A review of treatment modalities in gyrate atrophy of the choroid and retina (GACR)

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Review article

A review of treatment modalities in gyrate atrophy of the choroid and retina (GACR)

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ABSTRACT

Gyrate atrophy of the choroid and retina (GACR) is a rare inborn error of amino acid metabolism caused by bi-allelic variations in *OAT*. GACR is characterised by vision decline in early life eventually leading to complete blindness, and high plasma ornithine levels. There is no curative treatment for GACR, although several therapeutic modalities aim to slow progression of the disease by targeting different steps within the ornithine pathway. No international treatment protocol is available. We systematically collected all international literature on therapeutic interventions in GACR to provide an overview of published treatment effects.

Methods: Following the PRISMA guidelines, we conducted a systematic review of the English literature until December 22nd 2020. PubMed and Embase databases were searched for studies related to therapeutic interventions in patients with GACR.

Results: A total of 33 studies ($n = 107$ patients) met the inclusion criteria. Most studies were designed as case reports ($n = 27$) or case series ($n = 4$). No randomised controlled trials or large cohort studies were found. Treatments applied were protein-restricted diets, pyridoxine supplementation, creatine or creatine precursor supplementation, L-lysine supplementation, and proline supplementation. Protein-restricted diets lowered ornithine levels ranging from 16.0–91.2%. Pyridoxine responsiveness was reported in 30% of included mutations. Lysine supplementation decreased ornithine levels with 21–34%. Quality assessment showed low to moderate quality of the articles.

Conclusions: Based primarily on case reports ornithine levels can be reduced by using a protein restricted diet, pyridoxine supplementation (variation-dependent) and/or lysine supplementation. The lack of pre-defined clinical outcome measures and structural follow-up in all included studies impeded conclusions on clinical effectiveness. Future research should be aimed at 1) Unravelling the OAT biochemical pathway to identify other possible pathologic metabolites besides ornithine, 2) Pre-defining GACR specific clinical outcome measures, and 3) Establishing an international historical cohort.

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1. Introduction

Gyrate atrophy of the choroid and retina (GACR) (OMIM #258870) is a rare autosomal recessive disorder of amino acid metabolism. The disease is clinically characterised by a progressive vision loss in the early decades of life. First symptoms are often night blindness and constriction of visual fields due to peripheral chorioretinal degeneration, eventually leading to marked central vision loss and complete blindness when the macula is also affected. Although the precise incidence if GACR is not known it is estimated to be around 1:1,500,000 live births, with the highest incidence found in Finland (1:50,000) [1].

GACR is caused by bi-allelic pathogenic variants in the *OAT* gene, encoding the mitochondrial enzyme ornithine-δ-aminotransferase (OAT). OAT plays a central role in ornithine metabolism by catalysing the reversible reaction that converts ornithine and 2-oxoglutarate (α-KG) into glutamate- 5-semialdehyde (GSA) and glutamate (Glu). Glutamate 5-semialdehyde is in a chemical, non-enzymatic equilibrium with Δ^1-pyrroline-5-carboxylate (P5C), a precursor of proline and glutamate [2]. OAT is a vitamin B6-dependent enzyme which requires pyridoxal phosphate to catalyse its enzymatic function [3] (Fig. 1).

Pathogenic bi-allelic variants in *OAT* result in absent or decreased enzyme activity and thus impair the aforementioned metabolic process. As a result, markedly elevated ornithine levels can be observed in plasma and other bodily fluids of patients with GACR. Unfortunately, GACR is often diagnosed at a late stage of the disease, when the retina is already severely affected and vision is impaired. This is due to the rarity of the disease in combination with the great phenotypic heterogeneity among patients, even between siblings and groups with the same sex, age, or pathogenic variant [4].

The disease-causing mechanism of GACR is unclear and as of yet, there is no curative treatment. It has been suggested that the high levels of ornithine are toxic to the delicate structures of the retina and that early interventions that lower ornithine levels may prevent or delay disease progression [5]. Although GACR is mostly known for its ophthalmic problems a wider range of symptoms, such as neurological and skeletal muscle symptoms, have been reported [6].

However, due to the lack of high quality natural history studies, the full clinical spectrum of GACR is still not fully known. Typical eye findings include myopia, night blindness, and/or progressive vision loss. Another rather common manifestation includes cystoid macular oedema (CME). Chorioretinal degeneration leads to a progressive constriction of the peripheral visual fields and a loss of visual acuity (Fig. 2). Additionally, patients often develop (bilateral) cataracts [7,8]. In several patients, cognitive changes and structural and functional brain abnormalities on MRI and EEG have been reported, which might be related to secondary creatine deficiency as a result of hyperornithinaemia [6,9,10]. Skeletal muscle weakness and polyneuropathy have also been reported [11].

Currently applied therapeutic interventions are targeted at several steps within the ornithine pathway. These interventions are mainly nutritional, *i.e.* life-long dietary restriction of natural protein which thus includes arginine with the aim to reduce ornithine levels, in combination with other therapeutic measures including supplementation of pyridoxine, lysine, and creatine. Previously published manuscripts on therapeutic interventions in GACR are scarce and, due to the rarity of the disease, are mainly case reports or small case series with limited significance. Furthermore, no systemic review of the literature documenting all treatment modalities used in GACR has been published. The aim of this study was therefore to gain knowledge about currently applied treatment modalities for GACR and to provide an overview of published treatment effects.

In order to do so we performed a systematic review of all published international literature reporting therapeutic interventions in GACR patients.

2. Methods

2.1. Search strategy and eligibility criteria

A PRISMA-guided systematic PubMed search strategy was initiated to identify the studies of interest (last searched on December 22nd, 2020; Fig. 3) [12]. We also performed a hand search of bibliographies of included studies. The following MeSH terms were used: *OAT deficiency; Gyrate Atrophy; Therapy; Drug Therapy; Diet Therapy.* A search of PubMed as well as Embase was performed and results were restricted to manuscripts published in peer reviewed journals and performed in humans. Five coauthors (MJNB, BMB, MMB, EAF and CT) independently reviewed the 102 articles that emerged from the searches for potential

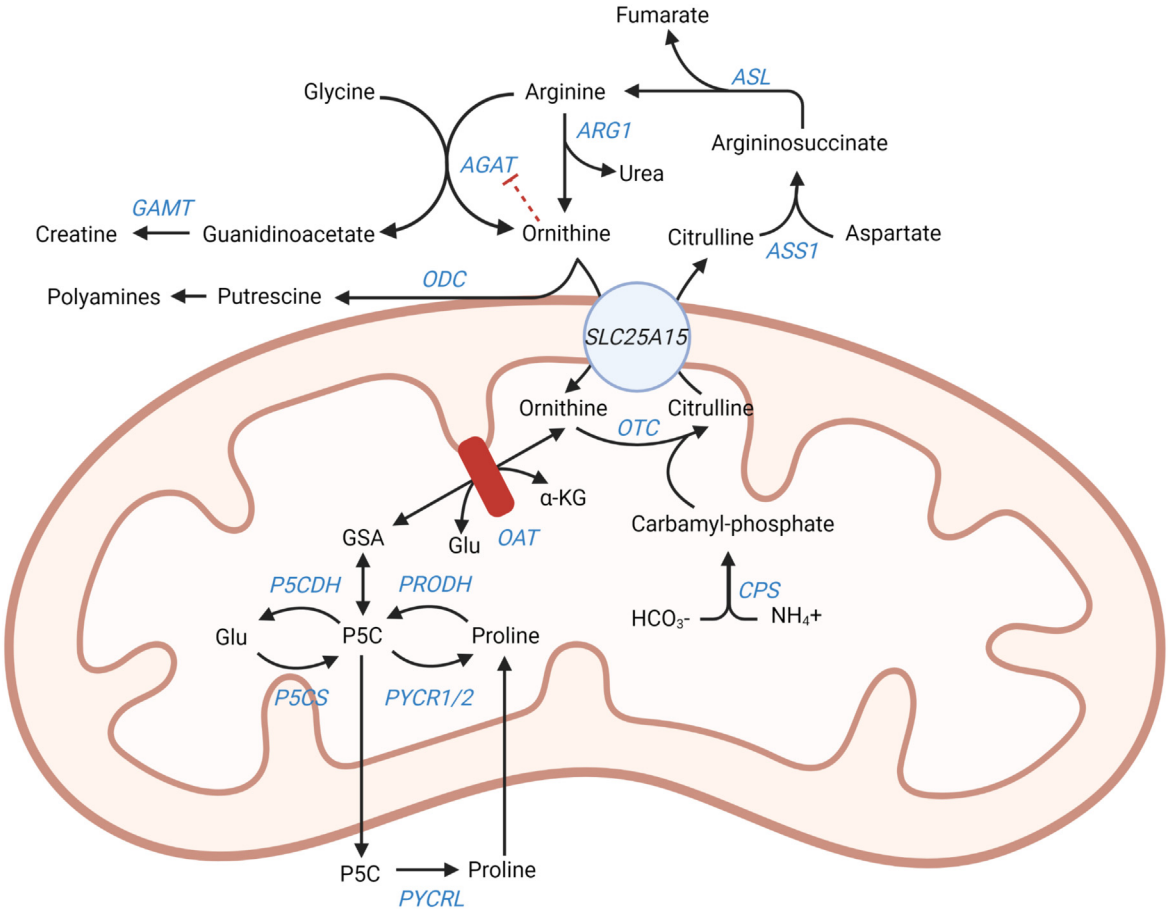

Fig. 1. Metabolic pathways involving ornithine.
Glu: glutamate. GSA: glutamate-5-semialdehyde. P5C: Δ1-pyrroline-5-carboxylate. OAT: ornithine aminotransferase. PRODH: proline dehydrogenase. P5CDH: Δ1-pyrroline-carboxylate dehydrogenase. P5CS: Δ1-pyrroline-carboxylate synthase. PYCR1/2: Δ1-pyrroline-carboxylate reductase ½. PYCRL: Δ1-pyrroline-carboxylate reductase-like. CPS: carbamoyl phosphate synthase. ASS1: argininosuccinate synthetase 1. ASL: argininosuccinate lyase. ARG1: arginase. OTC: ornithine transcarbamylase. AGAT: arginine:glycine amidinotransferase. GAMT: guanidinoacetate methyltransferase. ODC: ornithine decarboxylase.
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inclusion in review. Studies published in any language other than English were excluded as were articles in abstract form only. Other exclusion criteria were: lack of diagnostic confirmation according to the criteria proposed in Table 1; *in vitro* studies; animal or model organism studies.

2.2. Data extraction and synthesis

Data were extracted independently by five authors (MJNB, BMB, MMB, EAF, and CT) using a standardised form. Discrepancies were resolved by consensus. Terms used in different studies were standardised whenever possible. Pyridoxine responsiveness as described in table 3 was based on the definition the authors of the respective papers assigned to it. When DNA variant notations were not provided, these were deduced based on provided amino acid substitutions, where possible.

2.3. Data quality

All articles included were graded based on the Levels of Evidence for Therapeutic Studies (http://www.cebm.net). This grading system ranks articles based on how valuable the evidence provided is, with 1 being most valuable (systematic review with randomised controls) and 5 the least valuable (expert opinion). Additionally, the quality of articles was assessed. Case studies and case series were assessed according to the tool described by Murad et al. (2017) [13]. Other studies were assessed according to the Study Quality Assessment Tools described by the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). The articles were graded and assessed by four coauthors (BMB, MJNB, CT, MMB). Discrepancies were resolved by consensus.

3. Results

3.1. Search and quality of evidence

The literature search yielded 102 unique records. 49 records were excluded after screening title and abstract, leaving 53 articles for full-text reading. Of these 53 articles, 21 were excluded. The reasons for exclusion of these 21 articles were lack of diagnostic confirmation of GACR ($n = 2$); no treatment administered ($n = 5$); no pre-treatment measurements ($n = 3$); duplicate reports of patients also described in a more recent paper ($n = 5$); treatment of complications only ($n = 6$). One article was added after revision. Finally, 27 case reports, 4 case series, one long-term observational study and one cohort study were included in the analysis.

All included articles were rated on their quality and the validity of their evidence. Most articles were case reports corresponding with a level of evidence of most articles of 4 out of 5. The median score of the quality of articles was 4/8 (range 0/8–8/8). Scores are summarised in Table 2.

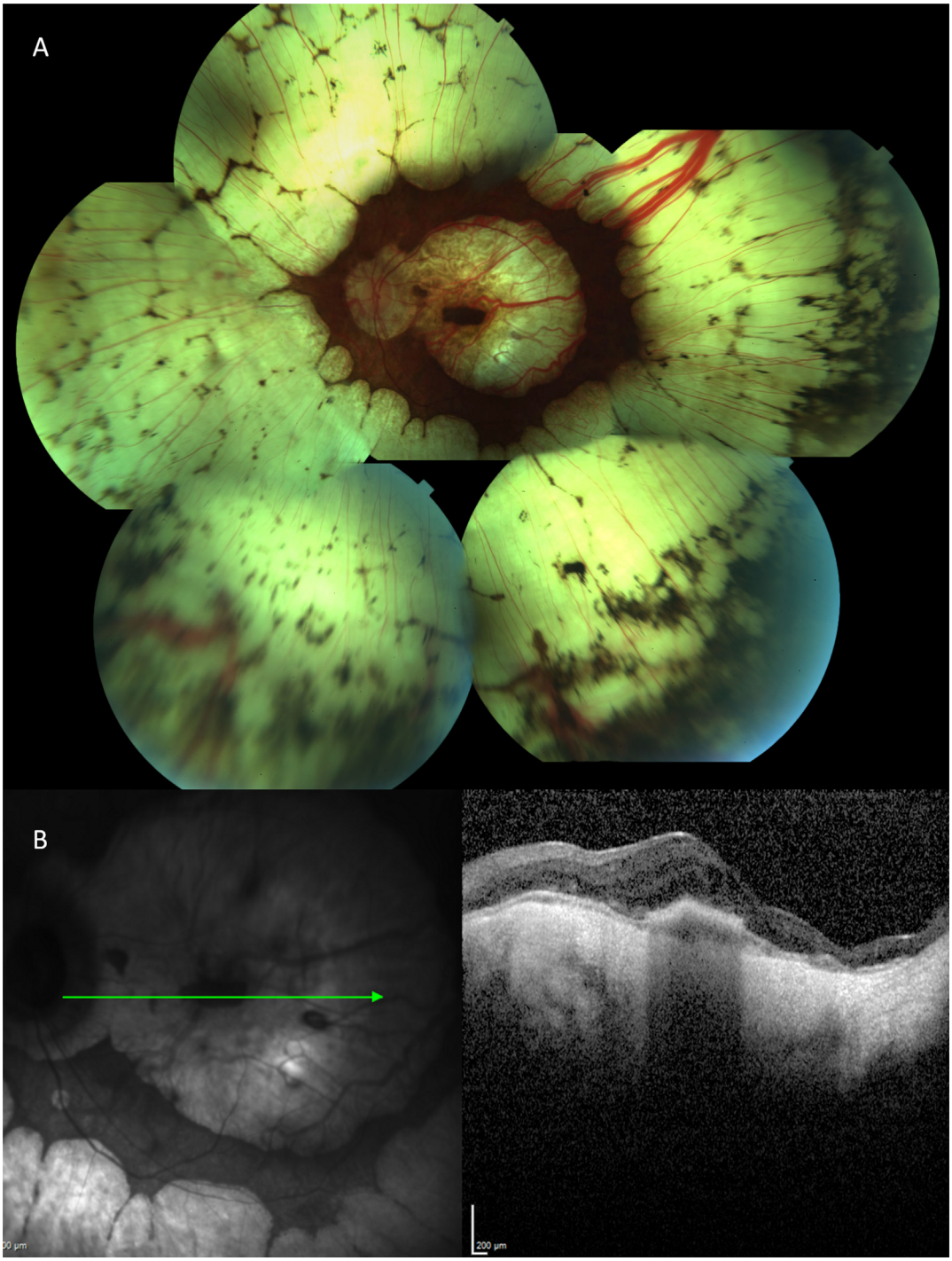

Fig. 2. A. Colour fundus photograph of a 55-year-old patient with advanced gyrate atrophy, showing round patches of profound peripheral chorioretinal atrophy. The macula also is profoundly atrophic, except for a small central island of relative sparing of the fovea, explaining the relatively preserved Snellen visual acuity of 20/30. B. Optical coherence tomography scan through the macula, showing relative structural sparing in the foveal area, some mild cystoid macular oedema, and profound chorioretinal thinning and atrophy in the surrounding area.

3.2. Clinical characteristics

In total, 107 individual patients were included, reported in 33 studies (Table 2) [3,14–45]. 43 were male (40%), 51 (48%) were female, and of 13 patients (12%) sex was not reported. Diagnosis of GACR was made based on plasma ornithine levels and the characteristic funduscopic lesions in all patients. Analysis of enzymatic function was performed in 29 patients (30%). Mutation analysis was performed in 41 patients (40%).

The median age of the included patients was 17 years (range 2–67). Kaiser-Kupfer et al. (2004) and Peltola et al. (2000) did not provide individual ages, instead they provided ranges [18,27]. The median age at diagnosis was 13 years (range 11 months - 67 years) and was provided for 47 patients. Nyctalopia (32%, $n = 34$) and progressive vision loss (32%, $n = 34$) were the most commonly described primary presentations. Other symptoms included central scotoma, sudden vision loss, photophobia, restriction of peripheral visual fields, astigmatism, and

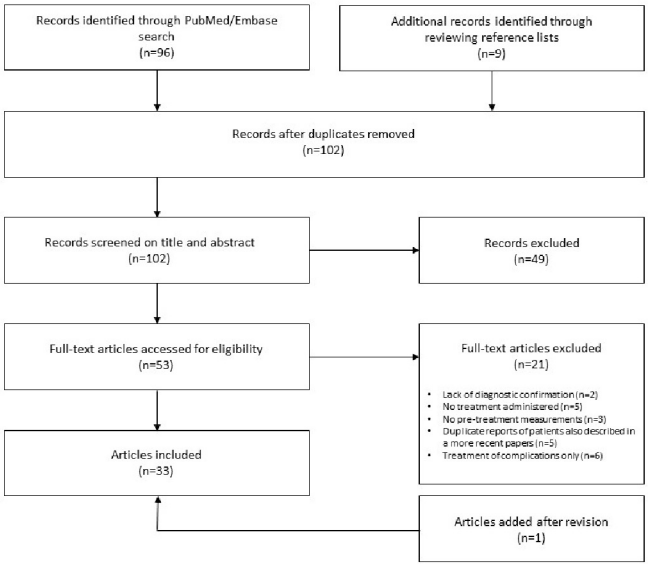

Fig. 3. PRISMA flow diagram depicting the process of inclusion of articles in this systematic review.

cataract. Nine out of 97 patients had neurological symptoms, ranging from mild muscle weakness to neurodevelopmental delay or epilepsy [14,16,17,28,29,31,33,37]. Rigante et al. (2010) presented a 4 year old patient with neurodevelopmental delay and severely reduced vision as primary presentation. She was diagnosed with GACR, however, neurological imaging also showed porencephaly, making it unclear which part of the visual impairment can be attributed to porencephaly and which to GACR [28].

In 56 patients, the initial clinical or biochemical presentation was not reported. Mean plasma ornithine at initial presentation was 823.0 μmol/L (range 370–1480 μmol/L), normal values for adults being 27–98 μmol/L.

3.3. Genotypes

In 68 GACR patients molecular analysis was performed (see table 3). Bi-allelic pathogenic variants were provided for 36 patients. Twelve patients were homozygous for variants in *OAT*, whereas the remaining patients were compound heterozygous. 5 patients described by Peltola et al. (2000) were said to have a "typical Finnish mutation" without further elaboration [27]. For 27 patients described by Kaiser-Kupfer et al., mutation analysis was only briefly mentioned in the discussion [18]. Thirty-two different pathogenic variants were reported, including 19 missense mutations [3,15,17,21,22,24,25,29,36,40,45], three nonsense mutations [20,24,26], five frameshift mutations [15,17,20,45], one deletion [37], one splicing defect [15], one unknown variant causing exon 5 skipping [22], one intronic variant with an unclear effect [21], and one translation initiation defect [17].

Of the 68 patients in whom molecular analysis was performed, 12 were reported as being pyridoxine-responsive [3,15,22,24,40,45]. These patients had missense, frameshift and nonsense variants, as well as a splicing defect and exon 5 skipping. In six patients, pyridoxine-responsiveness was unclear due to concurrent start of several treatment modalities [21,26,37,45]. Six patients were classified as pyridoxine-unresponsive by the authors [17,20,25,29,45]. In 17 patients, responsiveness was not tested or reported [17,20,27,36,45].

Table 1
Inclusion criteria for the diagnosis of gyrate atrophy of the choroid and retina.

Typical chorioretinal degeneration on fundus examination
Hyperornithinaemia (ornithine serum levels more than twice the reference value)
Enzymatic analysis of residual OAT function in fibroblasts
Mutation analysis of *OAT*

In the absence of mutation analysis of OAT in combination with enzymatic analysis, criteria in bold were used as minimal requirements for patients included in this review.

3.4. Treatment

Treatment was administered to 85 patients. The remaining 22 patients functioned as untreated controls. Seven patients had compliance issues or were lost to follow-up. The median duration of reported treatment was 1.25 years (range 7 days-26 years). The median duration of treatment with a natural protein-restricted diet was 1.25 years (range 1 month to 26 years), whereas patients treated with pyridoxine had a median treatment duration of 1.25 years (range 1 month to 7.1 years). Patients treated with pyridoxine monotherapy had a median treatment duration of 1.25 years (range 1 month to 18 years).

3.4.1. Outcome measures

The selected articles reported different biochemical and clinical outcome measures to assess treatment effect. Most papers provided plasma ornithine levels in order to monitor short-term biochemical treatment effect and compliance. Clinical response was measured using varying structural and functional ophthalmic parameters which are summarised in Tables 5 and 6. Best corrected visual acuity and funduscopic imaging were usually provided as ophthalmic outcome parameters. 16 out of 32 papers reported no side-effects as reported by patients [3,19,21,24,27,28,31–33,35,38,41–44]. One paper reported a symptomatic hyperammonaemia as a result of an acquired urea cycle disorder caused by severe arginine deficiency [23]. Other papers did not evaluate side-effects or safety of treatment. A minimal clinical important difference (MCID) to evaluate treatment effect was never pre-defined.

3.4.2. Protein-restricted diet

Of the 85 treated patients, 64 patients (75%) were prescribed a natural protein- or arginine-restricted diet with the goal of reducing ornithine levels (Table 4) [14,15,17–21,23,25,26,28,29,31–39,41,43,45]. In 9 papers, a dietary natural protein content in grams per kilograms per day was provided, with a mean protein content of 0.6 g/kg/day [14,15,17,23,26,29,33,37,39]. In five papers, a total protein content in grams per day was provided (range 10–35 g/day) [19,31,32,35,43]. In eight papers, the addition of essential amino acids (EEA) to the protein-restricted diet was mentioned [14,17,19,23,26,31,34,35].

Of these 64 patients, 50% received additional therapy, either pyridoxine supplementation or supplementation of creatine, lysine, or creatine precursors [15,21,23,25,26,28,31,32,34,35,37–39,43,45]. Median follow-up time was 1.25 years (range 1 month to 26 years). In 28 of 64 patients a decrease in plasma ornithine was witnessed (mean 911 to 398 μmol/L) [14,15,17,20,21,23,26,28,29,31,33–35,37,39,41,43]. In 15 out of 64 patients, a follow-up plasma ornithine level was not provided [25,32,36,38,45]. Of 18 patients no ornithine values were provided [18,19]. In three papers, the authors presented two patients on a protein-restricted diet but only provided ornithine values for one [23,26,39]. Of the 28 patients with a decrease in ornithine, 15 (54%) received additional therapy [14,15,17,21,25,26,28,31,34,35,37,39,43].

Fig. 4 shows the decrease in plasma ornithine levels in patients with a protein-restricted diet and patients with combination treatment. All degrees of protein restriction had an effect on ornithine levels varying from a decrease of 16.0% to 91.2% in patients on monotherapy (natural protein-restricted diet) and 4.5% to 78.3% in patients that received combination therapy. In 11 patients on a protein-restricted diet, serial best corrected visual acuity (BCVA) measurements were provided [15,17,19,20,23,25,36,41,43]. In 5 of these patients, an improvement in BCVA after initiation of treatment was reported with a treatment duration of 2 months to 7 years [15,17,19,36]. However, the patient described by Çavdarli et al. (2020) did not adhere to diet and

Table 2
Level of evidence of all included studies and demographic data.

Reference	Type of article	Level of evidence	Quality assessment	No. of patients	Patient sex (*n*)	Patient age (y, m)
H. D. Bakker et al. (1991)	Case report	4	5.5/8[a]	1	Female	12
M.I. Kaiser-Kupfer et al. (1991)	Case series	4	5/8[a]	12	Male (6), female (6)	Range (8y6m-61)
A. Javadzadeh et al. (2007)	Case report	4	4/8[a]	1	Male	28
R. Christopher et al. (1999)	Case report	4	2/8[a]	2	Male (2)	40, 47
X. Cui et al. (2018)	Case report	4	5/8[a]	1	Female	67
G. Casalino et al. (2018)	Case report	4	4/8[a]	1	Male	8
D. Heller et al. (2017)	Case report	4	7/8[a]	2	Male (1), female (1)	16, 28
M. I. Kaiser-Kupfer et al. (2004)	Long-term observational study	4	6/10[b]	27	Male (11), female (16)	Range(10–74)
F.Tanzer et al. (2011)	Case report	5	3.5/8[a]	1	Female	8
Y. Mashima et al. (1999)	Case series	4	0/8[a]	4	Female (4)	Not reported
M. Michel et al. (2015)	Case report	4	3.5/8[a]	2	Male (1), female (1)	5, 16
Y.R. Sharma et al. (2006)	Case report	4	2/8[a]	1	Male	28
R. Santinelli et al. (2004)	Case report	4	5/8[a]	1	Female	30
M. Zekušić et al. (2017)	Case report	4	6/8 [a]	1	Female	10
S. Katagiri et al. (2014)	Case report	4	6/8[a]	2	Male (2)	2, 6
D. Rigante et al. (2010)	Case report	4	1/8[a]	1	Female	4
K. Peltola et al. (2000)	Case series	4	6/8[a]	5	Male (5)	Range (16–45)
J. Michaud et al. (1995)	Case report	4	8/8[a]	1	Female	7
Y. Ohkubo et al. (2005)	Case report	4	4/8 [a]	1	Male	37
S. Doguizi et al. (2015)	Case report	4	2/8[a]	1	Male	9
S. Hayasaka et al. (1985)	Case reports	4	4.5/8[a]	5	Male (4), female (1)	Range (5–32)
R. Feldman et al. (1989)	Case report	4	3.5/8[a]	1	Female	26
S.P. Shrestha et al. (2010)	Case report	4	3.5/8[a]	2	Female (2)	15, 18
S.J. Kim et al. (2013)	Case report	4	2.5/8[a]	2	Female (2)	19
D. Valle et al. (1980)	Case report	4	6.5/8[a]	1	Female	35
M.I. Kaiser-Kupfer (1980)	Case report	4	4/8[a]	1	Female	36
I. Zhioua Braham et al. (2018)	Case report	4	1/8[a]	2	Female (2)	26, 30
V.E. Shih et al. (1981)	Cohort study	4	5/8[a]	5	Female (3), male (2)	Range (13−30)
O.N. Elpeleg et al. (2001)	Case report	4	4/8[a]	3	NR	Range (13–19)
R.R. McInnes et al. (1980)	Case report	4	4/8[a]	2	Male (2)	17, 30
G. Stoppoloni et al. (1982)	Case report	4	4/8[a]	1	Female	3
C. Çavdarli et al. (2019)	Case report	4	5/8[a]	1	Male	26
M. Doimo *et al* (2013)	Case series	4		10	NR	Range (3–40)

Levels of evidence (source www.cebm.net): 1a. Systematic review of randomised controlled trials (RCTs), 1b. Individual RCT, 1c. All or none. 2a. Systematic review of cohort studies, 2b. Individual cohort study, 2c. "Outcomes" research, 3. Systematic review of case-control studies, 4.Individual case-control study or case-series/report, 4/5. Single case report, 5. Expert opinion without critical appraisal.

[a] Study Quality Assessment Tool for case reports as adapted from Murad et al[1]

[b] Study Quality Assessment Tools for case series, cohort studies, and observational studies (source: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools):

concurrently received symptomatic local treatment for macular oedema, making it unlikely that this improve in BCVA is related to the protein-restricted diet [36]. The two patients described by Heller et al. (2017) reported improvement in BCVA after 4 months of a protein-restricted diet and pyridoxine supplementation. The authors attribute BCVA improvement to regression of cystoid macular oedema [15]. Other ophthalmic examination data are summarised in Tables 5 and 6.

Compliance was usually monitored *via* self-reporting and the trend of plasma ornithine levels. Of the 58 patients on a protein-restricted diet, eight patients could not adhere to dietary restrictions (age range 8–60 years).

Kaiser-Kupfer et al. (1991) reported a possible beneficial effect of early initiation of an arginine-restricted diet in two sibling pairs, where the younger sibling that started earlier with a protein-restricted diet showed less severe chorioretinal atrophy compared to the older sibling at a similar age [17]. Two of these pairs were followed up until 2002, which expanded the results of their study from 1991, showing that the younger sibling had experienced slower disease progression [50]. A long-term follow-up of 14 years of 27 GACR patients, of which 10 did not adhere to an arginine-restricted diet, showed that progression of disease as measured through electroretinography was slower in patients that adhered to the diet, compared to patients that did not [18].

Doimo et al. (2013) only briefly mentioned dietary treatment, therefore it is unclear to which extent and how long patients were treated [45].

3.4.3. Pyridoxine supplementation

42 patients received therapeutic pyridoxine, a precursor of pyridoxal phosphate which is a cofactor to OAT, with the aim of stimulating residual enzyme activity (Table 4) [3,14–17,21,22,24–26,28,30–32,37–40,43–45]. The mean dosage was 405 mg/day (range 100–1000 mg/day). Of these 42 patients, 33 patients (79%) received additional therapy [14,15,17,21,22,25,26,28,31,32,34,37–39,43–45]. 31 patients received a protein-restricted diet next to their treatment with pyridoxine, of which four received triple therapy with addition of creatine ($n = 2$) [26], lysine ($n = 1$) [37], or α-aminoisobutyric acid (AIB) ($n = 1$) [43]. Two patients received proline supplementation as an addition to their treatment with pyridoxine [44]. Nine patients divided over seven articles received pyridoxine monotherapy. These patients showed a decrease in plasma ornithine ranging from 19.2% to 68.8% [3,16,22,24,30,40,44]. In seven patients, no clinical features were described. Michaud et al. (1995) showed that after two years on pyridoxine, the funduscopic lesions of their patient were unchanged, although her BCVA had fallen [24]. One patient described by Hayasaka et al. (1985) showed a decrease of plasma ornithine without an effect on clinical parameters [44]. No pyridoxine-unresponsive patients on monotherapy were reported. Fig. 5 shows the decrease in ornithine levels of the aforementioned nine patients responsive to pyridoxine on pyridoxine monotherapy.

Of 12 out of the 32 aforementioned patients, serial BCVA measurements were provided [15,21,24,25,30,40,43,44]. In four patients, an improvement in BCVA could be seen 4 months to 5 years after initiation of treatment [15,44]. However, all these patients received additional therapy, either proline [44] or a protein-restricted diet [15]. Other ophthalmic investigations are summarised in Tables 5 and 6.

Several *OAT* variants are reported as pyridoxine responsive (see table 3). Mashima et al. (1999) presented four patients with a p.

Table 3
Patient characteristics.

Reference	Primary presentation	Other symptoms or diagnoses	Method of diagnosis	*OAT* variants Allele 1	*OAT* variants Allele 2	Pyridoxine responsive[a]	Plasma ornithine (μmol/L) at primary presentation
H. D. Bakker et al. (1991)	PVL, nyctalopia, photophobia	Epilepsy	AA, fundoscopy	NR	NR	No	1150
M.I. Kaiser-Kupfer et al. (1991)	BCE (n = 2), myopia, nyctalopia, CPVF, PVL	Keratosis pilaris atrophicans Diminished muscle mass	AA, EA, MA, fundoscopy	c.278G > T (p.(Cys93Phe)) c.163 T > C (p.(Tyr55His)) c.215-3048del (p.(His53fs (−1))) c.1031del (p.(Asn334fs (−1))) c.1A > C (translation initiation defect)	c.722C > T (p.(Phe241Leu)) ? c.215-3048del (p.(His53fs (−1))) c.1031del (p.(Asn334fs (−1))) c.1A > C (translation initiation defect)	No	764–1180
A. Javadzadeh et al. (2007)	PVL, nyctalopia	Muscle weakness	AA, fundoscopy	NR	NR	Yes	629
R. Christopher et al. (1999)	Myopia, PVL, CPVF, nyctalopia, BCE	NR	AA, fundoscopy	NR	NR	Yes	1008
X. Cui et al. (2018)	PVL, CPVF, nyctalopia, BCE	NR	AA, MA, fundoscopy	c.473A > C (p.(Tyr158Ser))	c.473A > C (p.(Tyr158Ser))	Yes	586
G. Casalino et al. (2018)	Difficulty reading	Failure to thrive	AA, MA, fundoscopy	c.1307 T > A (p.(Ile436Asn))	p.1307 T > A (p.(Ile436Asn))	No	528
D. Heller et al. (2017)	1: Nyctalopia, VI 2: PVL	NR	AA, MA	c.159delC (p.(His53Glnfs7*)) 2: c.800C > T (p.(Thr267Ile))	c.159delC (p.(His53Glnfs7*)) c.900 + 1G > A (splicing defect)	Unclear	697 879
M. I. Kaiser-Kupfer et al. (2004)	NR	NR	NR	NR	NR	NR	NR
F. Tanzer et al. (2011)	PVL, nyctalopia	NR	AA, fundoscopy	NR	NR	Yes	955
Y. Mashima et al. (1999)	NR	NR	AA, EA, MA, fundoscopy	c.952G > A (p.(Glu318Lys)) c.952G > A (p.(Glu318Lys)) c.952G > A (p.(Glu318Lys))	c.952G > A (p.(Glu318Lys)) c.521-2A > G (exon 5 skipping) ? (?)	Yes	NR
M. Michel et al. (2015)	Myopia, astigmatism	Short stature	AA, MA, fundoscopy	c.498C > A (p.(Thr166*))	c.498C > A (p.(Thr166*))	Unclear	877
Y.R. Sharma et al. (2006)	CPVF, central scotoma	NR	AA, fundoscopy	NR	NR	Yes	780
R. Santinelli et al. (2004)	NR	Delayed psychomotor and language development, speech defects, hyperactivity, distractibility, short attention span	AA, EA, MA, fundoscopy	c.271G > A (p.(Gly91Arg))	c.271G > A (p.(Gly91Arg))	No	1189 ± 105
M. Zekušić et al. (2017)	PVL, strabismus	Attention deficit	AA, MA, fundoscopy	c.868_870delCTT (p.(Leu290del))	c.868_870delCTT (p.(Leu290del))	Unclear	1039
S. Katagiri et al. (2014)	Nyctalopia	NR	AA, EA, MA, fundoscopy	c.504_505delAA (p.(Lys169Aspfs*11))	c.1276C > T (p.(Arg426*))	1: No 2: NR	1041 952
D. Rigante et al. (2010)	VI, nystagmus, esotropia	Neurodevelopmental delay	AA, fundoscopy, MRI	NR	NR	No	536
K. Peltola et al. (2000)	NR	NR	AA, MA, fundoscopy	“typical Finnish mutation”	?	NR	NR
J. Michaud et al. (1995)	VI	NR	AA, EA, MA, fundoscopy	c.677C > T (p.(Ala226Val))	c.1192C > T (p.(Arg398*))	Yes	652
Y. Ohkubo et al. (2005)	PVL	NR	AA, EA, MA, fundoscopy	c.710G > A (p.(Gly237Asp))	c.710G > A (p.(Gly237Asp))	Yes	1140
S. Doguizi et al. (2015)	Low visual acuity	NR	AA, fundoscopy	NR	NR	NA	622
S. Hayasaka et al. (1985)	NR	NR	AA, fundoscopy	NR	NR	1, 4, 5: Unknown 2: No	739 980

						3: Yes	524 984 853
R. Feldman et al. (1989)	PVL	NR	AA, fundoscopy	NR	NR	NR	818
S.P. Shrestha et al. (2010)	Frequent change of glasses	Petit mal epilepsy	AA, fundoscopy	NR	NR	Yes	741 462
S.J. Kim et al. (2013)	PVL, nyctalopia	NR	AA, MA, fundoscopy	c.425G > A (p.(Gly142Glu))	c.199 + 11_199dupAATTAA (?)	Unclear	783 831
D. Valle et al. (1980)	PVL, nyctalopia	NR	AA, EA, fundoscopy	NR	NR	No	964
M.I. Kaiser-Kupfer (1980)	NR	NR	AA, fundoscopy	NR	NR	No	964
I. Zhioua Braham et al. (2018)	PVL, pseudophakia	NR	AA, fundoscopy	NR	NR	Unclear	723
V.E. Shih et al. (1981)	NR	1: Muscle weakness 2: Minor motor seizures	AA, EA, fundoscopy	NR	NR	1–4: no 5: yes	76–1106
O.N. Elpeleg et al. (2001)	NR	NR	NR	NR	NR	No	662–1040
R.R. McInnes et al. (1980)	1: Myopia, BCE 2: PVL, nyctalopia	1: Elevated intraocular pressure	AA, EA, fundoscopy	NR	NR	No	750–1000
G. Stoppoloni et al. (1982)	NR	Mild developmental delay	AA, EA, fundoscopy	NR	NR	*In vitro* no, *in vivo* unclear	744.9
C. Çavdarli et al. (2019)	PVL	NR	AA, MA, fundoscopy	c.1253 T > C (p.(Leu418Pro))	c.1253 T > C (p.(Leu418Pro))	NR	379
M. Doimo et al. (2013)	PVL, nyctalopia	NR	AA, MA	c.994G > A (p.(Val332Met)) c.994G > A (p.(Val332Met)) c.152G > A (p.(Gly51Asp)) c.152G > A (p.(Gly51Asp)) c.991C > T (p.(Arg331*)) c.311A > G (p.(Gln104Arg)) c.1181G > A (p.(Cys394Tyr)) c.1307 T > A (p.(Ile436Asn)) c.596C > A (p.(Pro199Gln)) c.952G > A (p.(Glu318Lys))	c.994G > A (p.(Val332Met)) c.994G > A (p.(Val332Met)) c.1181G > A (p.(Cys394Tyr)) c.1181G > A (p.(Cys394Tyr)) c.991C > T (p.(Arg331*)) c.991C > T (p.(Arg331*)) c.1181G > A (p.(Cys394Tyr)) c.1307 T > A (p.(Ile436Asn)) c.1250CT (p.(Pro417Leu)) c.1311 G > A (p.(Leu437Phe)) c.952G > A (p.(Glu318Lys))	1,2,7: no 3,4: yes 5,6,8: not tested 9: partial reduction of ornithine levels	526–982

NR = not reported; NA = not applicable; SD-OCT = spectral domain optical coherence tomography; MRI = magnetic resonance imaging.
PVL = progressive visual loss, VI = visual impairment, CPVF = constriction of the peripheral visual fields, (B)CE = (bilateral) cataract extraction.
AA = amino acid profile, EA = enzymatic analysis, MA = mutation analysis.
a: As determined by the authors of the referenced articles.

Table 4
Treatment and therapy outcome.

Reference	Age at start therapy (Yrs)	Type of therapy	Protein content restricted diet	Pyridoxine	Other supplements	Duration of therapy	Side effects	Treatment stopped/adjusted prematurely	Ornithine level: before treatment	Ornithine level: after treatment	Other outcomes
H. D. Bakker et al. (1991)	12	ARD Pyridoxine	0.2 g/kg/day	1 g/day	EEA: 0.5 g/kg/day	4.5 months	NR	After 3 months protein intake to 1.2 g/kg/day, due to compliancy issues	1150 μmol/L	352 μmol/L	NR
M.I. Kaiser-Kupfer et al. (1991)	Range (11 m-4,5y) ($n = 2$)	PRD Pyridoxine	0.5 g/kg/day	400 mg/day, lowered to 200 mg/day	EEA: 0.3–0.5 g/kg/day	85 months	NR	No	886 μmol/L 1180 μmol/L	313 μmol/L 251 μmol/L	NR
	Range (2–8) (n = 2)	PRD	0.5 g/kg/day	NA	EEA: 0.3–0.5 g/kg/day	67 months	NR	No	818 μmol/L 971 μmol/L	121 μmol/L 106 μmol/L	NR
A. Javadzadeh et al. (2007)	28	Pyridoxine	NA	300 mg/day	NA	6 months	NR	No	629 nmol/mL	293 nmol/mL	NA
R. Christopher et al. (1999)	1: 47 2: 40	PRD Pyridoxine	1: already low protein intake 2: 0.2 g/kg/day	100 mg/day	NA	6 months	NR	Patient 2 was lost in follow up	Patient 1: 1008 μmol/L. Patient 2: 1856 μmol/L	Patient 1: 496 μmol/ Patient 2: Lost in follow up	1: Lysine and glutamate concentrations had increased after 6 months of therapy
X. Cui et al. (2018)	67	Pyridoxine	NA	400 mg/day	NA	2 years	NR	No	586 μmol/L	445 μmol/L	NA
G. Casalino et al. (2018)	8	ARD Pyridoxine	NR	500 mg/day	NA	3 years	NR	No	582 μmol/L	No decrease	After 18 months: chorioretinal atrophy had not progressed. Resolution of CME after 3 months
D. Heller et al. (2017)	1: 28 2: 16	PRD Pyridoxine	≤0.8 g/kg/day	500 mg/day	NA	3 months	NR	Patient 1 was unable to adhere to treatment	1: 697 μmol/L 2: 879 μmol/L	1: 450 μmol/L 2: 739 μmol/L	After 3 months: 1: marked improvement in CME 2: decreased central macular thickness
M. I. Kaiser-Kupfer et al. (2004)	NR	ARD	NR	NA	NA	Mean follow-up 13.9 years	NR	NR	NR	Diet group: 338 μmol/L Control group: 702 μmol/L	NR
F.Tanzer et al. (2011)	8	Pyridoxine and/or PRD	NR	500 mg/day	NA	1 month	NR	Difficulty in adherence to low-protein diet	955 μmol/L	375 μmol/L	>50% reduction of urinary ornithine excretion
Y. Mashima et al. (1999)	NR	Pyridoxine	NA	600–750 mg/day	NA	NR	NR	Patient 4 did not receive pyridoxine	640 μmol/L 570 μmol/L 770 μmol/L	340 μmol/L 250 μmol/L 340 μmol/L	Normalisation of lysine with treatment
M. Michel et al. (2015)	16	PRD, pyridoxine, creatine, dorzolamid eye drops	0.5 g/kg/day	300 mg/day	EEA: 12,5 g/day Creatine: 12 g/day in 3 doses	250–300 days	NR	NR	877 μmol/L	<500 μmol/L	NR
	5	PRD, pyridoxine, creatine	NR	NR	NR	250–300 days	NR	NR	>800 μmol/L	<500 μmol/L	NR
Y.R. Sharma et al. (2006)	28	Pyridoxine	NA	300 mg/day	NA	12 weeks	NR	Patient denied arginine-restricted diet	370 μmol/L	214 μmol/L	NR
R. Santinelli et al. (2004)	4	PRD	0.8 g/kg/day	NA	NA	26 years	NR	No	1189 μmol/L	469–742 μmol/L	NR
M. Zekušić et al. (2017)	6-9Y	PRD, pyridoxine, L-lysine, systemic corticosteroids,	Phase 1: no restriction	Phase 1: pyridoxine	Phase 3: Addition of	Phase 1: 3.5	NR	No	1039 μmol/L	Phase 1: 907 μmol/L	After phase 3: positive change in ERG, significant

		topical carbonic anhydrase inhibitors	Phase 2: 1 g/kg/day Phase 3: 0.6 g/kg/day	500 mg/day Phase 2: pyridoxine to 200 mg/day	L-lysine 12 g/day	months Phase 2: 2.4 years Phase 3: 7.5 months				Phase 2: 537 μmol/L Phase 3: 489 μmol/L	improvement of central macular oedema
S. Katagiri et al. (2014)	1: 6 2: 2	ARD	NR	NA	NA	16 years	NR	No	1: 1041 μmol/L 2: 952 μmol/L	1: 525 μmol/L 2: ~800 μmol/L	NR
D. Rigante et al. (2010)	4	ARD Pyridoxine	NR	300 mg/day	NA	6 months	No	No	536 μmol/L	512 μmol/L	Unclear how much of the visual loss is due to GA or due to porencephaly
K. Peltola et al. (2000)	Range (16–45)	Lysine	NA	NA	2 g 5× daily	1 week	No	2 patients stopped after day 1, reason not mentioned	910–2067 μmol/L, mean 1480 μmol/L	34% decrease of plasma ornithine	775% decrease of urinary ornithine (20–2767%)
J. Michaud et al. (1995)	5	Pyridoxine	NA	500 mg/day	NA	2 years	No	No	652 μmol/L	232 μmol/L	NR
Y. Ohkubo et al. (2005)	19	Pyridoxine	NA	300 mg/day	NA	18 years	No	No	1140 μmol/L	921 μmol/L	NR
S. Doguizi et al. (2015)	9	ARD	NR	NR	NR	2 years	No	No	622 μmol/L	55 μmol/L	NR
S. Hayasaka et al. (1985)	Range (4–32)	Pyridoxine Proline	NR	120–600 mg/day	3–10 g/day	1–5 years	No	No	739 μmol/L 980 μmol/L 524 μmol/L 984 μmol/L 853 μmol/L	649 μmol/L 1091 μmol/L 284 μmol/L 942 μmol/L 990 μmol/L	NR
R. Feldman et al. (1989)	30	PRD Pyridoxine, lysine, AIB	35 g/day	750 mg/day	Lysine: 1 g/day AIB: 3 g/day	20 weeks	No	No	818 μmol/L	587 μmol/L	NR
S.P. Shrestha et al. (2010)	15, 18	PRD Pyridoxine	25 g/day	160 mg/day	NR	5 years	No	No	741 μmol/L 462 μmol/L	NR	Patient with abnormal EEG does not require antiepileptic medication anymore
S.J. Kim et al. (2013)	19	ARD, pyridoxine	NR	300 mg/day	NA	15 months	No	No	1: 783 μmol/L 2: 831 μmol/L	1: 386 μmol/L 2: 408 μmol/L	NR
D. Valle et al. (1980)	35	ARD, AIB	10–20 g/day	NA	EEA: 20 g/day AIB: 5 g/day	At least 18 months	No	No	964 μmol/L	<426 μmol/L	Normal electromyogram, normal sensory and motor nerve conduction
M.I. Kaiser-Kupfer (1980)	35	ARD	10 g/day	NA	EEA: 20 g/day	20 months	No	No	964 μmol/L	176 μmol/L	NR
I. Zhioua Braham et al. (2018)	1: 26 2: NR	ARD, pyridoxine	NR	300 mg/day	NA	6 months	No	No	1: 723 μmol/L	NR	NR
V.E. Shih et al. (1981)	Range (12−30)	ARD (n = 5) Pyridoxine (n = 1)	15 g/day	300 mg/day	EEA: 20 g/day	8–55 weeks	No	1: after 8 wk. increase protein content to 20–25 g/day 5: stopped all treatment after discharge	706–1106 μmol/L	153–400 μmol/L	After stopping treatment, plasma ornithine in patient 5 rose to 870 μmol/L
O.N. Elpeleg et al. (2001)	Range (13–19)	Lysine	NA	NA	10–15 g/day	40–55 days	No	No	662–1040 μmol/L	525–724 μmol/L	NR

(continued on next page)

Table 4 (*continued*)

Reference	Age at start therapy (Yrs)	Type of therapy	Protein content restricted diet	Pyridoxine	Other supplements	Duration of therapy	Side effects	Treatment stopped/adjusted prematurely	Ornithine level: before treatment	Ornithine level: after treatment	Other outcomes
R.R. McInnes et al. (1980)	1: 39 2: 17	PRD, arginine	1 g/kg/day	NA	EEA 2: 125 mg arginine/day	1: 6 months 2: 5 weeks	2: Episode of hyperammonaemia which resolved after i. v. arginine	No	1: 1000 μmol/L 2: 750–1000 μmol/L	1: 247 μmol/L 2: 30–120 μmol/L	NR
G. Stoppoloni et al. (1982)	3y9m	PRD	0.8 g/kg/day	NA	NA	6 year 3 months	No	No	1180.9 μmol/L	744.9 μmol/L	NR
C. Çavdarli et al. (2019)	26	ARD Topical brinzolamide 1% nepafenac 0.1%	NR	NR	NA	2 months	No	Patient did not adhere to diet	379 μmol/L	NR	NR
M. Doimo et al. (2013)	Range (3–40)	Pyridoxine Diet	NR	NR	NA	NR	NR	NR	526–982	NR	Plasma ornithine levels could be normalised by diet alone

NR = not reported; NA = not applicable; OD = oculus dextra, right eye; OS = oculus sinistra, left eye; EEA = essential amino acids; AIB = α-aminoisobutyric acid; PRD = protein-restricted diet; ARD = arginine-restricted diet.

(Glu31Lys) variant. Studies with patient fibroblasts homozygous for the p.(Glu318Lys) variant or compound heterozygous a p.(Glu318Lys) variant and one that causes exon 5 skipping showed an increase of OAT activity in the presence of pyridoxal phosphate. Three patients received *in vitro* treatment with pyridoxine and showed a decrease of more than 50% in plasma ornithine [22]. Michaud et al. (1995) presented a patient with p.(Ala226Val)/p.(Arg398*) variants, with both *in vivo* and *in vitro* response to pyridoxine supplementation [24]. Ohkubo et al. (2005) presented a patient with a homozygous p.(Gly237Asp) variant whose plasma ornithine levels decreased with 20–30% and stabilised with long-term pyridoxine supplementation [3]. Doimo et al. (2013) presented three patients with different missense mutations that were classified as pyridoxine-responsive [45].

3.4.4. L-lysine supplementation

Ten patients received L-lysine supplementation [27,37,42,43]. Because lysine, cysteine, ornithine and arginine use a common renal transport channel, it is hypothesised that increasing plasma lysine concentrations might compete with ornithine and arginine reabsorption in the kidney. This may induce increased renal loss of ornithine and arginine, consecutively lowering plasma ornithine levels.

This hypothesis was tested by Peltola et al. (2000), who provided five pyridoxine non-responsive patients with L-lysine as part of a pilot study. Supplementation of oral L-lysine for 7 days led to a 34% decrease of plasma ornithine and a 775% increase of urinary excretion of ornithine. These patients were reported to have the "typical Finnish variant" [27]. Elpeleg et al. (2001) repeated this experiment in three patients, treated for 40–55 days. A 21–31% decrease in plasma ornithine was reported. No variants in *OAT* were provided for these patients [42].

3.4.5. Proline supplementation

Five patients described by Hayasaka et al. (1981) received proline as part of therapy. Proline is generated from P5C by the enzyme Δ^1-pyrroline-5-carboxylate reductase (PYCR/P5CR). P5C is reduced in GACR due to OAT deficiency. Proline is a highly preferred nutrient substrate for retinal pigment epithelium (RPE), leading to the hypothesis that proline deficiency plays a role in retinal atrophy associated with GACR [46]. One patient reported a subjective improvement of visual function after start of proline supplementation, although it is unclear to which extent. In the other patients, no improvement was reported [44].

3.4.6. Creatine and precursor supplementation

In order to treat secondary creatine deficiency caused by the inhibition of arginine-glycine amidinotransferase (AGAT) by high concentrations of ornithine, creatine can be supplied. Two patients described by Michel et al. (2015) received creatine supplementation as adjunct therapy to a protein-restricted diet and pyridoxine therapy. All treatments were started simultaneously and no neurological symptoms were reported, therefore a singular effect of creatine cannot be derived [26].

3.4.7. Combination therapy

Combination therapy was provided in 34 of the 85 treated patients. These 34 patients include patients mentioned earlier in the results section. Combination therapy usually consisted of a protein- or arginine-restricted diet in combination with pyridoxine or another form of supplementation [14,15,17,21,25,26,28,31,32,34,35,37–39,43–45]. Kaiser-Kupfer et al. (1991) compared two affected sibling pairs, one pair that was only on a protein-restricted diet of 0.5 g/kg/day and one pair that received additional pyridoxine supplementation, but found no benefit of the added supplementation on plasma ornithine levels and ophthalmic follow-up [17]. Casalino et al. (2011) described a patient that first received pyridoxine supplementation and was later put on an arginine-restricted diet, who did not exhibit a decrease in plasma ornithine, although there was resolution of central macular oedema despite the lack of specific ocular therapy [25]. The two siblings described by Michel et al. (2015), mentioned earlier in the review, received a low-

Table 5
Structural ophthalmological investigation.

Reference	Treatment	Follow-up time	Diagnosis			Follow-up		
			Ophthalmoscopy	Fundus autofluorescence	SD-OCT	Ophthalmoscopy	Fundus autofluorescence	SD-OCT
H. D. Bakker et al. (1991)	Arginine-restricted diet Pyridoxine	4.5 months	Vitreous detachment OD, cataract ODS, normal anterior segments.	Drusen of optic discs, attenuated retinal vessels, disciform macular lesions, diffuse atrophic changes in both posterior poles, circumferential chorioretinal atrophy	NR	NR	NR	NR
M.I. Kaiser-Kupfer et al. (1991)	Protein-restricted diet Pyridoxine	85 months	1: Multiple lesions 2:Not described	NR	NR	1: Minimal progression in both size and pigmentation of a few lesions 2: Solitary atrophic lesion ODS, small depigmented areas	NR	NR
	Protein-restricted diet	67 months	1: Multiple scatted atrophic and pigmented lesions 2:Not described	NR	NR	1: Minimal progression 2: Diffuse mottling and slight increase in pigmentation, no atrophic chorioretinal lesions	NR	NR
A. Javadzadeh et al. (2007)	Pyridoxine	6 months	Sharply demarcated areas of choroid and retinal atrophy in gyrate shape involving the midperiphery with the macula not affected. Tilted disc OD. Posterior subcapsular cataracts	Slight leakage from the margins of the choriocapillaris neighbouring the atrophic area. Normal posterior pole.	NR	NR	NR	NR
R. Christopher et al. (1999)	Protein-restricted diet Pyridoxine	6 months	1: Circular areas of complete chorioretinal atrophy 2: Circular areas of chorioretinal degeneration. Posterior subcapsular cataracts ODS	NR	NR	Unchanged	NR	NR
X. Cui et al. (2018)	Pyridoxine	2 years	Preservation of RPE around the macula with distinct borders. Preservation of RPE islands in the periphery. Very distinct borders.	Bilateral sharply demarcated RPE atrophy that encroached from the periphery and surrounds the central macula.	Extensive choroidal sclerosis and degeneration in the areas of RPE atrophy	Unchanged	Minimal disease progression	Spared RPE around the central macular with paramacular areas of RPE atrophy. Individual larger choroidal vessels from Sattler's and Haller's layers in areas of RPE atrophy
G. Casalino et al. (2018)	Arginine-restricted diet Pyridoxine	3 years	Patches of circumferential chorioretinal atrophy in the peripheral retina of both eyes	NR	Bilateral foveal-involving CME	NR	NR	Small fluctuations of residual intraretinal cysts with good foveal contour
D. Heller et al. (2017)	Protein-restricted diet Pyridoxine	3 months	1: Bilateral posterior subcapsular cataracts, bilateral sharply demarcated circular areas of chorioretinal atrophy involving the mid-periphery. Blunted foveal reflexes 2: midperiphery chorioretinal atrophic lesions, mild posterior subcapsular cataracts	1: Loss of autofluorescence corresponding to areas of atrophy, hyperautofluorescent ring within the macula. Pinkish-yellow lesions with spots of calcification over both optic discs 2: NR	1: Bilateral severe CME with central macular thickness measurements of 670 μm OD and 565 μm OS 2: Macular thickening with flattening of the foveal depression, CMT 403 μm OD and 352 μm OS	1: Stable 2: NR	1: Stable 2: NR	1: CMT 270 μm OD and 161 μm OS 2: CMT 323 μm OD and 305 μm OS, deepening foveal depression

(continued on next page)

Table 5 (*continued*)

Reference	Treatment	Follow-up time	Diagnosis			Follow-up		
			Ophthalmoscopy	Fundus autofluorescence	SD-OCT	Ophthalmoscopy	Fundus autofluorescence	SD-OCT
M. I. Kaiser-Kupfer et al. (2004)	Arginine-restricted diet	13.0 years	NR	NR	NR	NR	NR	NR
F.Tanzer et al. (2011)	Pyridoxine and/or protein-restricted diet	1 month	Sharply demarcated areas of choroid and retinal atrophy in gyrate shape involving the midperiphery with macular oedema	Leakage from the left fovea, bilateral hyperfluorescence in maculo-temporal area, cystoid macular oedema	NR	NR	NR	NR
Y. Mashima et al. (1999)	Pyridoxine	NR	NR	NR	NR	NR	NR	NR
M. Michel et al. (2015)	Protein-restricted diet Pyridoxine Creatine	250–300 days	Coalescent chorioretinal atrophic changes in the periphery	NR	Bilateral cystoid oedema	NR	NR	NR
Y.R. Sharma et al. (2006)	Pyridoxine	12 weeks	Bilateral full thickness macular holes with surrounding cuff of fluid along with concentric chorioretinal atrophy with scalloped margins	NR	Full thickness macular holes	Unchanged	NR	Unchanged
R. Santinelli et al. (2004)	Protein-restricted diet	26 years	Many round, sharply defined, whitish areas of choroid atrophy, 0.5–1 disc in diameter, partially pigmented borders	NR	NR	Normal optic disc and peripapillary region, no change of retinal peripheral aspect	NR	NR
M. Zekušić et al. (2017)	Pyridoxine, L-lysine, systemic corticosteroids	3 years	Numerous circular sharply limited atrophic zones in the retina	Bilateral macular oedema	Bilateral macular oedema	NR	NR	Improvement with only discrete oedema of the macula
S. Katagiri et al. (2014)	Arginine-restricted diet	16 years	1: Sharply demarcated circular areas of chorioretinal atrophy in the entire peripheral retina in both eyes 2: Retinal degeneration n superior peripheral area of both eyes	1: Hypofluorescence in the peripheral chorioretinal atrophic areas in both eyes, window defect near the macula 2: NR	1: Slight cystic changes in both macular areas 2: macular thinning	1: Posterior expansion of the chorioretinal atrophy 2: posterior expansion of chorioretinal atrophy	1: Loss of autofluorescence corresponding to chorioretinal atrophic areas 2: loss of autofluorescence in peripheral chorioretinal atrophic areas, ring-shaped hyperautofluorescence around macula	1: Moderate cystoid spaces within the inner nucleus layer, thinning of outer nuclear layer, splitting of inner nuclear layer in temporal area OD 2: moderate cystoid spaces within inner nuclear layer, abnormally thin outer nuclear layer
D. Rigante et al. (2010)	Arginine-restricted diet Pyridoxine	6 months	Bilateral large atrophic polycyclic scars associated with pigment accumulation, mostly in the posterior pole	NR	NR	Unchanged	NR	NR
K. Peltola et al. (2000)	Lysine	1 week	NR	NR	NR	NR	NR	NR
J. Michaud et al. (1995)	Pyridoxine	2 years	Typical GA lesions in the periphery of the retina	NR	NR	Unchanged	NR	NR
Y. Ohkubo et al. (2005)	Pyridoxine	18 years	Large atrophied area OD Retinal detachment OS due to accident	NR	NR	No exacerbation	NR	NR
S. Doguizi et al. (2015)	Arginine-restricted diet	2 years	Multiple bilateral, sharply defined, and scalloped chorioretinal atrophy areas in the midperipheral and peripheral zone	NR	Bilateral cystoid macular oedema	Unchanged	NR	NR
S. Hayasaka et al. (1985)	Pyridoxine (n = 3), proline (n = 4)	Range (2–5 years)	Sharply defined atrophy, cataract Normal (n = 1)	NR	NR	Increase in yellow-white spots ($n = 1$), vitreous opacity due to vitreous haemorrhage (n = 1), increase of chorioretinal atrophy (n = 1), unchanged (n = 2)	NR	NR

R. Feldman et al. (1989)	Protein-restricted diet Pyridoxine Lysine and α-aminoisobutyric acid	5 months	Scalloped areas of chorioretinal atrophy, attenuated retinal arteries, cystoid macula oedema and epiretinal membranes, mild posterior subcapsular cataracts, calcific degeneration, posterior vitreous detachments, shrinkage of vitreous gel, round opacities, veils, and patchy opcification of the posterior vitreous face	NR	NR	Expansion of chorioretinal atrophy	NR	NR
S.P. Shrestha et al. (2010)	Protein-restricted diet Pyridoxine	5 years	Confluent arcuate equatorial full-thickness lesions of the choroid and retina, separated by thin margins of pigment, early posterior subcapsular cataract ODS	NR	NR	Unchanged atrophic lesions but development of significant posterior subcapsular cataract ODS	NR	NR
S.J. Kim et al. (2013)	Arginine-restricted diet Pyridoxine	15 months	1: Bilateral posterior subcapsular cataracts, bilateral severe chorioretinal atrophy involving midperiphery 2: Similar	1: Leakage at the margin of chorioretinal atrophy and dye accumulation in maculae of both eyes 2: Similar	1: Disclosed cystoid macular oedema ODS 2: Similar	1: No progression of chorioretinal atrophy 2: No progression of chorioretinal atrophy	NR	NR
D. Valle et al. (1980)	Arginine-restricted diet α-aminoisobutyric acid	18 months	Characteristic lesions associated with GA	NR	NR	No progression of chorioretinal atrophy	NR	NR
M.I. Kaiser-Kupfer et al. (1980)	Protein-restricted diet	20 months	NR	NR	NR	NR	NR	NR
R.R. McInnes et al. (1981)	Arginine-restricted diet	24 weeks	Extensive peripheral retinal lesions of gyrate atrophy with near-normal appearance of the central area of each fundus	Minor transmittance of choroidal fluorescence	NR	NR	NR	NR
I. Zhioua Braham et al. (2018)	Arginine-restricted diet Pyridoxine	6 months	1: Multiple bilateral sharply defined chorioretinal atrophy areas in (mid) peripheral retina 2: Multiple, coalescent areas of peripheral chorioretinal atrophy sparing the posterior pole	1: Decreased autofluorescence that correlated with atrophic areas, no leak	1: Increased central macular thickness 398 μm OD 355 μm OS, suggestion of foveoschisis 2: Normal OD, macular pseudohole OS	1: No retinal changes observed 2: NR	NR	NR
V.E. Shih et al. (1981)	Arginine-restricted diet Pyridoxine	8–55 weeks	NR	NR	NR	No effect	NR	NR
O.N. Elpeleg et al. (2001)	Lysine	40–55 days	NR	NR	NR	NR	NR	NR
R.R. McInnes et al. (1980)	Protein-restricted diet Arginine	5 weeks-6 months	1: Area of atrophy above disc, typical scallops, peripheral geographic areas of choroidal atrophy 2: Area of atrophy above disc, scallops and peripheral geographic areas of choroidal atrophy	NR	NR	Unchanged	NR	NR
G. Stoppoloni et al. (1982)	Protein-restricted diet	6 years, 3 months	Many areas of chorioretinal atrophy in the periphery of the fundus	NR	NR	No progression of lesions	NR	NR
C. Çavdarli et al. (2019)	Arginine-restricted diet Topical brinzolamide 1% nepafenac 0.1%	2 months	Bilateral posterior subcapsular cataracts, peripheral-midperipheral sharp demarcated circular chorioretinal atrophic areas	Peripheral and midperipheral window defects	Bilateral IC-like cystoid macular oedema, CMT 540 μm OD 528 μm OS	NR	NR	Regression of ICs, CMT 397 μm OD 411 μm OS
M. Doimo et al. (2013)	Diet, pyridoxine	NR	NR	NR	NR	NR	NR	NR

Legend: NR = not reported; NA = not applicable; OD = oculus dextra, right eye; OS = oculus sinistra, left eye; SD-OCT = spectral domain optical coherence tomography.

Table 6
Functional ophthalmological investigation.

Reference	Treatment	Follow-up time	Diagnosis			Follow-up		
			BCVA	Visual fields	Electroretinogram	BCVA	Visual fields	Electroretinogram
H. D. Bakker et al. (1991)	Arginine-restricted diet Pyridoxine supplementation	4.5 months	0.16 OD 0.25 OS	Peripheral defects	Almost absent, small photopic response	NR	NR	NR
M.I. Kaiser-Kupfer et al. (1991)	Protein-restricted diet Pyridoxine supplementation	85 months	Patient 1 + 2: NR	Moderate constriction of 25^0–40^0 to a small test object (I4e) but normal to a large test object (V4e)	Reduced amplitudes when compared to controls	Patient 1: 20/32 ODS Patient 2: 20/25 OD 20/32 OS	Unchanged	Unchanged
	Protein-restricted diet	67 months	Patient 1: 20/60 ODS Patient 2: NR			Patient 1: 20/40 ODS Patient 2: 20/25 OD 20/32 OS		Amplitude reductions in cone-mediated ERG
A. Javadzadeh et al. (2007)	Pyridoxine supplementation	6 months	3/10 OD 1/10 OS	NR	NR	NR	NR	NR
R. Christopher et al. (1999)	Protein-restricted diet Pyridoxine supplementation	6 months	NR	1: Goldmann: concentric constriction of visual fields 2: Goldmann: concentric constriction of visual fields	NR	1: Unchanged 2: NR	1: Unchanged 2: NR	NR
X. Cui et al. (2018)	Pyridoxine supplementation	2 years	20/25 OD 20/50 OS	NR	Diminished scotopic rod-specific and maximal responses	20/40 OD 20/60 OS	NR	NR
G. Casalino et al. (2018)	Arginine-restricted diet Pyridoxine supplementation	3 years	20/40 ODS	NR	Abolished responses ODS	After 3 months: 20/25 both eyes. BCVA maintained after 3 years	NR	NR
D. Heller et al. (2017)	Protein-restricted diet Pyridoxine supplementation	3 months	Patient 1: 6/120 ODS Patient 2: 6/15 OD 6/12 OS	1: Constricted 2: Constricted	NR	1: 6/30 OD 6/12 OS 2: 6/12 OD 6/8.5 OS	1: Stable 2: Stable	NR
M. I. Kaiser-Kupfer et al. (2004)	Arginine-restricted diet	13.0 years	NR	NR	NR	NR	NR	Combined ERG: Diet group: 0.043 ± 0.012 log μV/y Control group: 0.123 ± 0.025 log μV/y Flicker ERG: Diet group: 0.034 ± 0.019 log μV/y Control group: 0.141 ± 0.048 log μV/y
F.Tanzer et al. (2011)	Pyridoxine supplementation and/or protein-restricted diet	1 month	3/10 ODS	NR	NR	NR	NR	NR
Y. Mashima et al. (1999)	Pyridoxine supplementation	NR	NR	NR	NR	NR	NR	NR
M. Michel et al. (2015)	Protein-restricted diet Pyridoxine supplementation Creatine supplementation	250–300 days	0.4 OD 0.5 OS	NR	NR	NR	NR	NR
Y.R. Sharma et al. (2006)	Pyridoxine supplementation	12 weeks	20/200 OD 20/120 OS	Goldmann & Humphrey: severe constriction of visual field in both eyes	Extinguished responses in both eyes	Unchanged	NR	NR
R. Santinelli et al. (2004)	Protein-restricted diet	26 years	Normal until 9 years old	Goldmann: contraction of isopters, confirming a loss of peripheral vision	OD: scotopic subnormal, photopic subnormal, flicker 40 μV OS: scotopic normal, photopic normal, flicker 40 μV	After menarche (9Y): 10/20 ODS	Unchanged	Lower than those of normal age-matched subject, remained constant over follow-up period
M. Zekušić et al. (2017)	Pyridoxine supplementation, L-lysine supplementation, systemic corticosteroids	3 years	NR	NR	Performed, results not reported	NR	NR	"Positive change"

Table 6 (*continued*)

Reference	Treatment	Follow-up time	Diagnosis			Follow-up		
			BCVA	Visual fields	Electroretinogram	BCVA	Visual fields	Electroretinogram
S. Katagiri et al. (2014)	Arginine-restricted diet	16 years	1: 1.0 ODS 2: 1.0 OD 1.2 OS	1: Constricted visual fields in the I-4 isopters with preserved visual fields of the V-4 isopters in both eyes 2: Constricted visual fields of I-4 and V-4 isopters	1: NR 2: rod, standard-combined, cone, and 30-HZ flicker responses were non-recordable	1: 0.6 ODS 2: 0.7 OD 0.9 OS	1: Constriction of both I-4 and V-4 isopters 2: Constriction of both I-4 and V-4 isopters	NR
D. Rigante et al. (2010)	Arginine-restricted diet Pyridoxine supplementation	6 months	Impossible due to age and psychomotor delay	NR	Non-recordable for scotopic and photopic conditions	NR	NR	Unchanged
K. Peltola et al. (2000)	Lysine supplementation	1 week	NR	NR	NR	NR	NR	NR
J. Michaud et al. (1995)	Pyridoxine supplementation	2 years	20/20 OD 20/40 OS	Normal	No response under scotopic conditions, low potentials with lengthened b-wave under photopic conditions	20/60 ODS	NR	NR
Y. Ohkubo et al. (2005)	Pyridoxine supplementation	18 years	NR	NR	NR	NR	NR	NR
S. Doguizi et al. (2015)	Arginine-restricted diet	2 years	20/80 ODS	NR	NR	Unchanged		
S. Hayasaka et al. (1985)	Pyridoxine (n = 3), proline (n = 4)	Range (2–5 years)	1: 0.3 ODS 2: 0.4 ODS 3: 0.03 OD 0.6 OS 4: 0.1 OD 0.08 OS 5: 0.1 ODS	1: NR 2: <40 degrees 3: <10 degrees 4: 10 degrees 5: <10 degrees	1–3: subnormal 4, 5: extinct	1: 1 ODS 2: blind OD 0.2 OS 3: 0.03 OD 0.06 OS 4: 0.08 OD 0.06 OS 5: 0.1 ODS	1: NR 2: <30 degrees 3: <10 degrees 4: 10 degrees 5: <10 degrees	1–3: almost extinct 4, 5: extinct
R. Feldman et al. (1989)	Protein-restricted diet Pyridoxine supplementation Lysine and α-aminoisobutyric acid supplementation	5 months	20/200 OD 20/80 OS	Goldmann: visual field restriction	NR	20/400 OD 20/200 OS	NR	NR
S.P. Shrestha et al. (2010)	Protein-restricted diet Pyridoxine supplementation	5 years	1: 20/60 ODS 2: 20/60 OD 20/80 OS	Humphrey: constricted	NR	NR	NR	NR
S.J. Kim et al. (2013)	Arginine-restricted diet Pyridoxine supplementation	15 months	1: 20/32 ODS 2: 20/25 OD 20/32 OS	1: Visual field constriction ODS (Goldmann) 2: NR	1: Marked impaired photopic and scotopic responses 2: Similar	1: Unchanged 2: Unchanged	NR	NR
D. Valle et al. (1980)	Arginine-restricted diet α-aminoisobutyric acid	18 months	20/30 OS, less in OD due to intravitreal haemorrhage	Severely constricted	NR	NR	NR	NR
M.I. Kaiser-Kupfer et al. (1980)	Protein-restricted diet Essential amino acid supplementation	20 months	20/30 OS, "counts fingers at 3 ft" OD	NR	Extinguished	20/200 OD 20/30 OS	Improvement	Improved, measurable rod and conse responses to Ganzfeld stimulation
R.R. McInnes et al. (1981)	Arginine-restricted diet	24 weeks	20/80 OS, hand movements at 45 cm OD	Constricted OD	NR	20/100 OD, OS stable	Increase in visual field 40′-55′ temper	No effect
I. Zhioua Braham et al. (2018)	Arginine-restricted diet Pyridoxine supplementation	6 months	1: 20/32 OD 20/100 OS 2: 20/20 OD 20/32 OS	1, 2: Peripheral alterations	1, 2: Reduced photopic responses, no recordable scotopic response	NR	NR	NR
V.E. Shih et al. (1981)	Arginine-restricted diet Pyridoxine supplementation	8–55 weeks	NR	NR	NR	NR	NR	NR
O.N. Elpeleg et al. (2001)	Lysine supplementation	40–55 days	NR	NR	NR	NR	NR	NR

(*continued on next page*)

Table 6 (*continued*)

Reference	Treatment	Follow-up time	Diagnosis			Follow-up		
			BCVA	Visual fields	Electroretinogram	BCVA	Visual fields	Electroretinogram
R.R. McInnes et al. (1980)	Protein-restricted diet Arginine	5 weeks-6 months	1: 20/60 OD 20/50 OS 2: 20/300 OD 20/70 OS	1: limited to 20 degrees from fixation 2: not performed	1: B amplitude 14 μV 2: B amplitude 2 mV	1: 20/50 ODS 2: 20/200 OD 20/60 OS	NR	1: B amplitude 2 μV 2: B amplitude 2 mV
G. Stoppoloni et al. (1982)	Protein-restricted diet	6 years, 3 months	NR	NR	Subnormal findings OD	NR	Slight reduction of visual fields	Normal
C. Çavdarli et al. (2019)	Arginine-restricted diet Topical brinzolamide 1% nepafenac 0.1%	2 months	20/100 ODS	NR	NR	20/50 OD 20/63 OS	NR	NR
M. Doimo et al. (2013)	Diet, pyridoxine	NR	NR	NR	NR	NR	NR	NR

BCVA = best corrected visual acuity; OD = oculus dextra, right eye; OS = oculus sinistra, left eye; NR = not reported; NA = not applicable.

protein diet in combination with pyridoxine supplementation and creatine supplementation, which lowered plasma ornithine in both patients. Unfortunately, no extensive ophthalmic follow-up was provided [26]. The patient described by Zekušić et al. (2014) received a protein-restricted diet combined with pyridoxine supplementation and L-lysine supplementation. Supplementing L-lysine lead to a decrease in plasma ornithine which was associated with a positive change in the patient's electroretinograms [37].

However, in most patients different treatment modalities were initiated at the same time, therefore efficacy of a single modality, as well as added benefit of another modality, could not be assessed.

4. Discussion and conclusions

This is the first systematic review on therapeutic interventions in GACR and therefore provides a unique overview of all administered therapies, as reported in the literature up until December 2020. GACR is a rare disease without evidence-based treatment recommendations. By summarising all therapeutic interventions and effects published regarding GACR patients we created an overview useful for clinicians in daily practice as well as a steppingstone to management guidelines and further research, even though the levels of evidence and quality of individual studies is low.

The low prevalence of GACR explains the large number of case reports, the lack of systematic randomised controlled trials and cohort studies, and the scarcity of high quality data. Furthermore, most studies did not provide predefined outcome measures. Despite GACR being a predominantly ophthalmic condition, a large portion of the papers did not provide any ophthalmic follow-up. Different interventions were often initiated at the same time, making it impossible to attribute a possible beneficiary effect to a single treatment modality. Follow-up regimens varied greatly across all studies.

Due to the lack of knowledge on the exact pathophysiology underlying GACR, all treatment options, with the exception of creatine supplementation, are aimed at decreasing ornithine levels. However, it is questionable whether ornithine is the right target for therapeutic interventions. The retinal pigment epithelium (RPE) is a critical barrier between the retina and the systemic circulation, regulating the flux of nutrients and oxygen between the choroid and the subretinal space. It has unique metabolic properties which serve, in a large part, the metabolic needs of the eye [47]. A 2011 review by Hayasaka et al. summarises the known risks of high-dose ornithine supplements for the retina as concluded from both *in vitro* and animal studies. They describe several *in vitro* studies where high-dose intravitreal injections of ornithine were toxic to retinal pigment epithelium (RPE) cells. Additionally, they described an animal study with OAT-deficient mice. The mice on arginine-restricted diets retained better ophthalmic function compared to the mice on normal diets [48]. However, no research has been performed which aims to unravel the broader metabolic consequences of OAT deficiency. Therefore, it is unclear whether plasma ornithine is actually the culprit in the process of chorioretinal atrophy or if there are more, yet unknown, metabolites involved. The only other disorder associated with hyperornithinaemia is hyperornithinaemia-hyperammonaemia-homocitrullinuria (HHH) syndrome. Ophthalmic

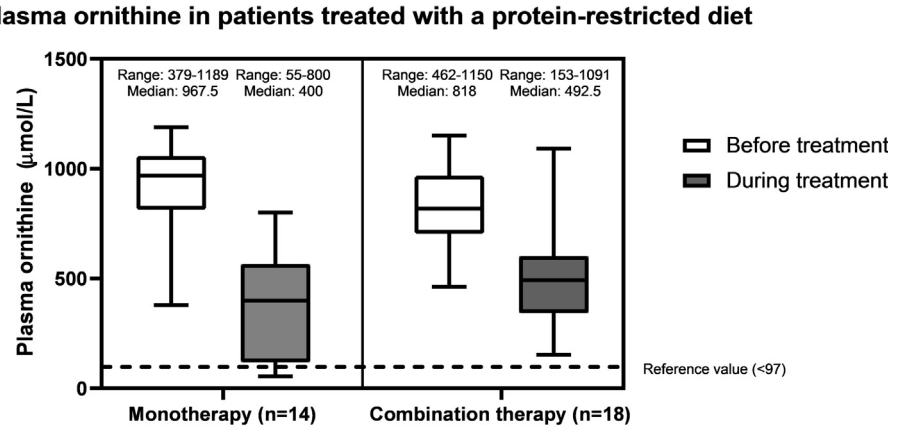

Fig. 4. Plasma ornithine before and during treatment in patients with a protein-restricted diet. On the left, patients that were only treated with a protein-restricted diet are depicted. On the right, patients with a protein-restricted diet and additional therapy are depicted.

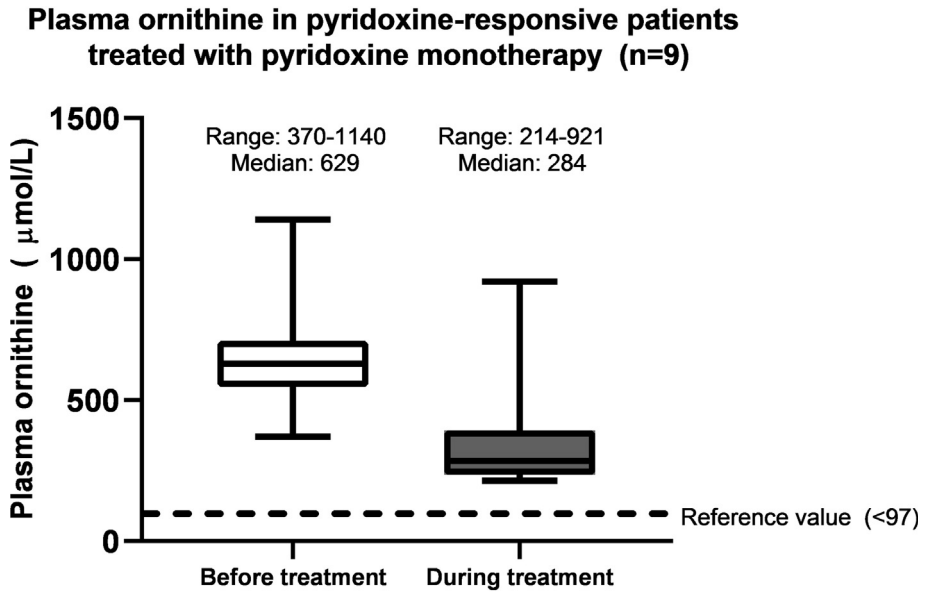

Fig. 5. Plasma ornithine levels before and during treatment in patients that received pyridoxine monotherapy and were classified by the authors of the respective papers as being pyridoxine-responsive.

changes are usually not reported in HHH syndrome. Interestingly, Morini et al. reported one patient with genetically confirmed HHH syndrome that developed tapetoretinal degeneration and decreased ocular function [49]. As HHH has a different cause, it is likely that the pathophysiological mechanism is different. Additionally, due to the unique metabolic properties of the retina, it is questionable whether plasma ornithine accurately reflects the retinal status.

The most frequently reported intervention is an arginine-restricted diet, usually executed in the form of a diet generally restrictive in natural protein with arginine-free supplementation of essential amino acids. The degree of protein restriction was often not mentioned, but when reported varied from 0.2–1 g/kg/day. The age at intervention is usually between adolescence and adulthood, because there is often a diagnostic delay due to unawareness of the disease phenotype and late manifestations. Biochemically, ornithine levels dropped during treatment independent of the degree of protein restriction [17–20,29,50]. Ophthalmic follow-up was often not reported. The patient that did receive ophthalmic follow-up measurements, were often on different treatment modalities at the same time, making it unlikely that possible beneficial effects can solely be attributed to therapy with a protein-restricted diet. Most of these studies did not provide a comparison with untreated controls. Nonetheless, two sibling studies suggest that early intervention favours a better outcome: the earlier a patient started on the protein-restricted diet, the slower the progression of the chorioretinal lesions was [17,50].

Compliance is a significant factor to consider when treating patients with a protein-restricted diet. Our review showed that nine patients with ages ranging from 8 to 60 years were non-compliant to the diet. Indeed, a study of 197 participants with other inborn metabolic diseases (IMDs) requiring a protein-restricted diet reported also variable compliance, with compliance decreasing significantly as age progressed [51]. It is likely that similar patterns exist within the GACR community, especially because there is limited research on the effect of a protein-restricted diet on disease progression and patients will not immediately notice an effect of following or stopping the diet.

Pyridoxine is an additional therapeutic modality used in GACR [43]. In a subgroup of patients with GACR it lowers ornithine levels, although it is as of yet unclear why. Pyridoxine might play a role in stimulating residual enzyme activity, but others propose that it might also have an additional chaperone function, leading to increased enzyme stability and thus improved enzyme function similar to tetrahydrobiopterin (BH4) in PKU patients [52,53]. *In vitro* experiments on HEK293 cells with the Val332Met pathogenic variant show that, after catalysis, this variant loses its B6 vitamer and quickly aggregates and unfolds [55]. Increasing concentrations of pyridoxal phosphate, the active form of pyridoxine, helps stabilise the enzyme. Another paper supports the notice of *in vitro* responsiveness of the Val332Met mutation [56]. However, discrepancies between *in vitro* and *in vivo* responsiveness have been reported. In their paper, Doimo et al. (2013) describe two patients that were homozygous for the Val332Met pathogenic variant and that did not respond to pyridoxine [45]. Montioli et al. (2021) argue in their recent review that a lack of consistency between *in vitro* and *in vivo* responses may suggest that pyridoxine has an (added) effect not directly related to OAT activity [1].

Valle et al. (2019) reported that <5% of GACR patients show clear *in vivo* and *in vitro* pyridoxine-responsiveness [54]. Our review shows a much higher responsiveness (30%) of patients carrying specific *OAT* variants. Pyridoxine-responsiveness was defined as a lowering of plasma ornithine levels. The decrease in plasma ornithine in responsive patients on pyridoxine monotherapy ranged from 19.2% to 68.8%. 79% of patients received additional therapy, which was usually started at the same time, making it difficult to estimate whether a decrease in ornithine levels can be attributed to pyridoxine, a natural protein-restricted diet, or the combination of the two. In 33% of patients where serial BCVA was provided an improvement was noted. There was no clear dose responsiveness.

Heller et al. (2017) described two patients that reported an improvement in BCVA and regression of cystoid macular oedema after treatment with a protein-restricted diet in combination with pyridoxine supplementation. These treatments were started concurrently, therefore it is difficult to establish which treatment regimen attributed to the improvement in BCVA [15].

The potential side effect of pyridoxine is a reversible peripheral neuropathy [57]. Interestingly, this is also reported as a possible feature of disease in 21 patients as reported by Peltola et al. (2002). These patients were not treated with pyridoxine, yet had abnormal results on neurography. These abnormalities associated with the severity of ophthalmic symptoms and the age of the patient [58].

Other supplementations, such as lysine and proline, have only been tested in small groups. Although their supplementation makes sense based on our current knowledge of the biochemical pathways involved

in GACR, it is important to further investigate the effect that these supplements truly have on clinical symptoms and disease progression.

Lysine is not commonly used in the treatment of other IEMs, although there are some cases where it is used in lysinuric protein intolerance (LPI) in order to correct low lysine levels [59]. A systematic review analysing the side effects of lysine reports little to no side-effects, although mild gastrointestinal complaints have been reported [60].

Proline supplementation has not been commonly reported as a therapeutic modality in IEMs. However, it might play an important role in a variety of biochemical and metabolic processes within the cell [61] and although very little research has been done on the role of proline within the treatment of GACR, it might be an interesting treatment modality. Especially as proline is one of the preferred nutrients of the RPE [46].

Supportive therapy such as intravitreal corticosteroids or intravitreal antivascular endothelial growth factor agents seem to have a good short-term result in the treatment of cystoid macular oedema (CME) [62–66]. This is comparable to the effect these treatments have in cystoid macular oedema in retinitis pigmentosa, another hereditary retinal atrophy [67].

Lastly, although only one patient included in the review received creatine supplementation, it is an important treatment modality to keep in mind. Hyperornithinaemia in GACR leads to an inhibition of arginine-glycine amidinotransferase (AGAT), which can be visualised with MR spectroscopy [68].

Creatine deficiency in primary creatine synthesis disorders leads to symptoms such as intellectual disability, motor impairments, and epilepsy [69]. In patients with GACR neurological abnormalities have been reported in a subset of patients [10,70]. Because GACR is usually considered to be a disease solely affecting the eye, there is no systematic neurological assessment of this this patient group.

Indeed correction of GACR-associated creatine deficiency is a tractable therapeutic target, distinct from the previous therapies as it is not directed at reducing ornithine levels. Heinänen et al. (1999) described five patients with GACR treated with methionine (420–1120 mg/day) and guanidinoacetate (330–880 mg/day), and four patient treated with creatine (1.5–2 g/day). MR spectroscopy showed almost normalised creatine phosphate/inorganic phosphate ratios in the muscles of these patients, when compared to healthy controls [10]. Näntö-Salonen et al. (1999) reported similar results with regards to creatine ratios in the brain in the same nine patients [70]. All patients responded similarly to creatine and creatine precursor supplementation, although some patients had higher doses compared to other patients. Clinical parameters were reported in neither of the two studies.

5. Limitations

Research on therapeutic interventions in GACR is limited and most studies are designed as observational open-label studies and published as case reports. This results in evidence level IV. No large historical cohort data is available, which obstructs comparison to untreated patients. Reasons for the lack of high evidence studies include the extremely small population size inherent to ultra-rare diseases, but also the lack of standardised protocols for treatment and follow-up. Meta-analysis or even comparison of individual case reports is not possible given the clinical and genetic heterogeneity, differences in type and duration of therapy, follow-up as well as outcome measures. Additionally, the patient population is very heterogeneous; clinical manifestations and age of apparent onset vary among individuals even within the same family. Furthermore, pre-analytical (fasting, time of day) as well as analytical differences are important to keep in mind when comparing ornithine levels as measured at different laboratories in different reports.

The lack of knowledge on the natural course of the disease further complicates the interpretation of results. Renner et al. (2012) reported a patient that did not receive any type of treatment during 39 years of life, yet she did exhibit periods of disease stabilisation [71]. Jasani et al. (2018) reported a patient that, despite not adhering to a protein-restricted diet, reported 18 years of progression-free disease [72]. This emphasises the importance of sibling studies such as performed by Kaiser-Kupfer (1991, 2002, 2004) [17,18,50] but even more the necessity of a physician-driven international patient registry.

The majority of studies had no predetermined ophthalmic outcome measure. Structural diagnostic tools such as funduscopy and optical coherence tomography (OCT) are relevant for diagnosing the characteristic lesions of GACR. With respect to functional tools, best corrected visual acuity (BCVA) and the measurement of visual fields is often used to assess visual function. Although the measures of visual acuity and visual fields are important, they do not convey all aspects of vision, such as dark adaptation and contrast sensitivity [73]. Specifically, they do not assess the degree of loss of rod cells, which is relevant in GACR as nyctalopia is usually one of the primary symptoms. Retinal damage due to GACR is probably not reversible. Improvement after initiating therapy is probably due to a decrease in macular oedema. The importance of standardised ophthalmic measures for follow-up has also been emphasised in retinitis pigmentosa and choroideraemia, two hereditary eye diseases that also display retinal atrophy [74–76].

In conclusion, this review shows that several treatment modalities used in GACR, namely a protein-restricted diet, lysine supplementation, and in a sub-group of patients, pyridoxine, are effective in lowering plasma ornithine. A protein-restricted diet may slow progression of disease. Creatine supplementation may normalise brain and muscle creatine. However, due to the lack of data and evidence, we cannot conclude an effect of therapy on disease progression.

6. Future directions

It is essential to improve GACR (clinical) research and subsequently care for patients with GACR. As this research has shown, the GACR study populations are often small and it is difficult to establish enough power to perform clinical trials. It is important to establish a historical cohort of GACR patients to gain insight in the progression of disease and the associated changes in outcome measures. Historical cohorts can also function as controls if needed in trials with small patient populations [77]. A physician-driven registry can help to develop a historical cohort and evaluate natural disease course. To assess any therapeutic effect it is necessary to obtain disease specific outcome measures amenable to change, as has been done for other degenerative (retinal) disorders [73–76]. Clinical endpoints recommended for other inherited retinal diseases are: BCVA, visual field sensitivity, retinal sensitivity, multiluminance mobility tests, electrophysiological measures such as ERG, OCT, and fundus autofluorescence [74].

Finally, it is needed to further unravel the OAT pathway and establish which substances truly affect OAT function. *In vitro* studies have shown that pyridoxine stimulates residual enzyme activity, however it is not known if there are more compounds that could affect OAT and thus affect plasma ornithine levels. High-throughput assays could help gain insight in the substances that rescue OAT function. To precisely establish the molecular and biochemical and cellular effect of ornithine on the retina and therapeutic testing, human retinal organoids could be used. Furthermore, to fully gain an understanding of the metabolic pathway and the breakdown of ornithine, stable isotopes could be used for *in vivo* and *in vitro* experiments.

By obtaining the missing clinical and biochemical links in GACR we might be able to perform intervention studies in GACR patients, eventually leading to the development of new therapeutic regimens that could give a new perspective to this debilitating chronic disorder.

Declaration of Competing Interest

The authors report no conflict of interest.

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