The importance of understanding the natural history of Usher Syndrome

Usher Syndrome is the leading genetic cause of deafblindness and represents a significant clinical and social challenge. Affected individuals experience a variable combination of hearing loss, progressive vision deterioration, and, in some cases, balance problems. Among the genes involved, MYO7A and USH2A play a central role: the former is responsible for more than 50% of Usher type I cases, the most severe form, while the latter is responsible for the majority of cases of the more common form, known as Usher type II. The natural history of these conditions has been increasingly described in recent years, thanks in part to multicenter studies such as Rush 2A, which examined the clinical evolution of patients with USH2A mutations.

Usher Syndrome type I presents a severe clinical picture from the outset: infants are born with profound sensorineural hearing loss, fail to acquire balance within the typical timeframe, and develop retinitis pigmentosa in early childhood. The retinal disease progresses rapidly, leading to significant visual field loss by adolescence. In many cases, legal blindness occurs within the third decade of life. The natural history of this form is therefore marked by a very early dual sensory disability, requiring intensive rehabilitation interventions from an early age.

Type II Usher Syndrome, caused by mutations in the USH2A gene, presents a different picture. Children with this form exhibit moderate or severe hearing loss from early childhood, but not profound deafness, and balance function is preserved. This allows for more typical language development and a greater degree of independence compared to type I. However, vision begins to deteriorate during adolescence or early adulthood, when the first symptoms of retinitis pigmentosa appear, such as difficulty seeing in the dark and progressive narrowing of the visual field.

A detailed understanding of this progression was also possible thanks to the Rush 2A study, one of the largest and most systematic studies on the natural history of Usher II. The study, conducted at numerous international clinical centers, followed patients with USH2A mutations over time to precisely describe the evolution of visual function. Rush 2A confirmed that visual field loss in USH2A patients is slow but

constant, and that central vision tends to remain relatively intact until the third or fourth decade of life. The study also identified sensitive parameters for monitoring progression, such as retinal sensitivity measured by microperimetry and photoreceptor thickness obtained by OCT. Another important contribution of the Rush 2A study concerns phenotypic variability: researchers observed that some USH2A mutations are associated with more rapid progression, while others produce a milder form or a predominantly retinal phenotype without significant hearing loss. These findings are crucial not only for understanding the natural history of the disease, but also help interpret clinical differences between patients and personalize follow-up and therapeutic interventions, allowing for the design of targeted clinical trials.

Research is opening up new avenues: for specific mutations in the USH2A gene, gene manipulation therapies based on antisense oligonucleotides are in advanced stages of study, while for MYO7A, a Phase 1/2 clinical trial is underway using a novel viral vector for gene replacement. Natural history studies are essential for evaluating the efficacy of these new strategies, allowing for the identification of the most specific clinical parameters for the disease.

On December 3, 2025, the "Workshop Outcome Measures for Gene Therapy" conference was held at the Bambino Gesù Children's Hospital in Rome. The conference examined the current state of knowledge and potential therapies for inherited retinal dystrophies and, through analysis of past and current studies, correctly defined the most sensitive clinical and instrumental parameters for assessing the efficacy of a specific therapy in clinical trials.

This conference, which saw the participation of national and international experts under the aegis of ERN-Eye (the European Reference Network for Rare Ocular Diseases) and representatives of patient organizations, such as USHER Italia A.P.S., emphasized the importance of natural history studies for better understanding disease progression and for being as precise as possible in establishing these parameters, which can vary significantly from disease to disease.

The presence of representatives of patient organizations, such as USHER Italia A.P.S., provided a comprehensive overview of the disease and the opportunity to express the public's expectations for research. affected through a comparison with specialists.

In conclusion, the natural history of Usher Syndrome linked to the MYO7A and USH2A genes demonstrates how two seemingly similar conditions can follow very different evolutionary paths. Understanding these pathways not only improves our understanding of the pathogenic mechanisms of a rare disease but also sheds light on the daily reality of people living with Usher syndrome and paves the way for interventions that, in the future, could significantly improve patients' quality of life.

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