

DOI: <https://doi.org/10.34921/amj.2025.2.026>**AKSENFELD-RİGER SİNDROMU: NEVROLOJİ ƏLAMƏTLƏRİ VƏ FENOTİPİK VARIABELLİYİ (KLİNİK MÜŞAHİDƏ)****M.Ya.Delva, K.V.Hrin, V.A.Pinçuk, Q.Ya.Silenko, İ.İ.Delva,
A.M.Krivçun, T.İ.Purdenko, K.A.Taryanik***Poltava Dövlət Tibb Universitetinin sinir xəstəlikləri kafedrası, Poltava, Ukrayna*

Məqalədə Aksenfeld-Riger sindromunun fenotipik variabelliyi və nevroloji simptomları haqqında müvafiq diaqnozu təsdiq edilmiş xəstə misalında məlumat verilmişdir. Burada Aksenfeld-Riger sindromunun yüngül klinik gedişli forması olan 45 yaşlı xəstədə müəlliflərin öz müşahidələri şərh edilir. Xəstədə nevroloji müayinələr aparılmış və funksional diaqnostika üsulları tətbiq edilmişdir. Təsvir edilən klinik təzahürlər Aksenfeld-Riger sindromuna dair müasir ədəbiyyat mənbələrində olan məlumatlara uyğun gəlir. FOXC1 genində müşahidə edilən patogen mutasiya bu sindromun diaqnostikası üçün təkbisedilməz sübutdur. Məlumdur ki, genetik xəstəliklərin diaqnostikasında çox zaman simptomatikanın polimorfizmi ilə əlaqəli olan çətinliklərə rast gəlinir. Buna görə müxtəlif xəstəliklərə çətinliklə diaqnoz qoyulur. Genetik xəstəliklərə diaqnozun erkən qoyulması və effektiv müalicə aparılması isə pasiyentlərin həyat keyfiyyətinin yaxşılaşdırılmasının əsasını təşkil edir.

Açar sözlər: Aksenfeld-Riger sindromu, genetik xəstəliklər, fenotipik variabellik

Ключевые слова: синдром Аксфельда-Ригера, генетическое заболевание, фенотипическая вариабельность

Key words: Axenfeld-Rieger syndrome, genetic disease, phenotypic variability

AXENFELD-RIEGER SYNDROME: NEUROLOGICAL SIGNS AND PHENOTYPIC VARIABILITY (CLINICAL OBSERVATION)**M.Y.Delva, K.V.Hryn, V.A.Pinchuk, G.Ya.Sylenko, I.I.Delva,
A.M.Kryvchun, T.I.Purdenko, K.A.Tarianyk***Department of Nervous Diseases, Poltava State Medical University, Poltava, Ukraine*

The article provides information about the phenotypic variability of Axenfeld-Rieger syndrome in a patient with confirmed neurological symptoms. The study aimed to characterize phenotypic variability and neurologic symptoms in a patient with genetically verified Axenfeld-Rieger syndrome. This paper presents a clinical case of Axenfeld-Rieger syndrome in a 45-year-old female patient with a mild clinical course. A neurologic examination was performed, and functional diagnostic methods were used. The reported clinical case demonstrates the matching of the patient's clinical presentation with the present-day described symptoms of Axenfeld-Rieger syndrome. The results of the molecular genetic study with the finding of a pathogenic mutation in the FOXC1 gene are definitive evidence of this syndrome. Diagnostic search in genetically caused diseases is often challenging, as polymorphic symptoms present in patients do not always allow for a definite diagnosis of a given pathology. Early diagnosis and effective therapy of genetic diseases are the key to saving the quality of life of patients.

Doctors of different specialties have to deal with the sequelae of genetic disorders. The significance and complexity of clinical cases of hereditary diseases encourage clinicians to team and multidisciplinary activities since the spectrum of clinical presentations in each particular case can be broad and not limited to single-disciplinary observation [1-5].

Axenfeld-Rieger syndrome (ARS) is a rare autosomal dominant inherited disorder with an incidence of up to 1:200,000. ARS was formerly known as Axenfeld anomaly, and this term was used to describe one of the three disease subtypes. Previously ARS was divided into: Axenfeld's anomaly, Rieger's anomaly, and Rieger's syndrome. The German ophthal-

mologist Theodor Axenfeld described Axenfeld's anomaly, which was characterized by posterior embryotoxic and peripheral attachment of the iris trabecular. Described by Austrian ophthalmologist Gerwig Rieger, Rieger's anomaly was characterized by posterior embryotoxon, iris hypoplasia, polycoria, and corneal ectasia. Rieger's syndrome was characterized by Rieger's anomaly with some systemic signs, including dental anomalies, facial bone changes (hypoplasia of the maxilla), umbilicus anomalies (excess skin around the umbilicus), hypospadias, and pituitary anomalies. Later, Axenfeld's and Rieger's anomalies and Rieger's syndrome were combined into a group of diseases, which is now called Axenfeld-Rieger syndrome (ARS) [6].

ARS syndrome includes dysgenesis of the anterior segment of the eye as well as systemic anomalies (dental, craniofacial, cardiac, and abdominal wall defects). The symptom presentation of this genetic disorder can vary among patients but often involves multiple organ systems. Visual organ pathology presents with varying degrees of anterior segment dysgenesis and has a high risk of glaucoma. Other systemic anomalies include cardiovascular malformations and pituitary abnormalities, which may be responsible for endocrinologic symptoms [7]. Recent advances in molecular genetics have identified two key genes, PITX2 and FOXC1, which have a wide range of mutations and are most commonly involved in ARS syndrome. However, there is evidence for the involvement of other genes in this genetic pathology [8].

No conclusive and definitive neurological markers of ARS syndrome we found in the literature. This fact led us to a scientific and practical medical study.

The study aimed to describe and illustrate phenotypic variability and neurologic symptoms in a patient with genetically confirmed Axenfeld-Rieger syndrome.

Materials and methods of research. The examination of a 45-year-old female patient was conducted after getting her written voluntary informed consent to participate in the study with full compliance with the principles of bioethics as stated in the Declaration of Helsinki "Ethical Principles of Medical Research Involving Human Subjects" and the "General Declaration on Bioethics and Human Rights" (UNESCO); taking into account the prin-

ciples stated in the materials for the clinical case reporting guidelines [9]. The study was approved by the Ethics and Biomedical Ethics Commission of Poltava State Medical University. In the description of the clinical case, we used the results of the patient's medical tests, including molecular genetic tests (performed by Invitae Laboratory - San Francisco, USA, Invitae Corporation). The patient venous blood was used as a material for the study. An anamnestic, clinical, and neurological examination was performed, also it was examined by a medical geneticist, ophthalmologist, and brain MRI.

Results. We represent the clinical case description of a patient with Axenfeld-Rieger syndrome. Patient S., 45 years old, applied to the Department of Neurological Diseases of Poltava State Medical University for the first time in 2023. On examination, complaints of recurring headaches, predominantly in the right side of the head, accompanied by nausea, pain in the eyeballs, severe dizziness and fainting, decreased vision, decreased hearing in both ears, memory loss, numbness of the hands, attacks of palpitations, pain in the joints. Anamnestic data. She regarded herself as a sufferer for more than 10 years when headaches started to occur.

The patient applied for neurological aid on several occasions and underwent treatment courses (nootropics, metabolic, and symptomatic therapy). In 2008 she was treated in a neurological inpatient department due to rheumatic arachnoencephalitis with liquor and venous distention, persistent cephalgic syndrome. In 2022, her condition worsened, she had attacks of sudden dizziness, for which she was repeatedly examined by emergency medical teams. According to the recommendation of a neurologist, a CT scan of the brain was performed in 2022, where signs of periventricular zones of leukoencephalopathy of the frontal-parietal lobes with the presence of hypodense zones of both hemispheres (foci of gliosis) were found. In 2023, the patient had a contrast MRI of the brain. MRI conclusion: signs of multifocal brain lesions, probably of post-inflammatory or demyelinating nature; focal changes in the white matter with predominance in the periventricular sections of both hemispheres of a confluent character. As the patient's condition worsened and there were no positive dynamics after the treatment, she was referred to the Clinic of Neurological Diseases at Poltava State

Medical University.

Based on neurological examination and neuroimaging data, a multifocal lesion of the brain white matter was diagnosed. She was appointed for additional examination: a blood test for HIV and consultation with a geneticist in the regional center of medical genetics. The molecular genetic study reports Axenfeld-Rieger syndrome (pathogenic mutation in FOXC1 gene p. 1157 dup CpAla 387AChg FS 141) with progressive vascular leukoencephalopathy, sensorineural hearing loss, migrainous paroxysms, anterior chamber dysgenesis, cognitive disorders, and thrombocytosis.

Past medical history: moderate bronchial asthma, chronic rheumatic disease, chronic normochromic anemia. At the age of 10 years, the patient suffered from rheumatic chorea.

Neurologic status. Consciousness is unchanged. Patient can have productive contact. No meningeal symptoms. Eye slits D=S. Photoreactions are vivid. There is a hypopigmentation of the right eye iris. No nystagmus. - Oculomotor activity is the norm. The face is symmetrical. The protruding tongue is along the center line. Muscle strength in the limbs is 5 points. Muscle tone in the limbs is the norm. Reflexes on the arms: hyperreflexia, D>S. Abdominal reflexes are absent. Knee and ankle reflexes are moderate, D=S. Babinski's symptom is positive on the right side. Finger-nose and heel-knee tests perform well enough. There is a slight staggering in the Romberg pose. General hyperesthesia.

Laboratory and instrumental investigation: general blood analysis, general urine analysis, biochemical blood analysis, and lipidogram - no abnormality. ECG - normal sinus rhythm.

Ophthalmologist conclusion: medium degree hypermetropia, mixed astigmatism, corneal opacity of both eyes, amblyopia of the left eye, bilateral optic disc atrophy. Photo of the eyeballs (Fig. 1) and the results of ophthalmoscopy (Fig. 2) are presented below. The ophthalmologist recommended surgical refractive replacement of both eye lenses. Otolaryngologist's examination: bilateral sensorineural hearing impairment. Therapist's examination: chronic rheumatic heart disease, bronchial asthma of medium severity, chronic anemia of medium severity, polyarthrosis with predominant lesions of the feet joints.



Fig 1. Photograph of the eyeballs of patient S., 45 years old

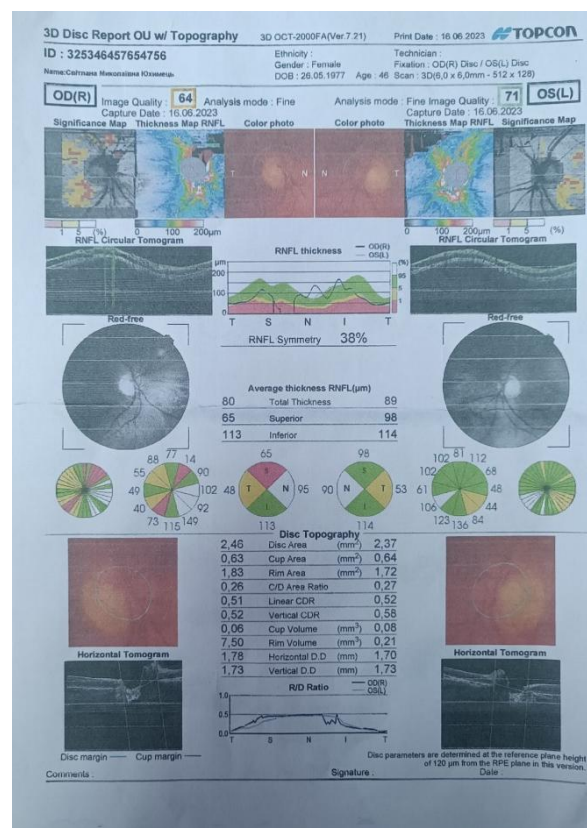


Fig. 2. Ophthalmoscopic examination

The patient has a son born in 2002. Since 2020, her son has had attacks of headaches in the frontal-orbital region with nausea, vomiting, and decreased work efficiency. Headache attacks are preceded by visual disturbances that last up to 5 minutes. Regarding these complaints, the patient consulted a neurologist, who was prescribed brain MRI and electroencephalography. According to neuroimaging, there were no mass, inflammatory, and demyelinating brain lesions. There were signs of low placement of cerebellar tonsils (Chiari malformation type 1). EEG revealed an epileptiform activity without a distinct epileptic focus. A neurologist diagnosed migraine with aura (attacks frequency 1-2 times a week) and

prescribed abortive treatment. An ophthalmologist diagnosed hypermetropic astigmatism in the right eye and iris coloboma in both eyes (Fig. 3).



Figure 3. Photograph of the patient's son's eyeballs

The medical history revealed a hypoxic-ischemic CNS lesion at birth and congenital coloboma of the irises of both eyes. Echocardiography examination diagnosed abnormal development of the chordal apparatus (extra chorda).

Psychophysical development has no deviations from the age norm. Physical examination revealed deformation of the teeth crowns (Fig. 4).



Fig. 4. Teeth crowns deformation.

Examination of the neurological status revealed no focal signs. There are signs of vegetative-vascular dysfunction.

Taking into account the complicated hereditary anamnesis, the patient was examined in 2023 by a neurologist, and by a specialist at the Regional Center of medical genetics. Molecular genetic analysis was recommended.

Discussion. ARS has an autosomal dominant inheritance pattern. ARS is diagnosed with mutations in different chromosomes, including mutations in chromosomes 2, 4, 6, 9, 13, 18 and 21. Mutations in the genes PITX2 (chromosome 11p13), FOXC1 (chromosome 6p25), RAX6 (chromosome 11p13), FOXO1A

(chromosome 13q14), and CYP1B1 (chromosome 2p22.2) are typical for ARS. The main abnormality in 40% of patients is mutations in the PITX2 or FOXC1 genes. The Forkhead-Box C1 gene (FOXC1) and the Pituitary Homeobox 2 gene (PITX2) are the most studied genes encoding an ARS-related transcription factor [10].

There are three types of ARS. Type 1 is due to a heterozygous mutation in the PITX2 gene located on chromosome 4q25. The PITX2 gene is a homeobox transcription factor critical for tooth and iris development. PITX2 is associated with splicing site mutations, skipping mutations, and chromosomal translocations in patients with ARS. Type 2 is associated with chromosome 13q14. Type 3 is associated with chromosome 6p25.3 involving the FOXC1 gene.

About 25-30% of ARS cases present with ocular pathology and correlate with mutations in the FOXC1 and PITX2 genes on chromosomes 6p25 and 4q25, respectively. PITX2 mutations in 4q25 are present in about 10-30% of patients with ARS. A distinct phenotype of ARS, called De Hauwere syndrome, is characterized by the presence of hydrocephalus, partially missing eye muscles, hypertelorism, joint pathology, psychomotor retardation, and sensorineural deafness [11].

Most cases of ARS are diagnosed before the age of 1 year. Children may have signs of congenital or early glaucoma (diagnosed in the first 3 years of life). But glaucoma may also be diagnosed in adulthood.

Congenital glaucoma is characterized by enlargement of the eyeballs, corneal distension with a predominantly blue color (buphthalmos), lacrimation, photophobia (caused by iris and pupil abnormalities), strabismus, and blurred vision (visual impairment with loss of the ability to distinguish details when looking far away or at close vision). Risk factors for visual deterioration in children with glaucoma include deprivation amblyopia, uncontrolled secondary glaucoma, strabismus, uncorrected refractive error, age at diagnosis of glaucoma <3 months, and preoperative interval >3 months [12].

The dental anomalies associated with ARS are: hypodontia (missing 1-5 teeth), oligodontia (missing more than five teeth), and microdontia.

ARS is characterized by distinctive facial features: mild craniofacial dysmorphism,

protruding forehead, telecanthus, hypertelorism, hypoplasia of the maxilla, thin upper lip, and broad, flat nose bridge. Skeletal anomalies in ARS include joint hypermobility, joint degeneration, scoliosis, and hip anomalies [13].

The clinical presentations of ARS 1 type are anomalies in the anterior segment of the eye, dental anomalies, excessive skin around the umbilicus, Meckel's diverticulum, craniofacial anomalies, and cardiovascular abnormalities. ARS type 2 is present with anomalies of the eye's anterior segment, glaucoma, developmental delay, and with other systemic anomalies. But these systemic anomalies for ARS type 2 are less specific than for ARS types 1 and 3. Clinical manifestations of ARS type 3 include anomalies in the anterior segment of the eye (e.g., Axenfeld-Rieger anomaly), glaucoma, hearing loss, heart defects (atrial septal defects, mitral valve defects), and renal anomalies. Other systemic presentations of ARS include hypospadias, excessive skin fold around the umbilicus, umbilical hernia, hydrocephalus, deafness, kidney anomalies, heart valve abnormalities, arachnoid cysts, pituitary anomalies (empty Turkish saddle), endocrine anomalies (short stature, height retardation), congenital hip dislocation [7].

Common neurological signs of ARS are brain white matter anomalies, Dandy-Walker syndrome (hydrocephalus, hypoplasia or aplasia of the cerebellum, cysts of the posterior cranial fossa), agenesis of the corpus callosum, ventriculomegaly and hydrocephalus, tortuosity/dolichoectasia of the arteries and arteriovenous malformation [14].

The phenotypic manifestations in the examined patients do not include the entire set of classical manifestations of Axenfeld-Rieger syndrome. However, an absolute confirmation of the ARS syndrome is the results of a molecular genetic study of patient S., which revealed pathology in the FOXC1 gene, corresponding to the type 3 disease.

Among the neurological manifestations that are present in the patient with confirmed ARS syndrome, we described cephalgic syndrome in the form of migraine headaches, autonomic dysfunction, periventricular zones of leuko-araiosis in the frontoparietal lobes, gliosis foci in both hemispheres on neuroimaging data.

Although the above-mentioned signs are not specific to ARS, they are quite common in this genetic pathology, as in this clinical case.

The perspective of further study is to perform molecular genetic, and neuroimaging investigation of the patient's son.

Conclusions. The presented case of moderate-to-mild Axenfeld-Rieger syndrome diagnosed in adult age is consistent with the evidence of genetic disease phenotypic variability.

The clinical case described herein demonstrates the matching of the patient's clinical manifestations with the described clinical symptoms of Axenfeld-Rieger syndrome. The results of the molecular genetic study with the detection of a pathogenic mutation in the FOXC1 gene are undeniable evidence of this syndrome.

Diagnostic workup for genetically determined diseases is often complicated, as polymorphic symptoms in patients do not always make it possible to accurately diagnose certain genetic pathology.

Relationship of the paper to scientific programs, plans, and themes. Financing of the study. The study is a fragment of the Department of Neurological Diseases research: "Neuro-psychological characteristics of pain phenomena in organic lesions of the nervous system and psyche impairment due to military operations". State registration number 0124U003351.

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Conflicts of Interest. The authors confirm that the study and the publication of the results were not related to any conflicts regarding commercial or financial relationships, relationships with organizations and/or individuals that could be related to the study, as well as the relationships of the co-authors of the paper.

Ethical Approval. The examination of the patient was carried out upon obtaining the informed consent from him to participate in the study with strict adherence to the ethical principles of medical research involving a person as a research object in accordance with the Declaration of Helsinki.

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СИНДРОМ АКСЕНФЕЛЬДА-РИГЕРА: НЕВРОЛОГИЧЕСКИЕ ПРОЯВЛЕНИЯ И ФЕНОТИПИЧЕСКАЯ ВАРИАБЕЛЬНОСТЬ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

М.Ю.Дельва, Е.В.Гринь, В.А.Пинчук, Г.Я.Силенко,
И.И.Дельва, А.М.Кривчун, Т.Й.Пурденко, К.А.Таряник

*Кафедра нервных болезней Полтавского государственного медицинского университета,
Полтава, Украина*

Резюме. В статье описана и продемонстрирована фенотипическая вариабельность и неврологические симптомы у пациентки с генетически подтвержденным синдромом Аксенфельда-Ригера из числа собственных наблюдений авторов – продемонстрирован клинический случай синдрома Аксенфельда-Ригера у пациентки 45 лет с мягким клиническим течением; проведено неврологическое исследование, использованы функциональные методы диагностики. Описанный клинический случай демонстрирует совпадение клинических проявлений, имеющихся у пациентки с описанными сегодня симптомами синдрома Аксенфельда-Ригера. Неоспоримыми подтверждениями данного синдрома являются результаты молекулярно-генетического исследования с обнаружением патогенной мутации в гене FOXC1. Диагностический поиск при работе с генетически обусловленными заболеваниями зачастую сложен, поскольку полиморфная симптоматика, присут-

ствующая у пациентов не всегда дает возможность четкой диагностики той или иной патологии. Ранняя диагностика и эффективная терапия генетических заболеваний являются ключом к сохранению качества жизни пациентов и их близких.

Author for correspondence:

Hryn Ekaterina Viktorovna - Department of Nervous Diseases, Poltava State Medical University, Poltava, Ukraine.

E-mail: k.hryn@pdmu.edu.ua

Автор для корреспонденции:

Гринь Екатерина Викторовна – кандидат медицинских наук, доцент кафедры нервных болезней Полтавского государственного медицинского университета, Полтава, Украина

E-mail: k.hryn@pdmu.edu.ua

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