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Asymptomatic retinal dysfunction in a patient with alpha-methylacyl-CoA racemase deficiency

Retinal abnormalities in AMACR deficiency

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Conflict of interest

All authors declare that they have no conflict of interest in this study.

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Brief summary

AMACR deficiency is a rare genetic condition that can potentially contribute to retinal dystrophy through various mechanisms. Additionally, it may lead to a wide spectrum of systemic signs and symptoms. Interestingly, in contrast to other reported studies, our patient was completely asymptomatic, with no evidence of systemic disorders.

Keywords: alpha methyl acyl-CoA racemase (AMACR) deficiency; genetics; retinal disorders

Abstract

Purpose: To present a case of a young female patient with asymptomatic retinal dysfunction associated with alpha-methylacyl-CoA (AMACR) racemase deficiency

Methods: Retrospective analysis of the medical notes of a single patient. Detailed slit-lamp examination was completed by Optos colour fundus photography and enhanced depth imaging optical coherence tomography (EDI-OCT). Genetic testing was conducted to establish the diagnosis, and the patient was also referred to the Department of Neurology for further assessment.

Results: Dilated fundoscopy and ophthalmic imaging revealed bilateral retinal pigment epithelium abnormalities that could be associated with a genetic retinal disorder. Indeed, genetic testing showed that this lady was homozygous for AMACR (OMIM 604489; Gene ID 23600) variant NM 014324.6: c.154T>C; p.(Ser52Pro). She had no detectable neurological deficit.

Conclusion: AMACR deficiency is a rare genetic condition that can potentially contribute to retinal dystrophy through various mechanisms. Additionally, it may lead to a wide spectrum of systemic signs and symptoms. Interestingly, in contrast to other reported studies, our patient was completely asymptomatic, with no evidence of systemic disorders.

Introduction

Peroxisomes are cellular organelles that play a crucial role in catabolic and metabolic processes, particularly in lipid metabolism **[1]**. The breakdown of phytanic acid, a dietary fatty acid with methyl branches primarily found in dairy products, meat, and certain fish, is accomplished through peroxisomal alpha oxidation **[1]**. This process generates pristanic acid, which is further degraded through peroxisomal beta-oxidation **[1]**. Peroxisomal beta-oxidation not only facilitates the synthesis of docosahexaenoic acid, an omega-3 fatty acid abundant in neuronal tissue and photoreceptor outer segments but also contributes to bile acid production **[1]**. Disorders associated with peroxisomes can be broadly categorized as either peroxisome biogenesis disorders, such as Zellweger syndrome, or deficiencies in specific peroxisomal enzymes, like alpha-methylacyl-CoA racemase (AMACR) deficiency **[2]**. AMACR is responsible for converting certain compounds that possess a 2R-methyl branch, including pristanic acid and bile acid intermediates, into their degradable S-stereoisomers through peroxisomal beta-oxidation. As a result, patients with AMACR deficiency exhibit significantly elevated levels of (2R)-pristanic acid and C27-bile acid intermediates, while phytanic acid may also be mildly increased **[3]**. The range of clinical manifestations encompasses neonatal cholestatic liver disease, giant cell hepatitis, or a combination of both, deficiency in fat-soluble vitamins, early-life bloody stool due to vitamin K deficiency, cognitive challenges, as well as neurological conditions such as encephalopathic episodes, sensory and motor neuropathy, seizures, and signs of cerebellar dysfunction **[1-9]**. Of the 16 previously reported patients, 10 were found to have clinically obvious pigmentary retinopathy **[3-9]**. A significant number of individuals previously identified as having visually evident pigmentary retinopathy were not

subjected to electrophysiology studies, and the available information was limited for those who were. In this case study, we present one patient affected by this uncommon condition with no evidence of systemic involvement, emphasizing the importance of assessing retinal function in such patients, even in the absence of reported visual issues.

Case report

A 32-year-old female patient was referred to our unit following a routine check-up with her optician. The optician noted bilateral retinal abnormalities and a slightly reduced sensitivity in her visual field. The patient was asymptomatic and in overall good health. Regarding her previous ophthalmic history, she reported only amblyopia in her left eye. She was systematically well with no history of neurological disease.

Her best-corrected visual acuity was 6/7.5 in the right eye and 6/12 in the left eye. Intraocular pressure was within normal limits in both eyes. Slit-lamp examination of the anterior segment did not reveal any pathological findings. Dilated fundoscopy revealed bilateral retinal pigment epithelium (RPE) mottling and flecks, which could potentially be indicative of the Stargardt disease spectrum. Ophthalmic examination was completed by retinal imaging including Optos photography **[Figure 1]** and EDI OCT **[Figure 2]**. Based on the clinical and imaging findings, it was determined that genetic testing should be conducted to investigate potential causes of macular dystrophy. Whole genome sequencing (illumina) was done via the Genomics England bioinformatics pipeline. This demonstrated that the patient was homozygous for AMACR (OMIM 604489; Gene ID 23600) variant NM 014324.6: c.154T>C; p.(Ser52Pro). A

neurological assessment did not detect any neurological deficits. Subsequent biochemical analysis identified a significantly raised pristanic acid at 95.6 umol/L (0.4-4 reference range).

Discussion

AMACR deficiency can potentially contribute to retinal dystrophy through various mechanisms. One such mechanism involves the elevation of pristanic acid, which can induce the production of reactive oxidative species and subsequent cell death in neural tissues, including the retina **[10]**. Additionally, cholestatic liver disease associated with AMACR deficiency can lead to poor absorption of fat-soluble vitamins, such as vitamin A. Deficiency in vitamin A, in turn, can result in retinal dysfunction. Another possible mechanism for retinal dystrophy in AMACR deficiency is the impaired synthesis of docosahexaenoic acid (DHA), an essential component of photoreceptor outer segments. Considering these factors, the presence of retinal dystrophy in individuals with AMACR deficiency is not surprising **[1-3]**.

In theory, dietary modification is considered a potential treatment approach for AMACR deficiency. The restriction of phytanic and pristanic acids, combined with the supplementation of cholic acid, has the potential to limit the development of retinal dystrophy and neuronal degeneration **[1-4]**. However, due to the rarity of this disease, conclusive evidence supporting the efficacy of this approach is currently lacking. We propose that multimodal imaging and electrophysiological monitoring of retinal function, even in individuals without evident pigmentary retinopathy, could serve to assess and track the response to dietary modification.

Although asymptomatic cases have been previously reported **[3]**, our case is also unique as there were no obvious systemic abnormalities associated with this genetic disorder. This

homozygous missense mutation in the AMACR has previously been reported to cause disease in the homozygous state **[11]**. Functional studies also predict it results in an inactive protein **[4]** and the patient had significantly raised pristanic acid. AMACR deficiency may cause a wide spectrum of systemic features with variable degrees of severity. This case highlights there may not be systemic features prior to ophthalmic pathology. However, ongoing systematic review is recommended in case systemic features develop later.

Patient anonymity

The patient's anonymity is carefully protected. This is an observational study and does not include any personal data or identifiable details.

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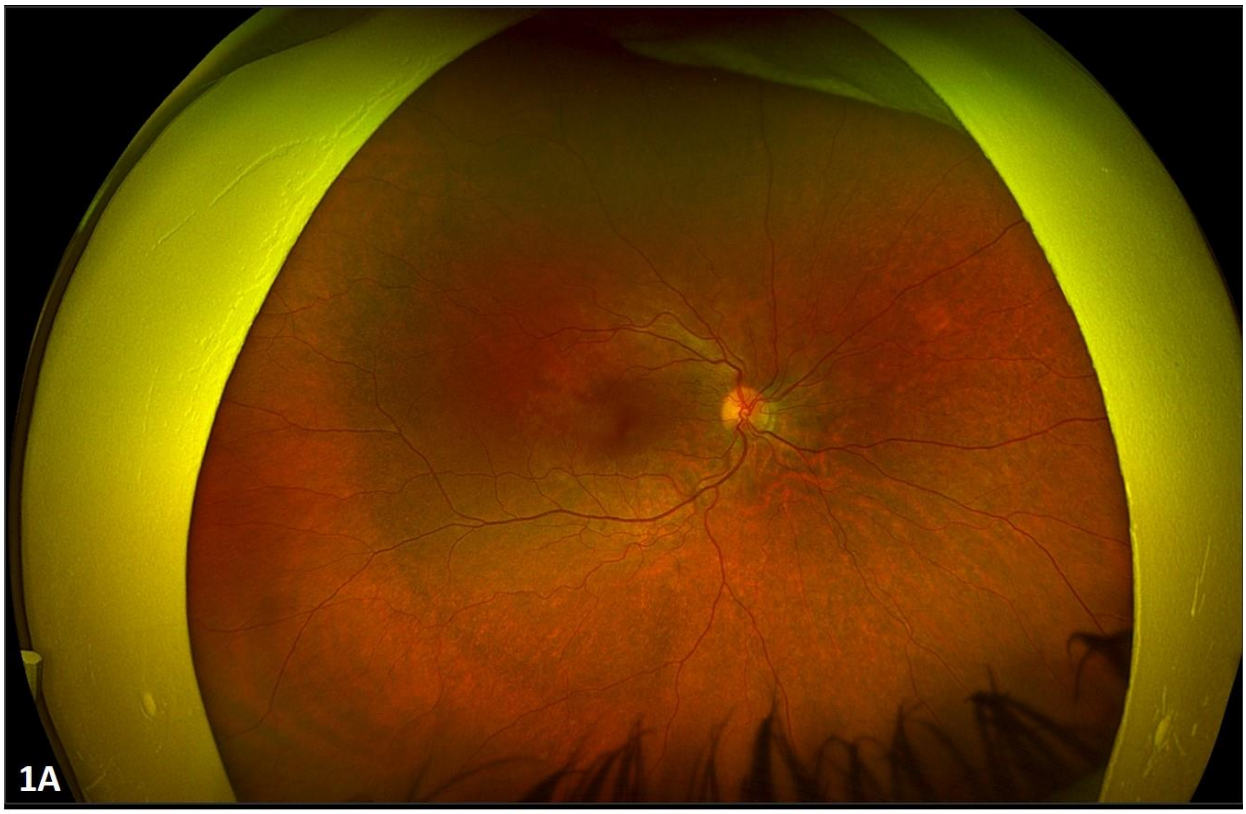
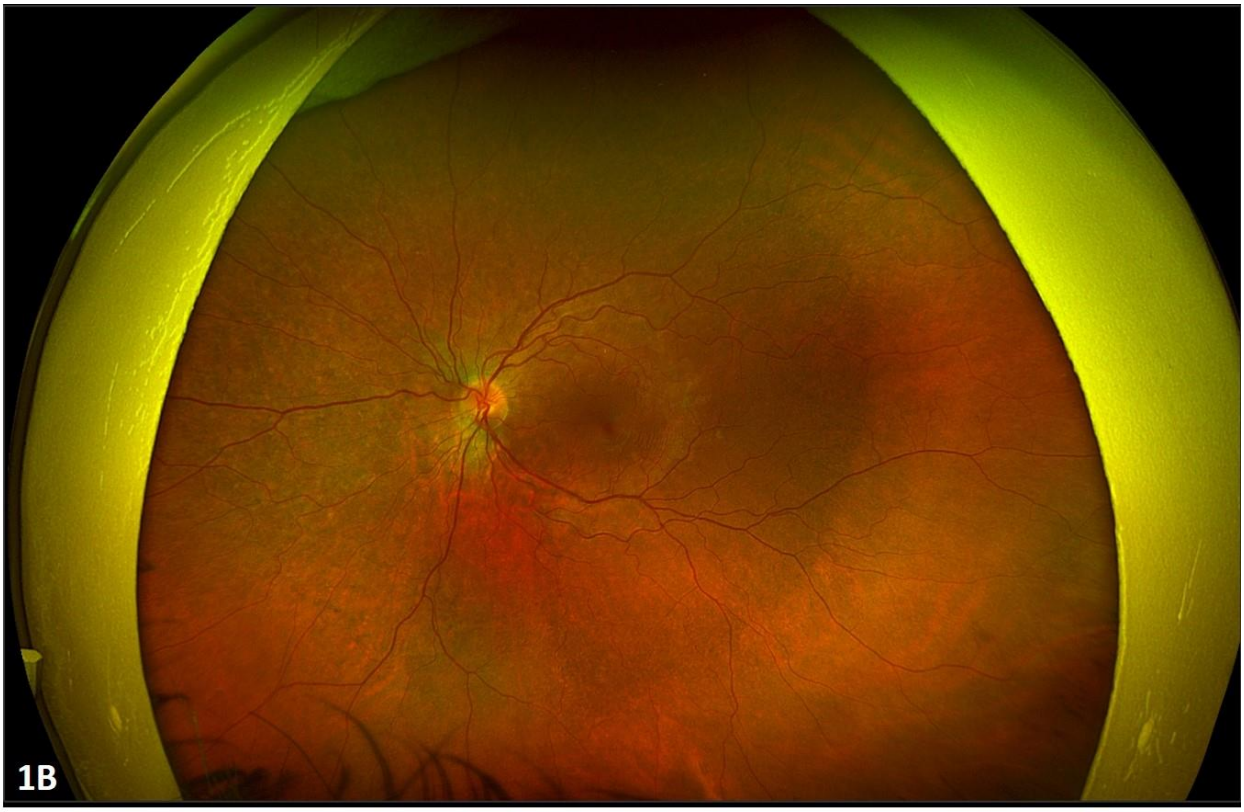
Figure 1 (a-d)

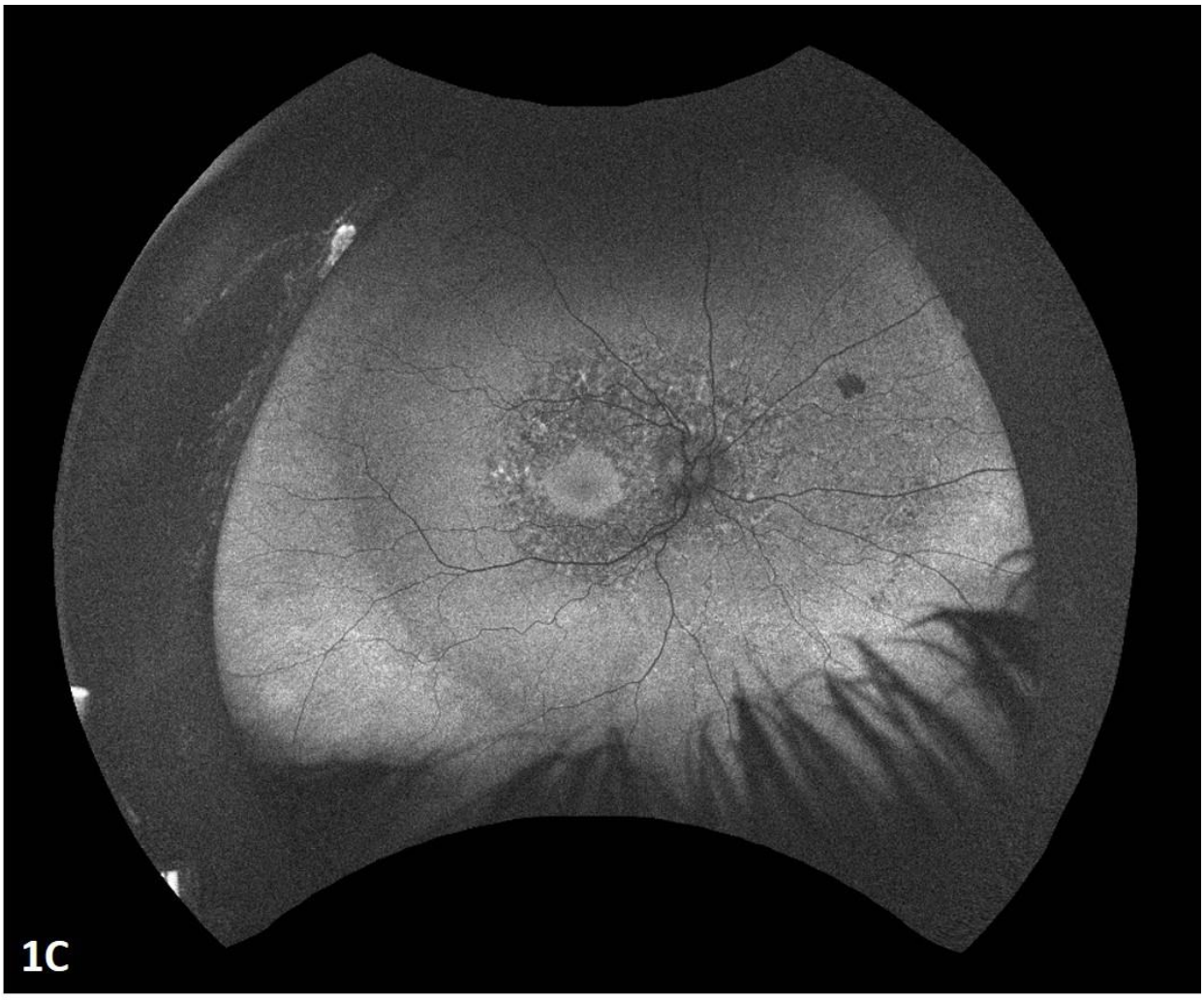
Optos ultra-widefield colour photography (a, b) and autofluorescence (c, d). Colour photography shows retinal pigmentary atrophic changes, whereas fundus autofluorescence demonstrates corresponding areas of hypo and hyperfluorescence pericentrally, sparing the central macula and the peripapillary area in both eyes.

a, c: right eye

b, d: left eye







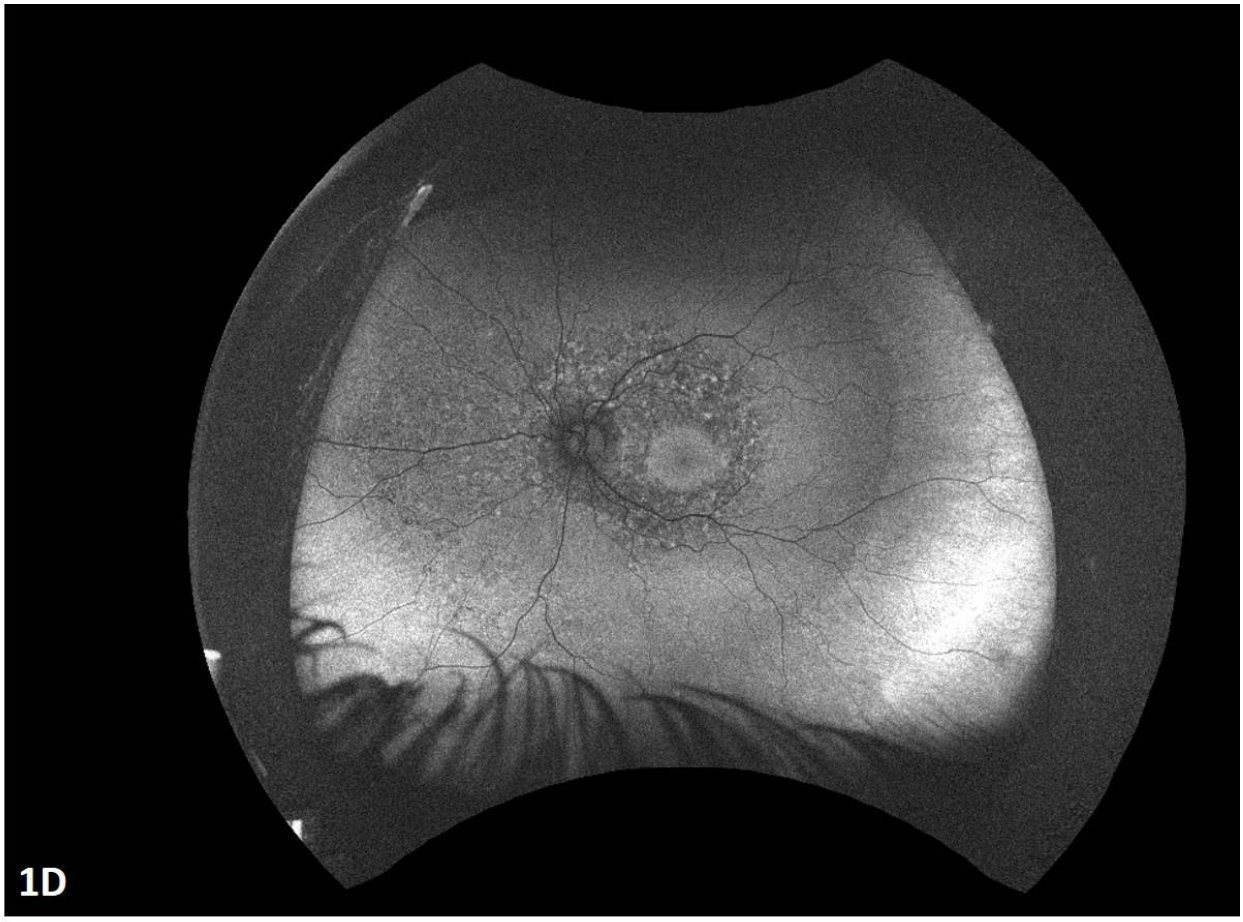


Figure 2 (a, b)

Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) demonstrates normal retinal structure of the central macula.

a: right eye, b: left eye