Characteristics of Late Onset Retinal Degeneration (L-ORD)

Abstract

Purpose: To provide a review of late-onset retinal degeneration (L-ORD).

Methods: Retrospective single case report with diagnostic imaging to include fundus photography, fundus autofluorescence, and spectral-domain optical coherence tomography

Patient: A 60-year-old female presented with difficulty in light adaptation, depth perception, night blindness and loss of central vision. She denies any pain or discomfort and does not experience any flashes or floaters. She has a positive family history of L-ORD.

Results: Ophthalmic examination revealed well-circumscribed, scalloped areas of atrophy in both eyes with central fibrotic CNVM in the left eye. SD-OCT showed outer retinal atrophy and subretinal fibrosis in both eyes. After diagnosis of L-ORD, patient was informed of the natural history and progression of the disease. The importance of close monitoring and decreased vision precautions were discussed. A follow-up evaluation in 3 months was scheduled.

Conclusion: L-ORD can be mistakenly diagnosed during the early stages as aged-related macular degeneration or confused with other retinal dystrophies. A thorough review of the patient's night vision difficulties, family medical history and retinal examination must be performed to ensure accurate diagnosis. Given unknown pathogenesis, treatment is not available but the disease course should be monitored closely for the development of secondary CNVM.

Keywords: Late-onset retinal degeneration; Lipid-rich drusen deposits; Scalloped areas of RPE atrophy; Night blindness; Rod-cone dystrophy

Review Article

Volume 6 Issue 4 - 2017

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Received: January 05, 2017 | **Published:** March 16, 2017

Introduction

Late-onset retinal degeneration (L-ORD), sometimes called late-onset retinal dystrophy is a rare autosomal dominant disorder, characterized by the presence of thick, lipid-rich deposits between the retinal pigment epithelium (RPE) and Bruch's membrane. The disease was first seen in the mid-1990s and has been linked to a mutation in the *C1QTNF5* gene. The *C1QTNF5* gene, located on 11q23 encodes a 281 amino acid protein and is highly expressed in the RPE, lens, and ciliary epithelium. Known cases of individuals with L-ORD have been seen in families from the United States, United Kingdom, and Canada [1,2]. Individuals with L-ORD often show no ophthalmic disturbances until midlife, around 50-60 years old. Clinically, early symptoms of the disease process include difficulty with light and dark adaptation with inability to see in dim light or at night. Progression of the disease then leads to loss of central and peripheral vision, choroidal neovascularization and retina-wide pigmentary retinopathy. Ultimately, the decline in visual acuity leads to complete vision loss.

Although ophthalmic examinations may initially be normal even after decline in night vision begins, as the disease progresses, the appearance of fine yellow-white drusen-like dots in the mid-periphery is the first ophthalmic indication of L-ORD. These drusen-like "dots" or deposits then form atrophic areas that spread throughout the retina. Fundus autofluorescence depicts extensive, well-defined scalloped areas of RPE and chorioretinal atrophy predominantly in the mid-periphery and in the posterior pole of the retina. The macula usually becomes atrophic but can sometimes form a disciform scar. The optic disc also changes into a pale color. The anterior pole is also affected with iris transillumination defects having a peri-pupillary distribution and abnormally long anterior zonular insertions. Spectral Domain OCT (SD-OCT) shows a vast amount of photoreceptor loss with absence of the ellipsoid zone and thinning of the outer nuclear layer. Electroretinography (ERG) performed on individuals with L-ORD show defects in rod-cone pattern, with greater macular involvement than seen in other rod-cone dystrophies. During the later stages of the disease, ERG results show reduced amplitude and delayed cone signals. At the level of the RPE and Bruch's membrane, there may be areas of relative preservation and hyper-reflective deposits [1,3]. The sub-RPE deposits seen in L-ORD are similar to those seen in patients with Sorsby fundus dystrophy (SFD) and age-related macular degeneration (AMD) in regards to their ultrastructure and lipid content [4]. The pale color of the optic disc combined with visual acuity abnormalities can lead to

the diagnosis of normal tension glaucoma [3].

Case Report

A 60-year-old female from Singapore presented with vision abnormalities due to issues in light adaptation, depth perception, night blindness, and loss of central vision over the course of a decade. Past ocular procedures include intravitreal ranibizumab injection (Lucentis) in the left eye for treatment of choroidal neovascular membrane (CNVM). Family history was remarkable for L-ORD-positively diagnosed in mother, brother and sister. Current medications include Eliquis, Ibuprofen, Klonopin, Metformin, ZyprexaZydis. A review of systems indicated osteoarthritis and history of psychosis.

Visual acuity was measured 20/25 in the right eye and count-fingers at 5 feet in the left eye with symmetrically reactive pupils and normal intraocular pressures. Retinal examination revealed well-circumscribed scalloped areas of atrophy in both eyes (Figure 1), particularly in the outer retinal and choroidal areas. The presence of a central fibrotic CNVM was also seen in the left eye. Spectral Domain OCT showed outer retinal atrophy and subretinal fibrosis with the left eye (Figure 2) to a greater degree than the right eye. Baseline diagnostic imaging was obtained to document the pathological course. Given the presence of sub-RPE deposits noted in the retina along with discerned areas of RPE loss and choroidal atrophy in the macula and periphery, the diagnosis of L-ORD was made for both eyes.

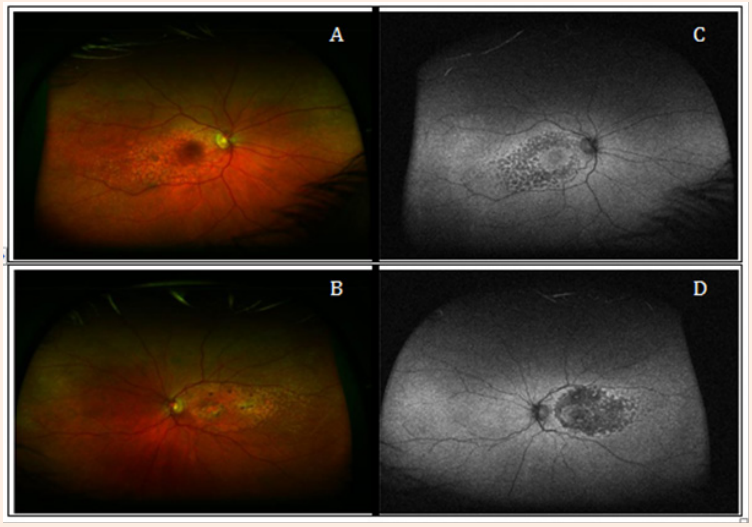

Figure 1: Fundus photo (A,B) and fundus autofluorescence (C,D) of the right eye and left eye showing well-circumscribed scalloped area of atrophy.

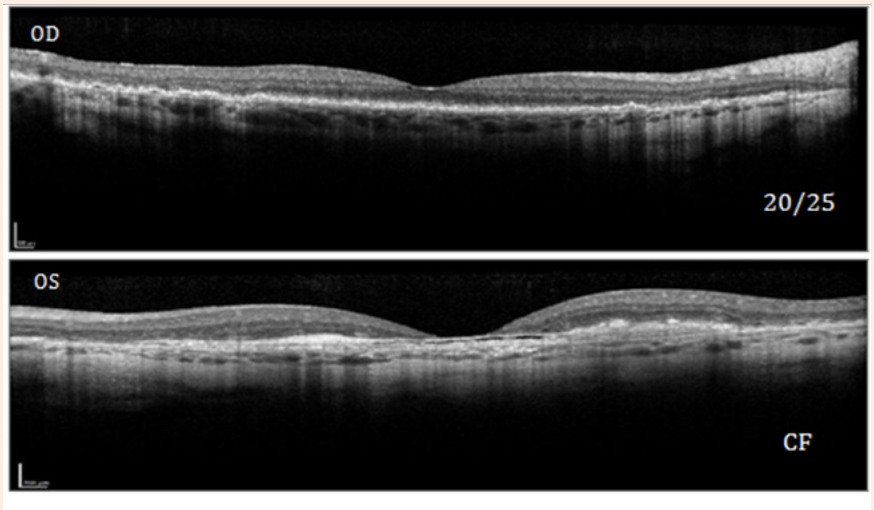

Figure 2: Optical coherence tomography of right eye and left eye confirming sub RPE deposits OU, outer retinal atrophy OU and subretinal fibrosis OS.

Citation: Crawford CM, Hwang Y, Wesley T (2017) Characteristics of Late Onset Retinal Degeneration (L-ORD). Adv Ophthalmol Vis Syst 6(4): 00185. DOI: 10.15406/aovs.2017.06.00185

Discussion

In diagnosing L-ORD, there should be a thorough review of the patient's detailed medical and family history, review of systems, ophthalmic and physical examination. If the patient's ophthalmic workup mirrors the clinical presentation described above or contains the defining features of sub-RPE deposits throughout the retina, the diagnosis of L-ORD can be made. During the early stages of the disease, L-ORD can often be confused with SFD or AMD. Symptoms of night blindness and a strong family history of L-ORD usually aids in the diagnosis. The loss of peripheral vision observed in patients with L-ORD is not usually seen in patients with AMD [3]. Although a mutation in C1ATNF5 has been linked to L-ORD, not all individuals who have L-ORD carry the C1ATNF5 mutation. Currently, the exact pathogenesis is unknown. Many electrophysiology studies show that rod-specific functions are the first to be compromised, while cone function is not affected until later in the disease progression [2].

Some studies have shown a positive effect of vitamin A supplementation in slowing the progression of L-ORD. This is based on the hypothesis that one part of the disease is caused by a disruption of the visual cycle which is due to the depletion of vitamin A stores in the RPE. Normally, C1ATNF5 is a glycoprotein that is secreted into the sub-RPE space and thought to take part in the adhesion of RPE cells to Bruch's membrane. RPE cells with heterozygous C1ATNF5 mutation contain abnormal protein that remains within the endoplasmic reticulum, leading to functional abnormalities. One disruption is the ability to efficiently generate vitamin A-derived materials essential for phototransduction. Post-mortem examination of donor eyes from individuals with L-ORD also contain thick, lipid-rich deposits that lie between the RPE and Bruch's membrane that is made up of collagen, elastin, and lipids. These deposits are thought to act as a barrier, preventing the transport of nutrients and metabolic products between the choriocapillaris and RPE, further disrupting the visual cycle [4,2]. Both of these mechanisms could explain the disturbances in light/dark adaptation and subsequent vision loss.

There has also been a positive correlation shown between deposit thickness and photoreceptor loss, which suggests that the light adaptation abnormalities may be a signal for future photoreceptor loss [4]. Because the exact pathogenesis of L-ORD is not well understood, there is no preventative or approved therapies to effectively slow the progression of this disease. In the presence of secondary CNVM, anti-vascular endothelial growth factor therapy has been used. In the advanced stages of this disease, the clinical course shows a poor visual prognosis with an impact on an individual's central and peripheral vision. After the discussion, the patient was informed of the natural history and progression of the disease. The importance of close monitoring and decreased vision precautions were discussed. A follow-up evaluation in 3 months was scheduled.

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Citation: Crawford CM, Hwang Y, Wesley T (2017) Characteristics of Late Onset Retinal Degeneration (L-ORD). Adv Ophthalmol Vis Syst 6(4): 00185. DOI: 10.15406/aovs.2017.06.00185