

# X-linked Juvenile Retinoschisis

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## Abstract

*X-linked retinoschisis is a congenital ocular disease secondary to an abnormal cleavage of the innermost layer of the retina. The frequency has been estimated at 1/28 000 in the North of France and 1/17 000 in Finland. This ocular disorder is characterized by a bilateral cystic macular lesion at the level of the posterior pole of the retina and, in more than one third of the cases, by a bullous elevation of the peripheral retina. This peripheral elevation or schisis can be associated with veils and preretinal vitreous condensations. The lesions are present at birth or appear during the first years of life. They have little tendency to progress. Whereas the peripheral lesions will eventually flatten and even disappear with time, the central lesion progresses towards atrophy. Vision slowly decreases with age, resulting in poor central vision after the fifth decade. No treatment is needed in the simple form. However, surgery should be considered in the presence of major complications, such as severe vitreoretinal traction resulting in haemorrhages, retinal tears or rhegmatogenous retinal detachment. This condition is inherited as a recessive X-linked trait. The gene has been localized (Xp22.2-p22.1) and numerous mutations have been identified. The physiopathology remains to be elucidated.*

## Keywords

Cataract; congenital peripheral schisis; discoïdine; foveolar cysts; hypermetropia; nystagmus; retinoschisin; rhegmatogenous retinal detachment; schisis; stellar shaped macula; strabismus; vitreoretinal veils; X-linked macular disease

## Diagnostic criteria/definition

X-linked retinoschisis is a bilateral retinal disease with a recessive X-linked mode of inheritance, characterized by a maculopathy which is present in all cases and is associated in somewhat less than 50% of the cases with

peripheral retinal and vitreous lesions. The retinal lesions are probably already present at birth or appear during the first months of life. The maculopathy consists of bilateral star-shaped microcystic macular changes. The retinal periphery is only involved in about 40% of cases,

and then presents an inferotemporal schisis, vitreous veils and condensations and, more rarely, vitreoretinal membranes.

### Synonyms

- X-linked congenital retinoschisis
- Hereditary juvenile retinoschisis
- X-linked juvenile retinoschisis
- Cystic retinal disease in children
- X-linked vitreoretinal degeneration
- XLRS
- RS

### Historical overview

In 1898, Haas was the first to describe the ophthalmoscopic appearance of what he called cysts in "wheel spokes". The familial nature of the disease was recognized by Pagenstecher in 1913 and several authors described the condition under different names. In 1935, Wilczek introduced the term retinoschisis (schisis -> cleavage).

### Excluded diseases

Dominant or autosomal recessive foveolar retinoschisis  
Goldman-Favre syndrome  
Peripheral vitreoretinal degeneration  
Senile peripheral retinoschisis

### Differential diagnosis

The macular lesion can be mistaken for sequelae of cystoid macular oedema (CMO), which can occur bilaterally in case of autosomal dominant CMO or as a complication of retinitis pigmentosa or allied diseases. An electronegative ERG can be found in congenital hemeralopia. The peripheral lesions may be reminiscent of those seen in Goldman-Favre disease. There are some similarities between the peripheral fundus lesions of X-linked retinoschisis and those of retinopathy of prematurity (ROP). Autosomal dominant as well as autosomal recessive macular retinoschisis have been described and should be considered in the differential diagnosis of X-linked retinoschisis with isolated macular lesions.

### Prevalence

The prevalence has been estimated at 1/28 000 in the North of France (Puech 1991) and at 1/17 000 in Finland (de la Chapelle *et al*, 1994).

### Clinical description

The diagnosis is seldom made in newborn babies, except when the disease is very disabling resulting in nystagmus and strabismus. If other family members are affected, the diagnosis can be made at an early age by the systematic examination of newborns. The diagnosis is most commonly made in early childhood, at the occasion of a school

examination revealing poor vision, strabismus or tractional retinal complications. Distant visual acuity may vary between 2 and 7/10, near vision being usually better. Hypermetropia, strabismus and nystagmus have been classically described but are not necessarily present.

The central retinal lesion consists of fine radial folds of the inner limiting membrane covering the macula and centered on the foveola. This configuration is stellar or "wheel-like". It is particularly obvious with the scanner laser ophthalmoscope (SLO). In the center of this stellar lesion, at the foveola, the striations are prolonged by small round and reddish microcysts. In 98% of younger patients, this central lesion is present in a more or less obvious fashion.

A peripheral retinoschisis is observed in somewhat less than half of the cases. It projects into the vitreous as a semitransparent bullous detachment, most often localized in the inferotemporal quadrant. This detachment is sometimes limited to one or more semitranslucent vitreous veils, which contain retinal vessels. The peripheral retinoschisis may be variable in size. In the most severe forms, it may reach and involve the macula, it may also look like a vitreoretinal traction fold between the retinal periphery up to the optic disc.

In female carriers, clinical signs signs have been described, such as loss of foveal reflex, hardly visible folds of the internal limiting membrane or irregular macular pigmentation, and were considered as "Lyonsation" phenomena. However the foveal reflex disappears in the adult around the age of 35 years, which corresponds to the mean age of mothers of affected children at diagnosis. Macular pigment irregularities can be observed in otherwise normal individuals over the age of 40 and the subtle macular folds have only been exceptionally noticed in female carriers. According to Kaplan (1991), female carriers frequently present with discrete peripheral retinal lesions similar to those seen in affected adult males.

The *visual field* shows a relative central scotoma and sometimes major peripheral constriction when the peripheral schisis is important.

The *color vision* is only mildly affected.

The *electroretinogram* is always affected and is electronegative. The photopic a-wave is larger than normal, especially in the beginning, and the b1-wave is small and negative; the scotopic b2-wave is also negative and markedly modified or even absent. It is noteworthy that Arden described in 1988 a rather complicated electrophysiological technique, which could diagnose female carriers. The electro-oculogram (EOG) is normal in 50% of cases and is markedly affected only at older age. The *visual evoked potentials* (VEP) are normal if the visual acuity is better than 2/10.

*Fluorescein angiography* does not generally show changes in children, except discrete fluorescence at the level of the foveola. In advanced forms, in adults, perimacular annular window defects are sometimes seen.

### Evolution

After the age of 40 years, the macular schisis becomes less obvious and is replaced by a macular atrophy with pepper and salt appearance and a prognosis similar to that of atrophic age-related macular degeneration. The peripheral schisis initially also progresses quite slowly. Classically, worsening occurs up to the age of 20 years, and is characterized by the extension of the surface of the schisis. Later, spontaneous reapplication may occur; the schisis fades whereas gradually expanding holes are formed in its wall. The periphery takes the aspect of an atypical atrophic degeneration with sometimes spotted areas with brownish or miccalike reflexes. Sheathed and occluded retinal vessels are sometimes seen, producing a lattice-like dendritic appearance. In such advanced cases, cataract is common and is considered as a classic complication. As in most peripheral retinal dystrophies, cataract appears at an early age. Other complications result from vitreous tractions, such as vitreous haemorrhages, retinal tears or rhegmatogenous retinal detachment. These complications may be present already at birth or appear later after one or two decades. In cases that are not associated with these complications, the disease progresses with flattening of the peripheral lesions and progressive replacement of the cystic macular lesion by atrophy (Turut 1991).

### Treatment

There is currently no specific treatment or prophylaxis for retinoschisis.

The rule is not to treat uncomplicated cases. The peripheral elevation spontaneously reapplies. The patient should regularly be examined to detect more severe complications. Traction by vitreoretinal veils may provoke retinal tears, massive vitreous haemorrhages or rhegmatogenous retinal detachment. Prophylaxis or treatment with laser photocoagulation must be considered. Although vitreous haemorrhages will generally disappear spontaneously, they can play a role in vitreoretinal proliferation. The major complication is retinal detachment, which has been reported to occur in 4 to 20% of the cases. It is often associated with vitreoretinal proliferation, thus necessitating not only conventional retinal detachment surgery, but also associated vitreous surgery (Turut 1991).

### Etiology

Histologically, it has been demonstrated that the lesions of juvenile retinoschisis are secondary to an abnormal cleavage of the retina at the level of its innermost layer, the nerve fiber layer (Yanoff 1968, Manschot 1972). This led to the hypothesis that the lesions resulting from cleavage are malformative in nature and congenital, especially as they could be detected in the newborn (Sauer 1997). In the light of this hypothesis, the disease would not progress further after birth, but tissues would be damaged by the initial malformations and degenerate. Epidemiological studies on the fertility of female carriers and the sex ratio (see "Genetics") seem also to support this hypothesis. There could be a pleiotropic action of the gene defective in retinoschisis, *XLR51*, affecting embryonic implantation and survival (Huopaniemi 1999). Immunohistochemistry however is not in favor of a pure malformation disorder, as it detects the gene product, the secreted retinoschisin, in the photoreceptor layer (Grayson 2000).

### Diagnostic methods

The disease's hallmark is the typical stellar macular lesions, which are found in almost 100% of cases. The diagnosis is confirmed by the observation of peripheral lesions, an electronegative ERG and a positive family history. A systemic examination of the family will enable detection of other affected members. In difficult cases, molecular biology will enable detection of female carriers.

### Genetics

Juvenile retinoschisis is an hereditary disorder with an X-chromosomal recessive mode of transmission. As a result, most of the detected cases are males. The few cases of affected females described in the literature were daughters of an affected father and a carrier mother. The sex ratio in sibships with retinoschisis and in children of carrier mothers is larger than 130, which means that there is a predominance of males in the offspring. The gene could therefore be involved in the mechanism of fertility (Huopaniemi 1999). A carrier female transmits the disorder to her sons in 50% of the cases, whereas 50% of her daughters become carriers. The penetrance is 100% in affected males, but the expressivity is variable. Late-onset milder cases as well as very serious early-onset blinding forms of the disease can be found within the same family.

The gene is localised to the chromosomal region Xp22.2-p22.1. The first mutation was described by Sauer (1997). The gene consists of six exons and encodes a 224 amino acids protein, which contains a discoidin domain indispensable for normal retinal development. Immunochemical techniques (Grayson 2000) have shown that the

gene is expressed in the photoreceptor layer and that the secreted protein (retinoschisin) is found in that layer and in the internal retinal layers. This suggests a primary role of the photoreceptors. The proposed role of Müller cells in the abnormal cleavage in the visual fiber layer and retinal vessels seems therefore unlikely.

Most of the ongoing research is coordinated by the Retinoschisis Consortium (1998), with teams from Germany, the USA, Great Britain, Denmark, Spain, Finland, France, the Netherlands, Italy.... These different teams can be contacted via Internet where the updated list of the different mutations so far identified (more than 80) is also available.

### Genetic counseling

Genetic counseling is necessary. It is often requested in severe forms, mainly for women closely related to the proband and susceptible to be carriers. A normal fundus does not exclude a carrier state, and search for mutations or haplotypes analysis is necessary. This search should take into account the whole family and must comprise at least one affected individual

### Detection of the gene mutations

These mutations are detected either by Southern blot or by microsatellite analysis. Gene alterations (substitution, deletion, insertion, rearrangement) are searched in the 6 exons. Although the spectrum of identified mutations is very heterogeneous, most patients will present with a typical clinical aspect. Molecular genetic investigation is required in the diagnosis of severe forms in children that are associated with *de novo* mutations or lack electrophysiological or familial arguments. Mutations detection is also justified in the screening of female carriers (see above). The families in which mutations have not yet been identified may have mutations affecting the transcription mechanism of messenger RNA or the introns (Retinoschisis Consortium 1998)

### Prenatal diagnosis

The vast majority of X-linked retinoschisis cases does not justify abortion.

There are neither rules nor recommendation for abortion in the most severe forms. In such cases, where blindness at birth is highly likely, an interruption of pregnancy may be considered, but the advice of an ethical committee should be requested.

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