(36)

X-linked retinoschisis – clinical manifestation, genetic and electrophysiological analysis of three generations with p.Arg197Cys mutation of *RS1* gene

Rozwarstwienie siatkówki związane z chromosomem X – obraz kliniczny, analiza genetyczna i elektrofizjologiczna trzech pokoleń rodziny z mutacją p.Arg197Cys *w genie RS1*

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Summary: The aim of the study is to present an atypical case of late-onset X-linked retinoschisis.
We present a case of a 37 year-old male patient with a few months' history of visual impairment. A clinical exam with optical coherence tomography and flash electroretinography (flash-ERG) was performed and the patient was diagnosed with X-linked retinoschisis. Genetic testing of the patient's family confirmed the disease and p.Arg197Cys mutation of *RS1* gene was identified.
In conclusion, optical coherence tomography and flash electroretinography enabled a proper diagnosis of X-linked retinoschisis in a patient with symptoms manifesting in the fourth decade of life. Genetic testing revealed male sufferers and female carriers among his family members.

Key words: X-linked retinoschisis, electroretinography, optical coherence tomography, genetic mutations.

Streszczenie: Celem pracy jest prezentacja pacjenta, u którego młodzieńcze rozwarstwienie siatkówki sprzężone z chromosomem X rozpoczęło się atypowo.
Do Samodzielnego Publicznego Klinicznego Szpitala Okulistycznego w Warszawie zgłosił się 37-letni mężczyzna, u którego od kilku miesięcy utrzymywała się obniżona ostrość wzroku. Pełne badanie okulistyczne, optyczna koherentna tomografia oraz elektroretinogram wywołany błyskiem (flash-ERG) pozwoliły postawić rozpoznanie rozwarstwienia siatkówki sprzężonego z chromosomem X. Badania genetyczne członków rodziny pacjenta potwierdziły obecność mutacji p.Arg197Cys w genie *RS1*.
Badania optycznej koherentnej tomografii i elektroretinogram wywołany błyskiem (flash-ERG) pozwoliły na postawienie rozpoznania rozwarstwienia siatkówki sprzężonego z chromosomem X u pacjenta, u którego objawy wystąpiły w czwartej dekadzie życia. Członków rodziny opisywanego przez nas pacjenta poddano badaniom genetycznym – w ten sposób w rodzinie zidentyfikowano mężczyzn chorujących na rozwarstwienie siatkówki sprzężone z chromosomem X oraz kobiety, które były nosicielkami mutacji.

Słowa kluczowe: rozwarstwienie siatkówki sprzężone z chromosome X, elektroretinografia, optyczna koherentna tomografia, badania genetyczne.

Introduction

X-linked retinoschisis (XLRS) was first described as an inflammatory disease in 1898, by the Austrian ophthalmologist Josef Haas (1). His documentation technique of fundus drawings, commonly used at that time, clearly shows a characteristic symptom of this disease – central retinal edema with a "bicycle wheel" structure. More than ten years later, Pagenstecher presented a family tree of related people afflicted with the disease, thus proving its relation to chromosome X (2). Until 1953, the disease had been known under several names, the present one was proposed by Jager (3).

X-linked retinoschisis is a bilateral disease, detected in 1 individual per 5000–30000, depending on studied population (4–6). Decreased visual acuity, related to hyperopia and astigmatism secondary to macular changes, is usually detected in school-age boys. A particularly high percentage of carriers

was found in Finland (morbidity – 14 cases per 10000) (7). A full expression of the mutated gene in these families can lead to symptoms noticeable as early as in infancy. Cases of infants with strabismus or nystagmus and bilateral retinoschisis presenting as large blisters with hemmorhage into the schisis cavity or the vitreous have even been reported.

Symptoms of the disease are found in male offspring of female carriers of mutated *RS1* gene, which is found in the short arm of chromosome X (Xp22.13). Very rarely female carriers of the mutation can also exhibit discrete fundus anomalies presenting as pigment alterations in the macula (8). Fovea is the most common site involved. Furthermore, other types are distinguished: foveal-perimacular, foveal-peripheral and mixed, involving the fovea, posterior pole and periphery (9).

The progression of XLRS is generally slow. Retinal detachment and vitreous hemorrhages are the most common sight-threatening complications.

Differential diagnosis, depending on predominant symptoms and age, includes: retinoblastoma, Norrie's disease, Bloch-Sulzberger syndrome, Goldmann-Favre syndrome, familial exudative vitreoretinopathy, Wagner's vitreoretinal dystrophy, X-linked retinitis pigmentosa, rod-cone dystrophy, as well as macular edema and age-related macular degeneration (4, 10, 11).

According to Leiden Open Variation Database, almost 200 mutations of *RS1* gene in XLRS sufferers have been detected so far. Molecular genetic testing allowed identifyication of the *RS1* mutation responsible for the disease on the short arm of chromosome X in position 22.13. The *RS1* gene, which consists of six exons, encodes a protein, known as retinoschisin, which is found on extracellular surface of inner photoreceptor segments, bipolar cells and plexiform layers of the retina. Retinoschisin plays an important role in retinal stability and organization.

Aim of the study

The aim of this study is to present an atypical case of XLRS and the currently available diagnostic possibilities.

Case presentation

A 37-year-old, previously healthy member of uniformed service came to the Department of Ophthalmology at the Warsaw Medical University due to visual acuity impairment persisting for a few months.

Best corrected visual acuity for distance, tested with Snellen chart, was 0.4 in the right eye and 0.7 in the left eye. Pupillary reflex was normal and symmetrical, anterior segment and the vitreous – regular. Dilated fundus exam (Volk's lens,

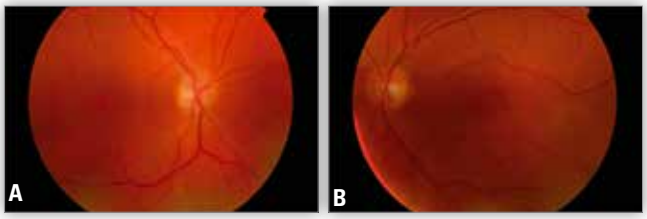

Fig. 1. Right (A) and left (B) eye fundus in a 37-year old patient with XLRS – hazy macular reflex.
Ryc. 1. Dno oka prawego (A) i oka lewego (B) u opisywanego 37-letniego pacjenta.

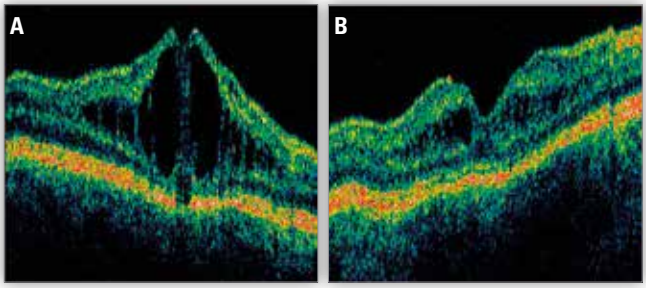

Fig. 2. Right (A) and left (B) eye OCT – intraretinal edema, central retinal thickness higher in the right eye.
Ryc. 2. OCT oka prawego (A) i oka lewego (B) – obrzęk śródsiatkówkowy, zwiększenie centralnej grubości siatkówki w oku prawym.

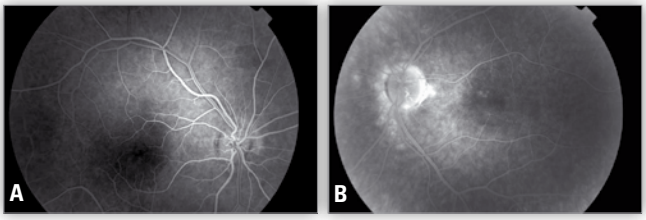

Fig. 3. Right (A) and left (B) eye fluorescein angiography (late phase) – no major anomalies.
Ryc. 3. Angiografia fluresceinowa oka prawego (A) i oka lewego (B) – bez istotnych odchyleń.

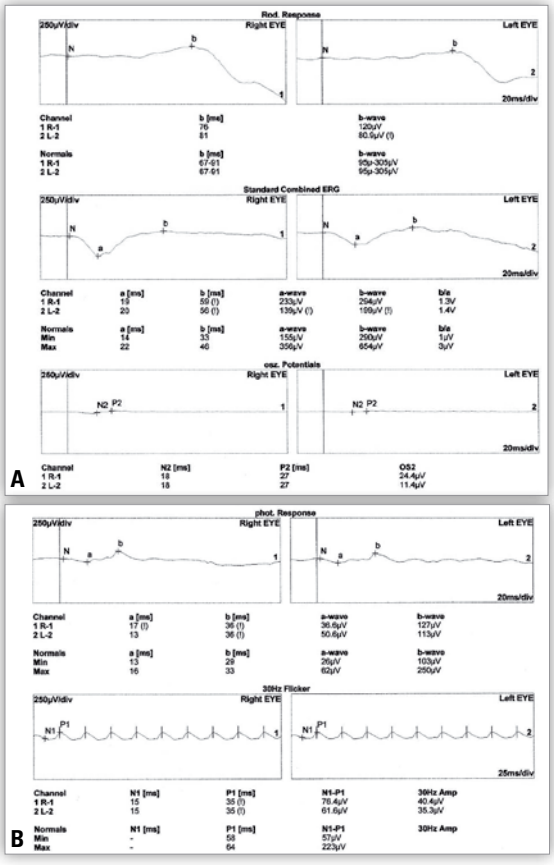

Fig. 4. Electroretinography in XLRS patient – scotopic (A) and photopic (B) response – reduced b-wave amplitude in rod and maximal responses (negative electroretinogram), significant reduction of oscillatory potentials.
Ryc. 4. Elektroretinogram u pacjenta z XLRS – odpowiedzi skotopowe (A) i fotopowe (B) – obniżona amplituda fali b w odpowiedziach pręcikowych i maksymalnych (elektroretinogram negatywny), znacząca redukcja potencjałów oscylacyjnych.

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Kinship/ Pokrewieństwo	BCVA RA/ LA najlepsza skorygowana ostrość wzroku OP/ OL	OCT	ERG	Conclusion/ Wniosek
Mother/ Matka	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Father/ Ojciec	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Mother's sister/ Siostra matki	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Patient/ Pacjent	0.4 / 0.7	Edema/ Obrzęk	Reduced b-wave amplitude/ Obniżona amplituda fali B	Sufferer/ Chory
Patients son 1/ Syn pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Patients son 2/ Syn pacjenta 2	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Patients daughter 1/ Córka pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Patients daughter 2/ Córka pacjenta 2	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Patient's sister 1/ Siostra pacjenta 1	0.9 / 0.9	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Sister's 1 son 1/ Syn1 siostry pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Sister's 1 son 2/ Syn 2 siostry pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Sister's 1 daughter 1/ Córka 1 siostry pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Sister's 1 daughter 2/ Córka 2 siostry pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Sister's 1 daughter 3/ Córka 3 siostry pacjenta 1	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Patient's sister 2/ Siostra pacjenta 2	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Sister's 2 son/ Syn siostry pacjenta 2	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy
Sister's 2 daughter/ Córka siostry pacjenta 2	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Patient's sister 3/ Siostra pacjenta 3	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Carrier/ Nosiciel
Sister's 3 son 1/ Syn 1 siostry pacjenta 3	0.5 / 0.4	Edema/ Obrzęk	Electronegative record/ Zapis ujemny	Sufferer/ Chory
Sister's 3 son 2/ Syn 2 siostry pacjenta 3	0.5 / 0.5	Edema/ Obrzęk	Electronegative record/ Zapis ujemny	Sufferer/ Chory
Sister's 3 daughter/ Córka siostry pacjenta 3	1.0 / 1.0	Normal/ Prawidłowy	Normal/ Prawidłowy	Healthy/ Zdrowy

Tab. I. Results of examination of the presented family with XLRS (BCVA RE/ LE evaluated using Snellen chart).
Tab. I. Wyniki badania członków rodziny pacjenta z XLRS (BCVA oczu prawego/lewego ocenana na tablicach Snellena).

three-mirror Goldmann's lens) showed retinal blurring in the macula with discrete edema, resembling the "bicycle wheel" sign (Fig. 1), while the retinal periphery appeared normal. In OCT intraretinal schisis cysts were found (Fig. 2), with no major anomalies observed in fluorescein angiography (Fig. 3) or in ultrasonographic imaging.

Flash ERG using the RetiScan RetiPort (Roland Consult) was performed according to the ISCEV standards. The reduced b-wave amplitude in rod and maximal responses was found (negative electroretinogram) with significant reduction of oscillatory potentials (Fig. 4).

Based on performed investigation, the patient was diagnosed with central retinoschisis. As we suspected the X-linked disease, the patient and his relatives were invited to both ophthalmic tests with optical coherence tomography (OCT) and genetic tests. Adult family members and mothers of under-age family members agreed to take part in all exams. The results of ophthalmic tests are shown in Table I.

Genetic testing results

Genome DNA was isolated from peripheral blood leucocytes of the patient and available family members (n = 14) using the standard method for desalting. Coding sections of *RS1* gene were amplified using PCR technique and then sequenced in both directions with the ABI PRISM 377 DNA Sequencer (Applied Biosystems, Foster City, CA) and the BigDye Termination Cycle Sequencing Kit v. 3.1 (Applied Biosystems) (12). Cytosine-tymine transition (c. 589 C>T; NCBI reference sequence: NM 000330.3) in *RS1* gene, previously described in XLRS sufferers, was found in the patient (Fig. 5) (13). As a result of this mutation, argininę is replaced with cysteine in codon 197 (p.Arg197Cys) and fully matched XLRS phenotype is expressed within the family. The patient's sons are healthy, his daughters carry the mutation. Carrier state of p.Arg197Cys in *RS1* gene was found in the patient's mother and her childless sister. The patient has three sisters; the oldest one (shown as 1 in the table) does not carry the mutation. This person, ho-

wever, was diagnosed with bilateral keratoconus and has had corneal transplantation in her right eye; currently her visual acuity is 0.9 in both eyes. Two other sisters carry the mutated gene. The first carrier sister (shown as 2 in the table) has a healthy son and a daughter who carries the mutation. The second, the youngest one (3 in the table), has two sons, aged 9 and 6, who were diagnosed with XLRS almost at the same time as our patient and a daughter who doesn't carry the mutation. The patient's mother also has two brothers who couldn't be tested due to poor health, but they have never presented with XLRS symptoms. The family tree is shown in Figure 6.

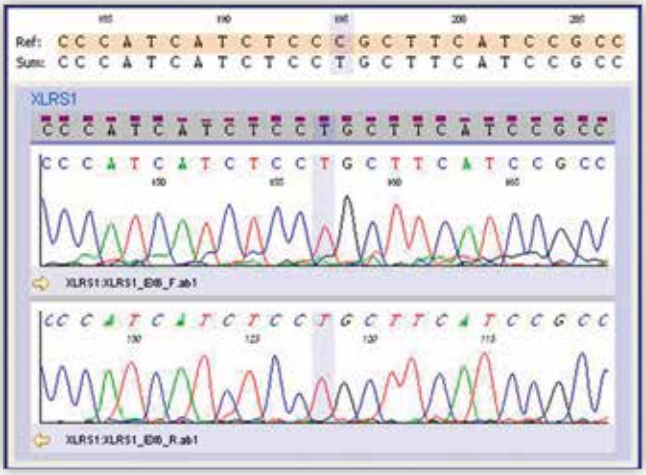

Fig. 5. *RS1* gene p.Arg197Cys mutation.
Ryc. 5. Mutacja p.Arg197Cys w genie *RS1*.

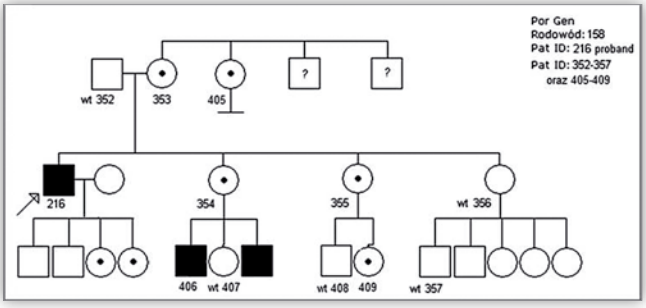

Fig. 6. Pedigree of the presented family with XLRS – black squares stand for sufferers and circles with black dots in the middle stand for carriers.
Ryc. 6. Rodzina pacjenta z XLRS: czarne kwadraty odpowiadają mężczyznom chorym na XLRS, czarne koła – nosicielkom mutacji.

Discussion

The congenital X-linked retinoschisis involves central retina thus leading to visual impairment in 98–100% of cases (14). Optical coherence tomography of macula shows microcysts within the inner nuclear layer, outer plexiform layer and outer nuclear layer (6, 9, 15–18).

Macular changes usually evolve and may lose their characteristic appearance in more advanced age, as dividing lines, circular patches of retinal pigment epithelium (RPE) atrophy or pigment regrouping with complete blurring of foveal structure appear. Sometimes, the lesions are so discrete that fundus is described clinically as normal (19, 20).

Peripheral retinoschisis, usually involving the inferior temporal quadrant, with atrophic holes in the inner layer develops in half of patients (5).

The blood vessels remaining in the outer, attached part of the retina and the inner atrophic layer, inserting into the outer hyaloid membrane, are visible as "veils". Sometimes, blood vessels become separated together with the inner, atrophic layer and seem suspended directly in the vitreous. Different lesions can be found in the periphery, such as perivascular sheaths, dendritic anomalies, exudative retinopathy, neovascularization and other retinal microvascular abnormalities. Vitreous haemorrhages are a rare complication (21, 22). Although very rare in XLRS, hole formation in the outer layer of divided retina, which is typical for senile retinoschisis can lead to retinal detachment, where itis a serious complication.

Structural differences between the central and peripheral retina lead to peripheral retinoschisis and macular schisis forming in different retinal layers. Histopathological studies of peripheral retinoschisis have shown schisis within the nerve fibre and plexiform layers (15, 23).

All sufferers from the described family presented with the decreased visual acuity and macular changes identified during the clinical assessment and on the OCT. None of them, though, has developed any peripheral abnormalities so far.

Many theories on the pathogenesis XLRS-related abnormalities can be found in literature. Some authors proposed a congenital defect of Müller cell (retinal glial cell) cytoplasm as the direct cause of disease (24, 25). Recent immunohistochemical research has shown that photoreceptors, retinal bipolar cells and the nerve fibre layer are all responsible for the secretion of retinoschisin, an adhesive protein coded by *RS1* gene. This protein is then transported by Müller cells and/or bipolar cells to other retinal layers, first of all to plexiform layers (9, 24–27). Retinoschisin is thought to connect the extracellular matrix with the surface of photoreceptors and other retinal cells, thus stabilizing the highly organized structure of this tissue (5). *RS1* mutations can lead to extracellular accumulation of retinoschisin, disrupt its spatial structure or impair its ability to form functional octamers. The impaired adhesion of retinal cells and development of schisis is the major consequence of dysfunctional retinoschisin (28–30).

The p.Arg197Cys mutation of *RS1* gene, identified in the examined family, involves 197 codon and arginine replacement with cysteine. Three other mutations of 197 codon have been found in XLRS patients, involving arginine replacement with serine (31), histidine (13) or proline (32). The existence of several different mutations of this codon indicates a hot spot for mutations in this part of *RS1* gene and suggests that arginine in position 197 is functionally or structurally important for normally developed retinoschisin molecules.

The p.Arg197Cys mutation of *RS1* gene has also been described in XLRS-affected families from Spain (33) and Korea (34). In both cases the 3–4-year-old boyshad lowered visual acuity which was followed by XLRS diagnosis. Similarly, both sick nephews of our patient, aged 9 and 6, also exhibited early signs of the disease. Reasons for the much later manifestation of XLRS in the patient himself seem to be related indirectly to the presence of p.Arg197Cys mutation, yet still remain unclear.

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Electroretinography (ERG) is an established basic diagnostic method in patients with suspected XLRS. A characteristic finding is the so-called negative electroretinogram, accompanied by the reduced oscillation potentials. In normal flash ERG, the b-wave amplitude dominates overe the a-wave amplitude. In a negative electroretinogram the a-wave is not as reduced as the b-wave. As a result, the a-wave amplitude is greater or equal to the b-wave amplitude and the b/a coefficient is reduced accordingly. The term "negative ERG" was coined by Karpe et al. in 1945 (35, 36). The b-wave amplitude is reduced due to the excessive extracellular accumulation of potassium ions as a result of Müller cell dysfunction. These cells are responsible for uptake and transport of extracellular potassium, which accumulates due to hyperpolarization of photoreceptors in response to a light stimulus; however, their function is impaired in XLRS (17, 37, 38).

Electroretinography performed in family members with clinical signs of XLRS showed the reduced b-wave amplitude in rod and maximal responses (negative electroretinogram) with significant reduction of oscillatory potentials.

XLRS therapy depends on disease location and severity. The isolated macular edema in foveal and foveal-perimacular types of the disease is currently treated with dehydrating agents such as topical dorzolamide. Laser treatment may be used as a part of retinal detachment prevention in cases with peripheral retinoschisis. Patients with spread retinal detachment, especially complicated with vitreous haemorrhage, are treated surgically withpars plana vitrectomy being the method of choice in most cases. Causal treatment of XLRS is still under investigation. Some future perspectives may include gene therapy. Laboratory research performed on mice with XLRS showed that replacement therapy including normal Rs1h protein supplementing may restore the normal ERG pattern in adult Rs1h-KO mice.

Conclusions

Congenital juvenile X-linked retinoschisis can sometimes have a benign course and manifest only in mature age.

OCT and flash ERG are useful tests for detecting congenital juvenile X-linked retinoschisis, especially in atypical cases.

Owing to genetic testing it is possible toconfirm the diagnosis and identify the sufferers and carriers of the mutated *RS1* gene, which is linked to XLRS development among family members.

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