X-linked Juvenile Retinoschisis: A Case Report and Review of the Current Approaches in the Diagnosis and Treatment

X'e Bağlı Juvenil Retinoskizis: Bir Olgu Sunumu ve Tanı ve Tedavideki Güncel Yaklaşımların Değerlendirilmesi

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SUMMARY

X-linked juvenile retinoschisis (XLRS) is a common cause of hereditary macular degeneration in male children and adolescents. We report a newly diagnosed case of XLRS in an adult patient. A 32-year-old man presented to our clinic with complaint of decrease in visual acuity since childhood. He had no systemic diseases and negative family history. His fundus examination revealed bilateral cystic lesions in the macula. Electroretinogram (ERG) and optical coherence tomography (OCT) images revealed XLRS. We confirmed the diagnosis with genetic analysis which revealed p.Glu72Lys (c.214G>A) mutation in the 4th exon of RS1 gene. We followed our patient with topical dorzolamide hydrochloride three times daily. No improvement was observed over a 1-year follow-up. Diagnosis of XLRS may be difficult in adults with negative family history due to the loss of characteristic macular appearance. Concurrent use of OCT and ERG is helpful in making diagnosis which can be further confirmed by genetic analysis.

Key Words: X-linked juvenile retinoschisis, cystoid macular lesion, electroretinogram, optical coherence tomography, genetic analysis.

ÖZ

X'e bağlı juvenil retinoskizis (XLRS) erkek çocuk ve ergenlerde görülen kalıtsal makular dejenerasyonun sık bir nedenidir. Bu yazıda yetişkin yaşta yeni tanı almış bir XLRS olgusu irdelenmiştir. Otuz iki yaşındaki hasta çocukluktan beri olan az görme şikayetiyle kliniğimize başvurdu. Fundus muayenesinde her iki gözde makulada kistik lezyonlar izlendi. Elektroretinogram ve optik kohorens tomografi görüntüleme sonuçlarına göre XLRS tanısı düşünüldü. Yapılan genetik analizde RS1 geninin 4. ekzonundaki p.Glu72Lys (c.214G>A) gösterilmesiyle tanıyı doğruladık. Hastayı günde üç kez topikal dorzolamid hidroklorid vererek takip ettik. Bir yıllık takip sonucunda hastada herhangi bir düzelme izlenmedi. Aile hikayesi olmayan yetişkinlerde karakteristik makula görünümünün kaybolması nedeniyle XLRS tanısı koymak güç olabilir. OCT ve ERG'nin birlikte kullanılması tanı koymada yardımcıdır, daha ileri doğrulama için genetik analiz yapılabilir.

Anahtar Kelimeler: X'e bağlı juvenil retinoskizis, kistoid makular lezyon, elektroretinogram, optik kohorens tomografi, genetik analiz.

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Geliş Tarihi - Received: 12.04.2015
Kabul Tarihi - Accepted: 10.07.2015
Ret-Vit 2016;24:83-85

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INTRODUCTION

X-linked juvenile retinoschisis (XLRS) is an early onset hereditary macular degeneration characterized by loss in visual acuity, splitting of retinal layers, and reduction in the b-wave amplitude of the electroretinogram (ERG). Because of the X-linked recessive penetrance of the disease, only males are affected. Female carriers are usually clinically normal.[1,2] XLRS is among the commonest causes of macular degeneration in male children and adolescents. The prevalence of the disease is estimated to vary from 1/5.000 to 1/25.000.[2] XLRS is usually diagnosed in patients presenting with moderate visual loss prior to or at the school age, but there are also several cases described in the first year of life.[1]

The most characteristic clinical finding is the radial streaks in the fovea, and macular changes are present in all patients. These radial streaks become less prominent in patients older than 30 years which causes difficulty in diagnosis.[1,2] Peripheral retinoschisis is the second most frequent finding in patients with XLRS, which is reported in 50% of the cases.[2]

X-linked juvenile retinoschisis was thought to result from an inherited defect in Müller cells in the past, but recent analysis have shown that photoreceptors and bipolar cells are primarily involved in the disease process.[1] RS1 is the only gene associated with the disease. This gene encodes retinoschisin (a protein composed of 224 amino acids) which binds tightly to the surface of photoreceptors and bipolar cells maintaining the structural organization of the retina.[3] Several mutations in the RS1 gene have been reported to associate with XLRS.[1]

Diagnosis of XLRS may be troublesome in patients older than 30 years because of the loss of characteristic foveal radial streaks, especially when the family history is negative. In this study, a late diagnosed XLRS case with prominent cystic lesions in the fovea and the current developments in the diagnosis and treatment of the disease are presented.

CASE REPORT

A 32-year-old man presented to our clinic with the complaint of reduced visual acuity in both eyes. He stated that his far vision was poor since school-age and he was told that he had lazy eye in his previous examinations. He had no systemic diseases, history of regular drug intake and smoking. His family history was nonspecific. In his ophthalmologic examination, best corrected distance visual acuity was measured 20/63 (+1.25+2.25 axis 160) in the right eye, and 20/160 (+1.75+2.75 axis 25) in the left eye (Snellen chart). There was no relative afferent pupillary defect. The intraocular pressure measured by applanation tonometer was 16 mmHg in both eyes. Biomicroscopic examination was normal and fundus examination with dilatation revealed bilateral cystic lesions in the macula (Figure 1). Optical coherence tomography (OCT) showed diffuse cystic lesions extending to the optic nerve (Figure 2). The fundus fluorescein angiography revealed no leakage (Figure 3). There was no detectable b-wave in the ERG (negative ERG) (Figure 4). We prediagnosed XLRS, and the genetic analysis of the patient revealed p.Glu72Lys (c.214G>A) mutation in the 4th exon of RS1 gene which confirmed our diagnosis. We followed our patient with topical dorzolamide hydrochloride three times daily for one year. There was no improvement, so we stopped the treatment upon the request of the patient and offered oral acetazolamide treatment. But he refused this treatment also and we called him for regular follow-up visits without treatment. We gave detailed information about the nature and possible complications of the disease and referred him to low vision service and genetic counseling.

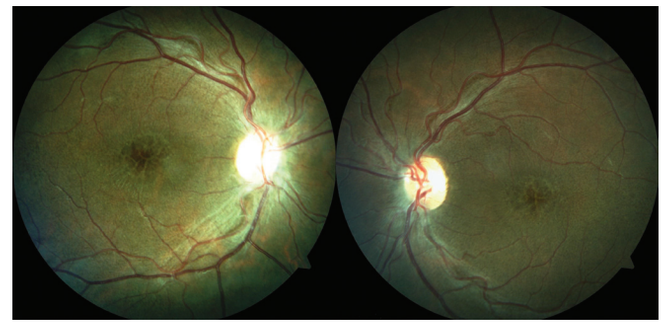

Figure 1: *Fundus images of the right and the left eyes showing cystoid macular lesions.*

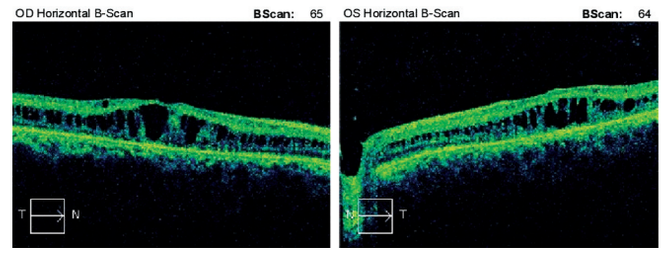

Figure 2: *Diffuse cystic lesions extending to the optic nerve are seen in the optical coherence tomography imaging.*

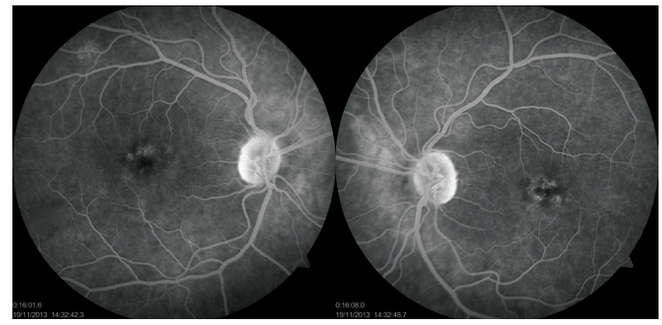

Figure 3: *Fundus fluorescein angiography images of the right and the left eyes.*

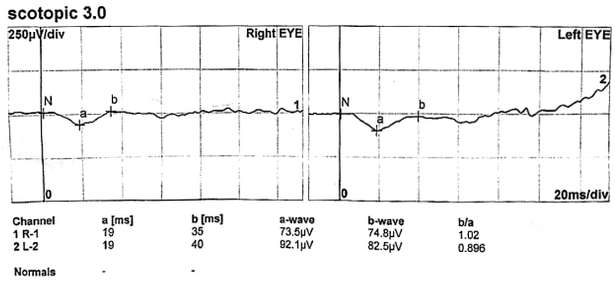

Figure 4: *Absence of b-wave in the electroretinography test (negative ERG).*

DISCUSSION

X-linked juvenile retinoschisis is a clinically heterogeneous disease and its diagnosis may not be easy in cases without prominent clinical features. Patients present with bilaterally reduced visual acuity which is usually stable until fifth or sixth decade when further deterioration occurs related with atrophic changes.[1] Although the most characteristic clinical finding is the presence of macular radial streaks, it is reported in a recent study that the typical radial streak pattern in the macula was present in 61% of the patients at the time of diagnosis.[4] Rather, especially in older patients, unspecific retinal abnormalities or cystic changes are reported.[1] These cystic changes are differentiated from cystoid macular edema by the absence of leakage in the fundus fluorescein angiography.[2] Our patient was aged 32 years at the time of the diagnosis although he had complaints of reduced visual acuity in both eyes since school-age. Honeycomb-like cystic appearance of the fovea was the most prominent finding in his fundus examination and there was no leakage in the fundus fluorescein angiography. Honeycomb-like cystic lesions are reported previously in some patients with X-linked juvenile retinoschisis, probably resulting from coalescence of smaller cysts during the course of the disease.[4]

Peripheral retinoschisis is reported in 43%-50% of the patients with XLRS.[2,4] Other findings rarely reported in patients with XLRS are perivascular sheathing, white flecks, dendritiform patterns, and Mizuo phenomenon (color change in the dark adapted retina after the onset of light).[1,5] Most patients with XLRS have hypermetropia.[1] Vitreous hemorrhage (4% to 40%) and retinal detachment (5% to 22%) are rare complications which may lead to sudden visual loss.[2]

The methods used in the diagnosis of XLRS have changed in recent years. Although ERG was accepted as the major diagnostic tool in the diagnosis of XLRS, demonstration of splitting of retinal layers with OCT is the major diagnostic method today.[1,2] In this case, OCT showed diffuse cystic lesions extending to the optic nerve. A negative ERG, a-wave larger than the b-wave, is characteristic for XLRS. Also, there was no detectable b-wave in the ERG (negative ERG) in our case. But, a negative ERG is also present in some other diseases such as congenital stationary night blindness.[6] Recent studies have shown that patients with RS1 mutations do not always have a negative ERG, therefore, a relatively normal ERG response does not exclude the diagnosis of XLRS.[1,4] RS1 is the only gene associated with XLRS and demonstration of mutations in the RS1 gene confirms the diagnosis.[2] The genetic analysis of our patient revealed p.Glu72Lys (c.214G>A) mutation in the 4th exon of RS1 gene which confirmed our diagnosis.

Although there is no definite therapy for XLRS currently, sustained application of topical dorzolamide is reported to be effective in some patients.[7] Surgery is indicated in patients with complications such as unclearing vitreous hemorrhage or retinal detachment, but prophylactic treatment of retinoschisis is not recommended.[1] We followed our patient with topical dorzolamide hydrochloride three times daily for one year. As there was no improvement in the best corrected visual acuity and OCT findings, we stopped the treatment upon the request of the patient. There are some reports in the literature demonstrating improvement with oral acetazolamide in patients with XLRS,[8] so we offered oral acetazolamide. Our patient refused this treatment and we called him for regular follow-up visits without treatment.

Gene therapy is under investigation for the treatment of XLRS. Supplementation of normal functioning retinoschisin protein is reported to induce improvement in retinal function and morphology. There are several studies investigating the efficacy of gene therapy in mouse models of XLRS, promising hope for future clinical trials.[2]

In conclusion, diagnosis of XLRS may be difficult in adults older than 30 years with negative family history. Concurrent use of OCT and ERG is helpful in making diagnosis which can be further confirmed by genetic analysis.

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