results. The difference was not statistically significant probably due to lack of power given than small sample size (n=31). Postoperative inflammation, higher dispersion of amyloid and its accumulation in the aqueous outflow pathway and increase oxidative stress in the trabecular meshwork may also contribute to the poorer results of patients with previous PPV. As overmentioned, it was shown that PPV increased the odds of glaucoma development.[14] In the present study, we demonstrate that previous vitrectomy also thwarts the outcomes of glaucoma surgery with AGV.

This study has some limitations. It is retrospective cohort study and has the drawbacks inherent to this design. Its lacks a comparison group of primary open-angle glaucoma with previous PPV to confirm the specific role of vitreous in hATTR disease. Also, despite some of the explanations given for our results can be translated to other types of glaucoma, such as conjunctival manipulation and free oxygen flow to the trabecular meshwork, other hypotheses are very specific of the disease, including increased amyloid deposition in the aqueous outflow pathway and in the conjunctival and episcleral vessels. A substantial number of eyes in both groups did not complete the follow-up period. This work has several strengths. We present a high number of patients, mostly considering that hATTR is a rare disease, and long-term follow-up data. Our groups were well balanced and the description of systemic and ocular features of the disease was comprehensive, strengthening our analysis and results.

CONCLUSION

In summary, the management of glaucoma secondary to hATTR is very complex and imposes a high burden. In our cohort, almost half of the patients were previously submitted to PPV which led to a lower success of AGV surgery over the 60 months of follow-up. Those patients might likely have a more aggressive phenotype, leading to earlier vitrectomy. PPV itself might also contribute to the lower success of surgery by increasing the amount of amyloid that can deposit in the trabecular meshwork and due to conjunctival manipulation.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

All authors provided substantial contributions to the conception and design of the work; AM and RV performed the acquisition of data; AF analyzed the data; all authors were responsible for the interpretation of data; AF drafted the manuscript; all authors reviewed the work for critically important intellectual content; all authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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