Inherited retinal diseases

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CHAPTER 13

SUMMARY

There has been a major thrust across the world in research into treatment of retinal degenerative diseases in recent years. With increase in the number of clinical trials to address the unmet need, outcome measures become important, not only to assess the efficacy of these treatment trials, but also to identify earlier time points where treatment can be instituted. The underlying genetic mutations of each disease are equally important before considering therapeutic interventions, especially gene therapy that is specific to each mutation.

This thesis addresses some of the newer imaging modalities that are being used in the management of IRDs. The thesis also looks into some of the genetic data from India, identifying mutations specific to the continent, and adding to the existing literature.

CHAPTER ONE provides an introduction to retinal dystrophies and outlines the aims of the thesis.

CHAPTER TWO is a detailed review of the current literature on inherited retinal diseases. We have discussed the clinical presentation of the common retinal dystrophies that include retinitis pigmentosa (RP), Stargardt disease and Leber congenital amaurosis. We have also discussed the current status of treatment into these conditions.

CHAPTER THREE is an overview of one of the newer imaging modalities, Adaptive optics (AO). In contrast to the axial resolution provided by optical coherence tomography, AO is able to provide excellent lateral resolution and therefore identify cellular details including cone count and structure. We have described the structural details noted in normal eyes, myopic eyes and those with retinal dystrophies.

CHAPTER FOUR describes the outer retinal tubules on the AO in patients with Bietti's crystalline dystrophy (BCD). First demonstrated in age-related macular degeneration, these tubules appear as hyporeflective ovoid spaces with hyperreflective borders in the outer nuclear layers on spectral domain optical coherence tomography (SD-OCT). These appear as elongated tubules of varying sizes, as a response to photoreceptor injury. This is the first study to demonstrate and describe these tubules in detail using AO in a retinal dystrophy.

CHAPTER FIVE investigated the structure-function correlation in the macula of patients with retinitis pigmentosa using a custom-designed software. The ultrastructure on the SD-OCT was related to function as measured by microperimetry (MAIA, Macular integrity assessment). We studied the retinal sensitivity at the macula using MAIA and the corresponding retinal thickness on SD-OCT, identifying changes that cause a reduction in function.

CHAPTER SIX studied the oxygen saturation profiles in patients with RP and macular dystrophy using the Oxymap T1 retinal oximeter. Arteriolar attenuation is a hallmark of RP. In addition to decrease in vascular diameters, we showed alteration in oxygen saturation profiles in all quadrants in the RP group but mainly in the infero-temporal quadrant in the macular group.

CHAPTER SEVEN studied a cohort of Indian patients with Stargardt disease. We presented the clinical information and identified five mutations in the ABCA4 gene, two of which were novel. This is the first study on genetic analysis of patients with Stargardt disease from India.

CHAPTER EIGHT investigated the results of exome sequencing in a family diagnosed with Neuronal ceroid lipofuscinosis or Batten's disease. NCL is a childhood onset neurodegenerative disease that often presents to the ophthalmologist first. We identified two novel MFSD8 mutations in the family. The chapter discusses the importance of exome sequencing in consanguineous families with neuronal ceroid lipofuscinosis.

CHAPTER NINE studied two Indian families identified with Choroideremia. We studied the clinical presentation and analysed their genetic mutations. SD-OCT showed loss of outer retina, preservation of the inner retina and choroidal thinning in the affected males and retinal pigment epithelial changes in the female carriers. Two known mutations were identified in the CHM gene. This is the first study to describe the genetic analysis of patients with Choroideremia from India.

CHAPTER TEN addresses the challenges of managing patients with retinal dystrophies in India. India faces several difficulties including lack of genetic counsellors and inadequate access to molecular genetic testing. This chapter describes the challenges and efforts to address these and the contribution of associations like the 'Organization for Rare Diseases India' towards addressing these problems.

CHAPTER ELEVEN is a review of various methods used to assess progression in RP. With many clinical trials and therapeutic interventions on the anvil, being able to monitor the progression and identify critical end points for these trials becomes crucial. Several relevant outcome measures including visual field assessment, electroretinography, OCT, fundus autofluorescence, microperimetry and AO were measured. We concluded that multiple modalities are required to arrive at meaningful outcome measures.

In summary, this thesis expostulates the expanding role of newer imaging systems in the management of inherited retinal diseases. It also adds to the existing literature of genetic mutations in the Indian population. The thesis has a special relevance to patients in India, given the exciting treatment options that are on the horizon.