Clinical and genetic examinations of X-linked juvenile retinoschisis

Doctoral thesis

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Introduction

X-linked juvenile retinoschisis (XLRS), firstly described by *Haas* in 1898, is one of the most common X-linked recessively inherited, incurable, bilateral, progressive vitreoretinal dystrophies limited almost exclusively to males.

On the basis of its estimated incidence (1:15000 and 1:30000) 330-660 persons can be affected in Hungary. The disease is often under- and misdiagnosed world-widely and this was the case in Hungary also.

The penetrance of the disease is 100% in affected males, but its phenotype, time of onset and course is pretty variable, which harden the right diagnosis.

The first typical complaint of the affected boys is reading difficulty, originated from uncorrectable decrease of central visual acuity (VA), usually noticed between 5-10 years of age. The first diagnosis is often uncorrect.

The boys' visual acuity is moderately variable and the difference between the two eyes is often remarkable. VA is usually between 0.2 and 0.4 at the first observation, then progrediates until the end of puberty, later on mostly turns to stabile. By the 6-7th decades decrease of VA may achieve the level of legal blindness (0.1).

The bilateral macular changes are present in almost 100% of patients. In the early stage of the disease in 98-100% of the affected patients intraretinal cystoid spaces (in the foveal area bigger, perifoveally smaller) are seen in a spoke-wheel configuration, with the absence of foveal reflex. In the following part of the study, for the mood of simplicity, the presence of cystoid spaces is called cystic stage. In the course of time cystoid spaces being gradually coalescing, the foveal schisis flattens and finally nonspecific macular atrophy evolves. The clinical symptoms alone are rather difficult to set up the right diagnosis in this stage.

In addition, approximately 50% of cases have peripheral retinoschisis, which typically affects the infero-temporal quadrant of the retina. The size of retinoschisis may progrediate significantly from fairly flat to extended bullous in childhood, but later on it mostly comes to a spontaneous regression.

XLRS inherits X-linked recessively and markedly affects boys/males only.

Mutation of *RS1* gene, being responsible for the development of the disease, was identified on the short arm of X-chromosome by *Sauer and co-workers* by positional cloning in 1997. *RS1* has six exons and encodes a 224 amino acid (AA) retina specific

extracellular adhesion protein, called retinoschisin (RS1). This protein is primarily expressed, then secreted by photoreceptors and bipolar cells. RS1 protein, which forms homo-octamer complex with intra and intermolecular disulfide bonds, plays a critical role in cell adhesion, cell signalling procession by its conservative discoidin domain.

Functional loss of retinoschisin due to mutations, then its intra- and extracellular accumulation leads to development of intraretinal cystoid spaces visible mainly in the inner nuclear layer (INL). All these mechanisms lead to disintegration of retinal structural integrity and to secondary degeneration of photoreceptors because of the damage of photoreceptor-bipolar synaptic structure.

The mutation spectrum of the disease is very heterogeneous and since identification of *RS1* gene, more than 178 different, mainly de novo XLRS causing mutations were referred, mostly affect exons 4-6, coding the discoidin domain.

New diagnostic methods of ophthalmology (optical coherence tomography= OCT, electroretinography= ERG) enable a more exact morphological and functional understanding and follow-up of the disease. Early diagnosis can help the affected persons to reduce the possible chance of development of complications.

Negative-type (characteristic decrease of b-wave amplitude with relative preserved a-wave amplitude) scotopic maximal response detected by Ganzfeld ERG is of differential diagnostic value in XLRS.

Real therapy of the disease has not been found in humans yet. As possible symptomatic therapeutical approach of the retina, application of multivitamins with anti-aging affect, or in complicated cases, vitrectomy is the therapy of choice.

In the course of widening molecular genetic knowledge in the field of XLRS, several animal trials have been starting with the goal of developing causative therapeutical methods instead of the palliative treatment of the disease. The aim of these methods is to treat XLRS similarly to other inherited retinal diseases (Leber's congenital amaurosis, retinitis pigmentosa, Stargardt's macular dystrophy, etc.) on gene level. Heartening morphological and functional rehabilitation was already achieved by animal trials in latter years. The first human experiments are going on.

Aims

Aim of our study was the extensive clinical analysis and the study of progression of XLRS with modern ophthalmological diagnostic equipments, and the exploration of genetic background for the first time in Hungary, by the help of Hungarian ophthalmologic centres.

During our examinations we set the following aims and searched for the answers to the undermentioned questions:

1. To collect patients with XLRS nationwide and to carry out detailed family tree examination in their families.
2. To asses retinal damage and age dependency (modelling time course) in different phenotypes with objective morphological and functional examinations. To compare the characteristics of different phenotypes with each other and with the normal age-matched controls.
3. To find correlation between the best corrected visual acuity (BCVA) and the morphological and functional examination results of the retina.
4. To make a new, more detailed classification system for easier assignment of the different phenotypes of the disease.
5. To reveal molecular genetic background in the possibly most patients with XLRS, to assess the prevalence of mutations, then compare the results with the international data.
6. To reveal spatial changes of the tertiary structure of mutant RS1 protein and to find correlation between the degree of structural changes and the severity of the disease.
7. To compare the clinical characteristic of cases with different genetic background (genotype-phenotype analysis).

Patients and methods

In a prospective study 107 members of 24 families (from 35 families) were involved in the study, which was carried out at the Department of Ophthalmology (Mária street) between September 1. 2005. and September 1. 2008. on members, who were observed at the Ophthalmologycal Departments of the University of Budapest, Pécs and Szeged. The results of morphological (fundus, OCT) and functional (VA, ERG) examinations of 51 family members (31 male patients, 19 asymptomatic female carriers, 1 female

patient) and molecular genetic examination of 107 family members were analysed for better understanding of the disease.

For a more correct assessment of the functional effect of morphological changes (i.e. from cystic to atrophic stage) - observable and exactly measurable by OCT -, patients were divided into two groups on the basis of their central foveal thickness (CFT) value.

Group I contains patients with cystic macular changes (23 patients, 45 eyes, mean age±SD: 16,2±9,8 years), whose CFT values were higher than the average CFT(+SD) value of the normal controls, that is > 173,2 μm.

Group II contains patients with atrophic macular changes (9 patients, 16 eyes, mean age±SD: 39,6±9 years), whose CFT values were lower than the average CFT(-SD) value of the normal control, that is < 140,2 μm.

A control group of 50 healthy age-matched normal subjects (mean age ±SD: 25,2±15,3 years) was examined using the same clinical and genetic protocol.

Examination methods are discussed in the order of examinations:

Subjective examination of retinal function - VA testing

Refraction of all participants was measured by automatic refractometer (Tomey RT-6000, Tomey Corporation, Nagoya, Japan), then decimal value of best corrected visual acuity (BCVA) was defined using Kettesy visual chart. For comparability and statistical processibility, BCVA values were converted to LogMAR (logarithm of the Minimum Angle of Resolution) units.

Subjective examination of retinal morphology - indirect ophthalmoscopy

Detailed indirect ophthalmoscopy was carried out at slit lamp with 90D SuperField® Volk® lens after pupil dilatation (0,5% cyclopentolate).

Objective examination of retinal morphology - optical coherence tomography (OCT)

For objective examination of retinal structure optical coherence tomography (OCT) was performed after pupil dilatation by 3rd generation OCT equipment (StratusOCT, Zeiss-Humphrey Instruments, Dublin, CA, USA), which examines the cross-section of retina with a transversal resolution of 20 μm and with an axial resolution of 10 μm.

Total macular volume (TMV) according to 6 mm long scans, and central macular volume (CMV) according to 3,45 mm long scans (in order to better characterizing of the foveal volume) were calculated automatically by the built-in software of the device. Retinal thickness (distance between ILM and RPE) was measured manually with caliper technique in order to a more accurate measurement. To measure the central foveal thickness (CFT), in case of central fixation, both cross marks of caliper were placed at right angles of retinal level in the intersection of 6 radial scans. In case of eccentric fixation, in cystic stage, or with irregular cystoid space, the highest, while in atrophic stage the lowest CFT were measured.

Objective examination of retinal function - electrophysiology

As an objective method, firstly Ganzfeld electroretinography (GfERG) was performed binocularly using corneal "ERG-jet" contact lens electrodes by the RetiPort ERG system of Roland Consult Company (Brandenburg/Wiesbaden, Germany), according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards. In the first part of the examination, function of rods was examined after 30 minutes dark adaptation. In the second part, function of cones was evaluated after 10 minutes light adaptation.

GfERG is suitable to diagnose and differential diagnose XLRS noninvasively. However, negative-type ERG is not observable in many genetically confirmed cases, and there are cases to know, when significant b-wave amplitude reduction is not detectable.

Afterwards multifocal electroretinography (mfERG) was carried out monocularly by the RetiScan ERG system of the same company after 15 minutes light adaptation, according to ISCEV standards. During mfERG 21" CRT display was used as stimulus source and a stimulus pattern consisting of 61 black-white hexagons and alternating with a special pseudorandome sequence was shown. Preparation of patients, applied electrodes and their installation happened by the same way alike GfERG.

The functional status of macula can be examined noninvasively and topographically by the help of mfERG and further follow-up of functional failure is possible. Since the mfERG is not specific for XLRS, it is not suitable for differential diagnosis and it can only be evaluated together with other examination results.

In both examinations amplitudes and implicit times of responses were measured.

Molecular genetic examinations

Genomic DNA was extracted from 6 ml peripheral blood leucocytes, then 6 exons and the flanking intronic regions of *RS1* were amplified using automated polymerase chain reaction (PCR) equipment (Thermo Hybaid PxE thermal cycler, Thermo Hybaid, Franklin, MA). The amplicons were genotyped by direct nucleotide sequencing on an automated DNA sequencer (ABI PRISM® 310 Genetic Analyzer, Perkin Elmer™; Applied Biosystems).

The tertiary structure of normal and mutant RS1 proteins were visualized by the predictive protein modelling software of CPHmodels 2.0 Server, while alternative splice site was determined by the NNSPLICE 0.9 predilection software of Berkeley Drosophila genome project.

Statistical analysis

Statistical calculations were carried out by Statistica 8.0 (StatSoft Inc., Tulsa, Oklahoma, USA), SPSS 15 (SPSS Inc., Chicago, USA) and Microsoft Office Excel 2003 (Microsoft® Corp.) software. Significance was accepted at the $p<0.05$ level. To assess significant changes of age, BCVA, OCT and ERG parameters among control persons, carriers and the two patient groups, we performed analysis of variance (one-way ANOVA) followed by Newman-Keuls post hoc analysis. Linear regression was performed to analyse the correlations between individual parameters and in several cases regression curves were fitted by Distance-Weighted Least Square (DWLS) method to a better visualizing the correlations between two variable parameters. The degree of correlations was described by Pearson's correlation coefficient (r). The CFT was examined in correlation with age by receiver operating characteristic (ROC) analysis and the cut-off point (with the best sensitivity and specificity) between cystic and atrophic stage was determined.

Results

Results of clinical and molecular genetic examinations of 24 Hungarian families suffering from XLRS were summarized and presented in this study, first in Hungary.

Results of clinical examinations

After detailed family tree examination, disease caused morphological changes were examined by OCT, functional changes by Ganzfeld and multifocal ERG in 31 male and in one female patient suffering from XLRS and in 19 female carriers.

Subjective examination of retinal function - VA examination

BCVA logMAR values of patients suffering from XLRS were significantly impaired (Group I<II) compared with controls and there was significant difference between the two patient groups.

Moderate negative significant correlation was detected between age and VA values of patients. Examining VA according to age in detail, a small improvement of decreased visual acuity of patients was observed until 13 years of age, while until 45 years a slow, later on an accelerating decline was observable.

The small improvement of VA in childhood was probably due to more efficient use of still functioning parafoveal retina (eccentric fixation), and would occur as a result of the plasticity of the developing visual system. This is also confirmed by the fact, that eccentric fixation was found nearly twice more in the younger group I, than in the older group II. Increasing visual acuity deterioration visible in older age was occur almost exclusively in cases with atrophic macula.

Subjective examination of retinal morphology - indirect ophthalmoscopy

Macular abnormalities were detectable in all patients suffering from XLRS in spite of the high inter- and intrafamilial variability.

Bilateral cystic retinoschisis was found in ¾ part of cases (almost exclusively under 28 years of age), while nonspecific foveal atrophy was found in more than ¼ part (over 28 years of age).

The characteristic infero-temporal peripheral retinoschisis was observable only in ¼ part of patients, in $^{2}/_{3}$ part bilaterally.

On the basis of fundus photographs and OCT measurements, bilateral (fundus albipunctatus-like) white flecks of the posterior pole of our patient (having the biggest OCT parameters) were proven to be columns, which creates the wall of cystoid spaces and considered to be Müller cells.

Objective examination of retinal morphology - optical coherence tomography (OCT)

Patients' OCT images and values showed large interocular and intrafamilial variability.

Macular cystoid spaces were managed to find more than 16.1% often by OCT than by indirect funduscopy.

Foveal cystic schisis was detected in ¾ part of eyes, while flat macular lamellar schisis - recognizable only by OCT - was detected in more than ¾ part. Nonspecific foveal atrophy was found in 12.9%.

In young age, in the cystic stage, the biggest cystoid spaces, thanks for the extra- and intracellular accumulation of pathological functioning RS1 protein, were always in the foveal area in the INL, surrounded para- and perifoveally by smaller and smaller cystoid spaces. However, smaller cystoid spaces were found in the ganglion cell (GCL) and in the photoreceptor cell layer (PRL) also.

On the basis of our modified classification scheme the most common phenotype of the disease (56.5%) was the foveo-lamellar type (type 3), in which retinoschisis was observable at the foveal and macular region in the INL, without peripheral schisis.

Analysing the age depending longitudinal changes of cystoid spaces, in early childhood only foveal retinoschisis was presented, then with age macular lamellar schisis was appeared, while later nonspecific atrophy was evolved in the macular area by the disappearance of foveal and macular lamellar schisis. The process was accompanied by the gradual decay of VA.

Analysing the age depending transversal changes of cystoid spaces, each of the three layers was affected. The biggest cystoid spaces were typically located in the INL, which layer was affected in every cystic case. By ageing - probably in association with their size - cystoid spaces were disappeared gradually, firstly small ones from GCL and middle ones from PRL, then later the biggest ones from INL. Finally nonspecific foveal and perifoveal atrophy was developed with unchanged parafoveal retinal thickness. In older age (over 28 years) the whole macula became atrophic, associated with the worst VA.

Analysing the time course of the disease, strong negative significant correlation was found between CFT and age. In young age, the significant CFT elevation (compared to control group's values) caused by cystoid spaces, stayed constant until the middle of the

twenty years. Thereafter CFT decreased significantly by disappearance of foveal cystoid spaces and in the atrophic stage it did not change with age.

Examining CFT in connection with age by ROC analysis, the cut-off value, belonging to the transition from the cystic to the atrophic stage was 28 years of age.

The tendency according to the age, detected when examining CFT, was milder in case of CMV and TMV.

Analysing results of patients with cystic and atrophic macula, the BCVA logMAR of the patient groups were significantly elevated compared to control values and to each other (Group I<II), but no sudden intense VA worsening was experienced in connection with the intense change of macular region (cystoid space→ atrophy).

Examining the CFT, CMV and TMV values of OCT, those of patients with cystic macula were significantly increased, while those of patients with atrophic macula were significantly decreased compared with controls being in accordance with the flattening of cystoid spaces visible with age.

Objective examination of retinal function - electrophysiology

All the amplitudes of scotopic and photopic responses of GfERG were significantly decreased in both patient groups (Group I<II) compared with values for controls.

Significant difference was found in the b-wave amplitudes of rod and maximal responses between the two patient groups (Group I>II).

The b-wave amplitude of scotopic maximal responses showed 56% decrease in average, while a-wave showed 21.1% decrease only. The decrease of maximal b-wave amplitude was primarily responsible for the differential diagnostic negative-type ERG (b/a ratio±SD: 0.85±0.1), found in 50% of affected eyes (Group I< II).

Implicit times of GfERG rod responses were significantly increased in group I, while implicit times of cone and 30Hz flicker responses were significantly increased in both patient groups, compared with controls.

Response densities (RD) of mfERG P1- (b) wave were significantly reduced in both patient groups in the whole examined retinal area (mainly in the two central rings correspond to the damaged fovea) compared with the controls, while implicit times were significantly increased in rings 3-5 in group I, and in rings 4-5 in group II,

compared with controls. There was no significant difference between response densities and implicit times of the two patient groups.

Main damage of INL and PRL was found by ERG, where the biggest schisis was found by OCT and where, normally, the functional RS1 protein can be detected in the greatest amount.

Amplitudes of patients' Ganzfeld and multifocal ERG responses showed significant weak and moderate negative correlation with age and with VA, in accordance with the decrease of retinal cell function and with the decrease of VA observed with the progress of age.

The areas of flat lamellar schisis (detected by OCT) and retinal functional impairment (measured by mfERG) showed the morphological and functional damage of retina in a greater part than would have been expected by funduscopy. All this indicates that OCT and mfERG is essential in the judgement of real measure and extension of retinal damage.

Results of molecular genetic examinations

Our present work is the first study to estimate the genetic background of patients with XLRS in Hungary as well.

In all patients suffering clinically from XLRS were managed to detect the disease causing *RS1* mutation. Altogether one novel intronic splice site (c.78+1G>C), two novel missense, one known frame shift causing insertion and nine known missense mutations were found in the *RS1* gene of 39 male patients and in 46 asymptomatic female carriers. The c.78+1G>C splice site mutation and the caused two possible alternative splicing mechanism was firstly described by us in men, which - in absence of human retinal sample - was confirmed by the result of an earlier published mutagenesis carried out in mice by others.

Contrary to the data of the Retinoschisis database (*exon 4: 42.7%*; exon 5: 16.3%; exon 6: 26.9%), in the Hungarian patient population the most often affected was exon 5 (exon 4: 28.2%; *exon 5: 35.9%*; exon 6: 30.8%), while the most different type mutations were in exon 6.

We demonstrated the spatial changes of the tertiary structure of mutant RS1 proteins, which did not correlate with the severity of the disease. This is in accordance with the

statement, that the absence of a functional RS1 protein is responsible for the development of the retinoschisis in men.

Examining the diseased caused morphological and functional changes linked to a mutation, obvious genotype-phenotype correlation was found in c.305G>A mutation, which was associated with the most pronounced morphological and functional changes (the highest OCT parameters, lowest GfERG maximal b/a wave amplitude ratios, lowest mfERG response densities).

The most often identified c.214G>A mutation was associated with highly impaired VA, increased OCT parameters and significantly decreased maximal a- and b-wave amplitudes of GfERG.

The c.527T>C mutation was associated with the least impaired VA and (cone specific) 30Hz flicker responses of GfERG.

Bilateral Mizou-Nakamura phenomenon was present in both patients with the novel intronic c.78+1G>C mutation.

The genetic examination of the one and only female patient, who initially was thought to suffer from XLRS by the characteristic spoke-wheel pattern of her macula, did not manifest any mutation in the *RS1* gene. Big cystoid spaces observable by OCT in the macular area were not located in the INL as opposed to XLRS, but in the OPL. Her FLAG examination showed pooling opposite the negative finding in XLRS. Beside normal GfERG responses, functional decrease was found in mfERG responses with central predominance. Based on the above, the case was concluded as the quite rare autosomal recessively inherited isolated foveal retinoschisis.

Conclusions - New results and their practical applications

1. We decided to collect families suffering from XLRS firstly in Hungary, then after detailed family tree examination modern clinical and molecular genetic examinations were carried out in the available patients and carriers (24 families, clinical examinations: 51 persons /31 males, 19 females/, genetic examinations: 107 persons /49 males, 58 females/).
2. We expanded the international classification scheme used earlier and on the basis of this we established the prevalence of the certain phenotypes and their correlation with age and VA in patients.

Genetic aspects

3. We examined firstly the genetic background of Hungarian patients suffering from XLRS. In all boys/males suffering clinically from XLRS were managed to manifest the disease causing mutation in the *RS1* gene. Three novel mutations were described (c.78+1G>C, c.575C>T, c.626G>T) and 10 known mutations were detected (in 39 males, 46 female carriers). We defined the prevalence of mutations and established that the Hungarian patients' mutational spectrum differs from that of the Western European type.
4. We described firstly the c.78+1G>C splice site mutation and the two possible alternative splicing mechanism in men.
5. Obvious genotype-phenotype correlation was found in four (1 novel, 3 known) mutations. Among these, bilateral Mizou-Nakamura phenomenon was observable in both patients with the novel intronic c.78+1G>C mutation.
6. We demonstrated the spatial changes of the tertiary structure of RS1 proteins developed by single mutations, which did not correlate with the severity of the disease.
7. We described firstly the clinical aspect of the rare autosomal recessively inherited isolated foveal retinoschisis in a female patient. Later on the case was differentiated from XLRS by proving the integrity of *RS1* gene by molecular genetic examinations.

Clinical aspects

8. We verified the known Ganzfeld (negative type maximal response) and multifocal (decreased amplitudes with central predominance and increased implicit times with peripheral predominance) ERG features of the diseases with modern equipments.
9. We confirmed by OCT and mfERG measurements, that the area of the disease caused morphological and functional damage was in a greater part of the retina than would have been expected by funduscopy. Flat macular lamellar schisis - recognizable only by OCT - was also detected in more than ¾ parts of our patients.
10. We analysed the location of intraretinal cystoid spaces on the basis of OCT examinations and we described firstly their transversal and longitudinal changes observable by the age and the VA associated to the single form of appearance.
11. We analysed statistically the time (28 years of age) belonging to the transition from the cystic to the atrophic stage on the basis of OCT examinations for the first time. Strong negative significant correlations were found between patients' OCT parameters and their age. Comparing the clinical condition of patient group I (cystic) and II (atrophic), significant differences were found between VA, OCT, rod and maximal b-wave amplitudes of GfERG (Group I>II).
12. Moderate negative significant correlation was found between age and VA of patients. After some improvement of patients' visual acuity lasting until 13th year of age, later, until 45 years a slow, then an accelerating decline was observable.
13. Aberrations found by OCT and ERG mainly affected INL and PRL of patients, in which layers functional RS1 protein can be detected in the greatest concentration in healthy individuals.
14. On the basis of fundus photograph and OCT measurements, bilateral (fundus albipunctatus-like) white flecks of the posterior pole of our patient were proven to be columns, which creates the wall of cystoid spaces and considered to be Müller cells.

Publications

Publications of the author in the scope of the present work

Papers

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2. **Lesch B**, Szabó V, Pámer Zs, Knézy K, Varsányi B, Vámos R, Somfai GM, Hargitai J, Farkas Á. (2006) X-linked juvenile retinoschisis - electrophysiological and molecular genetic features. 44th ISCEV Annual Symposium, Fontevraud Abbey, France
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