Usher Syndrome

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What is Usher Syndrome?

Usher syndrome (Usher, USH) is the leading genetic cause of combined deafness and blindness.

Disease characteristics

There are 3 clinical types of Usher syndrome named USH1, USH2 and USH3, based on the severity and age of onset of deafness and blindness, and in some patients, vestibular areflexia. USH1, the most severe form, is characterized by congenital, bilateral, profound sensorineural hearing loss (SNHL), vestibular areflexia, and adolescent-onset retinitis pigmentosa (RP). USH2 is the most frequent form characterized by congenital, bilateral SNHL that is mild to moderate in the low frequencies and severe to profound in the higher frequencies, intact vestibular responses, and RP that begins in the second-third decade of life. USH3 is characterized by post-lingual, progressive SNHL, late-onset RP, and variable impairment of vestibular function. The RP in all forms of USH is a progressive, bilateral, symmetric retinal degeneration that begins with night blindness and constricted visual fields (tunnel vision) and eventually includes decreased central visual acuity. The rate and degree of vision loss varies within and among families.

History

Albrecht von Gräfe first described Usher syndrome in 1858. However, it was named after Charles Howard Usher, a Scottish Ophthalmologist, who described the syndrome in 1914 on 69 patients with RP who were also hearing impaired, in an article called "On the inheritance of Retinitis Pigmentosa, with notes of cases" [1].

Who is affected by Usher syndrome?

The incidence of Usher is estimated at 1:20,000 individuals worldwide, although Kimberling et al (2010)[2] suggested it may be as high as 1:6000 in some populations. Approximately 3-6% of hearing impaired children have Usher. An estimated 10% of children born with profound SNHL have Usher. Current reports indicate that Usher accounts for more than 50% of people who are both deaf and blind.

What causes Usher syndrome?

Usher is inherited in an autosomal recessive manner. Both males and females can inherit Usher when he or she receives a mutation from each parent. Currently, 15 genes are associated with Usher. Nine different loci have been found to cause Usher syndrome type I (USH1). Genes at six of these loci have been identified: MYO7A (USH1B), USH1C (USH1C), CDH23 (USH1D), PCDH15 (USH1F), USH1G (USH1G), and CIB2 (USH1J). Mutations in three different genes are known to be associated with type II Usher (USH2): USH2A (USH2A), GPR98 (USH2C), DFNB31/Whirlin (USH2D); and two genes with type III Usher (USH3): CLRN1 (USH3A), HARS (USH3B).

How do you diagnose Ushers syndrome?

An Usher diagnosis is generally made based on clinical presentation. However, because there is typically a lag of 5 – 10 years between the onset of hearing and visual impairments, the average age of diagnosis is late teens for USH1 and adulthood for USH2 and 3. Early diagnosis is critical for adapted educational and management option. Genetic testing is available for most of the genetic mutations that cause Usher. **Figure 1**

Figure 1. Usher's syndrome patient (with permission)

Usher affects hearing, balance and vision. Diagnosis includes evaluation of all three senses. Evaluation of the eyes includes a visual field test, an electroretinogram (measurement of the electrical response of the retina), and a retinal exam by an ophthalmologist. An ear evaluation often includes an audiologic exam by an audiologist, and an otologic examination by an otolaryngologist. Sometimes an electronystagmogram can be done to measure involuntary eye movements to check for balance problems.

USH1

USH1 accounts for ~ 35% of all Usher. The hearing loss in USH1 is congenital, bilateral, and severe-profound. While it is autosomal recessive, the penetration is complete. Affected individuals do not develop speech without interventions. Vestibular areflexia is associated with the deafness and is a defining feature of this type. Because of vestibular areflexia, children with USH1 typically walk later than usual, at approximately age 18 months to two years. Older children may seem ‘clumsy’ and experience frequent accidental injuries or have difficulty with activities requiring balance, such as riding a bicycle or playing sports.

A child with USH1 is often misdiagnosed as having nonsyndromic deafness until tunnel vision and night blindness, the early signs of RP, become severe enough to be noticeable, either by parents and teachers or by the individual. Retinitis pigmentosa is progressive, bilateral, symmetric degeneration of the retina that initiates at the periphery. Rods (photoreceptors active in the dark-adapted state) are mainly affected first, causing night blindness and constricted visual fields (tunnel vision). Cones (photoreceptors active in the light-adapted state) may also be involved [3].

Visual fields become progressively constricted with time. The rate and degree of visual field loss show intra- and interfamilial variability. A visual field of 5-10 degrees is common for a person with USH1 who is age 30-40 years. Visual impairment worsens significantly each year [4]. However, it is unusual for the typical individual with USH1 to become completely blind, although cataracts sometimes reduce central vision to light/dark perception only.

USH2

USH2 accounts for 60-65% of all Usher, and is characterized by (1) congenital, bilateral sensorineural hearing loss predominantly in the higher frequencies that ranges from mild to severe; (2) normal vestibular function; and (3) late adolescent-to-adult onset of RP. One of the most important clinical distinctions between USH1 and USH2 is that children with USH1 are usually delayed in walking until age 18 months to two years because of vestibular involvement, whereas children with USH2 usually begin walking at approximately age one year.

USH3

USH3 is characterized by post-lingual progressive sensorineural hearing loss, late-onset RP, and variable impairment of vestibular function[5]. Some individuals with USH3 may have profound hearing loss and vestibular disturbance and thus be clinically misdiagnosed as having USH1[6].

Historical Perspective

The Acadians are descendants of the 17th century French colonists who settled in Acadia, what is now Nova Scotia, Canada. Many Acadians later settled in Louisiana, where their children, born in Louisiana became known as Cajuns. Clinical scientists have recognized some Acadian cultural isolation in Louisiana through an increased incidence of particular diseases in subpopulations of Acadian descendants, including Friedreich ataxia[7], Tay-Sachs disease[8], and Usher syndrome[9].

Dr. Kloepfer and his colleagues first reported Usher in Louisiana Acadian patients in 19669. Approximately 6-7% of USH1 is caused by mutations in the USH1C gene[10], however, nearly all cases of USH1 in the Acadian populations of Louisiana are cause by a single mutation the USH1C gene (c.216G>A). Because of founder affect, USH1C is suggested to have a higher incidence in the Acadian population than the general American population.

More than 30 mutations have now been reported, with most of them either located in an exon encoding a PDZ domain of the protein or affecting splicing. The most common USH1C mutation observed in persons from other ethnic origins is c.238dupC[11, 12]. A study of USHI patients in Spain identified two new mutations, one nonsense and one frameshift, and estimated that USH1C mutations are responsible for 1.5% of USHI in the Spanish population[13].

In addition to USH1C, a few cases of USH2 have been reported in the Louisiana Acadian population. A founder mutation has also been reported to cause USH2A (c.4338-4339delCT) in French Canadians from Quebec and New Brunswick (the former Acadia)[14]; however the prevalence in Louisiana Acadians is unknown.

Management of Usher syndrome patients

The key to management of patients with Usher syndrome is early diagnosis. Early diagnosis enables adapted educational and patient management options.

While there is no definitive cure for USH, there are a lot of treatments, and many of these treatments are most successful when begun early in life. The program is specific to each patient, is multidisciplinary, and is tailored to individual patient needs depending on the severity of the symptoms.

The team comprises specialists in Otolaryngology, Ophthalmology, Genetics, Audiology, Speech Therapy and Nursing.

Treatment of Manifestations

Current treatment focuses on rehabilitation of the auditory, vestibular and visual dysfunction.

Hearing

Hearing aids are usually ineffectual in individuals with USH1 because of the severity of the hearing loss. Cochlear implantation should be seriously considered, especially for young children[15]. Patients with USH 2 and 3 will benefit from traditional hearing aids, unless there is significant progression of the hearing loss with age.

Communication

It is imperative that children with hearing loss have good communication skills. As such, the affected children need to be identified early. Their new born screening should be assessed, and they need diagnostic testing as soon as possible. Once identified, they need communication started via an early intervention program so they can develop age appropriate communication skills.

Balance

Patients with USH1 who have impaired hearing, tunnel vision and night blindness combined with vestibular areflexia predispose patients to accidental injury. Children often benefit from physical therapy for their vestibular areflexia. Well-supervised sports activities may help a person with USH1 to compensate by becoming more adept at using the somatosensory component of the balance system. USH2 patients do not usually have any vestibular concerns, and USH3 patients may need interventions based on the severity of the vestibular areflexia.

Vision

Communication by sign language and lip reading becomes increasingly difficult over time as the RP progresses. Vision loss may progress to the point that the individual can only communicate through tactile signing. Routine ophthalmologic evaluation is recommended to detect potentially treatable complications such as cataracts.

Genetic counseling should be considered for families with Usher syndrome.

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