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ARTYKUŁ REDAKCYJNY/EDITORIAL ARTICLE

Usher syndrome as the most frequent cause of coexisting sight and hearing disorders genetically determined

Zespół Ushera jako najczęstsza przyczyna współistnienia zaburzeń wzroku i słuchu uwarunkowanych genetycznie

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ABSTRACT:

Usher syndrome is the most frequent cause of coexisting sight and hearing disorders genetically determined.

Depending on the type of the symptoms, we can single out 3 types of Usher syndrome. Among them the most advanced changes are described in first type. In final stage it leads to deafness and blindness with possible balance disorders.

This syndome is inherited in autosomal recessive way, but we have to note the occurence of genetical heterogeneity. It causes big diversity of symptoms intensification.

Correct diagnosis is important in view of giving genetical advice and eventual diagnostic and terapeutic procedure.

KEYWORDS: usher syndrome, retinitis pigmentosa, genetically determined hearing loss

STRESZCZENIE:

Zespół Ushera jest najczęstszą przyczyną współistnienia zaburzeń wzroku i słuchu uwarunkowanych genetycznie. W zależności od w zależności od objawów klinicznych, wyróżniamy jego trzy typy, wśród których najbardziej zawansowane zmiany opisywane są w typie I. W stadium końcowym prowadzą do głuchoty oraz ślepoty, z ewentualnie towarzyszącymi zaburzeniami równowagi.

Zespół Ushera dziedziczony jest w sposób autosomalny recesywny, przy czym zwraca się tu uwagę na występowanie heterogenności genetycznej. Wiąże się z tym duże zróżnicowanie nasilenia objawów wśród pacjentów.

Postawienie prawidłowego rozpoznania jest istotne zarówno z punktu widzenia udzielenia porady genetyczne, jak i ewentualnego postępowania diagnostyczno-terapeutycznego.

SŁOWA KLUCZOWE: zespół Ushera, retinitis pigmentosa, niedosłuch uwarunkowany genetycznie

INTRODUCTION

Usher syndrome is a rare genetic disorder associated with dysfunction of visual, auditory and vestibular systems [1,2].

The coexistence of the above-mentioned symptoms was, for the first time, described by German ophthalmologist Albrecht von Gräfe. However, it was only until 1914 when Scottish ophthalmologist Charles Howard Usher established the genetic character of the disease and described it in his work entitled "*On the inheritance of retinitis pigmentosa*" [2].

Usher syndrome is the most common cause of deafblindness, being diagnosed in half of deafblind patients. The diagnosis is

confirmed in 3%-6% of deaf patients and 18%-25% of patients with *retinitis pigmentosa*.

Genetic aspects of the disease and the inheritance pattern

Usher syndrome is inherited in an autosomal recessive pattern. The disease is genetically heterogeneous, which means that mutation of various genes can cause its symptoms. Thus far, seven genes related to Usher syndrome have been identified, located in 11 loci (Table 1). The most frequent are: USH1B and USH2A, accounting for 75% - 80% of all cases [3,4].

Due to advances in genetics, it became possible to clone genes, which allowed to detect USH homozygotes and heterozygous carriers. Until 1995, only one gene related to Usher syndrome had been cloned, i.e. USH1B. This gene encodes myosin VIIA, which is a protein present in sensory cells of the cochlea and vestibule, retinal pigment epithelium and photoreceptor cells. Damage to USH1B gene and consequent disruption of myosin VIIA production directly cause dysfunction of two major sensory organs (vision and hearing) as well as balance system [3]. Based on genetic research, the identified genes were associated with each type of the syndrome. Three genes are responsible for type I, two genes for type II, and a newly identified gene has been found responsible for type III disease [4].

Type I Usher syndrome

It is the most common type – found in about 90% patients with Usher syndrome. 3%-6% of patients suffering from congenital hearing impairment are diagnosed with type I Usher syndrome.

The characteristic clinical signs and symptoms among type I patients include:

- congenital sensorineural hearing loss of either profound (above 91dB HL) or severe degree (71-90dB HL), giving the so-called 'left-corner' audiogram [Fig.1];
- lack of improvement with a hearing aid;
- better reception of low frequency sounds compared to high frequencies;
- signs of *retinitis pigmentosa* before the age of 10;

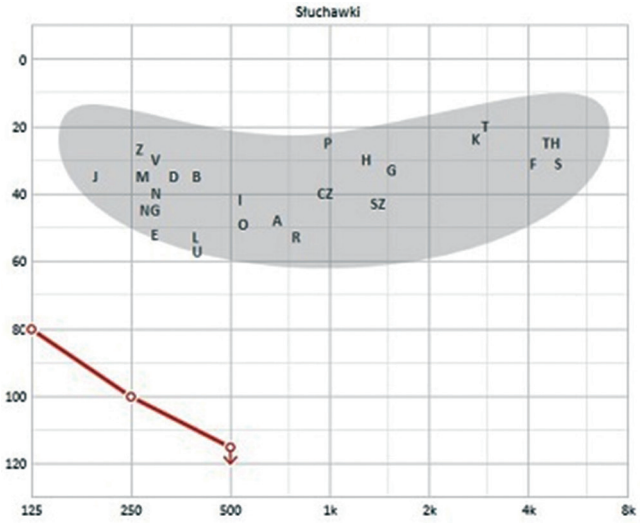

Fig 1. Sample audiogram typical for type I Usher syndrome.

- blindness in early middle age;
- vestibular system impairment manifesting itself in insecure gait, trouble maintaining balance in the dark;
- motor developmental delay (Table 2) [2,4].

Type II Usher syndrome

This type is found in ca. 9-10% of patients diagnosed with Usher syndrome. The hearing loss is lesser and no vestibular damage is present.

The characteristic clinical signs and symptoms among type II patients include:

- congenital sensorineural hearing loss of either moderate (41-70dB HL) or severe degree (71-90dB HL), usually stable over time [Fig.2];
- no damage to the balance system, thus no developmental delay of motor functions (a child begins to walk at about 12 months);
- symptoms of *retinitis pigmentosa* appear in adolescence or later; in childhood, difficulty seeing in the dark is present; blindness occurs in adulthood (Table 3) [2, 4].

Tab. I. Mutations causing Usher syndrome.

TYPE	USH1B	USH2A	USH3A	USH1C	USH1D	USH1F	USH1G
Locus	11q13.5	1q41	3q21-25	11p15.1	10q21	10q21-22	17q 24-25
Gene	MYO7A	USH2A	USH3A	USH1C	CDH23	PCDH15	USH1G
Protein	myosin VIIA	usherin	clarin-1	harmonin	cadherin 23 23	protocadherin 15	SANS

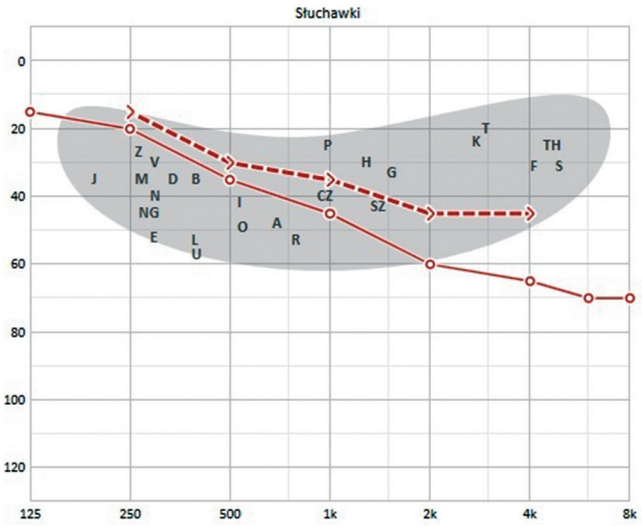

Fig. 2. Sample audiogram typical for type II Usher syndrome.

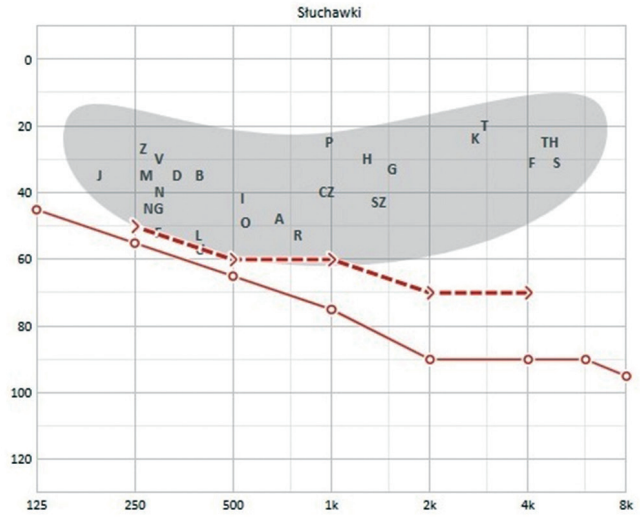

Fig. 3. Sample audiogram typical for type III Usher syndrome (end stage)

Type III Usher syndrome

Being extremely rare, this type accounts for only 1% of all diagnosed cases. It occurs most frequently in Finland (around 42% of all cases diagnosed in this country).

The characteristic clinical signs and symptoms in this type include:

- progressive sensorineural hearing loss ranging from severe (71-90dB HL) to profound degree (above 90dB HL). A child is often born with moderate or even mild hearing loss (12-40 dB HL), which worsens as the child grows and evolves to 'residual hearing' [Fig.3].
- variable function of vestibular system: usually normal, motor development of a child is unaffected; sometimes balance disturbances, which progress with age;
- intensity of *retinitis pigmentosa* lesions is also variable. Initially, nyctalopia (night-blindness) is always present and daylight vision remains normal. It means that a patient will at first experience trouble seeing in the dark and later the 'tunnel effect' or decline of visual acuity will occur (Table 4) [2,4].

Visual impairment in Usher syndrome

Most common abnormalities found in Usher syndrome include:

- Degeneration of retinal rod cells;
- Formation of bone-spicule lesions, i.e. deposits caused by migration and build-up of pigment in the retina;
- Obliterating arteriosclerosis of retinal arteries causing their narrowing;
- Optic disc discoloring leading to optic nerve atrophy [3].

Depending on the extent of lesions, visual decline in Usher syndrome may range from night-blindness and hypersensitivity of the retina to the light, visual field deficits to complete loss of vision.

Nyctalopia (night-blindness) is one of the earliest symptoms of the Usher syndrome. It usually manifests itself in infancy. In such cases, an infant cannot place a pacifier in their mouth in the dark. It is often accompanied by difficulties adapting to light with changing intensity, the eye becomes hypersensitive to light. It is caused by inability of rod cells to transmit signals of changing light intensity. The patient finds it difficult to adjust to seeing in the dark [5].

When the field of vision is narrow, it is referred to as a 'telescope' or 'tunnel' effect. Damaged rod cells on the retina are unable to analyze objects from the peripheral visual field. Thus the patient can see an object in front of them but is unable to notice things at the side. Normally, the diagnosis of *retinitis pigmentosa* is only made when the above-mentioned symptoms are present. The initial stage may proceed unnoticed or ignored by the patient, due to the compensation of visual deficits by eye movement. The decline of visual field progresses so rapidly that after a few years only 5° - 10° of visual field is left. This process is accompanied by cataract, glaucoma or myopia. As a result, visual acuity deterioration and loss of vision ensue. A narrowed field of vision is shown in Figure 4 [2].

Tab. II. Information summary for type I Usher syndrome

PREVALENCE	4 PER 100 000 LIVE BIRTHS
Hearing impairment	Profound congenital sensorineural hearing loss. Audiogram – 'residual hearing' and 'left-corner' diagram (patient responds only to very loud sounds with low frequency),
Visual impairment	Nyctalopia in early childhood. First symptoms before adolescence. Complete blindness in adulthood.
Dysfunction of balance system	Balance dysfunction leading to motor developmental delay. No excitability of vestibules.
Communication	As long as the patient can see, they use sign language, later the Lorm alphabet is introduced.
Inheritance pattern	Autosomal recessive. Usually, the patient is the first person suffering from the disease.

Tab. III. Information summary for type II Usher syndrome.

Prevalence	Less often than in type I.
Hearing impairment	Congenital dysfunction of the cochlea. Audiogram with a 'descending' curve (moderate loss in low frequencies, profound loss in high frequencies).
Visual impairment	Nyctalopia in childhood. Visual impairment before or just prior to adolescence. Total blindness in adulthood.
Dysfunction of balance system	Stable gait. Normal excitability of vestibules.
Communication	Patients equipped with a hearing aid can speak an oral language. Without a hearing aid, they use sign language.
Inheritance pattern	Autosomal recessive.

Tab. IV. Information summary for type III Usher syndrome.

PREVALENCE	RARELY OCCURRING, MOST FREQUENTLY IN THE FINNISH POPULATION
Hearing impairment	After birth, normal or mildly impaired hearing. Progressive sensorineural hearing loss with age, usually starting from age of 10. Audiogram with 'descending' curve.
Visual impairment	Clinical manifestation at various age. Nyctalopia always precedes daylight visual impairment.
Dysfunction of balance system	Variable vestibular excitability. Sometimes no balance disturbances, or mild manifestation in infancy, or progressively worsening with age.
Communication	Oral speech, sometimes unintelligible due to hearing loss.
Inheritance pattern	Autosomal recessive.

Dysfunction of balance system in Usher syndrome

Difficulties maintaining balance are caused solely by damage to the vestibules. Their dysfunction manifests itself soon after birth or in early childhood.

These symptoms affect patients with type I and III Usher syndrome. In case of type I, the lack of excitability of the vestibules can be found, while in type III the function of the vestibules varies and it is sometimes possible to notice certain dysfunction. There is also a relationship between the degree of hearing loss and the extent of vestibule dysfunction. In patients with total deafness, the function of the vestibules is affected, while in patients with normal hearing or mild hearing loss, normal excitability of the vestibules is found [3].

When difficulties with balance are present from birth, they constitute one of the major causes of developmental delay of motor functions. For this reason, children affected by type I Usher syndrome begin to walk only after 18 months [2].

Diagnosis of Usher syndrome

Diagnosis of Usher syndrome requires interdisciplinary team as well as multiple specialist tests. The most important part of this process is to select patients who are at risk of total loss of vision [3].

After preliminary head and neck physical examination, the patient requires audiological testing (auditory brainstem response – hearing levels, optoacoustic emission, impedance audiometry, pure tone audiometry). The decision to provide the patients with a hearing aid or cochlear implant is based on the results of these tests [5].

An essential diagnostic criterion for Usher syndrome, beside hearing loss and *retinitis pigmentosa*, is detection of balance dysfunction or the lack of thereof.

Diagnostic tests for balance performed in patients suspected of Usher syndrome may be categorized into five groups:

Ryc. 4. Normal field of vision (left) and a narrowed field (right)

- static tests: Romberg's test, Mann test;
- dynamic tests: pronator drift test, walking along a line;
- caloric test: ENG examination with Fitzgerald-Hallpike'a caloric test;
- kinetic tests: Barany chair test, oscillating chair test;
- computerized dynamic posturography (CDP) [3,6].

Ophthalmological tests in patients with suspected Usher syndrome include:

- acuity of vision (near and far);
- field of vision measured with ophthalmic perimeter or Goldman perimetry (GVF);
- contrast sensitivity;
- intraocular pressure;
- assessment of adaptation to darkness [7].

Other methods used include: electrooculography, direct ophthalmoscopy, biomicroscopy with a slit lamp, electroretinography and fundus photography [8]. Some of the tests ought to be run systematically in patients with Usher syndrome. An ophthalmologist should examine the acuity of vision, fundus and field of vision at least once a year [2].

TREATMENT

Usher syndrome is a genetic disorder, hence causative therapy is in this case impossible. It is worth noting that patients suffering from this syndrome require care from multiple specialists, including ophthalmologist, otorhinolaryngologist, pediatrician, psychologist and deaf educator [3]. The patient's family should also be subject to genetic counselling. Usher syndrome is inherited in an autosomal recessive pattern. It means that the probability of bearing a child afflicted by Usher syndrome is not sex-dependent and accounts to 25% in case of heterozygous parents (carriers); 100% in case both parents are diseased, and 50% - in case when one parent is a carrier of the mutation while the other suffers from Usher syndrome.

Depending on the degree of hearing loss, patients are offered either a hearing aid or a cochlear implant. Providing patients with such devices should take place as early as possible because of progressive visual deterioration. Doing so, it is possible to preserve one more communication channel for the patient. Otherwise, it is advisable to begin teaching Braille or Lorm alphabet (special alphabet designed for deaf-blind persons) [3].

The research conducted by the American scientists from the National Eye Institute proves that administration of high doses of vitamin A inhibits progression of *retinitis pigmentosa*. According to their guidelines, an adult patient should be given about 15,000 IU (international units) of vitamin A in the form of retinyl palmitate. Doses other than 15,000 IU do not bring advantages regarding the treatment of *retinitis pigmentos*a. It is worth mentioning that long-term administration of high doses of vitamin A causes liver damage [8].

CONCLUSIONS

Among genetic causes of hearing loss, visual-auditory syndromes may be distinguished. Concurrent dysfunction of two major sensory organs has a significant influence on the life of the patient. For this reason, it is important to broad-

en the knowledge in this field by medical practitioners and educators.

The most common among such disorders is the Usher syndrome. Patients suffering from this disease may be initially referred to an ophthalmologist, audiologist or otorhinolaryngologist, depending on the severity of their symptoms. Due to the heterogeneous character of the disease, the diagnosis of Usher syndrome may often be difficult. However, early diagnosis is crucial for the most effective treatment and rehabilitation of the patients, genetic counselling for the family and parents referral to support groups.

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