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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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Contents

| | | |
|--------|--|---|
| 1. | Introduction | 0 |
| 2. | Methods | 0 |
| 2.1. | Search strategy and eligibility criteria | 0 |
| 2.2. | Data extraction and synthesis. | 0 |
| 2.3. | Data quality. | 0 |
| 3. | Results | 0 |
| 3.1. | Search and quality of evidence | 0 |
| 3.2. | Clinical characteristics | 0 |
| 3.3. | Genotypes | 0 |
| 3.4. | Treatment | 0 |
| 3.4.1. | Outcome measures | 0 |
| 3.4.2. | Protein-restricted diet | 0 |
| 3.4.3. | Pyridoxine supplementation | 0 |
| 3.4.4. | L-lysine supplementation | 0 |
| 3.4.5. | Proline supplementation. | 0 |
| 3.4.6. | Creatine and precursor supplementation | 0 |
| 3.4.7. | Combination therapy | 0 |
| 4. | Discussion and conclusions | 0 |
| 5. | Limitations | 0 |
| 6. | Future directions. | 0 |
| | Declaration of Competing Interest | 0 |
| | Acknowledgments | 0 |
| | References | 0 |

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



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Fig. 1. Metabolic pathways involving ornithine.

Glu: glutamate, GSA: glutamate-5-semialdehyde, P5C: Δ^1 -pyrroline-5-carboxylate, *OAT*: ornithine aminotransferase, *PRODH*: proline dehydrogenase, *P5CDH*: Δ^1 -pyrroline-carboxylate dehydrogenase, *P5CS*: Δ^1 -pyrroline-carboxylate synthase, *PYCR1/2*: Δ^1 -pyrroline-carboxylate reductase 1/2, *PYCR1*: Δ^1 -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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[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

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 <i>OAT</i> |

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.

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



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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.

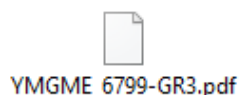


Fig. 3. PRISMA flow diagram depicting the process of inclusion of articles in this systematic review.

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.

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 al¹

^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>):

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 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

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, funduscopy | 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, funduscopy | 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, funduscopy | NR | NR | Yes | 629 |
| R. Christopher et al. (1999) | Myopia, PVL, CPVF, nyctalopia, BCE | NR | AA, funduscopy | NR | NR | Yes | 1008 |
| X. Cui et al. (2018) | PVL, CPVF, nyctalopia, BCE | NR | AA, MA, funduscopy | c.473A > C (p.(Tyr158Ser)) | c.473A > C (p.(Tyr158Ser)) | Yes | 586 |
| G. Casalino et al. (2018) | Difficulty reading | Failure to thrive | AA, MA, funduscopy | 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, funduscopy | NR | NR | Yes | 955 |
| Y. Mashima et al. (1999) | NR | NR | AA, EA, MA, funduscopy | 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, funduscopy | c.498C > A (p.(Thr166*)) | c.498C > A (p.(Thr166*)) | Unclear | 877 |
| Y.R. Sharma et al. (2006) | CPVF, central scotoma | NR | AA, funduscopy | 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, funduscopy | c.271G > A (p.(Gly91Arg)) | c.271G > A (p.(Gly91Arg)) | No | 1189 ± 105 |
| M. Zekušić et al. (2017) | PVL, strabismus | Attention deficit | AA, MA, funduscopy | c.868_870delCTT (p.(Leu290del)) | c.868_870delCTT (p.(Leu290del)) | Unclear | 1039 |
| S. Katagiri et al. (2014) | Nyctalopia | NR | AA, EA, MA, funduscopy | 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, funduscopy, MRI | NR | NR | No | 536 |
| K. Peltola et al. (2000) | NR | NR | AA, MA, funduscopy | “typical Finnish mutation” | ? | NR | NR |
| J. Michaud et al. (1995) | VI | NR | AA, EA, MA, funduscopy | c.677C > T (p.(Ala226Val)) | c.1192C > T (p.(Arg398*)) | Yes | 652 |
| Y. Ohkubo et al. (2005) | PVL | NR | AA, EA, MA, funduscopy | c.710G > A (p.(Gly237Asp)) | c.710G > A (p.(Gly237Asp)) | Yes | 1140 |
| S. Doguizi et al. (2015) | Low visual acuity | NR | AA, funduscopy | NR | NR | NA | 622 |

(continued on next page)

Table 3 (continued)

| 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 |
|--------------------------------|--------------------------------------|---|---------------------|---|---|--|---|
| S. Hayasaka et al. (1985) | NR | NR | AA, funduscopy | NR | NR | 1, 4, 5: Unknown 2: No 3: Yes | 739 980 524 984 853 818 |
| R. Feldman et al. (1989) | PVL | NR | AA, funduscopy | NR | NR | NR | 741 462 |
| S.P. Shrestha et al. (2010) | Frequent change of glasses | Petit mal epilepsy | AA, funduscopy | NR | NR | Yes | 783 831 |
| S.J. Kim et al. (2013) | PVL, nyctalopia | NR | AA, MA, funduscopy | c.425G > A (p.(Gly142Glu)) | c.199 + 11_199dupAATTAA (?) | Unclear | 831 964 |
| D. Valle et al. (1980) | PVL, nyctalopia | NR | AA, EA, funduscopy | NR | NR | No | 964 |
| M.I. Kaiser-Kupfer (1980) | NR | NR | AA, funduscopy | NR | NR | No | 964 |
| I. Zhioua Braham et al. (2018) | PVL, pseudophakia | NR | AA, funduscopy | NR | NR | Unclear | 723 |
| V.E. Shih et al. (1981) | NR | 1: Muscle weakness 2: Minor motor seizures | AA, EA, funduscopy | 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, funduscopy | NR | NR | No | 750–1000 |
| G. Stoppoloni et al. (1982) | NR | Mild developmental delay | AA, EA, funduscopy | NR | NR | <i>In vitro</i> no, <i>in vivo</i> unclear | 744.9 |
| C. Çavdarli et al. (2019) | PVL | NR | AA, MA, funduscopy | 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) Range (2-8) (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 |
| | | PRD Pyridoxine | 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 586 µmol/L | Patient 1: 496 µmol/L Patient 2: Lost in follow up 445 µmol/L | 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 | 582 µmol/L | No decrease | After 18 months: chorioretinal atrophy had not progressed. Resolution of CME after 3 months |
| 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 877 µmol/L | 340 µmol/L 250 µmol/L 340 µmol/L <500 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 | NR | NR | 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 |

(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 |
|--------------------------------|----------------------------|--|---|---|--|--|--------------|--|--|---|--|
| M. Zekušić et al. (2017) | 6-9Y | PRD, pyridoxine, L-lysine, systemic corticosteroids, topical carbonic anhydrase inhibitors | Phase 1: no restriction Phase 2: 1 g/kg/day Phase 3: 0.6 g/kg/day | Phase 1: pyridoxine 500 mg/day Phase 2: pyridoxine to 200 mg/day | Phase 3: Addition of L-lysine 12 g/day | Phase 1: 3.5 months Phase 2: 2.4 years Phase 3: 7.5 months 16 years | NR | No | 1039 µmol/L | Phase 1: 907 µmol/L Phase 2: 537 µmol/L Phase 3: 489 µmol/L | After phase 3: positive change in ERG, significant improvement of central macular oedema |
| S. Katagiri et al. (2014) | 1: 6 2: 2 | ARD | NR | NA | NA | 6 months | No | 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 |
| 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. Çavdarit et al. (2019) | 26 | ARD Topical brinzolamide 1% nepafenac 0.1% Pyridoxine Diet | 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) | | 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.

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.

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 fundoscopic 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 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].

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 funduscopy 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 $\mu\text{mol/L}$) [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 Çavdarlı et al. (2020) did not adhere to diet and 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 funduscopy 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

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 scattered 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 macula with paramacular areas of RPE atrophy. Individual larger choroidal vessels from Sattler's and Haller's layers in areas of RPE atrophy Small fluctuations of residual intraretinal cysts with good foveal contour |
| 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 in 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), | 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 opacification of the posterior vitreous face | NR | NR | increase of chorioretinal atrophy (n = 1), unchanged (n = 2) 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 μ m OD 355 μ m 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 |

(continued on next page)

Table 5 (continued)

| Reference | Treatment | Follow-up time | Diagnosis | | Follow-up | | |
|-----------------------------|--|-------------------|---|---|----------------|-------------------------|--|
| | | | Ophthalmoscopy | Fundus autofluorescence | Ophthalmoscopy | Fundus autofluorescence | |
| G. Stoppoloni et al. (1982) | Protein-restricted diet | 6 years, 3 months | Many areas of choriorretinal atrophy in the periphery of the fundus | NR | NR | NR | NR |
| C. Cavdatli et al. (2019) | Arginine-restricted diet Topical brinzolamide 1% nepafenac 0.1% | 2 months | Bilateral posterior subcapsular cataracts, peripheral and midperipheral window defects 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 |

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

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.(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].

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 Abolished responses ODS | 20/40 OD 20/60 OS | NR | NR |
| G. Casalino et al. (2018) | Arginine-restricted diet Pyridoxine supplementation | 3 years | 20/40 ODS | NR | | 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 NR |
| 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 menarcho (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 | 3 years | NR | NR | Performed, results not reported | NR | NR | "Positive change" |

(continued on next page)

Table 6 (continued)

| Reference | Treatment | Follow-up time | Diagnosis | | | Follow-up | | |
|----------------------------------|--|-------------------|--|--|--|---|--|---|
| | | | BCVA | Visual fields | Electroretinogram | BCVA | Visual fields | Electroretinogram |
| S. Katagiri et al. (2014) | corticosteroids 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 20/400 OD 20/200 OS | 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 | | | |
| 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: NR | 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 cone 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 |

Table 6 (continued)

| Reference | Treatment | Follow-up time | Diagnosis | | | Follow-up | | |
|-----------------------------|---|-------------------|---|--|--|--|-----------------------------------|---|
| | | | BCVA | Visual fields | Electroretinogram | BCVA | Visual fields | Electroretinogram |
| O.N. Elpeleg et al. (2001) | Lysine supplementation | 40–55 days | NR | NR | NR | NR | NR | NR |
| 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 μ V 2: B amplitude 2 mV | 1: 20/50 ODS 2: 20/200 OD 20/60 OS | NR | 1: B amplitude 2 μ V 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.

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-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,

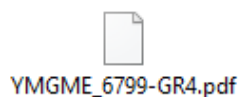


Fig. 4. Plasma ornithine before and during treatment in patients with a protein-restricted diet. On the left, patients that were only treated with a protein-restricted diet are depicted. On the right, patients with a protein-restricted diet and additional therapy are depicted.

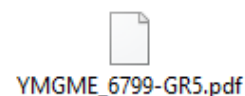


Fig. 5. Plasma ornithine levels before and during treatment in patients that received pyridoxine monotherapy and were classified by the authors of the respective papers as being pyridoxine-responsive.

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 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 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]. Nantö-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 choroideaemia, 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, multi-luminance 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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