ROSIŃSKI, Mateusz, ROSIŃSKA, Kamila, ŁOJEWSKA, Julia Natalia, JANICKA, Ewelina Justyna, PERKO, Agnieszka, NIEDŹWIEDZKA, Monika, BOCHENEK, Oliwia and ANDRZEJCZYK, Agata. Impact of Usher syndrome on athletic performance - navigating silence and darkness. Quality in Sport. 2024;24:54714. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.24.54714
https://apcz.umk.pl/QS/article/view/54714

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.08.2024. Revised: 08.09.2024. Accepted: 06.10.2024. Published: 07.10.2024.

Impact of Usher syndrome on athletic performance - navigating silence and darkness

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Abstract:

Usher syndrome (USH) is an autosomal recessive genetic disorder and a leading cause of simultaneous hearing and vision loss. The aim of this paper is to provide a detailed review of Usher syndrome, including its pathogenesis, clinical symptoms, diagnostic methods, the role of sport in the lives of athletes and sportspeople with Usher syndrome and available therapeutic options. Understanding this disease is crucial for early detection and the implementation of appropriate therapeutic interventions. Currently, Usher syndrome is classified into three main types (I, II, and III), differentiated by the degree and progression of hearing and vision loss. Type I is characterized by profound congenital deafness and early-onset retinitis pigmentosa. Type II presents with moderate to severe hearing loss and later onset of visual problems. Type III is the rarest, with progressive hearing and vision loss that occurs later in life. The genetic basis of Usher syndrome is linked to mutations in various

genes that affect proteins essential for the proper functioning of the inner ear and retina. Early diagnosis and an interdisciplinary approach to treatment are key to improving the quality of life for those affected by this disease. Ongoing research into the genetic mechanisms and potential therapies offers hope for future successful treatments.

Key words: Usher syndrome, retinitis pigmentosa, hearing loss, vision loss, hereditary genetic disorder, autosomal recessive.

Introduction:

Usher syndrome (USH) is the most common genetic disorder responsible for simultaneous hearing and vision loss, often accompanied by balance disorders and bilateral vestibular areflexia. This disease is inherited in an autosomal recessive manner. It was first described by Albrecht von Graefe in 1858 and later studied in more detail by Scottish ophthalmologist Charles Usher in 1914, after whom the syndrome is named. There are three main clinical types of this disease (I, II, and III), which differ in the severity of symptoms and the age of onset. [4,11]

Etiology:

The disease has a genetic basis and is caused by mutations in specific genes. To date, nine genes responsible for this disorder have been identified: MYO7A, USH1C, CDH23, PCDH15, and USH1G for type I; USH2A, ADGRV1, and WHRN for type II; and CLRN1 for type III. These genes encode proteins essential for the proper functioning of the inner ear and retina. Additionally, these proteins form a dynamic network, known as the "Usher interactome," which plays a crucial role in both the development and maintenance of the structure of stereocilia in the organ of Corti, as well as in the transport of molecules between the segments of photoreceptors in the retina. While some genes are clearly associated with Usher syndrome, others remain controversial. The expression of USH genes detected in various tissues suggests their involvement in additional, milder coexisting conditions. Understanding the genetics of Usher syndrome and the spectrum of mutations in USH genes is crucial for identifying genotype-phenotype correlations, which can lead to more precise diagnoses and potentially new therapies. [4,11]

Usher syndrome symptoms by type:

The symptoms of Usher syndrome primarily affect hearing, vision, balance, and sometimes movement. The manifestation of symptoms in these areas can vary in severity, occurrence, and rate of progression.

For Usher syndrome type 1 (Usher 1), the symptoms include:

- **Hearing**: Severe to profound, bilateral, congenital, usually non-progressive sensorineural hearing loss.
- **Balance**: Vestibular areflexia (lack of vestibular reflexes), leading to delayed motor development. Children typically do not walk independently before 18 months of age. Older children have a higher risk of falls and difficulty with balance-related activities such as cycling, affecting overall mobility.
- **Vision**: Retinitis pigmentosa (RP), typically developing before adolescence, leading to night blindness and progressive loss of the visual field. In Usher Syndrome Type 1D, there is a slowly progressive phenotype despite the early onset of symptoms. [6]

For Usher syndrome type 2 (Usher 2), the symptoms include:

- **Hearing**: Congenital, sensorineural hearing loss that is descending (higher frequencies are more affected), mild to moderate at low frequencies, and severe to profound at high frequencies. It may be progressive, especially in Usher 2A subtype.
- **Balance**: No balance problems. Vestibular function is typically preserved, allowing for normal motor development.
- **Vision**: Retinal degeneration, typically developing within the first two decades of life, leading to similar symptoms as in Type 1, but usually with a milder course.

For Usher syndrome type 3 (Usher 3), the symptoms include:

- **Hearing**: Late-onset, postlingual (after speech acquisition) hearing loss, typically detected in the first decade of life but can be delayed until adulthood. The hearing loss is progressive.

- **Balance**: Vestibular areflexia occurs in about half of the patients, but most achieve normal walking age.
- **Vision**: Retinitis pigmentosa usually develops after puberty, leading to similar symptoms as in other types, but typically later than in Types 1 and 2.

All types of Usher syndrome are characterized by progressive vision loss, with early symptoms like night blindness often preceding the full diagnosis of the syndrome. [27]

Additionally, a 2022 publication identified a new type of Usher syndrome, termed USH Type IV, caused by mutations in the ARSG gene. This type is characterized by a late onset of retinitis pigmentosa (RP) with primarily pericentral and macular changes and a late onset of sensorineural hearing loss (SNHL), but without vestibular dysfunction. Studies showed that mutations in ARSG lead to a loss of sulfatase activity, confirming that variants of this gene are responsible for this newly defined type of Usher syndrome. These findings support the expansion of the phenotypic classification of Usher syndrome. [29]

Diagnosis of Usher syndrome:

The diagnosis of Usher syndrome typically begins with the identification of clinical symptoms. Often, isolated hearing loss (NSHL) is initially diagnosed in family members until the oldest affected sibling shows signs of retinal degeneration, such as night blindness, difficulty adapting to darkness, contrast vision issues, changes in visual acuity, and narrowing of the visual field. This leads to the diagnosis of retinitis pigmentosa (RP). In younger family members, early pre-symptomatic signs of RP can often be detected during later eye examinations.

For children suspected of having NSHL, who also exhibit vestibular symptoms, vision tests are conducted to exclude or confirm the presence of RP, which may lead to further genetic testing. For Usher Syndrome Type 1 (USH1), diagnosis is based on electrophysiological tests and subjective tests of hearing and retinal function. These tests assess whether the patient's hearing and vision are impaired in a manner characteristic of Usher syndrome. The diagnosis can be confirmed by identifying pathogenic genetic variants in one of six genes (MYO7A, USH1C, CDH23, PCDH15, USH1G, CIB2). In some cases, when clinical symptoms are ambiguous, genetic testing is crucial for establishing a diagnosis.

It is also possible that a patient has inherited conditions characterized by both hearing loss and vision impairment, which may resemble Usher syndrome. However, in Usher Syndrome Type 2 (USH2) and retinitis pigmentosa (RP), caused by mutations in the USH2A gene, studies have shown that different mutations in this gene lead to distinct clinical symptoms. In cellular models, such as retinal organoids, it has been observed that RP leads to problems with photoreceptor differentiation, while in USH2, cone cell damage occurs. Studies on patients with the c.2610C>A mutation in the USH2A gene have shown that the rate of retinal degeneration varies. Most patients retain photoreceptors in the central part of the retina, while some have more advanced damage. This indicates the need for an individualized approach to monitoring and treating this disease. These findings help better understand the disease mechanisms and may serve as a basis for testing new gene therapies.

Therefore, it is necessary to consider differentiating from other diseases with a similar clinical picture. A genetic panel for hearing loss should be prioritized to detect genetic mutations associated with Usher syndrome, due to the progressive nature of the disease and potential physical and developmental deficits. [5,10,16,21]

The impact of Usher syndrome on quality of life

Usher syndrome significantly affects the quality of life of patients. Congenital or early childhood hearing loss, combined with progressive vision loss, creates serious challenges in daily functioning. For many patients, this means having to cope with sensory disabilities that substantially limit their ability to live independently and participate in social life. Patients with Usher syndrome often struggle with social isolation, which stems from both physical limitations and a lack of societal awareness about the condition. Social integration, including maintaining social relationships, can be particularly difficult, especially as vision and hearing loss progress. Patients often experience communication difficulties, which can lead to feelings of alienation and frustration. The ability to participate in social life is significantly limited by the severity of the condition. People with Usher syndrome may require specialized tools such as cochlear implants, hearing aids, as well as support in learning sign language and Braille. Despite this, communication and perceptual barriers often make full social integration difficult. Society is not always prepared to provide adequate support for people with this syndrome, which further deepens their isolation. The education of children with Usher syndrome requires an individualized approach and support from qualified specialists. Early

detection of the condition and the implementation of appropriate teaching methods can significantly improve the quality of life for these children. However, as the symptoms of Usher syndrome worsen, particularly vision loss, children may need specialized educational materials and adaptations to the school environment to continue their education. The lack of such support can lead to difficulties in achieving educational milestones, which in turn affects their future employment opportunities. In the job market, people with Usher syndrome face numerous barriers. Vision and hearing loss limit their ability to perform many jobs, and the lack of workplace accommodations often leads to difficulties in maintaining employment. Vocational support, such as workplace adaptation programs, assistance in acquiring qualifications tailored to the patients' abilities, and promoting the employment of people with disabilities, are key to improving their situation in the labor market. People with Usher syndrome and their families often need psychological support to cope with the challenges associated with the condition. The constant deterioration of health, especially vision loss, can lead to anxiety, depression, and a sense of helplessness. Access to professional psychological support, support groups, and organizations that assist people with Usher syndrome is crucial for maintaining the mental health of patients. Social support, including the opportunity to participate in communities focused on people with similar problems, can also play an important role in improving the quality of life. Usher syndrome has a multifaceted impact on the lives of patients, from daily challenges related to functioning in society, through difficulties in education and employment, to the need for psychological support. To improve the quality of life for people with this syndrome, a comprehensive approach is needed, encompassing education, access to medical and psychological care, and the promotion of social integration. Support for patients with Usher syndrome should be integrated and tailored to their individual needs, enabling them to fully participate in social and professional life, despite the challenges posed by this condition. [2,3,18,20,24,25,28]

The Role of Sport in the Lives of Athletes with Usher Syndrome

Athletes with Usher syndrome, which leads to hearing and vision loss, face unique challenges. Issues with balance, communication, and narrowed visual fields affect their ability to participate in various sports. This requires the use of specialized training methods, such as visual cues, vibrations, and assistive technologies. Examples of athletes like Mahadeo Sukhai,

a Canadian triathlete, and Kevin Frost, a blind speed skater, demonstrate that it is possible to achieve sports success despite significant health limitations. For individuals with Usher syndrome, sports not only improve physical fitness but also enhance self-esteem and support social integration, which is crucial for their quality of life.

Treatment methods, rehabilitation, and advances in Usher syndrome therapy:

Rehabilitation for individuals with Usher syndrome (USH) is complicated due to the simultaneous impairment of vision and hearing, which affects the ability to function independently in society. There is currently no cure for Usher syndrome, and treatment focuses on managing symptoms and supporting patients in daily life. The appropriate rehabilitation approach must address the patient's sensory, physical, and psychosocial needs to compensate for the loss of hearing and vision, as well as improve the quality of life. [4]

Key steps in the treatment and rehabilitation of Usher syndrome:

1. **Hearing**: Early introduction of cochlear implants (CI) for children with USH1 and individuals with USH3 later in life. Early fitting of hearing aids and audiological rehabilitation for patients with USH2. Learning sign language as an alternative form of communication in case of hearing loss. Children with Usher syndrome require intensive, individualized auditory therapy due to their additional vision impairment needs.
2. **Vision**: Early diagnosis using electrophysiology. Annual eye exams, including contrast and light sensitivity tests. Adjustment of lighting conditions and the use of sunglasses.
3. **Balance**: Rehabilitation to compensate for vestibular function loss through physical exercises focused on somatosensory and visual cues. Providing additional physical exercise in kindergartens and schools under the supervision of a physical therapist.
4. **Psychosocial Consequences of Deafblindness**: Considering psychosocial aspects in rehabilitation, with a focus on mental health, coping with problems, and social support. A multidisciplinary approach to rehabilitation, involving the family, school, and employer.
5. **Comorbidity of Physical and Mental Illnesses**: Treatment of physical symptoms such as fatigue, headaches, neck, and shoulder pain. Prevention and treatment of mental health problems, including suicidal behavior. There is speculation that the CDH23 gene, responsible for syndromic and non-syndromic hearing loss, associated with Usher Syndrome Type 1, may also be linked to symptoms similar to schizophrenia and bipolar

affective disorders. Therefore, doctors emphasize the importance of psychological and social support for individuals with this disease, as well as the need to develop genetic therapies in the future. Targeted education is needed for clinicians dealing with hearing and vision care. [2,3,18,20,24,25,28]

Advances in Usher syndrome therapy research:

Virus-based therapies, such as those using adeno-associated viruses (AAV) with low immunogenicity, have been tested to replace damaged genes responsible for Usher syndrome. Clinical studies have demonstrated their effectiveness in improving vision and hearing function, particularly in the case of mutations in genes such as MYO7A, USH1C, USH2A, USH2D, and USH3A. Additionally, gene editing techniques like CRISPR/Cas9 and zinc-finger nucleases have been successfully used in laboratories to repair mutations in cells. CRISPR/Cas9, utilizing the NHEJ pathway, can effectively improve the phenotype in living organisms, potentially leading to future therapies for patients with Usher syndrome. Successful studies provide evidence of the therapeutic potential of this method.

Furthermore, a new generation of drugs, such as modified aminoglycosides, has been tested in mouse models with mutations associated with Usher syndrome. These drugs have been shown to induce protein expression that improves sensory function. Additionally, antisense oligonucleotides (ASOs), such as QR-421a, have been tested in clinical trials on patients with mutations in the USH2A gene, which is relatively large. These therapies aim to reduce the effects of genetic mutations and protect against further vision loss. Moreover, cochlear implants and hearing aids have been tested in studies aimed at improving hearing as a means of partially alleviating hearing loss in patients with Usher syndrome. Results indicate benefits from the early use of these devices.

It is also worth mentioning a study on radiosensitivity dedicated to fibroblasts. While this research does not directly bring hope for new therapies for Usher Syndrome Type 1 patients, it provides information about cellular and molecular mechanisms related to radiosensitivity in these patients. Understanding how USH1 cells respond to DNA damage and what processes are disrupted in them may lead to the development of new therapeutic strategies in the future that better address the specific needs of USH1 patients.

Advances in Usher syndrome research focus primarily on gene therapies, gene editing, drugs that induce translation, and the use of ASOs. No curative therapy has yet been developed for patients with USH2A. In recent years, USH has become a target for gene and molecular therapy.

Several studies have shown that the gene in the adeno-associated virus ANC80L65 (AAV) or WHRN in AAV8 was successfully delivered to the inner ear of mice with USH1C to restore their hearing and vestibular function. In the case of USH1F, methods have been developed that use sequences encoding Mini-PCDH15 and PCDH15, which are housed on an adenoviral vector (AAV) and could be a useful therapy for deafness caused by USH1F. According to recent reports, there is also a gene therapy for Usher syndrome type 1B (USH1B), caused by mutations in the MYO7A gene, leading to congenital deafness, loss of balance, and blindness. As part of this therapy, an advanced lentiviral vector system has been developed that can deliver a large DNA fragment containing the MYO7A gene to the cells of the inner ear. In studies on mice with a mutation in the MYO7A gene, this therapy improved hearing and balance function, demonstrating its potential for treating the symptoms of Usher syndrome. Although there is no fully effective treatment yet, promising results in preclinical and clinical studies may significantly improve the quality of life for patients in the future. [1,7,8,9,12,13,14,15,17,19,22,23,26,30]

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All authors have reviewed and agreed to the publication of the final version of the manuscript.
Conflict of interest statement: No conflicts of interest.
Funding statement: The study did not receive any specific funding.
Informed consent statement: Not applicable.
Ethics committee statement: Not applicable.

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