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Genetic and phenotypic presentation of Usher syndrome - a case report

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ABSTRACT

Usher syndrome is a genetic, clinically heterogeneous condition characterized by sensorineural hearing loss, progressive retinal degeneration, and vestibular dysfunction. There are three phenotypically recognizable types of Usher syndrome. Individuals with Usher syndrome type 1 have no vestibular function and profound sensorineural hearing loss. Individuals with Usher syndrome type 2 have normal vestibular function and mild-to-severe hearing loss with visual impairment that is presented later in life. People with Usher syndrome type III experience hearing and vision loss beginning later in life. In this case report, we are reporting a 7-year-old boy consulted for progressive hearing loss and bilateral vision impairment, and fundus exam revealed mild bilateral retinal vessel attenuation and bone spicule deposits in both eyes. A molecular genetic test done by next-generation sequencing identified a homozygous pathogenic variant in the CDH23 gene (NM_022124.5:c.2255del variant coordinate with amino acid change of p.(Gly752Valfs*13)), confirming the diagnosis of autosomal recessive Usher syndrome type ID (USH1D). The patient had a remarkable improvement with visual and optical aids. Genetic counseling, including reproductive counseling, was provided to the parents. Clinical evaluation, visual hearing tests, and genetic workup confirmed Usher syndrome, which is a rare but dangerous cause of hearing loss and visual impairment that needs to be thoroughly evaluated by a multi-disciplinary team approach.

Keywords: Genetic, Phenotype, Usher syndrome, Vision Loss, Hearing Loss

INTRODUCTION

Usher syndrome is a genetic condition that is inherited as an autosomal recessive pattern. It permanently and severely affects the senses of hearing, vision, and balance. Three clinically distinct types of Usher syndrome have been identified, decreasing in severity from Type 1 to

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3, with symptoms of sensorineural hearing loss, retinitis pigmentosa, and vestibular dysfunction [1]. Deafness is often congenital. The eponym for the disease has been credited to Charles Usher, who, in 1914, described two variants of the disease. However, the first description of this syndrome was by Albrecht von Graefe in 1858 [2]. Usher syndrome type I is an autosomal recessive condition characterized by profound congenital hearing impairment with unintelligible speech, early retinitis pigmentosa (usually evident within the first decade), and constant vestibular dysfunction [3]. Usher syndrome is the most common hereditary form of deaf–blindness, with a global prevalence of 4 to 17 cases per 100,000 individuals; it accounts for more than half of all hereditary cases of deaf–blindness and 3–6% of all cases of childhood hearing loss [4]. Pathogenic variants of nine usher syndrome genes have been initially reported: MYO7A, USH1C, PCDH15, CDH23, and USH1G for USH1, USH2A, ADGRV1, and WHRN for USH2, and CLRN1 for USH3, Based on the co-occurrence of hearing and vision deficits, the list of USH genes has been extended to few other genes, but with limited supporting information [5].

Three clinical subtypes of Usher syndrome have been defined, Type 1, Type 2, and Type 3, based on the presence, severity, and progression of auditory, visual, and vestibular symptoms. Type 1 Usher syndrome accounts for approximately one-third of Usher syndrome cases and is the most severe form, with profound sensorineural hearing loss and vestibular dysfunction from birth, as well as progressive retinitis pigmentosa. Mutations in at least six genes can cause Usher syndrome type I. The most common of these are MYO7A gene mutations, followed by mutations in the CDH23 gene [1]. Usher syndrome type 2 patients typically have moderate sensorineural hearing loss from birth and retinitis pigmentosa, which starts during late puberty or early adulthood [6]. Although Usher syndrome was originally characterized as having non-progressive deafness, recent studies have shown that patients may suffer from increased loss of hearing over time, indicating symptoms can be progressive [7]. Three responsible genes have been identified so far, as well as Usher syndrome 2B, which was originally mapped to the short arm of chromosome 3, although following molecular analysis, this gene is no longer recognized as an Usher syndrome loci [8]. Patients with Usher syndrome type 3 typically exhibit symptoms by mid-life, including progressive sensorineural hearing loss and retinitis pigmentosa, usually with loss of night vision, constriction of the visual field, as well as variable, progressive vestibular dysfunction [9]. Though Usher syndrome is mostly associated with balance impairment, the patient in this case report was particular in having intact vestibular functions. Therefore, our case report will serve to inform healthcare providers of this rare but also diverse syndrome.

CASE PRESENTATION

This is a report of Usher syndrome in a 7-year-

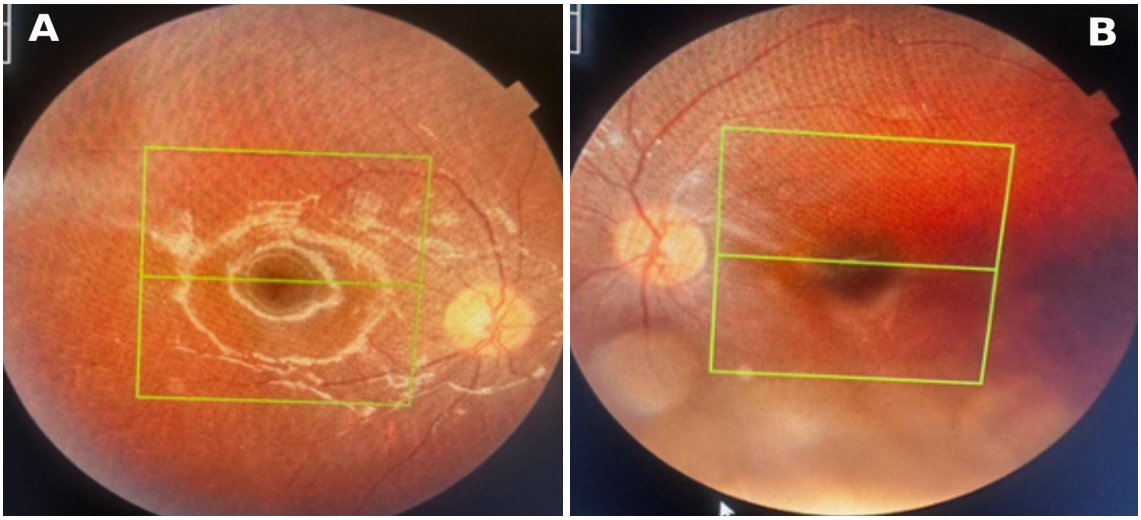

Figure 1: Funduscopic examination of both right (A) and left (B) eyes, showing mild bilateral retinal vessel attenuation and bone spicule deposits in both eyes.

old male pediatric Rwandan patient with a visual field defect, optic atrophy in the fundus exam in favor of retinitis pigmentosa. The developmental history and family history were unremarkable. The patient had hearing impairment, but her vestibular functions were preserved. Clinical evaluations and comprehensive testing of hearing, vestibular function, and visual function.

The funduscopic examination revealed mild, bilateral retinal vessel attenuation and bone spicule pigment deposits in the mid-periphery of both eyes (Figure 1).

A molecular genetic done by next-generation sequencing identified a homozygous pathogenic variant in the CDH23 gene (NM_022124.5:c.2255del variant coordinate with amino acid change of p.(Gly752Valfs*13)), confirming the diagnosis of autosomal recessive Usher syndrome type ID (USH1D). The patient had a remarkable improvement with visual and optical aids. Genetic counseling, including reproductive counseling, was provided to the parents.

DISCUSSION

Our report of one case of Usher syndrome adds to the growing literature on this disease; our patients' history suggests that the onset of the illness was in early childhood. Usher syndrome, while not a cause of early mortality, subjects the affected person and their supportive family to lifelong suffering and, hence, poor quality of life. Usher syndrome is a rare hereditary condition distinguished by a blend of auditory impairment and visual deficiency [2]. In this case, a blood sample was collected, and next-generation sequencing was performed, genomic DNA enzymatically fragmented, and regions of interest enriched using DNA capture probes. The final indexed libraries were sequenced on an Illumina platform, and a homozygous pathogenic variant was identified in the CDH23 gene. The genetic diagnosis of autosomal recessive Usher syndrome type ID (USH1D) was confirmed after combining molecular genetic tests and comprehensive clinical exams. The identified CDH23 variant c.2255del p.(Gly752Valfs*13), in our patient, creates a shift in the reading frame starting at codon 752. The new reading frame ends in a stop codon 12 positions downstream.

The Usher syndrome type 1D (USH1D) causative gene, CDH23, encodes cadherin 23 [10], which is a member of the cadherin superfamily of calcium-dependent cell adhesion molecules. It is a non-classical cadherin characterized by its long extracellular domain required for the development and correct morphology of the inner ear hair cell bundles and, along with protocadherin 15, forms the tip links between stereocilia [11].

The pediatric patient in this case report displayed typical indications of Usher syndrome, such as visual field abnormalities and optic atrophy detected during a fundus examination confirming the presence of retinitis pigmentosa, explaining hearing impairment and loss of vision both associated with Usher syndrome [7,8]. The hearing loss could range from slight to total.

Despite these vision and auditory problems, the patient's developmental and family history were ordinary, though the vestibular functions remained intact, setting this case apart from certain types of Usher syndromes that also impact balance [2].

Genetic testing is essential for accurately diagnosing Usher syndrome, as it is genetically diverse and caused by several gene mutations [12,13]. Therefore, the presence of homozygous pathogenic mutations in the CDH23 gene has confirmed the diagnosis of Usher syndrome, aligning with the patient's clinical presentation. Studies indicated that homozygous pathogenic mutations in the CDH23 gene are associated with hearing loss, vision loss, and problems with balance and coordination, collectively well-known signs and symptoms of Usher syndrome [14,15]. The fact that vestibular functions are maintained in this particular example contradicts certain literature that discusses Usher syndrome subtypes, which might potentially lead to vestibular impairment. This highlights the diverse range of symptoms that can be observed within the illness.

The patient demonstrated significant improvement with the use of visual and optical aids, underscoring the criticality of timely identification and intervention in the management of Usher syndrome. Usher syndrome patients can greatly improve their quality of life by utilizing visual aids like glasses and adaptive technologies [16,17]. Although there is no cure for the syndrome, using supporting measures such as rehabilitation services can help alleviate the effects of sensory impairments on everyday activities [17]. Cochlear implants are currently used to reduce the burden

of hearing loss in severe-to-profoundly deaf patients, but many promising treatments, including gene, cell, and drug therapies to restore the native function of the inner ear and retinal sensory cells, are under investigation [18].

The parents of sick children with Usher syndrome received genetic counseling in accordance with the latest recommended methods. Genetic counseling is necessary in cases of Usher syndrome to address the hereditary pattern, the likelihood of recurrence in subsequent pregnancies, and appropriate choices for family planning [19,20]. Families gain empowerment in making informed decisions about their reproductive options by comprehending the genetic foundation of the illness [20].

CONCLUSION

This case report provides significant insights into the clinical manifestation, diagnostics, and treatment of Usher syndrome in a pediatric patient from Rwanda. Confirming the presence of homozygous pathogenic mutations in the CDH23 gene underscores the significance of genetic testing for an accurate diagnosis. The positive outcomes achieved through the use of visual and optical aids highlight the need for early intervention to enhance the patient's quality of life. Healthcare experts can assist families in making well-informed decisions regarding their future reproductive choices by offering genetic counseling. This case study emphasizes the necessity of a multidisciplinary approach that includes ophthalmologists, audiologists, and genetic counselors in order to provide comprehensive care for persons diagnosed with Usher syndrome.

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