Factors Associated with Visual Acuity in Patients with Cystoid Macular Edema and Retinitis Pigmentosa

Short title: Associations with VA in Retinitis Pigmentosa

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Abstract

Purpose. Retinitis pigmentosa is the most common inherited retinal dystrophy. The factors associated with visual acuity in patients with other retinal diseases are well known, but are poorly understood in patients with retinitis pigmentosa. This knowledge is useful for prognosis and to support secondary endpoints in clinical trials.

Methods. We conducted a cross-sectional study of consecutive patients recruited from the inherited retinal disease service from January 2012 to December 2012. Central macular thickness (CMT) was measured using spectral domain optical coherence tomography.

Results. Data were available for 81 patients and 162 eyes. After multivariable analyses, older age, earlier age of onset of symptoms, and thicker CMT were associated with lower visual acuity. Gender and inheritance pattern were not associated with visual acuity. Each decade older age, younger age of onset, and thicker CMT was associated with 0.12, 0.10 and 0.11 worse LogMAR units of visual acuity, respectively (P<0.05 for all).

Conclusions. Age, age of onset, and CMT are associated with visual acuity and important factors to measure in studies of retinitis pigmentosa.

Introduction

Retinitis pigmentosa (RP) or rod cone dystrophy is the most common inherited retinal dystrophy. It is

a heterogeneous, progressive disorder with no proven treatments despite much ongoing research.[1;2]

Cystoid macular edema is a known complication that can occur in patients with RP.[1] Unlike other

retinal diseases where cystoid macular edema also occurs such as age-related macular degeneration

and diabetic retinopathy, little is known about the factors associated with good visual acuity in

patients with RP. Such information is useful as it provides insights into pathophysiology and suggests

secondary or surrogate endpoints for testing new treatments. For example, the association between

central macular thickness (CMT) and visual acuity is well established in age-related macular

degeneration, diabetic macular edema and retinal vein occlusions and CMT is a recognised

secondary endpoint in treatments trials of these diseases.[3-5] The association between CMT and

visual acuity has been studied in patients with RP, but results have been inconsistent, partly because

studies included patients with and without cystoid macular oedema.[6-9] We therefore performed a

cross sectional study to determine the factors associated with visual acuity in patients with RP and

thickened central macula from cystoid macular edema.

Methods

We collected data on 81patients seen in the inherited retinal disease clinics at Moorfields Eye

Hospital NHS Foundation Trust, London, UK from January 2012 to December 2012 inclusive. Patients

were included in the study if they had macular oedema secondary to RP. Exclusion criteria included

macular edema secondary to other causes such as epiretinal membrane or vitreous traction. The

study was approved by the Human Research Ethics Committee of Moorfields Eye Hospital NHS

Foundation Trust and adhered to the tenets of the Declaration of Helsinki. Further details are

provided elsewhere.[10]

The diagnosis of RP was based on a history of nyctalopia, peripheral visual field constriction, characteristic fundus findings on ophthalmoscopic examination, fundus autofluorescence abnormalities such as peripheral hypoautofluoresence and central peri-macular hyperautofluorescent rings, and in some cases full field electroretinogram testing. Electroretinogram testing was performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.[11] Pedigrees were constructed and RP was categorised as autosomal dominant (e.g. one affected parent or child, equal gender distribution), autosomal recessive (e.g. no affected parents, multiple affected siblings, consanguinity) and X-linked RP (e.g. males only, no male-to-male transmission, mothers may have signs). [1] A limited number of patients had a molecular diagnosis. Snellen best-corrected visual acuities were documented and converted into logarithm of the minimal angle of resolution (logMAR) values for statistical analysis. The Spectralis HRA + OCT with viewing module version 5.1.2.0 (Heidelberg Engineering, Heidelberg, Germany) was used to acquire autofluorescence images as well as SD-OCT images. The SD-OCT protocol included a dense horizontal linear scan centered on the fovea and values of CMT were taken from the $1mm^2$ central retinal subfield.

SAS version 9.2 (SAS Institute, Cary NC) was used for analyses. Multivariable models were constructed with LogMAR visual acuity as the outcome variable, and age, gender, age of onset, inheritance pattern and CMT as the study variables. Generalised estimating equation models were used to account for the correlation between eyes. Pearson correlation coefficients were calculated for factors associated with visual acuity. Scatterplots were constructed using Excel.

Results

Table 1 shows the baseline characteristics of the 81 patients (162 eyes) included in the study. The mean age of patients was 41.9 years, and mean age of onset of symptoms was 23.4 years. Females comprised 44.4% of the sample, 29.6% of patients had an inheritance pattern consistent with autosomal dominant inheritance, 69.1% consistent with autosomal recessive and 1.2% with X-linked inheritance.

We examined the independent associations of the factors above with visual acuity and found that older age, earlier age of onset of symptoms, and thicker CMT were associated with worse visual acuity (Table 2). Gender and inheritance pattern were not associated with visual acuity. Each decade older age, younger age of onset, and thicker CMT was associated with 0.12, 0.10 and 0.11 worse LogMAR units of visual acuity, respectively (P<0.05 for all). Figure 1 shows the scatterplot of visual acuity and CMT with a trendline showing increasing LogMAR visual acuity with increasing CMT. The correlation between visual acuity in LogMAR units and age, age of onset, and CMT was r=0.10 (p=0.19), 0.15 (p=0.14) and 0.20 (p=0.01), respectively. (data not shown).

Discussion

Knowledge of the factors associated with visual acuity in retinal diseases can provide insight into prognostic indicators and suggest secondary endpoints for clinical trials of therapeutic agents. This has been examined extensively in other major retinal diseases, but few studies have investigated this in RP. We report that in patients with retinitis pigmentosa and cystoid macular edema, older age, earlier age of onset and thicker CMT are associated with worse visual acuity. Gender and inheritance pattern (autosomal recessive versus autosomal dominant) were not associated.

Older age and earlier age of onset are associated with poorer visual acuity as these are markers of longer duration of disease and greater degree of photoreceptor degeneration. Earlier age of onset may also be a measure of more severe disease,[1] and decline in photoreceptor function may accelerate with age.[1;12] Greater CMT is an indicator of more severe cystoid macular edema and is associated with poorer vision in neovascular age related macular degeneration,[13] diabetic macular oedema[14] and retinal vein occlusion[15] due to distortion of photoreceptors and bipolar cells. The correlation of CMT with visual acuity in our study was weak at r=0.20, which is comparable to that reported for cystoid macular edema in neovascular age-related macular degeneration (r=0.25)[13] and lower than that reported for diabetic macular edema (r=0.56)[14]. A study in patients with RP but

without clinical cystoid macular edema (i.e visible cysts on OCT) reported a U shaped relationship where patients with severe retinal thinning (due to loss of outer retinal and photoreceptor layers) and mild retinal thickening (from presumed subclinical cystoid macular oedema) were found to have poorer vision than those with normal retinal thickness[6]. Our results extend this to show there is a clear relationship between retinal thickening from clinical cystoid macular oedema and visual acuity. Together these results suggest that SD-OCT CMT may be a useful objective endpoint for clinical trials of treatments for RP.

Strengths of this study include the moderately large number of patients, careful phenotyping, pedigrees to determine inheritance, objective measurement of CMT on SD-OCT and multivariable adjustment in analyses. A limitation of the study is that there were very few patients with X-linked inheritance and we are unable to draw conclusions regarding this form of disease. The majority of patients did not have a molecular diagnosis. Genotype may be an important factor associated with visual acuity, but over 100 genes/loci have been identified in RP and testing for all of them is currently prohibitively expensive.[2] This may become a more feasible option for future studies as the cost of genotyping continues to decrease. Another limitation of this study is that electrophysiology was only performed in patients in whom there was uncertainty regarding the diagnosis. The amplitude of the central segment of multifocal electroretinograms may correlate with visual acuity but was not routinely measured in this study.[16]

Conclusion

We report that age, age of onset of symptoms, and CMT are independently associated with visual acuity in patients with RP and cystoid macular edema. Data on these factors should be collected in clinical trials and other studies of patients with RP.

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Figure Legends

Figure 1. Scatterplot of LogMAR visual acuity against central macular thickness. The trendline shows a modest positive correlation.