

Neurodegenerative Maculopathy Associated with GLUT1 deficiency syndrome

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Purpose: The purpose of this case report is to raise awareness about the association between GLUT 1 deficiency syndrome and maculopathy, as well as to emphasize the need for comprehensive evaluation and genetic testing in patients presenting with unexplained vision loss or macular abnormalities.

Method: The patients medical history, clinical presentation, ophthalmic findings and genetic testing results were reviewed and analysed.

Results: Both patients were found to have mutations in the SLC2A1 gene, confirming the diagnosis of GLUT1 deficiency syndrome. Ophthalmologic examination revealed bilateral macular abnormalities, including degenerative cavitations in the fovea.

Conclusion: This case report highlights the association between GLUT1 deficiency syndrome especially in young patients, with maculopathy which is detected in the presence of accompanying neurological problems and movement disorders.

Keywords: GLUT1, müller cells, neurodegeneration.



Introduction

Glucose is a crucial energy source for cell vitality (1). Glucose transporter 1 (GLUT1), a transmembrane

protein, facilitates glucose uptake into cells (2). Glucose transportation across the blood-brain barrier is mediated by the GLUT1 protein. Apart from brain neurons, this protein enables glucose passage through

tissue barriers in high quantities of glial cells, erythrocytes, lens epithelium, and the retina (3). GLUT1 deficiency syndrome is a rare neuro-metabolic disorder caused by mutations in the SLC2A1 gene on chromosome 1. Restricted glucose transport leads to energy deficit, resulting in impaired brain functions (4). The disease manifests in two phenotypes: 90% classical, and the remaining non-classical. Classical symptoms include early-onset resistant epilepsy, developmental delay, acquired microcephaly, paroxysmal eye-head movements, ataxia, and spasticity. In the less common non-classical type, milder movement disorders are observed without seizures (5). Retina, that is one of the most metabolically active tissues in the body, requires glucose for daily renewal of photoreceptor cell outer segments. GLUT1, present in retinal vascular endothelial cells and pigment epithelium, is responsible for glucose transport across the inner and outer blood-retina barrier (6). For this reason, retinal abnormalities are possible to be observed in addition to neurological disorders, but degenerative changes in the macula are quite rare in individuals with GLUT1 deficiency syndrome.

In this study, 2 sibling patients with maculopathy secondary to GLUT 1 deficiency syndrome are presented.

Cases

A 16-year-old female patient presented with a one-month history of blurred vision in both eyes. Patient had walking disorder since the age of 10, diagnosed as flat feet (pes planus) and used orthotics. No known systemic diseases were reported. There was no history of illness in her parents, and they were not related.

Ophthalmic examination revealed hypermetropia as a refractive error, with best-corrected visual acuity of 20/32 in both eyes. The anterior segments of both eyes were normal. Direct and indirect light reflexes were

normal, and there was no color vision deficiency. Intra-ocular pressure was within normal limits. Fundus examination showed normal optic discs and maculas. In infra-red reflectance imaging, a hyporeflective halo at the fovea was observed, while fundus autofluorescence imaging (FAF) revealed hyperautofluorescence in the fovea (Figure 1). Optical coherence tomography (OCT) showed cavitations in the fovea covered with the internal limiting membrane and irregularities in the ellipsoid zone (Figure 2). Retinal nerve fiber thickness was within normal limits. Topical nepafenac was initiated four times a day. One month showed no improvement in visual acuity, and OCT still revealed cavitations in the fovea. Fundus fluorescein angiography showed no leakage. Cranial and orbital computed tomography revealed no abnormalities. Visual field testing showed no defects. Flash electroretinogram showed no abnormalities. However, multifocal electroretinography indicated decreased central responses.

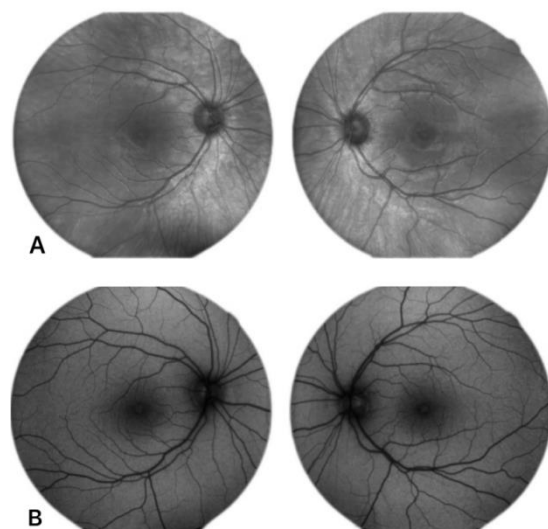


Figure 1. *A. Infrared reflection imaging shows a hyporeflective halo appearance at the fovea. B. Fundus autofluorescence imaging (FAF) revealed hyperautofluorescence at the fovea.*

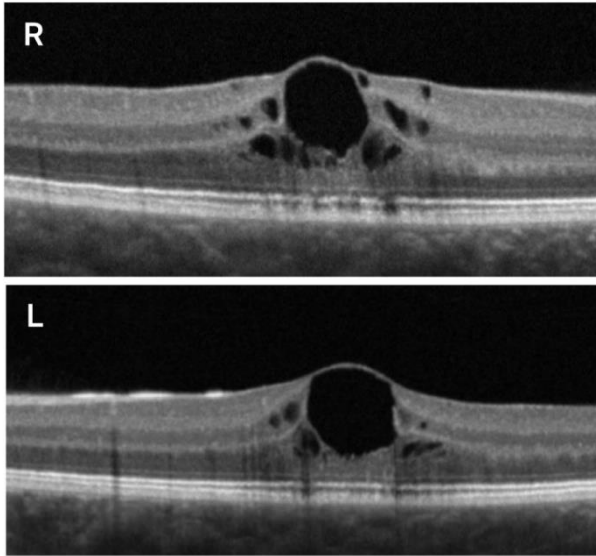


Figure 2. On OCT imaging, significant hyporeflective cavities at the right (R) and left (L) fovea and the appearance of ILM drape.

The patient's brother, a 30-year-old male with spastic paraparesis since childhood, was examined. His visual acuity was 20/20 in both eyes, and anterior and posterior segment examinations were normal. However, optical coherence tomography revealed degenerative cavitations in the fovea (Figure 3). Genetic testing confirmed a heterozygous mutation in the SLC2A1 gene for both siblings, leading to the diagnosis of neurodegenerative maculopathy associated with GLUT1 deficiency syndrome.

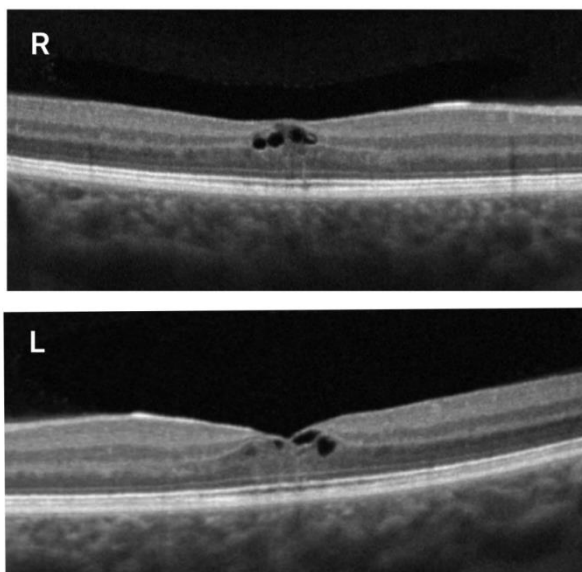


Figure 3. Hyporeflective minor cavitations at the fovea in the right (R) and left (L) eyes monitored on OCT imaging

Discussion

In GLUT1 deficiency syndrome, early-onset epileptic seizures occur due to a lack of energy in the brain, and impairment of cognitive function and movement disorders are added in the later stages. Although rare in the literature, retinal complications can be observed. In our two cases, the fovea in both eyes was significantly affected, and cavitations presumed to be related to the degenerative process.

In a 20-year-old female diagnosed with classical type GLUT1 deficiency syndrome, OCT imaging revealed increased thickness in the retinal pigment epithelium layer at the fovea and thinning in the perifoveal retinal thickness. Hyperautofluorescence was observed outside the fovea in FAF, while OCT angiography (OCT-A) showed a decrease in perimacular vessel density (7). In our cases, cavitations were observed in the fovea on OCT and hyperautofluorescence was observed in FAF. As the leakage was not detected on FFA imaging, cavitations in the fovea may be related to Müller cell and photoreceptor dysfunction.

Swarup et al. in a mouse study in which they created a Glut1 defect in about two-thirds of retinal epithelial cells, they showed that the measured glucose level in the retina decreased by 32% compared to normal. Immunohistochemical examination revealed a 50% thinning in the outer nuclear layer due to the death of rod photoreceptor cells, and a waviness in the outer nuclear layer on OCT imaging. They concluded that photoreceptor cone cells were less sensitive to glucose deprivation. In the same study, when GLUT1 was not expressed in half of the RPE cells, glucose levels in the retina were found to be similar to controls. Normal a

and b waves were observed in scotopic ERG measuring the rod response. They suggested that this could explain why neurological problems occur in patients but visual disturbance does not (6). In our cases, no significant changes were observed in ERG responses. In another GLUT1 deficiency animal model, although a decrease in the number of cone cells was not observed, a significant decrease in b-wave response in photopic ERG was detected (8).

Müller cells, prevent the progression of retinal damage through the release of neurotrophic factors and antioxidants. They enable neural tissue regeneration by differentiating into progenitor/stem cells (9,10). These cells require glucose to sustain their metabolic activity, and low glucose levels lead to metabolic stress (11). After the death of photoreceptor cells, reactive gliosis develops through Müller cells. In one study, it was shown that GFAP, which is a stress indicator, increases in Müller glial cells in RPE regions that are not expressed GLUT1, even if there are no photoreceptor cells (6). It is assumed that the pathology observed in the fovea in our cases is related to the loss of viability of Müller glial cells and the formation of structural cavitations.

Retinal cells require glucose for the production of NADPH, which is involved in the antioxidant defence system. When GLUT1 expression is absent, glucose uptake into cells decreases, and unpreventable oxidative stress leads to degeneration in photoreceptor and Müller cells (8).

Although GLUT1 is expressed in all retinal cells, it is mainly responsible for glucose transport in rod, cone, and Müller cells. GLUT3 is predominantly found in the inner retina, where amacrine, bipolar, horizontal, and ganglion cells are located. When GLUT1 expression decreases, compensatory GLUT3 increase is not observed. The continuation of viability in some

retinal cells is met by the uptake of amino acids and fatty acids into cells and their oxidation to obtain energy (6,8). The application of a fat-rich ketogenic diet in the treatment of GLUT1 deficiency syndrome has been associated with a decrease in epileptic seizures and improvement in cognitive and motor functions (12). However, the impact of this diet on the retina is unknown, and planning a ketogenic diet for the patient will be done in consultation with pediatric expertise to prevent systemic side effects.

The disease is genetically caused by heterozygous mutations that can be sporadic or inherited in an autosomal dominant manner in the SLC2A1 gene, but rare cases of autosomal recessive transmission have been reported (13). Homozygous mutations are not observed as they are presumably incompatible with life (4). In heterozygous mutations, the clinical manifestations vary according to the affected GLUT1 ratio, and the macular neurodegeneration observed in the cases was greater in the sister and reduced the level of vision, while it did not affect vision in the brother.

In conclusion, the decrease in glucose intake leads to dysfunction of RPE, loss of Müller cells and photoreceptor cells, and the development of neurodegenerative maculopathy. Especially in young patients, when maculopathy is detected in the presence of accompanying neurological problems and movement disorders, neurodegenerative processes should be considered. After detailed ophthalmological examination and investigations, guidance should be provided for medical genetic screening.

Conflict of interests

The author declares that there is no conflict of interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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None.

Study association

This study is not associated with any thesis or dissertation work.

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