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Short communication

# Retinitis pigmentosa as a clinical presentation of LCHAD deficiency: A clinical case and review of the literature☆

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ABSTRACT

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency is a rare metabolic disease caused by a specific mutation in the HADHA gene, which leads to an alteration in the metabolic pathway of fatty acids. Its most frequent form of presentation at the ophthalmological level is retinitis pigmentosa, and in some cases the ophthalmologist could be the first one to alert the other paediatric specialties to carry out a multidisciplinary approach to the case. The case is presented of a patient with long-chain 3-hydroxyacyl-CoA dehydrogenase deficit detected in neonatal screening, and which clinically debuted as pigmentary retinosis with no alteration in visual acuity as observed in the fundus images and optical coherence tomography of the retina provided. Finally, a review of the literature of this potentially lethal pathology is presented, and the main pathological and clinical features are highlighted.



## Retinosis pigmentaria como clínica de presentación del déficit de LCHAD: caso clínico y revisión de la literatura

*Palabras clave:*
3-hidroxiacil CoA-deshidrogenasa de cadena larga
Retinosis pigmentaria
Cribado neonatal
Betaoxidación

RESUMEN

El déficit de 3-hidroxiacil CoA-deshidrogenasa de cadena larga es una enfermedad metabólica poco frecuente debido a una mutación específica en el gen HADHA, lo que provoca una alteración en la vía metabólica de los ácidos grasos. Su forma de presentación más frecuente a nivel oftalmológico es la retinosis pigmentaria, y en algunos casos el oftalmólogo podría ser quien alerte a las demás especialidades pediátricas para llevar a cabo un abordaje multidisciplinar del caso. Presentamos el caso de una paciente con déficit

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de 3-hidroxiacil CoA-deshidrogenasa de cadena larga detectado en el cribado neonatal que inició clínicamente como retinosis pigmentaria sin alteración de la agudeza visual y del que se aportan imágenes de fondo de ojo y de tomografía de coherencia óptica de la retina. Por último, se expone una revisión de la literatura de esta enfermedad potencialmente letal y se destacan las principales características anatomopatológicas y clínicas.



## Introduction

Fatty acids are fundamental lipidic molecules in living beings that intervene in the structure of cellular membranes and are a source of basic energy for tissues such as the heart, for the skeletal muscle in situations of greater caloric expenditure (for example, in prolonged exercise or in infections) or as the main resource during fasting. Catalysis of free fatty acids produces acetyl-CoA at the mitochondrial level, molecules that after being oxidized originate adenosine triphosphate, the final product that provides energy to most of cellular metabolic activities.[1]

There is a heterogeneous group of diseases that affect the metabolism of fatty acids and, more specifically, their beta-oxidation. This degradation process consists of 2 phases of oxidation followed by a phase of hydration and a last phase of thiolysis, where the mitochondrial trifunctional protein, or TFP, composed of 4 alpha and 4 beta subunits, catalyzes 3 of these reactions. It intervenes through 3 enzymatic functions: the 3-hydroxiacil CoA-deshydrogenase of long chain (LCHAD), the long chain enoyl CoA-hydrate and the long chain thiolase.[2,3]

LCHAD deficit has autosomal recessive nature. It is produced by a specific mutation in the HADHA[2] gene, located on the short arm of chromosome 2 (2p23). This is a rare condition, with a prevalence of approximately one per 100,000 live births, combined with TFP deficiency.[4] It usually expresses during episodes of illness or fasting and is characterized by lactic acidosis, encephalopathy, hypoketotic hypoglycemia and liver dysfunction. Other complications include rhabdomyolysis, cardiomyopathy, peripheral neuropathy, mental retardation and death.[2,3] The ophthalmological condition expresses as pigment chorioretinopathy that could evolve to chorioretinal atrophy.

It is usually detected in neonatal screening programs with the determination of acylcarnitine in plasma or organic acids in urine by mass spectrometry, among other tests, and diagnosis can be confirmed with DNA study.[3]

Management consists mainly in avoiding fasting, diets restricted to long chain fatty acids and supplementation with medium chain triglycerides, as well as essential fatty acids.[5]

Our objective, based on the following case report, is to increase knowledge of the main characteristics of the disease and to provide specific imaging tests in order to help ophthalmologists to suspect the disease when no previous diagnosis is available.

## Case report

The case of a 4 year old patient, born after uneventful pregnancy and delivery, is presented. Gestational age was 40 weeks and 5 days, with a weight of 3400 g. Neonatal screening detected a fatty acid beta-oxidation disorder and the genetic study evidenced a mutation in the HADHA gene in homozygosis (c.1528G>C).

The asymptomatic patient visited the Ophthalmology room at the age of 3 for follow-up treatment from another hospital. Visual acuity was 20/20 with Pigassou optotype in both eyes. Cover test and anterior segment examination by biomicroscopy were normal. Homogeneous, symmetrical and bilateral hyperpigmentation in the fundus was observed in the fovea and perifoveal hypopigmentation (Fig. 1) and pigment aggregates in the peripheral retina (Fig. 2). Optical coherence tomography (3D OCT-1 Maestro, TOPCON, Tokyo, Japan) showed retinal pigment epithelium (RPE) hypertrophy at the foveal level associated to photoreceptor layer and perifoveal RPE atrophy (Fig. 3).

The electroretinogram recorded responses with discreetly diminished amplitude and bilateral disintegrated morphology as indicative findings of moderate intensity bilateral retinopathy.

No alterations were observed in the study of visual evoked potentials that indicated injury to the optic nerve.

Since birth and the diagnosis of the disease, the patient has kept a strict dietary and metabolic control that has not prevented her from experiencing 3 metabolic crises including an episode with rhabdomyolysis due to the disease and which required hospital admission for recovery.

## Discussion

At the ocular level, LCHAD deficit is clinically manifested in the form of retinopathy of the pigment retinosis type, this being one of the earliest expressions[6] as in the present case. At the onset of the disease, the retina exhibits normal characteristics. The first findings are peripheral pigment aggregates, associated or not to background hypopigmentation and/or pigment accumulations in the macula, evidenced in the fundus images of our patient. AS the disease advances, chorioretinal atrophy appears, finally reaches the fovea. The appearance of staphyllomas in the posterior pole, myopia, cataracts are also described. Some authors have tried to classify these findings.[6]

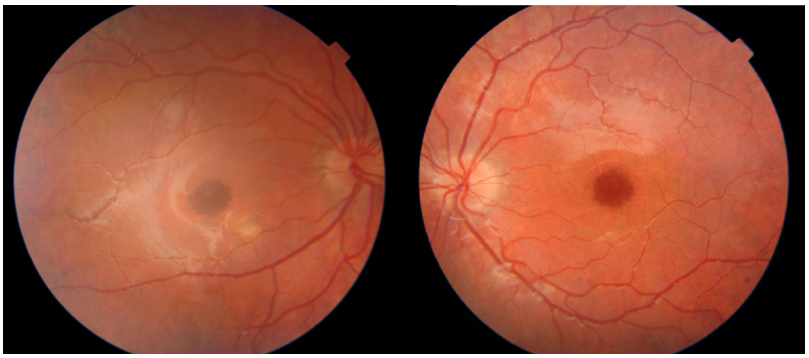

**Fig. 1 – Images of the right (left) and left (right) fundus showing homogeneous hyperpigmentation of the foveal area and perifoveal macular hypopigmentation.**

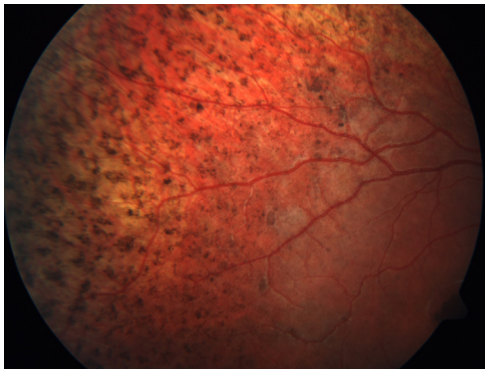

**Fig. 2 – Image of the upper temporary retina of the right eye. Pigment aggregates are observed in the periphery.**

At present, the exact physiopathological mechanism of chorioretinopathy is not known but it is thought that it could be due to a possibly toxic effect of the accumulation of metabolites by incomplete beta-oxidation. In vitro immunohistochemical antibody studies have revealed that, in addition to RPE, TFP has activity in other retinal layers such as photoreceptors and ganglion cells.[7] This suggests that damage to photoreceptors plays a role in the development of retinopathy in LCHAD deficit, although it is RPE that is most affected and the first layer to be compromised.[8] This matches with the tomographic alterations of the case. Other authors have demonstrated a destructuring of the inner plexiform layer in initial stages.[9]

Likewise, the elevation of long-chain 3-hydroxyacylcarnitines has been associated with the progression of chorioretinopathy and retinal dysfunction as measured by electroretinogram.[10]

It is interesting to point out the lack of correlation between retinal dystrophy and visual function in some occasions, as shown in our case in which, despite extensive involvement of the ocular fundus, the patient maintains adequate visual acuity.

Despite the exhaustive dietary control of our patient, acute metabolic decompensations (inherent to the course of the dis-

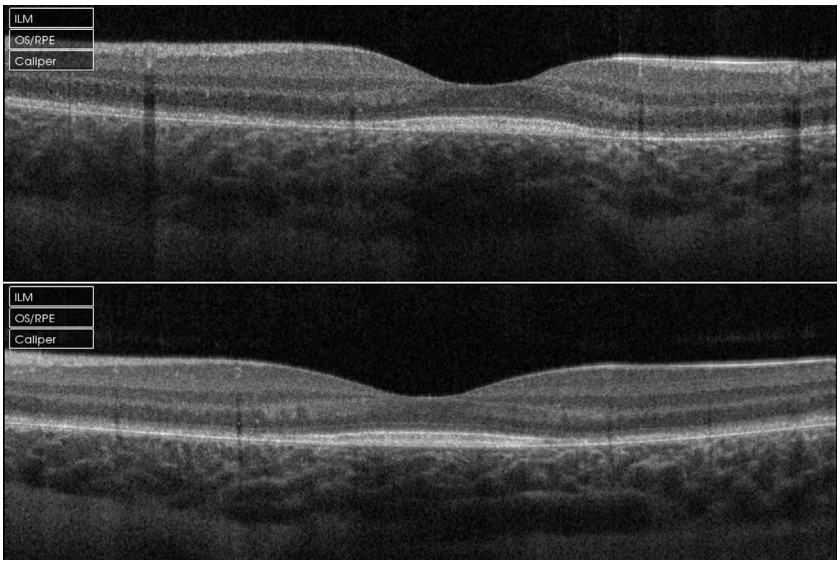


**Fig. 3 – Macular optical coherence tomography of the right eye (above) and the left eye (below) showing atrophy of the photoreceptor layer and the perifoveal pigment epithelium and hypertrophy of the retinal pigment epithelium at the foveal level.**

ease) could not be avoided. This gives rise to suspect that the advanced state of retinal involvement could be related to successive subclinical crises that are not detected, but which do favor the progression of the process and would justify the shorter life expectancy of these patients.

Finally, the ophthalmological knowledge of this disease is of vital importance because, although ocular compromise is very rarely the first finding in our environment in neonatal screening protocols, we could have a less privileged population arriving from other countries where these screening programs are not available. In these cases, the ophthalmologist must detect the possible underlying systemic condition, which may have an impact on the patient's life prognosis. For this purpose, a correct and complete anamnesis is essential in every pediatric patient with retinitis pigmentosa. Once the diagnostic suspicion is reached, it is our obligation to alert other specialties since this entity requires multidisciplinary management and follow-up.

## Conflict of interest

No conflict of interests was declared by the authors.

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