

# X-linked retinoschisis (XLRS) – A review of current scientific evidence

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## Summary:

X-linked juvenile retinoschisis (XLRS) is a rare, hereditary retinal dystrophy caused by mutations in the *RS1* gene, which encodes retinoschisin. Abnormal function of this protein disrupts retinal organisation and structural integrity, particularly in the macula, leading to retinoschisis and progressive visual acuity loss. Current management is primarily symptomatic and focuses on treating the disease's complications. Although carbonic anhydrase inhibitors have a beneficial effect on retinal cystic changes, the resulting anatomical improvement does not always translate into improved visual function. The development of gene therapy aimed at restoring normal *RS1* gene expression currently represents the most promising avenue of research into a causative treatment for XLRS. Results from preclinical and early clinical studies to date indicate the potential efficacy of this strategy; however, further analysis regarding its long-term safety and effectiveness is required.

## Key words:

X-linked juvenile retinoschisis (XLRS), *RS1* gene, retinoschisin, retinoschisis, gene therapy.

## Introduction

X-linked retinoschisis (XLRS) is an early-onset, progressive, hereditary retinopathy that primarily affects males. The clinical picture is dominated by changes within the macula, including the formation of cystic spaces and retinoschisis, which leads to a decline in visual acuity. The disease is caused by loss-of-function mutations in the *RS1* gene encoding retinoschisin, located on the X chromosome (*RS1*, MIM 30083).

Retinoschisin (RS1) is a protein encoded by the *RS1* gene, located on the X chromosome. It plays a key role in the normal development, organisation, and maintenance of retinal structure. This protein is secreted primarily by photoreceptors and bipolar cells, and it contributes to maintaining the integrity of connections between retinal cells [1].

This disease was first described in 1898 by the ophthalmologist Josef Haas, who documented the condition in two young brothers [2].

Although severe forms of XLRS are sometimes diagnosed as early as three months of age, the condition is most commonly diagnosed in school-aged boys. Few cases of XLRS have been diagnosed in women, which is due to the X-linked recessive inheritance pattern of the disease [3].

The typical clinical features of XLRS include the early appearance of intraretinal spaces caused by retinal detachment, particularly in the central macula. Characteristic changes are also observed on electroretinography (ERG) [4, 5].

In nearly all patients with XLRS, bilateral retinal layering (retinoschisis) of the macula is observed, which is the most common symptom of this disease. Diagnosis is possible during a fundus examination, while optical coherence tomography provides the most precise assessment of pathological changes. A typical fundus appearance includes a radial pattern of microcystic lesions radiating from the central part of the macula [6].

## Diagnostic

The diagnosis of XLRS is a multi-step process. Among the 90 patients included in a retrospective observational study with an in-depth phenotypic analysis conducted by Georgiou M et al., characteristic findings included macular detachment with the formation of lesions described as a spoked-wheel pattern, as well as detachments in the peripheral retina. Characteristic changes

were also observed on electroretinography (ERG) in patients with XLRS. These include a reduced b/a amplitude ratio and an electronegative nature of the combined rod-and-cone response to a high-intensity flash, observed in 72.2% of patients after adaptation to darkness. It should be noted, however, that among patients in the study group with a confirmed *RS1* gene variant, ERG results were sometimes normal as well, which may indicate that the absence of abnormalities on ERG does not rule out a diagnosis of XLRS [7].

Widely available optical coherence tomography (OCT) is of paramount importance in the diagnosis and follow-up of patients with XLRS. In a study by Hahn et al., involving 340 patients with XLRS, it was demonstrated that optical coherence tomography (OCT) allows for a more accurate assessment of retinal detachment and atrophic changes than ophthalmoscopy. The authors also demonstrated that a decline in visual acuity correlates with a shortening of the photoreceptor outer segment (PROS) and disruption of the continuity of the external limiting membrane (ELM) and the photoreceptor ellipsoid zone (EZ). These results suggest that the parameters assessed by OCT may serve as useful indicators of the severity of structural changes in the course of XLRS [5].

## Differential diagnosis

In patients with severe peripheral retinal detachment, it is essential to consider other conditions associated with early retinal detachment in the differential diagnosis.

The most important of these include X-linked Norri syndrome, characterised by complete retinal detachment present from birth and significant visual impairment, as well as familial exudative vitreoretinopathy (FEVR), which can lead to retinal detachment as a result of abnormalities in the peripheral vasculature. FEVR can occur in both X-linked and autosomal dominant forms and is caused by mutations in genes such as *NDP*, *FZD4*, *LRP5*, and *TSPAN12*. Despite certain clinical similarities, the ophthalmoscopic findings in FEVR differ from those observed in XLRS.

Pigment retention syndrome should also be considered in the differential diagnosis, although this condition is virtually absent in males. Furthermore, other causes of congenital or juvenile retinal detachment, such as trauma or retinopathy of prematurity, should be ruled out, primarily based on a thorough medical history and clinical presentation [1, 8, 9].

## Complications

Most patients experience a gradual decline in visual acuity, which in some cases leads to blindness around the age of 60 years. This process is associated with progressive atrophy of the macula, dysfunction of the retinal pigment epithelium, and pigmentary changes. In 5–20% of patients, complications such as pre-rupture retinal detachment and recurrent vitreous haemorrhages develop. Glaucoma and optic disc pallor are also reported, though less frequently [5, 7].

A retrospective study conducted by Wood et al. demonstrated that, despite a relatively stable disease course in most patients, 7.5% of the eyes analysed developed pre-rupture retinal detachment requiring surgical treatment during long-term follow-up. This complication occurred primarily in patients with phenotype type 3 and appeared as a late complication of the disease, on average after several years of follow-up. Phenotype type 3 corresponded to the form of XLRS characterised by the presence of peripheral retinal detachment [10].

## Treatment

### Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (CAIs) are one of the few pharmacological treatments used for retinal dystrophies, where they are employed to reduce cystic macular oedema.

In a prospective interventional study conducted by Apushkin and Fishman, it was reported that treatment with 2% dorzolamide led to a reduction in foveal thickness and a decrease in cystic spaces on OCT in 7 out of 8 patients. This effect was observed after one month of therapy in both eyes of 4 patients and in one eye of one patient, while similar changes were observed in two additional patients after 1–2 months of treatment. Among the patients who showed improvement on OCT, 5 additionally demonstrated clinically significant improvement in visual acuity, defined as an increase of  $\geq 7$  letters on the ETDRS scale [11].

A retrospective observational study conducted by Verbakel et al. evaluated the efficacy of carbonic anhydrase inhibitors (CAIs) in 9 children (18 eyes) with X-linked retinoschisis (XLRS) and cystic macular changes. The authors evaluated treatment with carbonic anhydrase inhibitors administered topically or orally (primarily dorzolamide, and in some patients, acetazolamide as well). The primary endpoint was the change in foveal zone thickness (FZT) as assessed by SD-OCT, with a reduction of  $\geq 22.4\%$  defined as a significant response. A significant morphological improvement was observed in 5 of 9 patients (55.6%), with a median treatment duration of 6.8 months (range 1–23 months). Importantly, in most of these patients (80%), a reduction in FZT was already evident within the first month of therapy. Overall, an improvement in visual acuity was observed in 5 eyes (27.8%) belonging to 3 patients (33.3%), suggesting that the anatomical effect does not always directly translate into improved visual function [12].

The results obtained by Verbakel et al. indicate that regression of structural changes within the macula does not necessarily correlate with a proportional improvement in visual function. In contrast, a retrospective observational study by Testa et al. observed simultaneous improvement in both structural and functional parameters of the retina following treatment with oral carbonic anhydrase inhibitors. An increase in best-corrected visual acuity (BCVA;  $p = 0.013$ ), a reduction in central retinal thickness ( $p = 0.004$ ), and a significant improvement in macular sensitivity ( $p < 0.001$ ) were noted. Additionally, mfERG analysis revealed an increase in P1 wave amplitude in 3 of the 6 analysed rings, indicating a partial improvement in retinal function. The authors emphasise that oral CAI can effectively reduce cystic changes in the macula in patients with XLRS, restoring its more normal architecture [13].

## Surgical treatment

Invasive procedures, including vitreoretinal surgery, are reserved for patients with severe complications, such as retinal detachment or a significant retinal membrane within the macula.

Sen P et al. analysed the records of 34 eyes from 28 patients with XLRS who underwent surgery for rhegmatogenous retinal detachment (RRD). Analysis of the treatment outcomes showed that vitreoretinal surgeries performed for RRD in patients with XLRS yield satisfying anatomical and functional results. In most patients, retinal reattachment was achieved, along with improvement or stabilisation of visual acuity. At the final follow-up, retinal reattachment was achieved in 27 eyes (79.4%). Regarding visual acuity, improvement was observed in 20 eyes, stable results in 6, and deterioration in 8. It should be emphasised, however, that due to the complex nature of the condition, some patients required further surgical interventions [14].

## Gene therapy

The limited effectiveness of carbonic anhydrase inhibitors in improving visual function has led researchers to focus on causal therapies. Current research focuses primarily on correcting the *RS1* gene mutation, and the monogenic nature of the disease, along with its relatively predictable clinical course, make XLRS an attractive target for the development of gene therapies.

Experiments conducted on mice with the *RS1* gene knocked out provided evidence of the efficacy of therapy using the AAV8-*RS1* vector. Following intravitreal administration, vector penetration into the retina, closure of the schisis, restoration of its normal organisation, and improvement in the functional transmission of visual signals at the synaptic level were observed [15].

In a phase I/IIa clinical trial conducted by Cukras et al., the safety and tolerability of gene therapy involving the delivery of a functional copy of the *RS1* gene to the retina using the AAV8-*RS1* viral vector were evaluated in patients with X-linked retinoschisis (XLRS). In this clinical trial, patients received the AAV8-*RS1* gene vector via intravitreal injection. The therapy was generally well tolerated, although higher doses caused transient inflammation of the eye. No cases of uveitis or retinal detachment were reported. In summary, this study confirmed the efficacy of the intravitreal route of administration for the AAV8-*RS1* vector [16].

Andres-Mateos E et al. demonstrated that the new AAV.SPR capsid, characterised by its ability to spread laterally within tissue, enables effective transduction of photoreceptors within the macula and fovea in primates without causing central retinal detachment. Following subretinal administration, transgene expression was observed beyond the injection site, and the use of the AAV.SPR-hGRK1-*RS1* construct resulted in proper expression of the *RS1* protein within the fovea as well. Studies in a mouse model with an *RS1* gene knockout demonstrated a dose-dependent improvement in retinal structure and function following treatment with ATSN-201, while toxicology studies conducted in primates confirmed a favourable safety profile even at the highest doses evaluated. The results obtained indicate that the AAV.SPR vector may represent a promising platform for gene therapy of XLRS and other hereditary retinal diseases [17].

In a study by Hahn et al., it was noted that in most patients with XLRS, the loss of visual acuity progresses relatively slowly. Combined with the results of preclinical studies, in which gene therapy slowed photoreceptor degeneration in animal models, this suggests the existence of a relatively broad therapeutic window allowing for the initiation of treatment before irreversible changes in the retina occur. The authors emphasised that the greatest benefits of the therapy are likely to be achieved in patients who have not yet experienced significant photoreceptor loss or deterioration

in visual acuity. Based on an analysis of the disease course, the authors suggest that the optimal time for intervention is most likely during the first 2–3 decades of life, before the development of advanced retinal atrophy [5].

## Conclusion

X-linked retinoschisis (XLRS) is a rare inherited retinal disease caused by mutations in the *RS1* gene, leading to structural abnormalities in the retina and the formation of detachments, particularly within the macula. The disease can cause progressive deterioration of visual acuity and the development of complications; therefore, the search for new therapeutic strategies, including causal therapies, represents an important area of research on XLRS.

Currently, there is no effective causal treatment for this condition, and available therapies mainly focus on preventing or treating complications associated with the disease.

In many retinal dystrophies, carbonic anhydrase inhibitors (CAIs) are effectively used to reduce cystoid macular oedema. Available studies show positive effects on retinal structure; however, it should be noted that anatomical improvements do not always directly translate into improved visual function.

In recent years, particular attention has been focused on gene therapy, which aims to introduce the correct version of the *RS1* gene and restore the function of the retinoschisin protein. Results from preclinical and early clinical trials suggest that this approach may contribute to improvements in both retinal structure and function. Although further research is needed to confirm the long-term efficacy and safety of these therapies, gene therapy is currently considered a promising avenue for the development of treatments for XLRS.

## Disclosure

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