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CASE REPORT

Multimodal imaging and genetic screening in Mexican patients with Gyrate atrophy: identification of novel *OAT* pathogenic variants

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Abstract

Purpose Description of retinal phenotype by structural and functional testing, ornithine plasma levels and mutational data of *OAT* gene in patients with Gyrate Atrophy (GA).

Methods Ophthalmologic examination, fundus photography (CFP), autofluorescence (FAF), spectral-domain optical coherence tomography (SD-OCT), Goldmann perimetry (GP), full-field electroretinogram (ffERG) and chromatic perimetry (CP) testing were performed. Ornithine plasma levels were measured. Sanger sequencing mutational analysis of the coding exons and exon–intron junctions of the *OAT* gene were analyzed.

Results Twelve eyes of seven Mexican patients with GA were included. CFF showed peripheric patches of chorioretinal atrophy; FAF revealed peripheric oval areas of hypoautofluorescence; SD-OCT exhibited outer retinal tubulations in 58%, cystoid macular edema in 50%, epiretinal membrane in 42%, foveoschisis and staphyloma in 17%, and hyperreflective deposits in 100% of the eyes; GP showed constricted visual fields in 100% of the eyes; ffERG revealed preserved photopic response in 17% and preserved scotopic response in 17% of the eyes; CP exposed a deficit in generalized response of rods and cones in 100% of the eyes. Mean ornithine plasma levels were 509.5 µmol/L. One patient with genetic confirmation of GA had normal ornithine plasma levels (48 µmol/L). Molecular findings in *OAT* gene detected two novel pathogenic variants: c.796 C > T (p.Gln266*) and c.721_722dupCC (p.Asp242ArgfsTer6).

Conclusion This study provides new information regarding functional and structural diagnosis in patients with GA, expands the understanding of retinal phenotype in patients with GA, reports two novel mutations and presents the first case of GA confirmed by genetic testing with normal ornithine levels.

Keywords Gyrate atrophy · *OAT* gene · Ornithine · Dystrophy · Molecular analysis · Hereditary eye diseases

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Introduction

In 1896, E. Fuchs described for the first time a progressive degeneration of the retina and choroid in young patients which was named "atrophia gyrata chorioideae et retinae"[1]; since then, this rare autosomal recessive chorioretinal dystrophy has been widely studied, exhibiting variable clinical characteristics [2]. To date, more than 200 individuals with Gyrate atrophy (GA) have been reported in the literature, of which one third corresponds to the Finnish population. Chorioretinal atrophy in GA is generated by increased levels of ornithine due to a deficiency of ornithine-δ-aminotransferase (OAT) which normally removes ammonia from the cells by the conversion of L-ornithine to proline and glutamic acid [3–5]. GA is caused by biallelic mutations in the *OAT* gene, with more than 60 different mutations reported to date in individuals from diverse ethnic origins and with no apparent genotype–phenotype correlation [6]. GA is clinically characterized by night vision impairment and loss of peripheral visual field starting in the first and second decades of life. In addition, myopia, cataracts and cystoid macular edema (CME) are common early features [7]. Initial fundoscopic changes are well described as round sharply defined areas of retinal and choroidal atrophy in the periphery and equator which in late stages tend to coalesce and spread centripetally [5, 7–10]. These lesions lead to a marked separation between healthy/normal and atrophic retina with loss of external layers, retinal pigment epithelium, choriocapillaris and most of the medium and large choroidal vessels [11]. Studies in GA mouse models and humans have demonstrated that early correction of ornithine levels, being abnormally elevated up to 20-fold in typical cases, can slow long-term progression of the retinal degeneration [12, 13]. Dietary plans including restricting arginine and low protein intake adding or not supplementations such as vitamin B6 or l-lysine, have been reported useful to lower and stabilize ornithine levels showing good results in vision improvement and slowing the progression. [2, 14–18]. While some case reports and a few case series of GA patients from diverse ethnic groups have been clinically and molecularly characterized [16, 17, 19–21] no information from Latin American patients do exist.

The aim of this study is to describe the retinal phenotype by functional and structural retinal testing in a Mexican cohort of patients diagnosed with GA and to report the pathogenic *OAT* variants identified in them. This is the first case series of GA reported in the Mexican population and our results expand the understanding of retinal phenotype and the mutational spectrum associated with GA.

Methods and materials

The study was approved by the Institutional Ethics Committee of the Institute of Ophthalmology "Conde de Valenciana" in Mexico City and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The inclusion criteria included patients with clinical characteristics of GA and clear media that allowed adequate clinical and multimodal imaging evaluation of the eye. Patients with suspected GA but no mutation in *OAT* gene were excluded.

Clinical ophthalmological evaluation

The patients were evaluated at the Clinic for Inherited Retinal Degenerations of the Institute of Ophthalmology Conde de Valenciana by a retina specialist by means of a full ophthalmological evaluation that included slit lamp examination, intraocular pressure measurement by applanation tonometry, and dilated funduscopic evaluation. Demographic data as well as a complete clinical questionnaire were reported. All patients underwent best-corrected visual acuity measurement (BCVA) using Snellen Chart and then converted to Logarithm of Minimum Angle of Resolution (logMAR) values.

Structural retinal evaluation

Wide field color fundus photography (CFP) (Optos California, USA) and a 55 grade color fundus photography (Spectralis; Heidelberg Engineering GmbH; Heidelberg, Germany) or a 45 grade color fundus photography (DRI OCT Triton, Swept source OCT, TOPCON Corporation; Tokyo, Japan) were taken to each patient. To estimate retinal pigment epithelium (RPE) status, retinal autofluorescence (FAF) was obtained using the 488 nm (Spectralis; Heidelberg Engineering GmbH; Heidelberg, Germany) and the 532 nm (Optos California, USA) imaging softwares. Retinal horizontal and vertical cross-sections were

obtained with the spectral domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering GmbH; Heidelberg, Germany). A 9-mm line scan along the horizontal and vertical meridians crossing the fovea was performed in all patients. The total area of the outer nuclear layer (ONL) in both meridians crossing the fovea, the subfoveal ONL thickness in the horizontal meridian, and the eccentricity of the ellipsoid zone (EZ) line in both meridians were determined by manual segmentation using the Spectralis built-in measurement software.

Functional retinal evaluation

Goldmann kinetic perimetry (GP) was performed in all patients without nystagmus (MonCvONE, Metrovision; Pérenchies, France). Full field ERG (ffERG) (MonPackONE, Metrovision; Pérenchies, France) was performed in all patients using the International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Topographical retinal function of cones and rods were determined by photopic and scotopic visual field testing (Chromatic perimetry; CP) (MonCvONE, Metrovision; Pérenchies, France) under light and dark-adaptation, respectively, in the eye with better BCVA in each patient.

Biochemistry measures

Blood samples were obtained to quantify ornithine plasma levels in all patients and were analyzed by an independent external laboratory.

Mutation screening of OAT gene

Genetic analysis was performed at the Laboratory of Molecular Genetics of the Institute of Ophthalmology Conde de Valenciana. For all patients, genomic DNA (gDNA) was extracted from peripheral blood leukocytes using standard methods after obtaining informed consent. The 9 coding exons and exon–intron junctions of the *OAT* gene were amplified by PCR using pairs of primers and temperature conditions available on request. Amplicons were sanger sequenced by the dideoxy chain method using a Compact System Sequencer (Promega, Madison, USA). Obtained OAT sequences were manually compared with the canonical gene transcript NM_000274.4. In compound heterozygous cases, available first relatives were also genetically screened for confirmation of *trans* configuration of the pathogenic variants.

Results

Clinical, structural and functional results

A total of seven patients 12 eyes were included in the study, including 4 females and 3 males. The mean age at the time of the first examination was 34.2 years old (age range, 10–66). The mean age of first symptoms reported by the patients were at 9.2 years old (age range, 5–20), being nyctalopia (N = 3) the main visual symptom in 42.8% of the patients as well as blurry vision in 42.8% (N = 3). Associated systemic features included muscle weakness in 29% (N = 2) of patients, cognitive deficit in 14% (N = 1) of patients, and history of otitis media associated and some degree of hearing loss in 29% (N = 2) of patients. 29% (N = 2) of the patients in the study were related (siblings) (P2 and P3). None of the patients were born to consanguineous parents.

Within the ophthalmological clinical findings, the mean BCVA was 0.5 LogMar (range between 0.0–1) (Snellen 20/63; range between 20/20 and 20/200). 29% (N = 2) of the patients had only one functional eye, one eye had an untreated chronic rhegmatogenous retinal detachment (RRD) with no light perception (P2) and the other eye was eviscerated due to an open ocular trauma (P7). 67% (N = 8) of the eyes had myopia and 50% of the eyes (N = 6) underwent early intervention of cataract surgery (mean age at 20 years) (Table 1).

Fundoscopy revealed typical changes of GA in 100% (N = 12) of the eyes, showing sharply demarcated, circular areas of chorioretinal atrophy predominantly distributed in the peripheral retina. 75% (N = 9) of the eyes had macular involvement at the time of the first evaluation of which 25% (N = 3) the fovea was affected. P6 presented a round-shaped atrophic area in the macula with some preserved central foveal tissue with an evident ring-shape area of preserved retina between the coalescent peripheral patches and the posterior pole atrophy (Fig. 1).

All the patients presented round or oval areas of hypoautofluorescence mainly in the periphery that tend to coalesce, spreading to the macula and partially sparing the peripapillary region, leaving some

Table 1 Clinical characteristics and ornithine plasma levels

Patient No	Gender	Age at examination (yrs)	Age at presenting symptoms	Main symptom	Visual acuity (LogMar)		Cataract surgery		Ornithine in plasma (µmol/L)
					Right eye	Left eye	Right eye	Left eye	
P1	F	10	6	Visual field constriction	0.2	0.1	No	No	916
P2*	M	16	6	Blurry vision	–	0.2	-	No	552
P3*	M	20	15	Blurry vision	0	0	No	No	583
P4	F	27	6	Nyctalopia	0.4	0.5	Yes	Yes	636
P5	M	47	20	Nyctalopia	0.9	0.7	Yes	No	48
P6	F	54	7	Blurry vision	1	1	Yes	Yes	353
P7	F	66	5	Nyctalopia	0.6	–	Yes	–	479

*Patients 2 and 3 are sibs

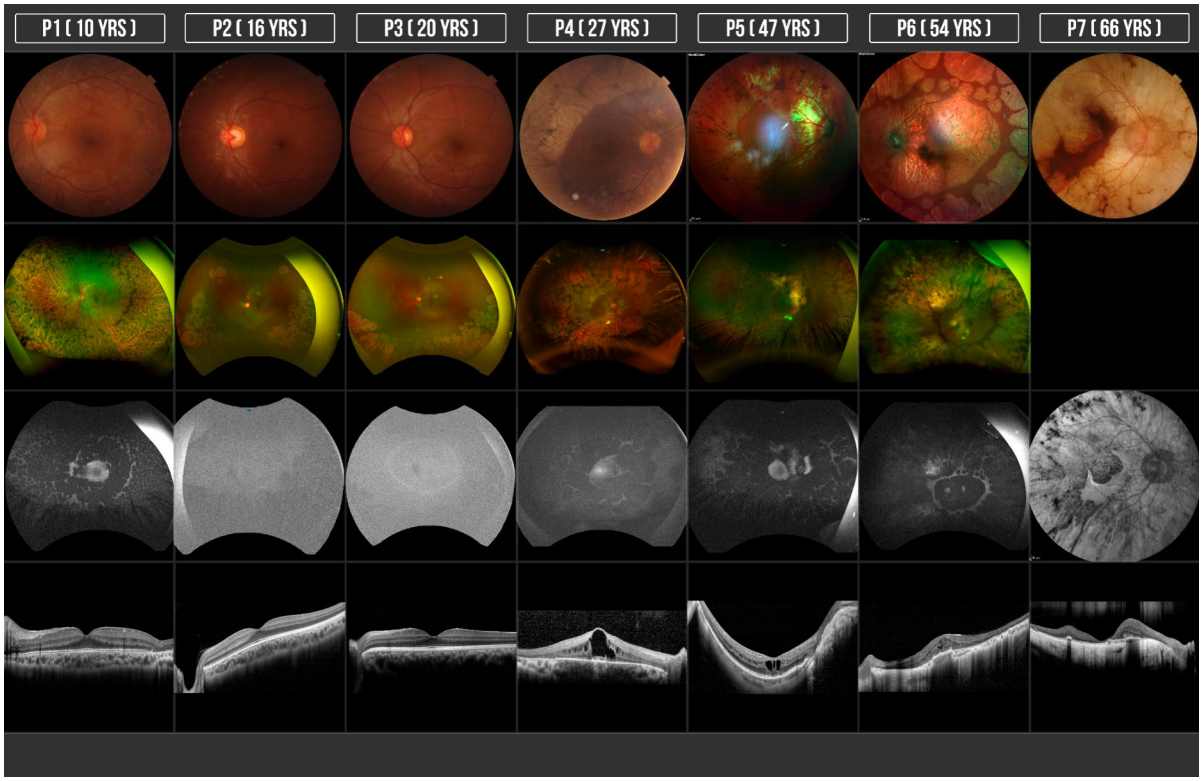

Fig. 1 Structural retinal evaluation: CFC, FAF and SD-OCT of patients with GA. Each column corresponds to the case number (patients 1 through 7) and patients are numbered according to age (youngest to oldest)

areas of hyperautofluorescence and also at the border of preserved retina in the macular area. P2 and P3 had an hyperautofluorescent ring outside the arcades separating the posterior retina with normal autofluorescence from hypoautofluorescence in the mid-periphery which did not correspond to the hypoautofluorescence of the patchy atrophic lesions in the far periphery (Fig. 1).

The structural features of the retina by SD-OCT evaluation demonstrated structural changes that were

concordant between eyes in all patients. In the areas of chorioretinal atrophy we found evident thinning of the retina predominantly the external layers with complete loss of photoreceptor inner segment outer segment junction IS/OS outer retinal as well as the interdigitation zone and external limiting membrane as well as evident choroidal thinning in the most advanced cases, outer retinal tubulations (ORT) were found in 58% (N = 7) of the eyes, cystoid macular edema (CME) was found in 50% (N = 6) of the eyes, 42% (N = 5) of the eyes had an epiretinal membrane (ERM), 17% (N = 2) of the eyes presented foveoschisis and a staphyloma. None of the eyes (N = 0) had focal choroidal excavation. Diffuse hyperreflective deposits were found in 100% (N = 12) of the eyes, most of them were found within the inner retina, mainly in the ganglion cell layer and the inner nuclear layer. These lesions were more evident in the two patients with CME, appearing as a band-shape zone in the ganglion cell layer closer to the inner plexiform layer (P4 and P5) (Fig. 1).

The GP test showed constricted visual fields in the isopters I4e and V4e in 100% (N = 12) of the eyes, P3 had an almost preserved V4e visual field in both eyes. P5, P6 and P7 who presented with a more advanced disease had a markedly constricted visual field with a small central visual field in the isopter V4e corresponding to the preserved retina in the fovea (Fig. 2).

The ffERG revealed a preserved photopic response in 17% (N = 2) of the eyes and a preserved scotopic response in 17% (N = 2) of the eyes. These nearly preserved responses were observed in two of the younger patients (P2 and P3).

Regarding the functional evaluation by the scotopic and photopic visual field test we could see that all of the patients presented some degree of deficit in the generalized response of rods and cones (more evident in the scotopic tests), finding a more reduced response in patients with more advanced disease, in P2 and P3 with a structural well-preserved macula we found an initial but significant mean deficit in the photopic evaluation (cone response) of 25 dB and 23 dB, respectively, which correlates with the subnormal findings in the electroretinogram test (Fig. 2).

Ornithine plasma levels results

Mean ornithine plasma levels were 509.5 µmol/L, (ranges between 48 and 916 µmol/L) this reflects an increase of up to more than 4 times its normal value (< 107 µmol/L). *Normal ranges vary between laboratories (22–115 µmol/L are considered normal). An

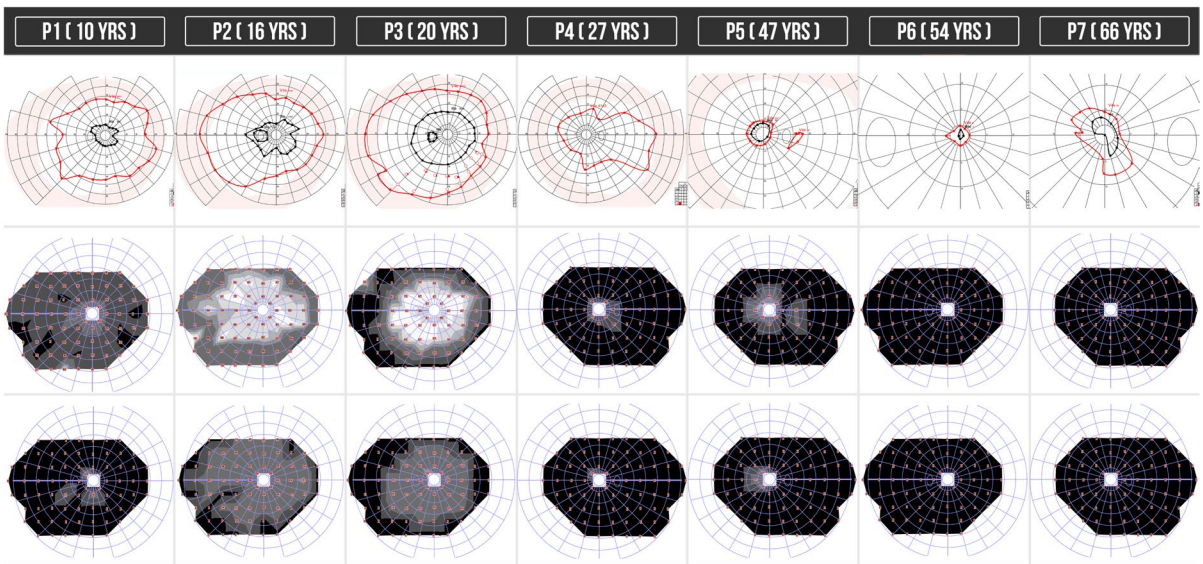

Fig. 2 Functional retinal evaluation: GP and CP of patients with GA. (ffERG not shown). First CP image reports the scotopic response and second CP image reports the photopic response. Each column corresponds to the case number (patients 1 through 7) and patients are numbered according to age (youngest to oldest)

interesting finding is that one patient has ornithine plasma levels within normal ranges (P5) (Table 1).

Molecular findings

Biallelic *OAT* mutations were identified in all seven patients, including a pair of affected sibs (P2 and P3). A total of three compound heterozygous and three homozygous phenotypes were identified in the 7 probands. Two novel *OAT* pathogenic variants were identified: c.796 C > T (p.Gln266*) and c.721_722dupCC (p.Asp242ArgfsTer6). The c.721_722dupCC variant was observed in 6 out of 12 pathogenic alleles in our cohort. The most commonly mutated *OAT* exon in our series was exon 6, harboring 9 out of all 12 disease-causing variants. All three cases of compound heterozygosity demonstrated to carry biallelic *OAT* mutations (trans configuration) by genetic screening of first-degree relatives (data not shown). Two previously identified mutations in *OAT*, c.991C > T(p.Arg331*) and c.677C > T (p.Ala226Val) were also recognized (Table 2).

Discussion

In the present study we described the anatomical and functional characteristics of seven patients 12 eyes with GA and performed a genetic analysis finding two novel pathogenic variants in the *OAT* analysis. Most of the features in the patients studied are consistent to previous reports such as age of first symptoms (second decade of life), being night blindness the most common reported symptom, also most of the phakic eyes had mild to high myopia and some degree of cataract with the need of intervention in 50% in the third decade of life [19, 22].The study by Peltola K et al. made in 35 finish patients reported the mean age of diagnosis at 18 years old, in our study the mean age was 34.2 years old which can translate to a late diagnosis. Central and peripheral nervous system abnormalities (muscular weakness, cognitive and hearing impairment) have been demonstrated in patients with GA by electrophysiological studies and these findings were also presented in some patients in our study [23, 24].

In the ophthalmological evaluation the mean BCVA of 0.5 logMar (Snellen 20/63) was worse than a similar case series of 7 patients with GA where a mean BCVA of 0.26 logMar was reported, this can be explained by the small number of patients studied in both series and the heterogeneity of disease severity. P2 16 years old was blind in one eye secondary to an untreated RRD, interestingly some cases have been reported related to this finding in pediatric patients with GA, with a novel *OAT* mutation confirmation in one case [25, 26], as pediatric RRD is uncommon even in myopic patients and GA has a very low prevalence worldwide it is important to evaluate if this complication might be another feature included in the clinical manifestations of GA.

Table 2 *OAT* pathogenic variants identified in Mexican GA patients. Two novel mutations were identified

Patient no	AGE	EXON	*OAT* variant	Zygosity	ACMG classification	References
P1	10	6	c.721_722dupCC; p.Asp242fsTer	Homozygous	Pathogenic	Novel
P2*	16	7	c.796 C > T; p.Gln266Ter	Compound heterozygote	Pathogenic	Novel
P3*	20	8	c.991C > T; p.Arg331Ter		Pathogenic	Kaczmarczyk et al. [35]
P4	27	6	c.721_722dupCC; p.Asp242ArgfsTer6	Compound heterozygote	Pathogenic	Novel
		7	c.796C > T; p.Gln266Ter		Pathogenic	Novel
P5	47	6	c.677C > T; p.Ala226Val	Homozygous	Pathogenic	Michaud et al. [36]
P6	54	6	c.721_722dupCC; p.Asp242ArgfsTer6	Compound heterozygote	Pathogenic	Novel
		8	c.991C > T; p.Arg331Ter		Pathogenic	Kaczmarczyk et al. [35]
P7	66	6	c.721_722dupCC; p.Asp242ArgfsTer6	Homozygous	Pathogenic	Novel

*Patients 2 and 3 are sibs

In the fundoscopy all eyes presented patches of chorioretinal atrophy in different amounts which tended to be more coalescent in the older patients except for P1 who was 10 years old and presented an advanced stage of the disease. Another clinical finding which needs a special mention was presented in P6 (54 years old), with a well-defined area of atrophy in the macula separated from the peripheral atrophic patches by an area of preserved retina at the equator in both eyes, this is different to what has been classically described where the atrophy starts in the mid-periphery and spreads to the macula and the ora serrata in the more advanced stages [7], as we don't have previous images of this patient we can only suggest but not proof a different pattern of atrophic changes in patients with GA that also start at one point of the disease in the posterior pole and not only in the periphery (Fig. 1). We found this pattern with similar characteristics by the fundus image of two patients presented by Sergouniotis et al. [19].

FAF findings were consistent to the atrophic area in all cases, with some degree of hyperautofluorescence in the border of the preserved retina as mentioned before [19]. With the use of ultra-wide field autofluorescence, P2 and P3 (siblings) showed an interesting pattern with an evident hyperautofluorescent ring outside the arcades that separated the retina with normal autofluorescence posteriorly from the mid-periphery retina anteriorly with subtle hypoautofluorescence that did not show the same degree of autofluorescence found in the chorioretinal patches in far-periphery retina (Fig. 1). By this finding in these two patients 3 eyes, we can suggest that an initial RPE damage that is not clinically visible can precede the chorioretinal patches of atrophy which might be evidenced by the FAF. Measuring this hyper-AF ring in patients with initial damage could work as an indicator of progression and to do a more accurate follow-up.

In our study, CME was found in 50% of the eyes studied which differs from the 100% of eyes described in Sergouniotis et al. case series [19]. This specific finding can be explained by a disruption of the outer blood-retinal barrier in the parafoveal area leading to a diffusion of fluid toward intraretinal spaces, maybe a lower incidence of this finding in our study could be attributed to the fact that the patients who did not present intraretinal cyst had a more preserved parafoveal area. CME in this type of retinal dystrophy has been treated with topical and oral carbonic anhydrase inhibitors, topical non-steroidal anti-inflammatory drugs, intravitreal or subtenon steroid injections, restriction of arginine in diet and vitamin B6 supplementation with widely range of response [27, 28]. Half of the patients presented ORT, the youngest patient (P1, 10 years old) with very advanced damage also presented this finding which demonstrates that the ORT can be considered as an indicator of the stage and marker of severity of the disease as mentioned before [29]. The intraretinal hyperreflective deposits found in the ganglion cell layer had been reported previously [19], usually found near the chorioretinal atrophy, in our study found these deposits along all the preserved macula, a gliotic process due to cell death has been hypothesized in a mice model study. In our study we found more accumulation of these deposits in the patients with chronic macular edema, where they seem to coalesce and form a band-shape zone.

Interestingly, the visual field constriction found in the GP mainly in isopter I4e and the generalized decrease in sensitivity response by the topographic functional evaluation of the cones and rods response separately with scotopic and photopic perimetry in all of eyes was more severe than the clinical changes visible on fundoscopy, making these two functional objective studies parts of the follow-up evaluation of patients with GA (Fig. 2).

Although it was not possible to make a correlation between the severity of retinal degeneration and ornithine levels as the measurements were done in a cross-sectional manner, we found a lower mean of elevated plasma ornithine levels of 586 µmol/L (excluding the patient with normal values) than reported in the finnish and japanese case series, 960 and 975 µmol/L respectively [19, 22], nevertheless the variability of the disease's severity was quite similar. The possible explanation for this finding could be related to the differences in diet between populations, but this must be properly studied. Furthermore, P5 (47 years old) with a homozygous *OAT* pathogenic variant had normal ornithine plasma levels at the time of the diagnosis, without any diet modification or treatment (Table 1). Previous studies have reported patients with normal ornithine levels and clinical findings corresponding to GA but with no genetic confirmation [30–34] naming these patients "GA-like phenotype".

To date, this is the first reported case of GA confirmed by genetic testing with normal ornithine levels. It is important to note that we didn't have the opportunity to repeat the ornithine level measurements in this patient. In such cases, it is recommended to perform the measurements at least three times to confirm the results. This supports the theory proposed by the authors mentioned before that there might be more than one pathophysiological mechanism within the metabolic pathways of ornithine and arginine, leading to an accumulation or a decrease of substrates that eventually produce chorioretinal degeneration. This should be evaluated in more studies in the future.

Pathogenic *OAT* variants were identified in all GA patients from this cohort. Interestingly, 50% of disease-causing mutations (6/12) corresponded to the novel c.721_722dupCC (p.Asp242ArgfsTer6) variant, which was observed homozygously in two cases and in compound heterozygosity in two additional patients. While additional haplotype studies will be needed, our preliminary data supports that the c.721_722dupCC variant could be a founder *OAT* mutation in Mexico. A second novel *OAT* variant, corresponding to c.796C > T (p.Gln266*), was identified in a single allele in this group of patients (Table 2).

Patients included in this study were referred to a specialist in metabolic nutrition to implement an arginine-restricted diet, ensuring careful consideration of nutraceutical components to prevent malnutrition-related disorders. This dietary intervention was meticulously designed to balance the reduction of arginine intake while providing all essential nutrients, thereby safeguarding against the potential risks of dietary insufficiencies. The collaboration with nutritional experts highlights the importance of a multidisciplinary approach in managing complex metabolic conditions.

In conclusion, the present study expands our knowledge of the clinical and genetic features of GA in the Mexican population. This study provides new information regarding functional and structural diagnosis to use in the future and evaluate if these tools can help us make a more accurate diagnosis on staging of the disease and a better follow-up to the patients under treatment. The most frequent mutations as well as the novel molecular findings in the Mexican population have important implications for the future genetic diagnosis of GA, allowing us to identify carriers of the disease and also study the genotype–phenotype correlation in larger studies in the future.

Clinical studies on retinal dystrophies are imperative for a deeper understanding of the disease's clinical course. Identifying the most precise clinical variables that measure disease progression is crucial, as these indicators are integral to the meticulous planning of gene therapy clinical trials aimed at slowing or halting disease advancement. Such trials depend heavily on accurate, reproducible clinical endpoints that not only reflect the true nature of the disease's progression but also offer measurable targets for therapeutic intervention.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish The authors affirm that human research participants provided informed consent for publication of the images in this manuscript.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki.

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