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DIAGNOSTIC APPROACHES FOR MACULAR DYSTROPHY USING OCT AND VEP: A CASE SERIES

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ABSTRACT

Introduction: *Macular dystrophies (MDs) consist of a heterogeneous group of disorders that are characterized by bilateral symmetrical central visual loss. Clinical manifestation including atrophy in macula. This cases series provides clinical manifestation and characteristics in ancillary testing for better approach to macular disease*

Case report: *Case 1 is 13-year-old girl with decrease visual acuity, uncorrected visual acuity (UCVA) was 2/60 on both eyes. The ophthalmologic examination showed an area of atrophy at macula accompanied with yellowish flecks on both eyes. Optical coherence tomography (OCT) shows thinning in all areas of macula and loss of outer nuclear layer (ONL) and photoreceptor. From VEP, there were low amplitude N75, P100, and N145 waves without any latency. Case 2 is 39-year-old woman with decrease of visual acuity, UCVA was 6/60 on both eyes, accompanied with partial colour blindness and red-green deficiencies. From ophthalmology examination showed large atrophy area at macula. OCT examination shows thinning in most of macula area and decrease of ONL thickness and photoreceptor. VEP showed normal wave without any latency.*

Discussion: *There were a gradual central vision loss, at a more advanced stage, color blindness can occur due to photoreceptor damage in the macular area. From the posterior segment there was a yellowish spot on the macula which suggested lipofuscin deposition on the retinal pigment epithelium (RPE). From OCT, there ware loss of ONL and VEP showed low amplitude or normal waves. This findings suggested macular dystrophy due to Stargardt disease.*

Conclusion: *OCT and VEP can be used to detect anatomical and physiological abnormalities that can aid in the diagnosis of macular dystrophy in the case of incomplete ancillary testing tools.*

Keywords: Macular dystrophy, Macular thinning, Genetic, Stargardt Disease, OCT, VEP
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INTRODUCTION

Macular dystrophy is a heterogeneous disease characterized by abnormalities in the macula that cause a person to experience a loss of visual acuity in both eyes. Inherited macular dystrophy generally appears at a young age, around the second decade of life. The disease is characterized by remarkable vision loss due to damage or atrophy of the macular area in both eyes. Based on the inheritance pattern, we can divide this disease into three major groups: autosomal dominant, autosomal recessive, and X-linked.[1]

The most common macular dystrophy is Stargardt's disease, Best Vitelliform Macular Dystrophy, Adult Vitelliform Macular Dystrophy, Autosomal Dominant Drusen, and Pattern Dystrophy.[1] Stargardt disease is the most common type of macular dystrophy. This is an autosomal recessive disease that can occur in 1:6578 people worldwide, affecting both men and women.[2] According to a Minnesota study, Best Disease (BD) is the second most common, with a prevalence of 1:16,500 to 1:21,000. [2,3]

Diagnostics of macular dystrophy can be differentiated based on clinical manifestations and physiological and histological abnormalities. Subjective and objective eye examinations can be performed to help diagnose macular dystrophy. Currently, the diagnosis of macular dystrophy is made through the classical clinical signs of each type. [4]The standard retinal imaging in this case is fundus autofluorescence (FAF) and electrophysiological examinations such as electroretinography (ERG). [1]Nevertheless, these two examinations are not available in all health facilities. Optical coherence tomography (OCT) is a more frequently available examination tool in health facilities. Visual evoked potential (VEP) is one of the electrophysiological examination modalities that available at this center.

Until now, there has been many research in therapeutic approaches for these diseases. Genetic engineering and stem cell therapy are still being investigated.[5] Accurate diagnosis related to the type of macular dystrophy is needed to determine the appropriate genetic therapy target. This case series describes the use of OCT and VEP in identifying retinal abnormality and electrophysiology changes in macular dystrophy and characteristic signs that can be found to determine a proper diagnosis especially Stargardt disease.

CASE REPORT

CASE 1

A 13-year-old girl visited the eye clinic at Saiful Anwar Hospital with a complaint of blurred vision in both eyes that had persisted for a year. She had difficulty seeing objects in the distance and had to read up close to see clearly. Despite wearing spectacles, she continued to have difficulty seeing clearly. The patient did not report any other issues with her eyes. She has been wearing spectacles since 2018. The most recent spectacles prescribed in 2019 for the right eye was S- 2.50 D C-1.50 D x 0° and S-3.00 D C-1.50 D x 0° for the left eye. There were no records of any previous injuries or surgical procedures. The patient was the youngest of three siblings. No other family members experienced similar complaints. Based on the patient's mother's, there were no issues during pregnancy and the patient was born without any complications.

Uncorrected visual acuity (UCVA) for both eyes were 2/60. The best corrected visual acuity (BCVA) used the S-3.00 D C-2.50 D x 0° lens to correct both eyes, resulting in a visual acuity of 6/60. The anterior segment examinations revealed no abnormalities. Meanwhile, for her posterior segment examination, yellowish flecks and beaten bronze appearance were spotted on both of the macula. There was no colour vision deficiency in her both eyes. The macular OCT revealed that the entire macular area was thinning. The B-scan showed prominent foveal atrophy in both eyes. Additionally, there was a loss of the outer nuclear layer (ONL) and neurosensory layer. Both eyes also showed hyperreflective foci on the choroidal layer. This could be seen due to thinning of the overlying retinal tissue.

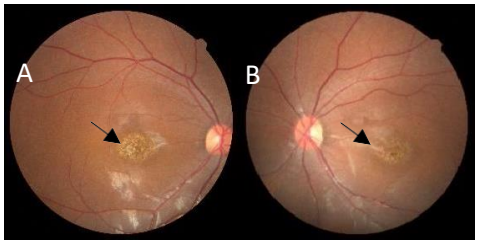

Figure 1. Funduscopy photo. A, right eye, and B, left eye. It was seen the appearance of beaten bronze with yellowish flecks around it (arrows).

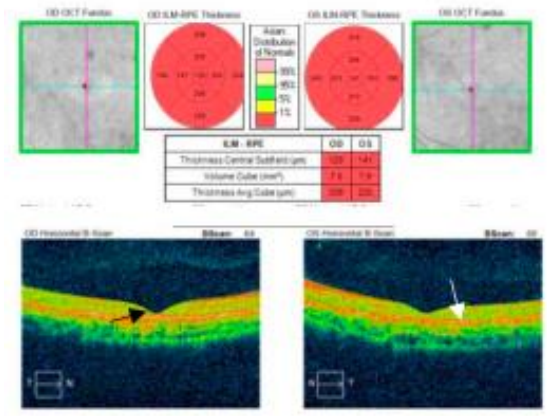

Figure 2. Macular OCT photo. It appeared prominent foveal atrophy (black arrow) and loss of the ONL layer (white arrow).

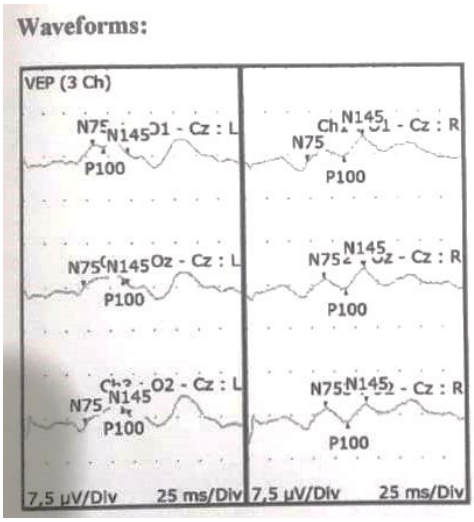

Figure 3. Visual Evoked Potential (VEP) Examination Results. There were low amplitude N75, P100, and N145 waves without any latency showed bilateral mild optic nerve neuropathy.

The laboratory examination was within normal limits. A VEP examination showed there was no latency from N75, P100, and N 145 waves, although the waves came with low amplitude, suggesting there was bilateral mild optic neuropathy. Fundus autofluorescence could be performed for a more precise description of the distribution of the lesions. In addition to seeing the retina's response to light, electro-retinography and electrooculography examinations could be done to see RPE function. Still, the examinations were not carried out due to the unavailability of tools.

Based on the clinical and supporting examinations that have been carried out, the patient was diagnosed with OU macular dystrophy due to moderate degree of Stargardt's disease and compound myopic astigmatism. The patient was planned to be given spectacles for improving quality of vision.

CASE 2

A 39-year-old woman has been complaining about blurred vision for the past three years, and it has gotten worse in the last year. She experienced blurriness in both her far and near vision, despite already wearing spectacles. She has a 20-year history of wearing spectacles.

For both eyes, the last prescribed spectacles were S-0.50. There was no history of trauma or surgery. In the family history, the patient's older brother also experienced blurry eyes during junior high school, a condition that worsened until he lost vision in both eyes.

Uncorrected visual acuity (UCVA) were 6/60 for both eyes. Visual acuity were 6/90 for both eyes using previous prescribed spectacles. The BCVA examination resulted in the right eye's correction to 6/24 with an S-2.00 D lens and the left eye's correction to 6/45 with the same lens. The anterior segment examination was within the normal limit. Ishihara's examination revealed a partial red-green color vision deficiency (CVD) in both eyes. Examination of colour blindness was then continued using Hardy-Rand-Rittler (HRR) pseudo-isochromatic plates; it was found that the patient had mild degree deutan-type CVD. The funduscopic examination of the posterior segment revealed clear media and a normal optic nerve. In the macula, a negative fovea reflex and macular atrophy were found in both eyes.

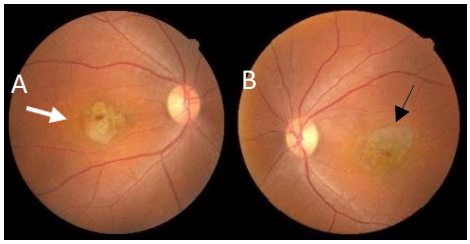

Figure 4. Funduscopy photo. A, right eye, and B, left eye. Atrophic areas on both macules were visible (black arrow), accompanied by yellowish spots around the atrophic area (white arrow).

OCT examination of the macula found thinning in almost the entire macula area when viewed through the macular map, both in the right and left eyes. Additionally, the shape of the fovea changed. On the B-scan of the right macula, ONL was still visible, whereas on the left macular, there was no ONL. The RPE layer in both eyes displayed hyper-reflection, and no photoreceptor structures were visible.

Laboratory tests was within the normal limits. A VEP examination found waves N75, P100, and N145 in this patient. In the P100 wave, a wave rate of 25ms was obtained in both eyes. It showed no decrease in the conduction velocity of the optic nerve.

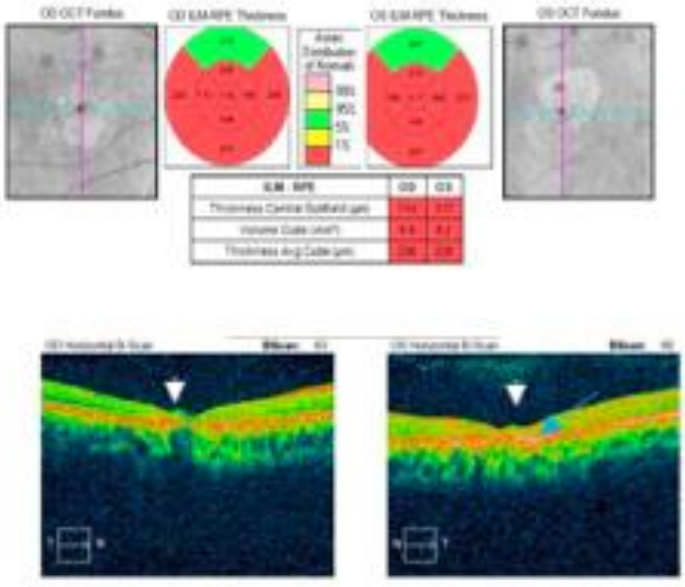

Figure 5. Macular OCT photo. There were changes in fovea shape (white arrow), ONL thinning, and loss of photoreceptor structure (blue arrow).

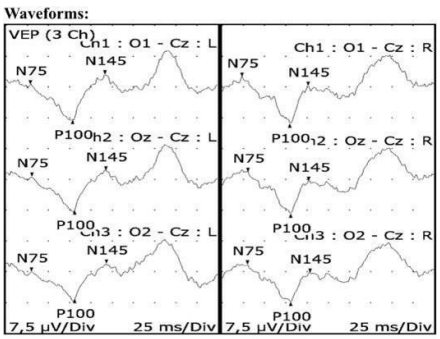

Figure 6. Visual Evoked Potential (VEP) Examination Results. There were N75, P100, and N145 waves without any latency.

Based on the results of the examinations, the patient was diagnosed with OU macular dystrophy, due to severe degree of Stargardt's disease and myopia. The patient was planned to be given spectacles for improving quality of vision.

DISCUSSION

These patients experienced gradual decrease in visual acuity in both eyes. Both cases describe macular dystrophy that appears at different ages with different degrees of severity. First case is a girl with yellowish flecks and beaten bronze appearance on macula, whereas second case is a woman with macular atrophy accompanied with yellow flecks around it. The characteristic sign of clinical examination is that yellowish fleck points to Stargardt disease. This disease is inherited through an autosomal recessive pattern associated with defects in the ABCA4 gene. This gene plays a role in the active transport of various substrates across the cell membrane. As a result of damage to ABCA4, there is a disruption in the transport of retinoids, which causes the accumulation of lipofuscin and metabolic waste products in the RPE and photoreceptors. It causes cell dysfunction, and over time, the cell will die.[6]

Although this disease generally appears in the second decade of life, symptoms can appear during adulthood. Stargardt can be classified into three presentations: childhood onset, adulthood onset, and late onset. The prognosis is poorer for individuals with an earlier presentation. [4–6]

Patients complained loss of central vision in both eyes slowly. Based on literatures, patients with Stargardt commonly present with progressive bilateral central vision loss. Visual acuity can range from 0.1 to 0.05. On physical examination of the patient, we could see that examination of the posterior segment showed a yellowish spot on the macula. In a more advanced stage, as seen in the second patient, an image of the area of atrophy was obtained. In Stargardt, it is found lipofuscin deposition on the RPE presented the classic fundus appearance of spots on the retina, especially in the macular area. The presence of atypical fishtail-shaped flecks indicates further development of the disease; then, it can also be an atrophic area of RPE in the shape of a flat oval (1.5-2 times the size of the optic disc) resembling a "beaten bronze" or "snail slime." In addition, it can find a "bull's eye" caused by RPE atrophy and geographic atrophy around normal RPE.[5,7]

The variation in the clinical manifestation between the first and second patients can be attributed to the disparity in the severity of the disease, which is influenced by age at the time of their visit to the eye clinic. The range of diseases varies greatly in terms of the age at which they begin. Common clinical presentations include colour vision problems, sensitivity to light (photophobia), and poor adjustment to darkness (dark adaptation).[1]

In the second case, the macular abnormalities had likely appeared long before, but the patient did not feel any significant complaints. Along with the increasing extent of the atrophic area on the macula and damage to almost all retina layers, the patient's complaints worsened. It was also characterized by the presence of red-green CVD disorders. It was consistent with the course of Stargardt's disease, where at a more advanced stage, color blindness can occur due to photoreceptor damage in the macular area.[8]

Thorough examinations are essential for clinical diagnosis and monitoring, which involve fundus photography, fundus autofluorescence (FAF) imaging, spectral-domain optical coherence tomography (SD-OCT), fundus fluorescein angiography (FFA) and electrophysiological testing (including pattern, full-field and multi focal electroretinograms; PERG, FFERG, mfERG). Fundus autofluorescence examination may show more clinically significant findings such as hypo-fluorescent lesions in the central macula, peripapillary sparring of RPE changes, and a longer course of the disease may show hypo-fluorescent lesion extending to the periphery. Another test that can be helpful is fluorescein angiography (FFA),

in which 80% of Stargardt patients show a "dark choroid" appearance due to masking from lipofuscin deposition in the RPE.[1,9]

In this case, FAF, FFA and ERG couldn't be done because unavailability of these device in this health care. Instead, this case series used OCT and VEP to determine the anatomical and physiological changes. OCT is a powerful tool for diagnosing and quantifying outer retinal loss (photoreceptor layers) and RPE atrophy in macular disorders, such as Stargardt.[1]In the first case the characteristics from OCT are loss of the outer nuclear layer (ONL), neurosensory layer. This finding is accurate with some literature, OCT images show the RPE as the deposition site, accompanied by atrophy of the outer retinal layers in the fovea and parafovea areas. In mild Stargardt, there is a "bulls' eye" maculopathy with the central fovea still in normal shape; there is already damage to the outer retina, ellipsoid zone, and RPE. In a moderate degree of Stargardt's disease, the prominent foveal atrophy, with hyperreflective in intra-RPE and/or sub-RPE. Regarding the prominent foveal atrophy, the first patient classified as moderate degree. In advanced stages, extensive atrophy in the macular area can be seen. This suitable with the findings from the second case, at a more mature age, more disruption occurred, such as macular thinning suitable with atrophy area from clinical examination, disruption of foveal contour, and no photoreceptor structures were visible.[10]

From electrophysiology examination, early stages of the disease, ERG examination can show normal results. In the advanced stages of Stargardt, the ERG examination will demonstrate abnormalities of the a-waves and b-waves in both photopic and scotopic vision. Meanwhile, on the electrooculography (EOG) examination, changes in the Arden index will be seen in severe RPE damage.[1] A lot of studies have investigated how macular disorders affect the pattern VEP (pVEPs).[11] However, the findings are not entirely in agreement. Several macular disorders, including age-related macular degeneration, macular hole, central serous chorioretinopathy, branch retinal vein occlusions, and macular dystrophies, exhibit attenuated pVEPs and delayed latencies.[11,12] A study conducted by Hanazono et al showed decreased pVEPs in some cases of macular dystrophies. The delayed latency and lowered amplitude indicate a significant contribution of the central cone route to pVEPs.[13] This was also found in first patient VEP where there was no latency but low amplitude in three waves (N75, P100, N145). For the second patient, the result showed that there was no wave latency. It follows some of the theory that at Stargardt, the VEP examination shows normal because damage occurs more often in the RPE layer.[14]

Differential diagnosis in the patient above can be best vitelliform dystrophy, the second most common macular dystrophy disorder that occurs at an early age.[9] But in best vitelliform dystrophy, the typical clinical picture is bilateral egg yolk (vitelliform) lesions on the fovea. The second differential diagnosis is adult vitelliform dystrophy which can appear in the fourth to sixth decades of life, where this does not match the patient's age. Moreover, in OCT, adult vitelliform shows a dome in the sub fovea, which was not found in both patients.[10] The third differential diagnosis is an Autosomal dominant drusen where the OCT shows hyperreflexia of the RPE-Bruch membrane complex, with damage to photoreceptor integrity, which resembles the OCT picture in the second patient. But in ADD, the typical sign is a drusen appearance.[1] Another differential diagnosis is pattern dystrophy, where in this disease, the complaints that appear are loss of central vision and abnormalities occurring in the RPE layer. But in terms of age, it does not meet the disease that appears in the fourth to fifth decades of life.[4]

Other investigations that should be carried out to help establish the diagnosis are FAF, ERG, EOG, and genetic tests. In conditions where these examinations are unavailable, using funduscopic and OCT photos is beneficial in viewing existing structural abnormalities. OCT can be a tool for evaluating the degree of damage to the retinal layer. Until now, there has been no treatment for this disease. Pharmacotherapies targeting the visual cycle are under development. Several studies are also exploring the possibility of using stem cells in RPE replacement.[15]

Education regarding a healthy diet, without additional consumption of vitamin A, needs to be emphasized for the patients. In addition, patients are advised to reduce exposure to ultraviolet light, which can accelerate worsening. Routine investigations are needed every 6 months to 1 year to see progress and prevent any complications that can occur.[16]

CONCLUSION

Macular dystrophy can be diagnosed with a comprehensive history, the results of a standard clinical examination, and a supportive examination. In the case of incomplete supporting instruments, OCT and VEP can be used to detect anatomical and physiological abnormalities that can aid in the diagnosis.

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