• Letter to the Editor •

Follow-up and multimodal imaging in long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency

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Received: 2017-12-13 Accepted: 2018-05-14

DOI:10.18240/ijo.2018.10.25

Citation: Espinosa-Barberi G, Miranda Fernández S, Valdés Martín ME, Betancor Perdomo MA, Aguilar Rosales CJ. Follow-up and multimodal imaging in long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. *Int J Ophthalmol* 2018;11(10):1730-1732

Dear Editor,

The deficit of 3-hydroxyacyl-CoA dehydrogenase (LCHAD) is a disease whose incidence is approximately 3 cases/100 000 births[1], with autosomal recessive inheritance[2]. The genes involved encode an enzyme that contributes to the production of energy, thanks to the metabolism of long-chain fatty acids[3]. This patology presents different complications of early onset, liver damage, cardiomyopathy, rhabdomyolysis and even death. Symptoms typically appear during childhood and include decay, hypotonia, and hypoglycemia[4].

The deficiency in this enzyme complex called mitochondrial trifunctional protein (MTP) is the only one known of the B-oxidation that produce retinopathy. There are 4 stages proposed by Tyni *et al*[5]. In stage 1, there is normal retinal function with a hypopigmented fundus. Visual acuity (VA) is maintained in stage 2, but there is dysfunction in the electroretinogram (ERG) and there is a foveal pigment. In stage 3, loss of night vision and colors accompanied by central chorioretinal atrophy. In final stage 4, loss of vision is seen with absence of photoreceptors and visualization of choroidal vessels at central level[6].

This deficiency can be detected in prenatal screening through the analysis of chorionic villi and in neonatal analysis by mass spectrometry. In our country, neonatal screening is only available in Galicia[6]. The usual way to monitor the retinopathy of these patients is through ERG and retinography. An 18-year-old male patient with ophthalmological follow-up at 7 year of age due to LCHAD deficiency, diagnosed from birth as a result of vomiting and diarrhea, in treatment since 5mo with a docosahexaenoic acid supplement, carnitine and a low-fat diet, but rich in carbohydrates. The genetic study carried out reveals the G1528C heterozygote mutation.

The first ophthalmologic examination shows a VA of 20/20 in both eyes (OU) and both pole anterior and posterior normal. Subsequently, the revisions were normal. At age 14, coinciding with a period of therapeutic failure of two years, among which there was a loss of follow-up, he began with distal weakness of the lower limbs and myopathic gait, which improved after the resumption of treatment, reaching the conclusion of that it is an axonal motor sensory polyneuropathy secondary to its metabolopathy. In the ophthalmological examination the VA was normal, but in the funduscopy (OF), granular alterations of the pigmentary epithelium at the posterior pole are observed. A visual field (VF) is requested, in which there is an increase in the blind spot in the right eye (RE) and a slight paracentral alteration in the left eye (LE). The color test and the ERG were normal, but the electrooculogram (EOG) has an Arden index of 1.79 in RE and 1.65 in the left one. At 16y of age the VA is reduced, being 20/40 in RE and 20/32 in LE. In the examination of OF, diffuse and extensive alteration of the pigment epithelium affecting mid-periphery is observed, the macula acquiring a coppery color. In optical coherence tomography (OCT) there is involvement of the outer layers of the retina.

Currently, the VA is 20/40 in OU, in the OF there is a retinopathy in salt and pepper with large areas of chorioretinal atrophy and increased macular pigmentation (Figure 1A, 1B). Fundus autofluorescence showed multiple hypo-autofluorescent areas (Figure 1C, 1D). In the OCT there are alterations of the external and choroidal layers with a hyper-reflective choroid secondary to atrophy (Figure 1E-1H). OCT angiography (Figure 2) allows the visualization of the choroidal vessels due to atrophy, as well as alterations at the level of the outer layers. The VF shows progression.

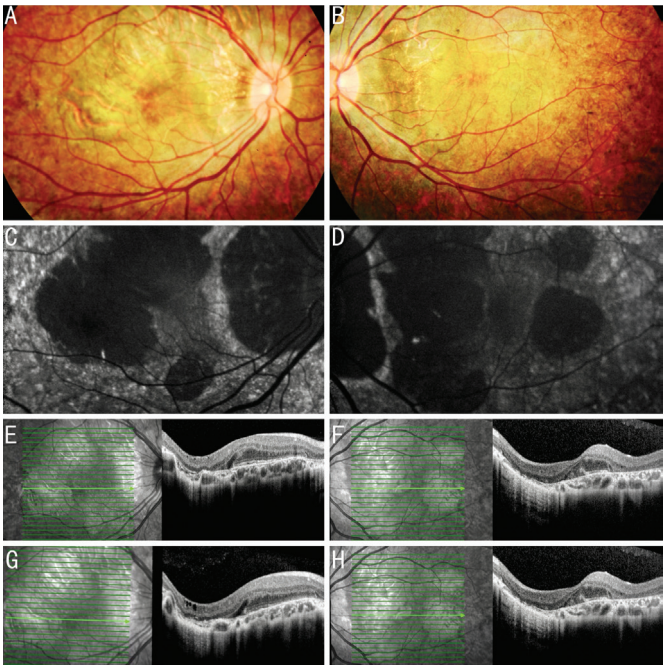

Figure 1 Multimodal exam A, B: Great chorioretinal atrophy, which mainly affects the posterior pole and peripapillary region; C, D: Fundus autofluorescence showing extensive areas of hypo-autofluorescent atrophy surrounded by healthy retinal pigmentary epithelium patches; E, F: OCT 4y ago with great affectation of the external retina and choroid; G, H: Currently, affectation persists and intraretinal cysts appear in the right eye.

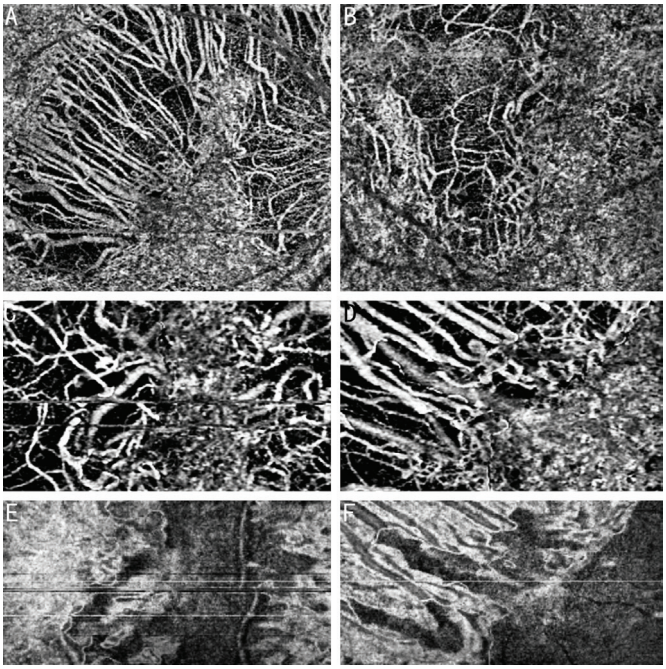

Figure 2 Current analysis through OCT angiography A, B: 8×8 OCT angiography at level of the choriocapillaris showing choroidal vasculature. C, D: 3×3 En-face OCT angiography with geographical atrophy and loss of the choriocapillaris; E, F: 3×3 En-face OCT angiography at level of the ellipsoids layer showing the large rods-cones distrophy.

There is a response in scotopic conditions of amplitude and latency of wave b within normality in the ERG, but the mixed response showed an amplitude below normal limits in OU,

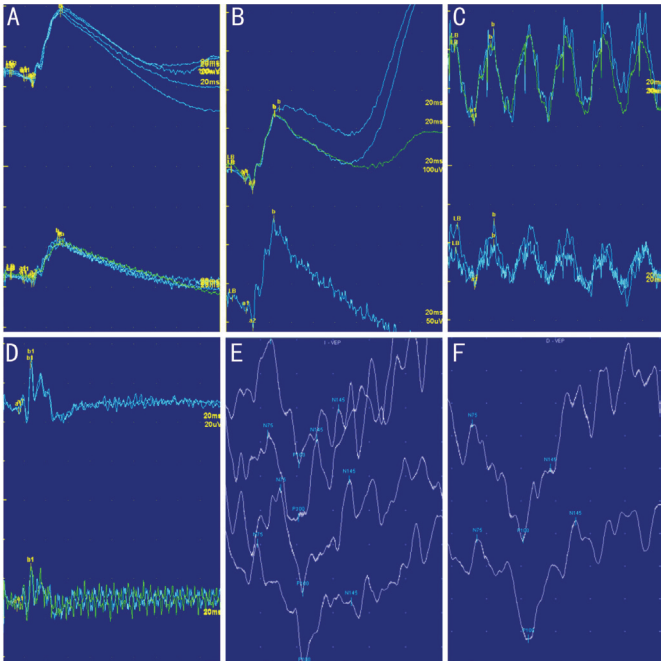

Figure 3 Neurophysiological tests ERG in scotopic conditions (A) within normal and the mixed conditions (B) with limits under of normality in right eye. Flicker at 30 Hz (C) of low amplitude and oscillating potentials (D) of borderline amplitude in left eye and reduced in right eye. Visual evoked potentials with bilateral and symmetric increased latency (E-F).

with latencies of the waves a1, a2 and b in limits of normality. The oscillatory potentials showed a preserved morphology. In photopic conditions, the response of the cones showed latencies in limit values and reduced amplitude in RE, while the flicker at 30 Hz presented a latency in the high limit of normality, with a borderline amplitude in LE and reduced in RE. There is an Arden index of 1.5 in both EOG and in the visual evoked potentials (VEP) a results with irregular morphology and the P100 latency increased symmetrically (Figure 3).

Long-chain LCHAD deficiency is a rare mitochondrial oxidative disorder, of potentially lethal course and autosomal dominant inheritance, whose coding genes are found on chromosome 2[2,7].

In studies carried out, it has been possible to demonstrate that patients who survive at 2 year of age develop ocular involvement, which usually manifests commonly as chorioretinopathy, being evident from puberty, as well as peripheral neuropathy[7]. The correct early diagnosis, as well as the therapeutic treatment with supplement of L-carnitine and docosahexaenoic acid, although they do not prevent the appearance, have been shown to delay the progression of the different complications of this disease; and as it has been described in our case, non-compliance can accelerate the appearance of symptoms[8].

The genetic study of our patient revealed the existence of the G1528C mutation, which is the most frequent in this disorder[9]. During the follow-up, he developed the typical

retinal alterations described, characterized by diffuse granular maculopathy and great chorioretinal atrophy[10].

It can be said that in the presently presented case we are in a stage 3, where there are extensive areas of chorioretinal atrophy, with more or less preserved retinal periphery and alterations in central vision, evidenced in the VF as an increase in the scotomas[5].

In some cases, where it has been possible to obtain a long-term follow-up of affected patients, the appearance of early cataracts, posterior staphyloma, myopic development has been demonstrated; and some isolated cases of subretinal neovascular membrane[6].

Among the limitations presented in the study, we can mention the retrospective nature, the reduced sample (due to the infrequency of this pathology) and the short follow-up period in previously presented articles.

In summary, we have reported a case of retinopathy associated with LCHAD deficiency in which modern multimodal imaging techniques have been used to better assess photoreceptors distrophy. Because it is a progressive and incurable disease, with multiple affectations and ophthalmological complications that can be manifested throughout life, in various publications annual ophthalmological monitoring is recommended for life.

ACKNOWLEDGEMENTS

Conflicts of Interest: Espinosa-Barberi G, None; **Miranda Fernández S,** None; **Valdés Martín ME,** None; **Betancor Perdomo MA,** None; **Aguilar Rosales CJ,** None.

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