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A Review On Usher Syndrome

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Abstract: Usher syndrome (USH) stands out as the predominant hereditary condition leading to concurrent impairment of both hearing and vision. In certain instances, individuals affected by ush also experience balance irregularities and bilateral vestibular areflexia. Initially documented by Albrecht von Graefe in 1858, the syndrome earned its moniker from charles usher, wh o extensively presented cases exhibiting a combination of hearing loss and retinopathy in 1914. Ush is clinically categorized into three primary types, denoted as 1, 2, and 3. These variations arise from mutations in distinct genes and further subdivide into specific subtypes. Currently, a total of nine causative genes have been unequivocally identified as contributors to the syndrome when undergoing mutation: MYO7A, USH 1C, CDH23, PCDH15, and USH 1g (sans) for Usher type 1; USH 2A, ADGRV1, and when for Usher type 2; CLRN1 for Usher type 3. The inheritance pattern of USH follows an autosomal recessive trait. This comprehensive review delves into the causative forms, diagnostic approaches, prognostic considerations, ongoing research, and emerging treatments in the realm of USH.

Key Words: Retinities pigmentasa, USH genes, USH protien, inner ear hair cells, charles Usher, vestibular dysfunction.

INTRODUCTION: Usher syndrome is a genetic condition characterized by both sensorineural hearing loss and vision loss. While considered rare in humans, the condition involves a specific type of hearing impairment known as sensorineural hearing loss, resulting from abnormalities in the inner ear(refer to figure-1)[1].

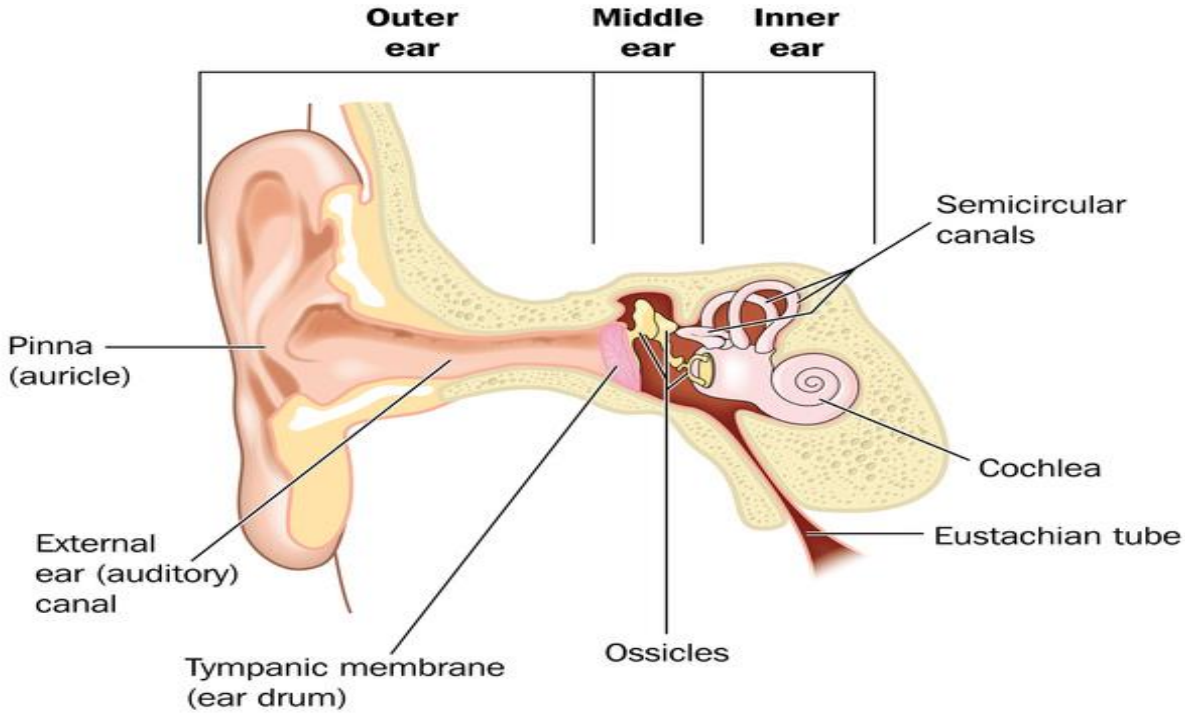

Figure no-1: Inner ear

Vision loss in usher syndrome is attributed to a condition known as retinitis pigmentosa(Refer to figure-2), an eye disease that impacts the light-sensitive tissue layer at the back of the eye[(2)]. This disease gradually breaks down the light-sensing cells of the retina, initiating the loss of night vision as the initial symptom [(3)]. Subsequently, blind spots develop in the peripheral vision. Over time, these blind spots enlarge and converge, leading to tunnel vision. Additionally, in certain cases, further impairment of vision may occur due to the clouding of the eye's lens[(4)].

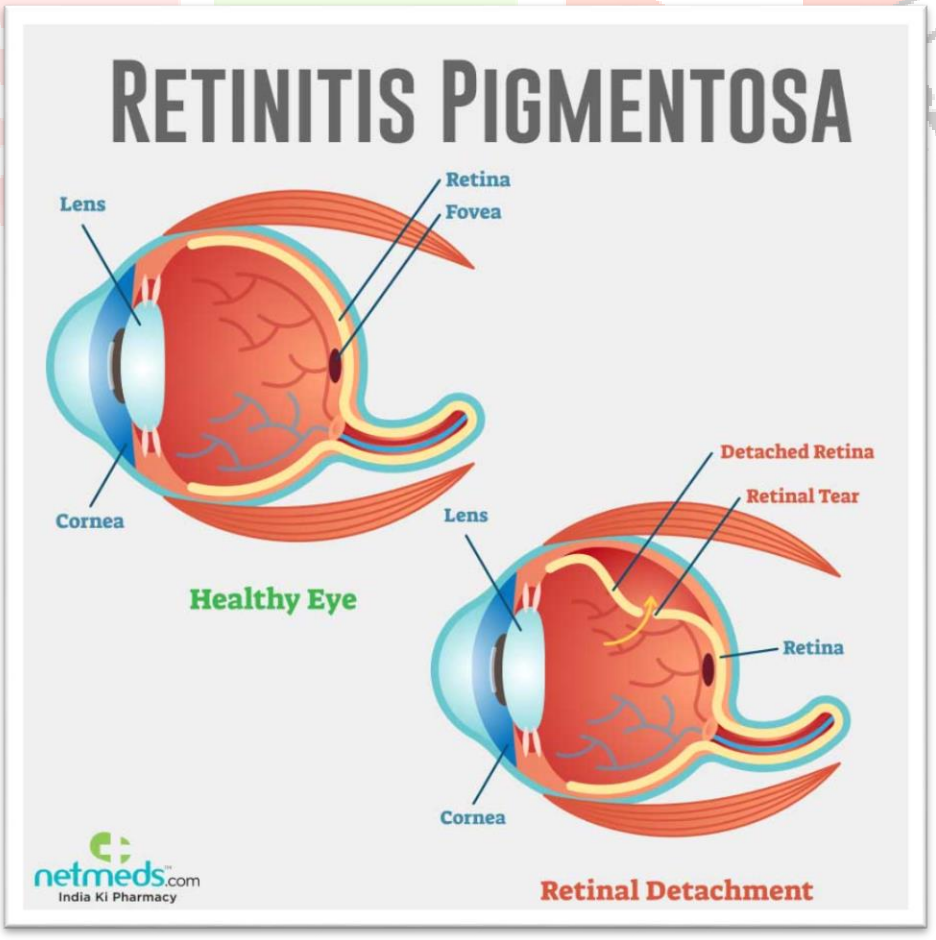

Figure no-2: Retinitis pigmentosa

Usher syndrome stands as the predominant cause of deaf-blindness globally, affecting 4 to 17 in every 100,000 individuals at birth. It is responsible for 3% to 6% of childhood deafness. Vestibular dysfunction, a common cause of combined sight and hearing loss, contributes to over half of deaf-blindness cases [5]. To inherit usher syndrome, both parents must carry the syndrome genes.

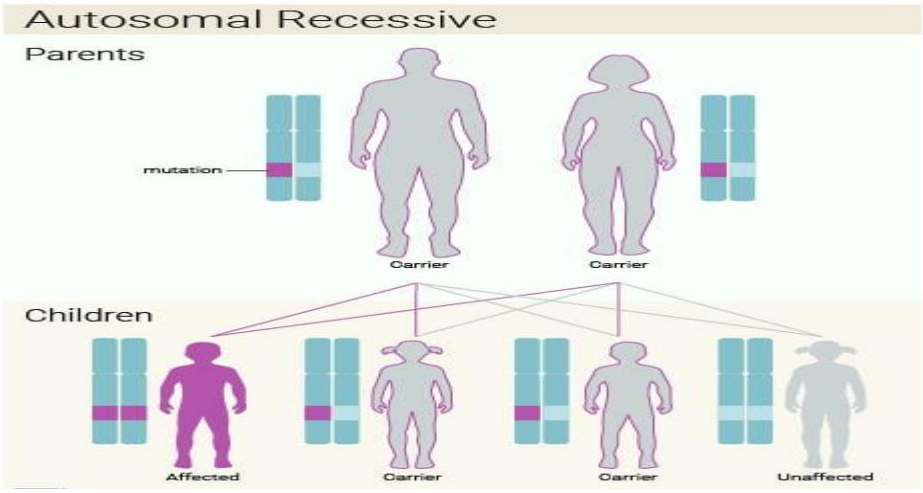

Figure no-3: Autosomal Recessive

All types of usher syndrome follow an autosomal recessive inheritance pattern(Refer to figure no-3), requiring mutations in both copies of a gene in each cell[6] . Parents, while carriers of one mutated gene, do not exhibit symptoms of the condition. Symptoms of Usher syndrome vary in severity and onset, contingent on the specific type[7].

Symptoms: Common symptoms include:

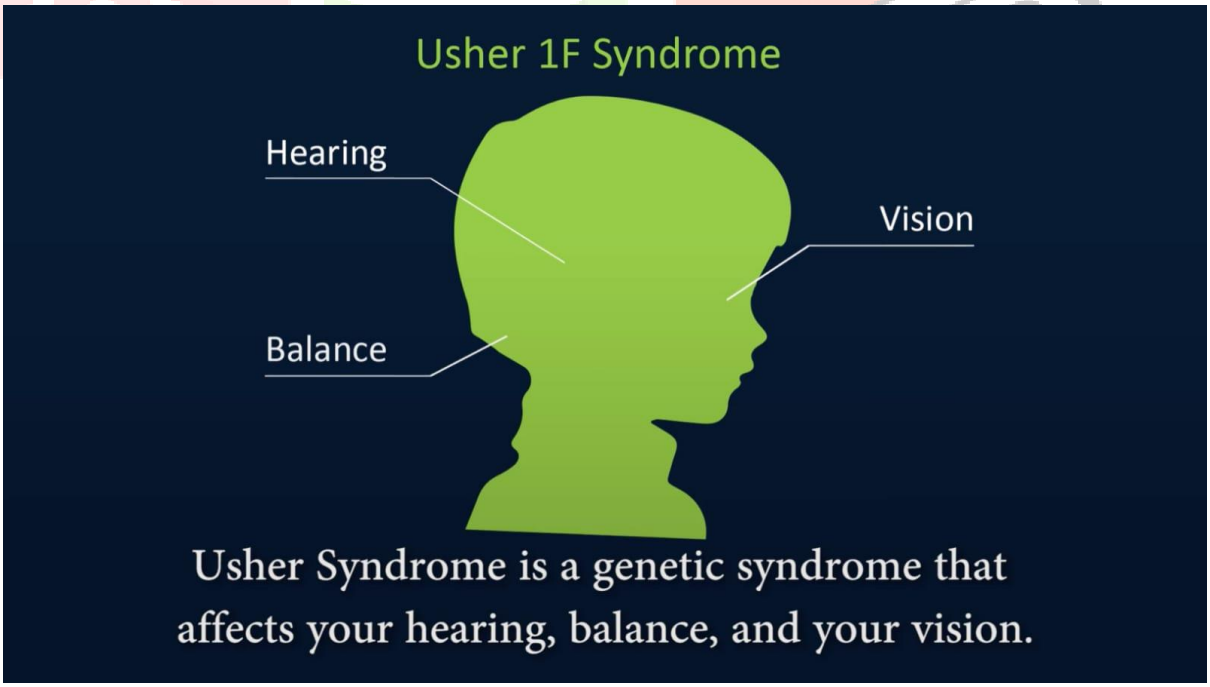

Figure no-4: symptoms of Usher syndrome

Hearing loss: Individuals may be born with severe hearing impairment(refer to figure-4).

Vision loss: Retinitis pigmentosa leads to worsening vision loss, particularly affecting peripheral vision[8] (refer to figure-4).

Balance problems: Damage to the eyes and inner ear can result in difficulties with balance and coordination[9] (refer to figure-4).

TYPES OF USHER SYNDROME:

Usher syndrome is categorized into three clinical subtypes: usher syndrome type-1, type-2, and type-3, based on the severity and onset of hearing loss and vestibular dysfunction[10].

Graphical representation was given on figure-5.

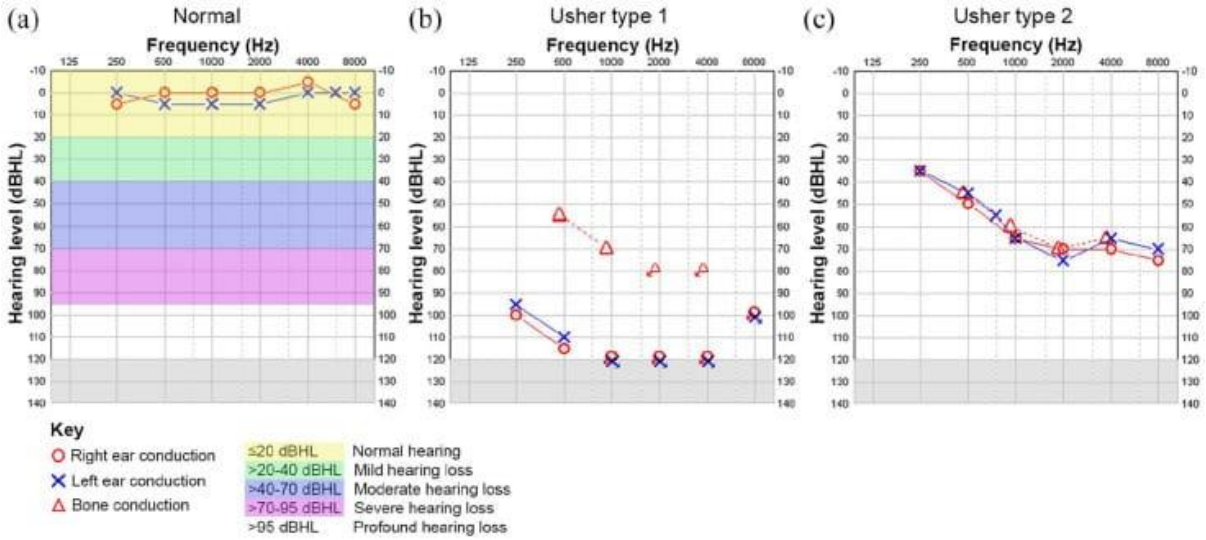

Figure no-5: Frequency of Usher syndrome

- **Usher syndrome type-1**: Individuals are born with severe to profound congenital sensorineural hearing loss. Vision loss due to retinitis pigmentosa becomes apparent in childhood[11]. Causative genes include MYO7A, USH 1C, CDH23, PCDH15, and USH 1G, CLB2. Diagnosis typically occurs in the second decade, with legal blindness occurring in the fourth decade. Vestibular abnormalities lead to delayed motor development, with children walking after 18 months of age[12].
- **Usher syndrome type-2**: Hearing loss manifests in adolescence or adulthood, ranging from mild to severe. Mainly affects the ability to hear high-frequency sounds. No associated vestibular abnormalities affecting balance[13]. Causative genes include USH2A, ADGRV1, when[14]. The pie chart presentation and progression of symptoms within usher syndrome types can vary widely among individuals and families was given on figure-6.

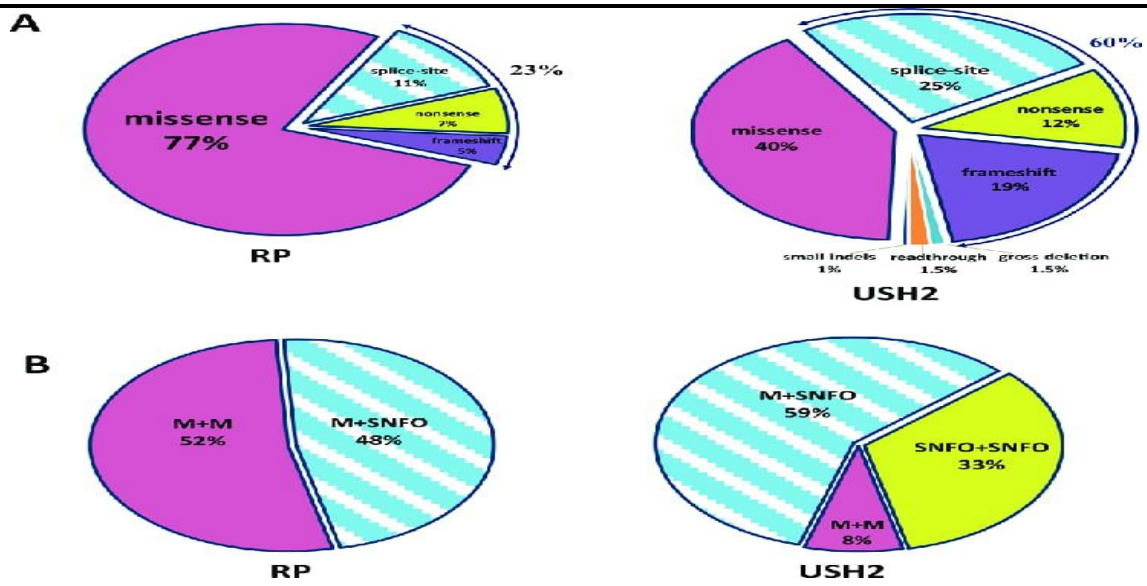

Figure no-6: Causative gene of Usher syndrome type-2

Individuals with usher syndrome type-3 encounter hearing and vision loss later in life. The causative gene for this type is CLRN1. In contrast to other usher syndrome forms, type-3 is generally linked to normal hearing at birth[15]. Hearing loss typically commences in late childhood or adolescence, after speech development, progressing to profound hearing loss by middle age. Vision loss due to retinitis pigmentosa also emerges during late childhood or adolescence, with some individuals developing vestibular abnormalities affecting balance.

Usher syndrome was initially described in 1858 by German ophthalmologist Albrecht von Graefe but later named charles usher syndrome, who presented by large number of cases with hearing loss and retinopathy in 1914[17].

DAGNOSISS: Behavioral and objective measures of the auditory system are within the audiologist's purview. Objective testing includes a direct examination of the retina, revealing attenuated blood vessels, a waxy pallor, and clumps of dead retina cells called bone spicules. The definitive test for retinitis pigmentosa is an electroretinogram[18], akin to an auditory brainstem response from the rods and cones of the retina(Refered to Table-1). While genetic testing is available, it can be costly. Upon a usher syndrome diagnosis, genetic testing is an option to determine the specific genetic type[19].

TREATMENT:

- Hearing aids and cochlear implants: (refer to figure-7)Hearing aids may be used to manage hearing loss. In some cases, cochlear implants can be considered for individuals with severe to profound hearing loss(Refer to table-1).
- Vision support: Individuals with usher syndrome may benefit from low vision aids, orientation and mobility training, and other resources to help them cope with visual impairments.
- Educational and psychological support: Support from educators and mental health professionals can help individuals with usher syndrome navigate the challenges associated with their condition.
- Genetic counseling: Usher syndrome is a genetic disorder, genetic counseling can be beneficial for affected individuals and their families. It can provide information about the inheritance pattern, the likelihood of passing the condition to offspring, and potential options for family planning.
- Research and clinical trials: As of my last update, research into potential treatments and therapies for Usher syndrome was ongoing.
- While there is no cure for usher syndrome, treatments can assist in managing vision, hearing, and balance issues[20]. It is crucial to promptly consult with a child's doctor upon noticing symptoms.

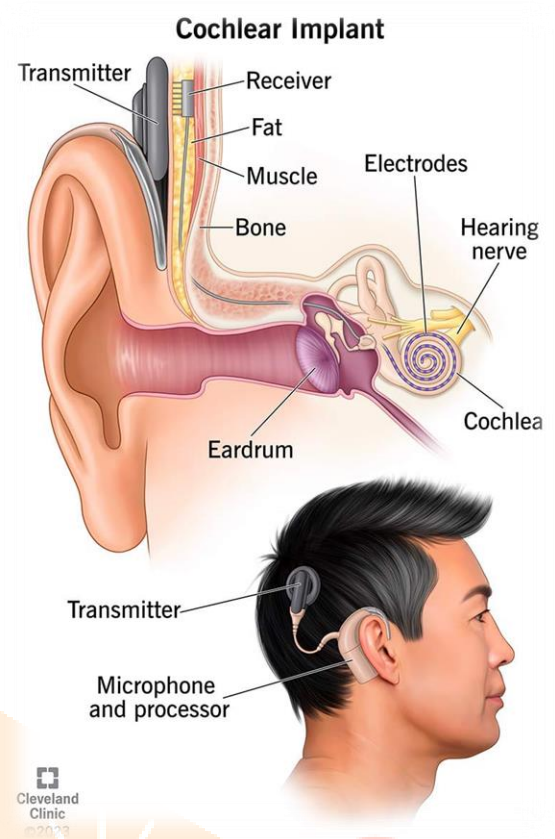

Figure no-7: Cochlear Implant

It's important to note that medical information and treatments can evolve, and there may have been developments or updates since my last knowledge update in january 2022. If you or someone you know is affected by usher syndrome, it's recommended to consult with healthcare professionals who specialize in genetic disorders, hearing loss, and visual impairments for the most up-to-date information and personalized guidance(21).

Table-1: Daignosis of Ear

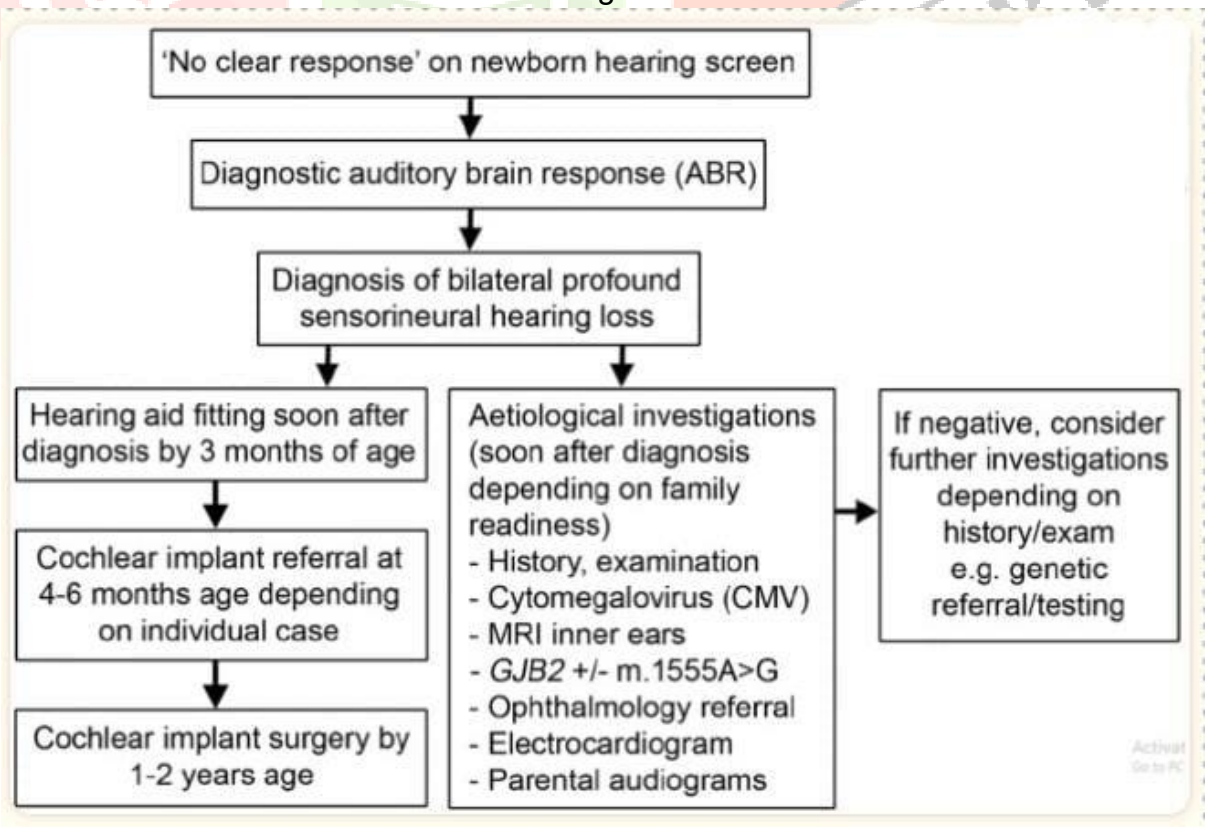

Table-2: Types of Usher syndrome

Usher subtypes	Causative genes	Sensorineural hearing loss	Retinitis pigmentosa	Vestibular function
Usher -1	MYO7A, USH1C , CDH23, USH1G, C1132	Congenital severe to prefound	Prepubertal on set, Average age of diagnosis in 2nd decade, Legal blindness in 4th decade	Vestibular hypo function, Moter development may be delayed Infants typically do not walk before 18 months of age .
Usher -2	USH2A, ADGRV1 WHRN	Congental moderate to severe high frequencies most affected	On set in 2nd decade average age of diagnosis in 3rd decand, legal blindness in 6th decade	Normal vestubular function
Usher -3	CLRN1	Post lingual onset Progressive variable.	Variable onset typically in 2nd decand	Variable; vestibular abnormalities in 50% of patients useally mild

A. Usher proteins in the hair bundle: Usher proteins play a pivotal role in the hair bundle of the inner ear, contributing to various pathogenic phenotypic features. The cochlear hair bundle undergoes dynamic changes during development and maturity. Transient apical lateral links, ankle links, and kinocilial links vanish after bundle maturation in mice, with top connectors persisting. The tip link, a distinctive fibrous link connecting stereocilia, is present in both developing and mature hair bundles[22]. The kinocilium, characterized by a 9+2 axoneme pattern, typical motile cilium structure, is absent in mature hair bundles. Ush proteins, such as cadherin 23 and protocadherin 15, form tip links, and ush2 proteins are crucial for ankle links(Refered to table-2), which disappear in mature auditory hair bundles[23]. The role of ush3a in the met channel complex remains unclear.

B. Usher protein defects and phenotypic abnormalities:

Usher protein defects result in a spectrum of physiological, morphological, and molecular abnormalities. For ush1, phenotypic findings include various impairments. The sem micrograph for ush3 illustrates these abnormalities[24].

To diagnose usher syndrome in a child, healthcare providers conduct comprehensive tests:

- ✓ Hearing test: Otolaryngologists and audiologists assess hearing ability using tests that cover a range of sounds and frequencies[25].
- ✓ Genetic tests: Definitive diagnosis involves genetic testing, identifying mutations in the nine known usher syndrome genes. A simple blood test can be employed for this purpose[26].
- ✓ Eye tests: Electroretinography (erg) measures the electrical activity of retinal cells in different lighting conditions[27].

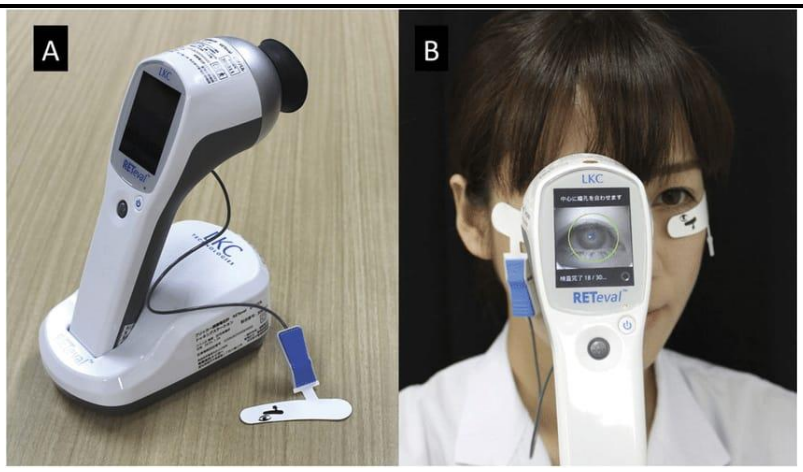

Figure no-8: Fundus autofluorescence

- ✓ Fundus autofluorescence (FAF)(refer to figure-8)imaging uses blue light absorption by blood vessels to identify damaged areas in the eye, appearing as dark regions[28].
- ✓ Optical Coherence Tomography (OCT) employs infrared light to generate a detailed image of the retina(refer to figure-9). This noninvasive technique captures an image by quantifying the reflection of dim red light off the retina and optic nerve[29].

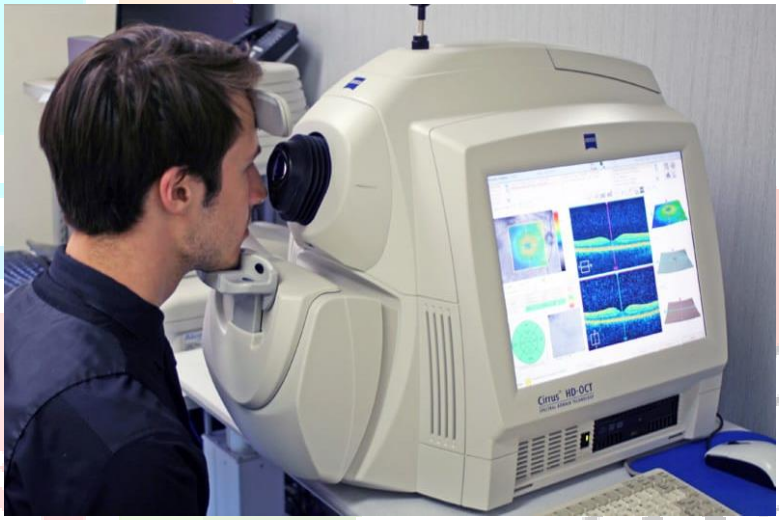

Figure no-9; Optical coherence tomography test

- ✓ Videonystagmography tests (VNG) assess a specific type of involuntary eye movement known as nystagmus(refer to figure-10). Nystagmus involves uncontrolled eye movements, manifesting as lateral, vertical, or circular motions[30].

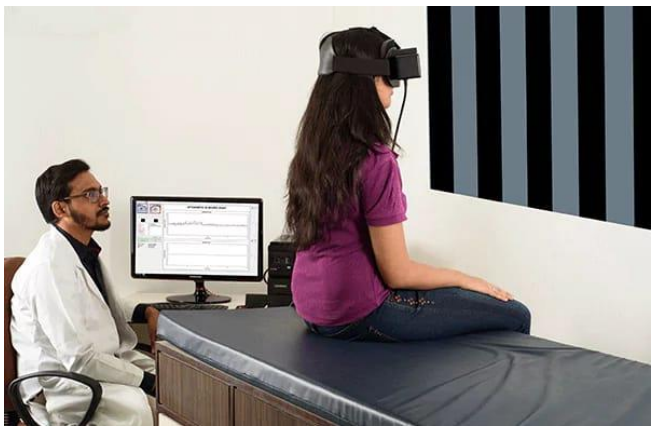

Figure no-10: Videonystagmography test

Conclusion: USH is one of the most common autosomal recessive syndromes associated with double-sense impairment, hearing, and vision. This combination creates a unique entity of deaf-blindness. Genetics has enabled significant advances, accurate diagnosis, and improved

understanding of the pathology and is expected to provide innovative treatments for gene therapy. Next-generation sequencing has also helped in new conceptions and knowledge of the field.

The recovery process for these individuals is intricate and demands specialized expertise and training. While bioengineering continually advances in providing support for the retina, the optimal treatment avenue still revolves around hearing rehabilitation through the use of hearing aids and cochlear implants (CIS). Bilateral devices show promise in partially reinstating spatial orientation and bolstering residual visual capabilities. Although experimental animal models have yielded promising outcomes in gene therapy, this method has not yet been integrated into current clinical practices. Nevertheless, additional research is imperative to formulate novel strategies and amass information concerning usher syndrome (USH)

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