Answers to Audience Questions - WSPOS World Wide Webinars

WWW 18 – Season 2 – Inherited Retinal Diseases: The Child Who Doesn't See


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1. Do we need to work up every patient with nystagmus?

   AD: I recommend a workup on every patient with INS because a large number of patients will have an underlying ocular cause for their nystagmus. Some of them are not obvious by doing a clinical exam alone and in some cases, there might be a treatment. If due to economic restraints the workup (including electrophysiology in some cases) is not possible, families should know that over time additional signs and symptoms may point towards an inherited eye disorder. They also should counsel about the risk of having another affected child.
   https://www.aao.org/disease-review/clinical-guidelines-childhood-nystagmus-workup

   ET: A good clinical exam is essential. The causes are often flagrant. More often than not, one finds iris transillumination defects that indicate albinism. An OCT is easy to obtain and may show foveal hypoplasia. The type of nystagmus also gives a clue to the etiology, and so do associated signs and symptoms. Light sensitivity and color vision defects suggest achromatopsia while very poor vision and night blindness suggest other types of retinal dystrophies. Finally a family history of other affected males in the family may suggest X-linked nystagmus.

   SC: A good clinical work up along with a detailed history and pedigree is always helpful. While it may not be immediately beneficial to the patient, these would provide good opportunities to undertake genetic testing and genotype-phenotype correlation to assess prognosis in the future.

   HLS: Evaluations for children with infantile nystagmus are worthwhile. A thorough examination, medical history, and family history will help direct the assessment. Previous research has shown that electrodiagnostic testing, ophthalmic imaging, and molecular testing have a good diagnostic yield (Bertsch M et al. The clinical evaluation of infantile nystagmus: what to do first and why. *Ophthalmic Genet* 2017; 38(1):22-33. PMID: 28177849).

2. What do you tell patients and parents when genetic testing does not find anything? What do you do then?

   AD: It is very important to know what is covered in the genetic testing that was performed and what is not included. It is also very important to establish a clinical diagnosis before genetic testing is ordered. If your clinical diagnosis is solid and the genetic testing coverage is good, the patient still has the disease, but the gene might be yet unknown or not tested in the test.
   If the clinical diagnosis is broad (which sometimes happens at a young age), like rod-cone dystrophy, the tests might be incomplete.
   With current knowledge and technology, we are only able, to find the disease-causing mutation in about 60% of the cases, so the families should be counselled on that.
   Ultimately, some diseases that look inherited, might be just developmental, like -atypical optic nerve coloboma or atrophy, congenital infections.

   ET: I take a fresh look at the patient and see if I have missed anything else that would suggest a post-inflammatory condition. Sometimes it is indeed genetic but the test did not cover all the bases, so I go back and see what the panel covered. Sometimes there is a need for a while exome or genome sequencing if the case for a genetic disorder is very strong.

SC: The patients and parents need to be appraised of genetic testing and its outcomes ahead of time. Simple and legible conversations between the patients, clinicians and genetic counsellors on the pros and cons of genetic testing go a long way in building accurate expectations. Additionally, the genetic testing labs should also provide some evidence-based data on the likelihood of a positive test for certain chosen conditions that exhibit strong genotype-phenotype correlation. When the patients are mentally prepared of the outcomes of their genetic testing, it is not too difficult to deal with negative results that could be either due to a failed test procedure, improper coverage of the gene (or genome), possibility of involvement of other genes that are yet unexplored or assignment of a wrong test due to a misdiagnosis.
In cases of negative or unexpected results, the genetic counsellor needs to appraise the clinician about the possible reasons for discordance. The next course of action could be to conduct a retest in case of failure or additional test depending on the presentation of the phenotype. If single gene or multiple gene (through targeted panel) screenings are negative, one should plan for whole exome (or whole genome) sequencing, depending on the need and based on the judgement of the clinician and the genetic counsellor. The outcome of the initial genetic testing is conveyed to the patient in lay language and once they are convinced, a fresh consent is taken for additional testing.

HLS: Pre-test counselling in which the potential outcomes of testing are discussed is the first step in addressing this question. When patients and families are informed that genetic testing can be positive, inconclusive, or negative, it sets expectations and establishes baseline knowledge for a results discussion. Depending on available data, precise numbers for detection rates can be offered, which can also assist in the understanding of the likelihood of different outcomes. When a genetic test has returned as negative, it is important to review the limitations of testing technology and the exact test ordered and acknowledge yet unknown genetic causes for the condition. I offer the ability or chance to pursue a different genetic test (if appropriate based on the clinical circumstance), either as a next step or in the future. I encourage patients and families to continue to inquire about genetic testing as it relates to their situation and I follow these cases long term to continue the discussion and provide updated genetic counselling and care, when possible.

3. What is the cost of all this testing? Do families pay or insurance around the world?

AD: Genetic testing could be fee-for-service (paid by insurance), research-based, or paid by various companies/foundations and the coverage varies. The same is true with other testing including electrophysiology, visual fields, photos, etc. In the United States, most insurance will cover at least some of it. One good source of finding the availability for testing is: https://www.ncbi.nlm.nih.gov/gtr/

ET: In the US it has become easier to find coverage. Not sure what it is like in other countries.

SC: The cost of genetic testing varies worldwide and is generally paid by the patient or their families unless these are covered under a clinical trial or a research program. In the developing world, insurance does not pay for genetic testing. The cost proportionately increases from single gene testing to screening a targeted panel with multiple genes and is the highest for whole exome and whole genome sequencing at any given laboratory.
Patients could see the genetic registry databases for genetic testing labs or clinical trials databases, where testing might be offered for free. Patients residing in the United States with a confirmed diagnosis of inherited retinal degeneration can avail free genetic testing for certain chosen retinal diseases under the open access genetic testing program (https://www.fightingblindness.org/open-access-genetic-testing-program#who-is-elegible-for-testing-512) supported by the Foundation Fighting Blindness.

HLS: It is critical to evaluate the insurance and financial situation prior to proceeding with genetic testing. This is because costs are essentially guaranteed to be passed along to the patient, particularly if the steps to pre-authorize the testing were not taken. In the United States, coverage of genetic testing by many payors is now possible (again, with the caveat of authorization). While there are some limitations, these are plan dependent. In my experience, genetic tests can be as affordable as a few hundred dollars or be as expensive as tens of thousands of dollars. If insurance coverage precludes patients from pursuing genetic testing, many laboratories offer patient assistance plans and payment options.

4. Status of gene therapy globally?

AD: The only FDA-approved product to this date is LUXTURNA (voretigene neparvovec-rzyl) for bi-allelic *RPE65* related Leber Congenital Amaurosis and Retinitis Pigmentosa. There are centres for treatment around the world.
One way of contacting a centre is by filling out a referral form on the Spark website. This will trigger a referral to the appropriate (usually closest) centre unless you or the patient request otherwise. Once that happens Spark may be able to provide financial and logistic assistance for the consultation visit.
Usually, this referral form will also require attaching the genetic testing that confirms the causative *RPE65* variants.https://mysparkgeneration.com/pdf/Luxturna_EnrollmForm_iPDF.pdf

SC: Globally, gene therapies across multiple disease conditions are currently at various stages from experimentations to translations and are yet to become the preferred practice patterns in treatment. Some of these such as achromatopsia are currently in clinical trials pending FDA approval. Gene therapy for correcting biallelic mutations in the *RPE65* gene in LCA is the major success story across all IRDs, which is currently in use (Luxturna) and approved by the FDA.

HLS: Gene therapies are continuing to emerge across the world, at the bench, in animal models, and in human trials. These therapies can change quickly, both toward the next phase or as a discontinuation of the research. It is important to stay apprised of the opportunities and establish a protocol to contact with patients with molecular confirmation to ensure that when a relevant opportunity emerges, they can be informed of an opportunity.

5. Does nystagmus improve post gene therapy?

   AN: Yes, it seems so but we haven't measured this quantitatively.

   AD: In my experience, yes.

   ET: In the dog model of RPE65, it does. I am not sure about humans.

   HLS: Defer to my colleagues who have direct experience.

6. In very young children child like the 22-month-old Dr. Aaron mentioned, do you depend on handheld ERG testing before genetic testing...or you would want to order genetic testing right away.

   AN: If we have a strong suspicion for an IRD we go straight to genetic testing.

   AD: It depends on the logistics available to you. I prefer the awake, full-field dome ERG (Espion E2 V5; Diagnosys LLC system with Colordome stimulator) with DTL electrodes rather than the handheld ERG. That is because the recordings of the handheld ERG are about 30% lower amplitudes and can lead to diagnosis error.
   ERG is just one step in the diagnosis. If the report is equivocal, or the test is not easily available to you, and you suspect LCA, proceeding with genetic testing without an ERG is a good option. Patients will not be treated with gene therapy, regardless of their ERG results, unless they have a complete genetic test to confirm their bi-allelic *RPE65* status.

   ET: I would go straight to genetic testing.

   SC: The ERG testing would provide a quantitative clinical attribute, which provides is a measure of the phenotype. These are important parameters to correlate with the genotype (obtained through genetic testing) to arrive at a disease diagnosis and also prognosis.
   Thus both these measures are important and should be done in parallel, as indicated in this editorial, Genotypes need Phenotypes (https://jamanetwork.com/journals/jamaophthalmology/article-abstract/426047).

   HLS: ERGs are an important component of the evaluation of children with retinal disorders and should be obtained, when possible. However, if it is not available or the child is uncooperative and if other relevant clinical signs or symptoms of retinal dystrophy are present, then I would proceed to genetic testing. That being said, phenotypic information is very important in evaluating genetic variants, particularly in the setting of multiple findings or variants that are likely pathogenic or of uncertain significance.

7. How long it takes to see the effect of gene therapy?

AN: sometimes within 1 week of treatment!

AD: In my experience, the nystagmus and visual responses improve within the 1st month and continue to improve for a while.

SC: It depends on the response of the patients and several other factors including the choice of vectors for delivery. The effect of gene therapy is assessed through some defined tasks that a normally sighted person would do. The accomplishment of these tasks by the patients undergoing gene therapy indicates its measure of success and can be witnessed at the completion of therapy to few weeks.

HLS: Defer to my colleagues who have direct experience.

8. Is there an International registry for patients who would be willing to enter trials for new gene therapies?

AD: Not that I know of, although would be a good idea. Clinical trials are usually listed on https://clinicaltrials.gov/. One has to be careful when recommending clinical trials to your patients because not all the trials listed on the website are FDA approved or IRB approved.

SC: The details on the latest clinical trials on gene therapy and recruitments can be seen at the following websites: a) http://www.genetherapynet.com/ b) https://clinicaltrials.gov/)

9. Any repetition of therapy needed?

AD: Not up to this point. The patients from the original clinical trial are now about 6 years from their therapy and most of them have maintained their gains.

SC: Only in some chosen conditions, multiple injections may be required.

HLS: Defer to my colleagues who have direct experience.

10. In what diseases could you use genetic therapy?

AD: The only FDA-approved product to this date is LUXTURNA (voretigene neparvovec-rzyl) for bi-allelic RPE65 related Leber congenital amaurosis and retinitis pigmentosa.
Hopefully, many others will follow soon.

ET: At this time, it is only approved for RPE65-related retinal disease. Several other gene therapy trials are underway.

SC: Currently, it is available only in Mendelian diseases, where mutations in a single gene are presumed to be implicated in the disease pathogenesis.