Abstract

Objective: To improve diagnostic accuracy in the work-up of patients with both deafness and decreased vision by analyzing patient data from a Genetic Eye/Ear clinic.

Design and Method: Retrospective chart review.

Patients: Patients of a single paediatric ocular genetics clinic with sensorineural deafness.

Results: In total, 17 patients (11 [64.7%] males, 6 [35.3%] females) were included in the study. Referral diagnoses included Usher syndrome (9), nonspecific dystrophy (3), dominant optic atrophy (1), optic nerve atrophy (1), cone dystrophy (1), fourth nerve palsy/ esotropia (1), and ocular motor apraxia (1). Of the 9 patients with suspected Usher syndrome, seven were confirmed to truly have the condition.

Conclusion: Usher syndrome is the best known and most common of the eye-ear genetic disorders, but there are others that should be considered in the differential diagnosis. ERG is helpful but often not diagnostic. Molecular genetic testing provided the most accurate diagnosis, but requires parental blood samples and detailed analysis of DNA variants for accuracy.

Introduction

Children with combined hearing and vision loss often are referred to the paediatric genetic eye disease service. We have created a combined Genetic Eye/Ear clinic to reduce the need for multiple visits, and to allow collaboration between our Genetic Eye and Ear departments at the University of Iowa. Because Usher syndrome is one of the most commonly recognized genetic disorders presenting with both vision and hearing loss, these patients are often given an initial diagnosis of Usher syndrome before complete workup is performed. However, there are other conditions that should be considered in the differential diagnosis for children who are presenting in this manner.

A misdiagnosis may be as difficult to disprove as the correct diagnosis is to prove. We sought to identify the hearing loss and vision loss were most common in our patient population to design the most effective work-up. Additionally, we goal was to generate a differential diagnosis along with a proposed protocol for evaluating these children.

Methods

This study is a retrospective chart review (2012 through 2014). It is a single centre study and is approved by the University of Iowa IRB Ethics Board. We looked at all patients referred to the Paediatric inherited eye disease services for evaluation of an ocular disorder associated with hearing loss. Most of these patients have been seen in a combined Genetic Eye/Ear clinic.

Collected data included the following:

1. Demographic data: age, gender, ethnicity
2. Family history: history of ocular and/or auditory disease in question
3. Medical Genetic testing results: most patients had testing by OtoSCOPE, an exome sequencing panel of known hearing loss genes
4. Clinical exam findings: visual acuity, pupil motility, ocular motility, anterior segment exam findings, slit lamp exam findings
5. Ancillary test results: electroretinogram (ERG), fundus photos, optical coherence tomography (OCT), visual fields, and visual evoked potentials (VEP)
6. Audiogram findings – presence and type of hearing loss
7. Reading ability and previous diagnostic, if any
8. Final diagnosis

Children with hearing loss, especially those that require cochlear implants, are often referred for Usher syndrome because it is the most common, and possibly also the most well-known, condition that presents with hearing and vision comorbidities. Approximately 10% of profoundly congenitally deaf children have Usher syndrome. However, multiple genes can cause Usher syndrome, several of which are highly polymorphic. Furthermore, it is a recessive diseases and many different phenotypes are carried by the same genotype. We found that some pre-diagnosed Usher cases indeed had a gene mutation but only in one allele, thereby leading us to the conclusion that genetic testing can be inconclusive in misleading, even for experienced geneticists.

There are many other conditions that also present with hearing loss and visual complaints. Our study showed the second most common condition to be Waardenburg syndrome type II. Waardenburg syndrome may present like Usher syndrome with decreased vision and hearing loss. However, multiple exome sequencing panels have been run in the last two years, and recently, for many patients with Usher syndrome and Waardenburg syndrome, a second gene has been found in the same patient.

Our study also diagnosed dominant optic atrophy (DOA). A previous study has found approximately 20% of OPN1 mutation carriers to be of the “plus” form with extra-ocular features such as hearing loss. Our patient (patient 12) mutation (p.R445H) has been described as one of the mutations causing both optic nerve atrophy and hearing loss. There have been reports in the past, we believe this could be another cause of hearing loss.

We also found only one case of congenital stationary night blindness and isolated hearing loss co-existing by chance in the same patient. Rare conditions including Harboyan syndrome, Cockayne syndrome, and Baraitser-Winter syndrome may cause hearing and vision loss. Recent advances in exome sequencing have shown that these rare diseases can be a part of a wider spectrum of diseases. These rare diseases are seen in our small sample of only 17 patients, but were only detected because the unusual combination of clinical features (including corneal thickness of 900 micrometers in patient 9) were combined with an exome panel which includes all known hearing loss genes in the patient.

Conclusion

Based on our survey of 17 paediatric patients with combined hearing loss and vision loss, we recommend the following work up: (1) complete eye examination with ancillary testing such as ERG and OCT as indicated. If the diagnosis is still unclear, this can be followed by (2) an exome sequencing based screen of known hearing loss genes. Great care must be taken in the interpretation of the genetic results, taking into account pathogenicity of variants, the fact that Usher syndrome genes are polymorphic and that two copies of the same gene with definite disease-causing mutations must be found in order to make the certain diagnosis. If this is non-diagnostic and ERG is abnormal, (3) exome sequencing panel of ocular genes, including retinal should be considered. Careful attention must be paid to every structure of the visual system since there are disorders which combine hearing with caval (e.g. Harboyan), optic nerve (e.g. DOA), iris (e.g. Waardenburg, Baraitser-Winter), and neural (e.g. Usher, Baraitser-Winter) features. Careful attention to extra-ocular structural changes such as in the vestibular system (e.g. Waardenburg) may also be useful.

Discussion

Patients

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Referring Dx</th>
<th>Final Diagnosis</th>
<th>Usher Allele</th>
<th>Other Molecular Genetics</th>
<th>ERG</th>
<th>Hearing Apparatus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dominant Optic atrophy</td>
<td>Saraval-Winter Syndrome</td>
<td>None</td>
<td>-</td>
<td>ACTG1</td>
<td>Hearing aids</td>
</tr>
<tr>
<td>2</td>
<td>Superior Oblique Palsy</td>
<td>Superior Oblique palsy with unilateral hearing loss</td>
<td>CDH2 (single allele)</td>
<td>-</td>
<td></td>
<td>Hearing aids</td>
</tr>
<tr>
<td>3</td>
<td>Usher Syndrome</td>
<td>Usher Syndrome Type IA</td>
<td>MYO7A (two alleles)</td>
<td>-</td>
<td></td>
<td>Cochlear implants</td>
</tr>
<tr>
<td>4</td>
<td>Usher Syndrome</td>
<td>Usher Syndrome Type 2A</td>
<td>USH2A (two alleles)</td>
<td>-</td>
<td></td>
<td>Cochlear implants</td>
</tr>
<tr>
<td>5</td>
<td>Usher Syndrome</td>
<td>Usher Syndrome Type 2A</td>
<td>USH2A (two alleles)</td>
<td>-</td>
<td></td>
<td>Cochlear implants</td>
</tr>
<tr>
<td>6</td>
<td>Usher Syndrome</td>
<td>Usher Syndrome Type 2A</td>
<td>USH2A (two alleles)</td>
<td>-</td>
<td></td>
<td>Cochlear implants</td>
</tr>
<tr>
<td>7</td>
<td>Usher Syndrome Type 2C</td>
<td>Waardenburg Syndrome</td>
<td>GPR98 (single allele)</td>
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<td></td>
<td>Cochlear implants</td>
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<tr>
<td>8</td>
<td>Dominant Optic atrophy</td>
<td>Saraval-Winter Syndrome</td>
<td>None</td>
<td>-</td>
<td></td>
<td>Hearing aids</td>
</tr>
</tbody>
</table>

ERG is helpful but not diagnostic in children with combined hearing and vision loss. Molecular genetic testing using OtoSCOPE, an exome sequencing panel of known hearing loss genes was the best first step, followed by an exome panel of vision loss genes if the former was negative and ERG was abnormal. Molecular genetic testing is vital but requires parental blood samples and detailed analysis of DNA variants to arrive at an accurate diagnosis.

References