A Review of Treatment Modalities in Gyrate Atrophy of the Choroid and Retina (GACR)


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Introduction

Autosomal recessive inborn error of amino acid metabolism
- Ornithine-δ-aminotransferase deficiency

Primarily ophthalmic phenotype:
- Progressive chorioretinal atrophy
- Cystoid macula oedema
- Early (bilateral) cataract
- Myopathy, neuropathy

Biochemically characterised by:
- Hyperornithinaemia
- Secondary creatine deficiency

Treatment of GACR has several aims

- Lowering plasma ornithine
- Correcting secondary creatine deficiency
- Treating local ophthalmic complications

Creatine and creatine precursor supplementation, Cataract extraction, eye drops, correction of refractive error, intravitreal injections
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Methods

PRISMA-guided search strategy of PubMed and Embase.

Records identified through search n=96

Added from systematic search of references n=9

Number of records after exclusion of duplicates n=102

Screened based on title and abstract n=102

Excluded based on title and abstract n=49

Screened based on full-text n=53

Excluded based on full-text n=21

Included n=33

Added after revision n=1

Results and conclusions

- N=107, 85 treated patients
- Median duration of 1.25 years (7d-26y)

Protein restriction lowered plasma ornithine in 44% (n=28) of treated patients
- 64 treated patients
- 50% received additional therapy

30% (n=32) of all patients were classified as pyridoxine-responsive
- 42 treated patients
- 79% received additional therapy
- Mean dosage of 405 mg/day

L-lysine (10-15 g/day) lead to a 21-34% decrease in plasma ornithine
- 10 pyridoxine-unresponsive patients

Creatine supplementation (1.5-2 g/day) can correct intracerebral and intramuscular creatine deficiency
- No research performed on patient-reported outcome measures

Colour fundus photograph of a 55-year-old patient with advanced gyrate atrophy, showing round patches of profound peripheral chorioretinal atrophy. The macula is also profoundly atrophic, except for a small central island of relative sparing of the fovea, explaining the relatively preserved Snellen visual acuity of 20/30.
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Discussion

- The rarity of GACR partly explains the lack of high-quality data and evidence-based guidelines.
- Mechanisms underlying pyridoxine responsiveness have not been completely elucidated.
- Pyridoxine might play a chaperone role, in addition to stimulating residual enzyme activity.
- Ornithine might not be the best target for therapeutic efficacy.
- Different metabolites might play an additional role in chorioretinal atrophy in GACR.
- Plasma ornithine might not correspond to intravitreal ornithine due to the blood-retina barrier.
- Creatine supplementation is a tractable therapeutic target with a distinct aim.
- A patient registry provides a natural history cohort and insight on genotype-phenotype relation.
- Establishing standardised (ophthalmic) outcome measures is essential to improve research.

Future directions

- Physician-driven patient registry
- Retinal models to facilitate organ-specific research
- Unraveling underlying metabolic changes due to OAT deficiency
- Connecting the GACR community

Our team