

Natural History of Retinal Changes in Patients with Usher Syndrome Type 1C

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Purpose: Usher syndrome (USH) is the most common cause of hereditary deaf-blindness. Type 1 is the most severe, with deafness and vestibular areflexia at birth and early adolescent onset of retinitis pigmentosa. Type 1C (USH1C) is caused by mutations in the *USH1C* gene, including the Acadian founder c.216G>A. However, the natural history is not known. We are conducting studies of visual loss in USH1C across the lifespan in an attempt to prepare USH1C patients for therapy trials using the most robust and repeatable functional and structural endpoints. Here, we aim to characterize retinal structural changes using optical coherence tomography (SD-OCT) imaging.

Methods: Demographic, ophthalmic history, and genetic data were obtained prospectively, and routine and novel measures of visual function were performed in adolescent, young adult, and adult USH1C patients. SD-OCT images were obtained and analyzed.

Results: Currently, 24 consenting participants (adolescent (n=6), young adult (n=12, 1 excluded due to nystagmus), adult (n=6), 50% female) with genetic confirmation of USH1C disease are enrolled in our prospective study. Visual Acuity (ETDRS) was 0.15 logMAR (20/28 Snellen) for adolescents, 0.22 logMAR (20/34 Snellen) for young adults, and 2.43 (CF/HM) for adults. Low Luminance Visual Acuity (LLVA) was 0.28 logMAR (20/38 Snellen) for adolescents, 0.35 logMAR (20/44 Snellen) for young adults, and 2.62 (CF/HM) for adults. Baseline OCT mean central foveal thickness (CFT), outer nuclear layer (ONL) thickness, and ellipsoid zone (EZ) horizontal width declined with age. 50% of adolescent eyes and 50% of young adult eyes exhibited shortening of EZ width (<4000 μ m), and all adults exhibited total atrophy of the EZ. Decreasing EZ width on OCT was moderately correlated with a decline in VA, LLVA, and blue-red full-field stimulus sensitivity threshold difference. 15/26 USH1C pediatric patients (2-5 years (n=4), 6-12 years (n=9), 19-21 years (n=2); 40% female) had meaningful retrospective OCT data. 40% (the youngest aged 6 years) exhibited retinal atrophy with or without ERM, and 40% exhibited CME (the youngest aged 3 years).

Conclusion: SD-OCT imaging is a useful tool for monitoring retinal disease progression in USH1C patients throughout the lifespan and can detect subclinical changes in retinal structure, including in asymptomatic pediatric patients. Our data suggest that USH1C retinal disease can start in childhood.