

## Sialidosis: Bilateral Cherry-Red Macular Spot

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### Abstract

Sialidosis is a lysosomal storage disease caused by autosomal recessive mutation eliminating the function of the sialidase enzyme. In this case report, we describe the clinical presentation, diagnostic workup, and examination findings of a male patient who entered our care at age 31. We examine the findings of ophthalmic diagnostic procedures and the utility of genetic testing to aid the diagnosis in the setting of a patient with bilateral cherry red macular spot.

**Keywords:** Sialidosis; Bilateral Cherry Red Macular Spot

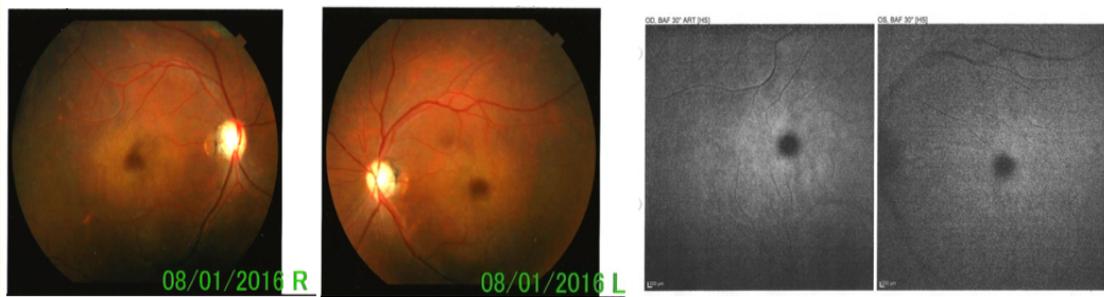
### Introduction

Sialidosis is a lysosomal storage disease caused by autosomal recessive mutation eliminating the function of the sialidase enzyme. Bilateral cherry red macular spot has a wide and complex differential diagnosis including inherited lysosomal storage diseases [1]. It is present in nearly all patients with GM2 gangliosidosis (Tay-Sach's disease and Sandhoff disease), in 100% of patients with type I and 75% of patients with type II sialidosis and in galactosialidosis. It is also encountered but far less frequently in Niemann Pick disease, Krabbe disease, Fabry disease, infantile form of GM1 gangliosidosis, Gaucher disease, Farber disease, and metachromatic leukodystrophy.

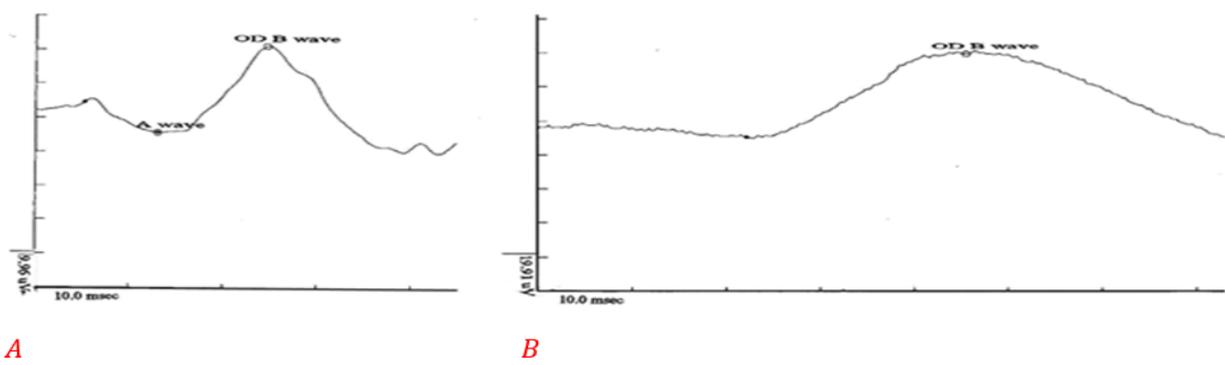
### Case Report

A 31 year old male with a past medical history of seizures, myoclonus, and dysarthria presented to the clinic with a chief complaint of decreased visual acuity in both eyes gradually over the previous year. Best-corrected visual acuity was right eye 20/60 and left eye 20/50.

Pupils, ocular motility, and ocular pressure were unremarkable. Anterior segment examination revealed right lower eyelid fasciculations, bilateral punctate opacities of the lens nucleus and posterior subcapsular cortex, and rare pigmented cells in the anterior vitreous. Retinal examination showed bilateral cherry red spot. Figure 1 shows color fundus photographs and autofluorescence images. Full-field ERG showed normal light- and dark-adapted b waves (Figure 2). Flash visual evoked responses showed delayed P100 responses in both eyes (Figure 3). SDS OCT of the macula showed increased reflectivity of the nerve fiber/ganglion cell layers (Figure 4).

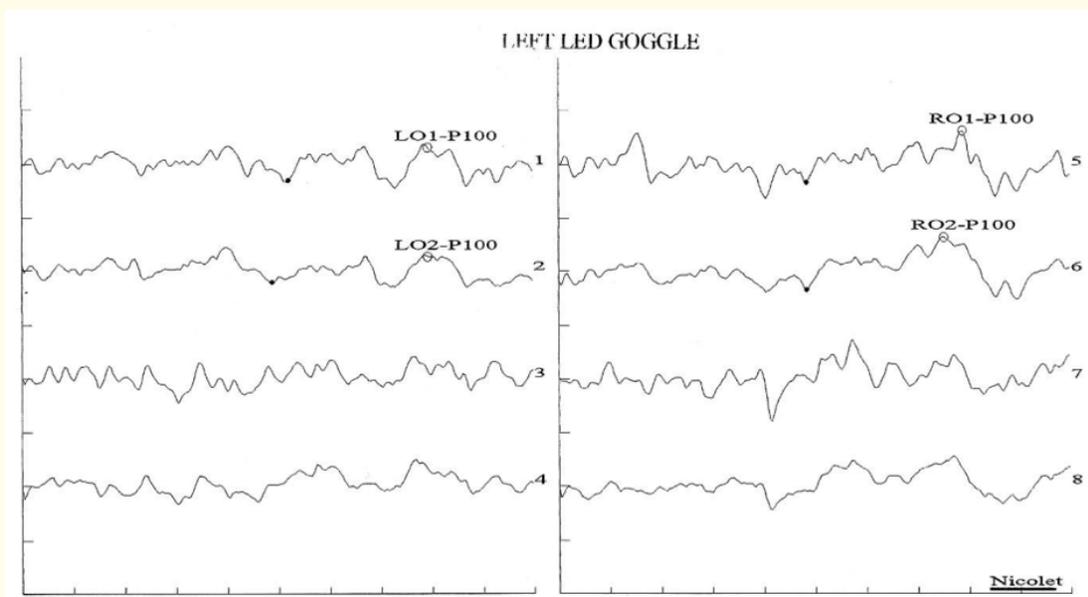


**Figure 1:** Bilateral cherry-red macular spot. Fundus photograph and autofluorescence.



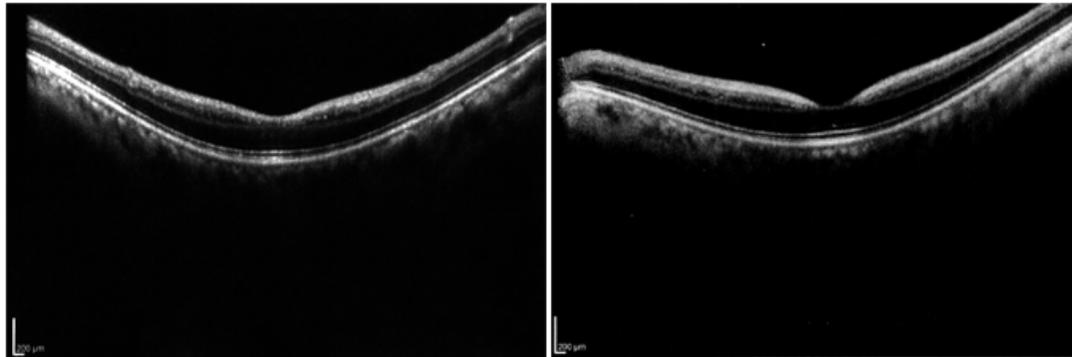
**Figure 2:** Full field ERG responses (Right eye).

A: Light-adapted B wave - 24.60 ms, 25.5uV (normal < 25 ms and 20 - 60 uV).  
 B: 3-minute dark-adapted B wave - 46.60 ms, 50.9 uV (normal < 40 ms and 20 - 50 uV).



**Figure 3:** Flash VER.

P100: Left eye: 158 ms, 3.2 uV (1), 158.40 ms, 2.57 uV (2).  
 Right eye: 158 ms, 4.9 uV (1), 150.40 ms, 5.10 uV (2).  
 (Normal <135 ms and 5-20 uV).



**Figure 3:** OCT macula (right, left eye).

An array of assays for enzymatic activity of various lysosomal enzymes revealed the patient's carrier status for beta-galactosidase enzyme deficiency only. Whole genome chromosome SNP microarray analysis was then performed and identified multiple extended areas of contiguous homozygosity. One candidate gene, *NEU1* - coding for the sialidase enzyme, was found to be located within one of the aforementioned homozygous regions. The patient was tested for sialidase activity and found to have none. Final diagnosis for the patient was type II sialidosis.

## Discussion and Conclusion

### Diagnosis

Bilateral cherry red macular spot has a wide and complex differential diagnosis including inherited lysosomal storage diseases [1]. It is present in nearly all patients with GM2 gangliosidosis (Tay-Sach's disease and Sandhoff disease), in 100% of patients with type I and 75% of patients with type II sialidosis and in galactosialidosis. It is also encountered but far less frequently in Niemann Pick disease, Krabbe disease, Fabry disease, infantile form of GM1 gangliosidosis, Gaucher disease, Farber disease, and metachromatic leukodystrophy.

These entities are due to disabling mutations in a vast array of lysosomal storage enzymes required for proper and complete metabolism of cellular substrates. Age of onset typically correlates with the degree of residual enzymatic function for the individual genotype, with partial deficits allowing for survival into adulthood while full deficits typically result in death in infancy. Each condition has unique clinical and ocular features in addition to cherry red macular spot - e.g. GM1 gangliosidosis presents with coarse facies, skeletal deformity, and hepatosplenomegaly while GM2 gangliosidosis are associated with ataxia, muscle atrophy, spasticity, and seizures. Corneal opacification and discoloration of the anterior lens capsule are seen in Niemann Pick disease.

### Pathophysiology

Sialidosis is caused by a homozygous recessive defect in the expression of the *NEU1* gene (chromosome 17: 34.93 - 34.94 Mb) that codes for sialidase, an enzyme responsible for cleaving the terminal sialic residues in modified proteins and lipids. Deficiency of sialidase causes a buildup of sialyl-oligosaccharides in neurons, including the ganglion cells of the retina, resulting in visual and neurological symptoms and consistent with delayed P100 on VEP in the face of a normal full-field ERG. Two major phenotypes have been identified - type I with adult onset, myoclonus, and little to no dysmorphism or intellectual disability as presented in our patient and type II, which is characterized by infantile onset, severe disabilities, and dysmorphism [1].

In addition to the dilated funduscopic examination, new imaging modalities can serve as a powerful tool in documenting retinal changes associated with sialidosis: OCT of the macula shows increased reflectivity and thickening of the ganglion cell layer due to accumulation of indigestible substrates in lysosomes of ganglion cells [2]; Fundus autofluorescence images show bilateral hyperfluorescent perifoveal areas which may be due to increased accumulation of phospholipids suspected to be present in the ganglion cell layer surrounding, but not within the anatomical fovea [2].

### Treatment

No definitive treatment currently exists for sialidosis. Therapies under consideration include proteosomal inhibitors that would prevent mutant sialidase from being digested and chaperone proteins that could help correctly fold mutant sialidase in an effort to salvage activity of the sialidase enzyme [3,4].

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### Competing Interests

The authors declare no competing interest.

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