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Full-field stimulus testing: Role in the clinic and as an outcome measure in clinical trials of severe childhood retinal disease

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ABSTRACT

Disease mechanisms have become better understood in previously incurable forms of early-onset severe retinal dystrophy, such as Leber congenital amaurosis (LCA). This has led to novel treatments and clinical trials that have shown some success. Standard methods to measure vision were difficult if not impossible to perform in severely affected patients with low vision and nystagmus. To meet the need for visual assays, we devised a psychophysical method, which we named full-field stimulus testing (FST). From early versions based on an automated perimeter, we advanced FST to a more available light-emitting diode platform. The journey from invention to use of such a technique in our inherited retinal degeneration clinic is reviewed and many of the lessons learned over the 15 years of application of FST are explained. Although the original purpose and application of FST was to quantify visual thresholds in LCA, there are rare opportunities for FST also to be used beyond LCA to measure aspects of vision in other inherited retinal degenerations; examples are given. The main goal of the current review, however, remains to enable investigators studying and treating LCA to understand how to best use FST and how to reduce artefact and confounding complexities so the test results become more valuable to the understanding of LCA diseases and results of novel interventions.

1. Introduction

In the many eras before the recent emergence of some therapeutic strategies for inherited retinal degenerations (IRDs), the emphasis was mainly on disease classification. Advances occurred over the years in methods to document a patient's disease, such as fundus photography, standard visual assays or clinical electrophysiology (Marmor et al., 1983). The clinicians evaluating patients with IRDs also tended to make progress in retinal electrophysiology, electroretinography (ERG). The clinical ERG became a relatively well-investigated tool for subclassification of IRDs (for example, Berson and Simonoff, 1979). Clinical progress in understanding disease expression was possible when there was sufficient visual function for the usual tools to capture. Patients with severe low vision, however, could not perform traditional spatial vision and visual field tasks and the recourse was to use less quantitative grading systems; a practical purpose was to qualify individuals for disability assistance (Colenbrander and Fletcher, 1995).

With progress in genetics and the identification of molecular causes of IRDs, the well-known Mendelian forms of IRD became molecularly-named diseases and thoughts turned to specific therapies based on the underlying genes and mechanisms. One of the earliest IRD targets for gene-based therapies has been Leber congenital amaurosis (LCA), a heterogeneous group of retinal disorders considered among the more severe IRDs. LCA typically manifests congenital visual impairment, nystagmus, and ERGs showing non-detectable signals (den Hollander et al., 2008; Kondkar and Abu-Amero, 2019).

The proof-of-concept research that clearly showed efficacy of subretinal gene therapy in the *RPE65*-LCA canine model (Acland et al., 2001) opened the door to the possibility of translation to human LCA due to mutations in the *RPE65* gene. More was known about the canine and murine versions of this disease at that time, however, than about the human patients. The race was therefore on to try to understand whether common molecular causation meant disease equivalence. LCA patients with *RPE65* mutations were generally more severe in disease expression but there was a feature of their phenotype that permitted comparison to the animal models – a dissociation of structure and function. Unlike in the animal models in which there were great expanses of normal-appearing retina, patients had only patches of preserved retina

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